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War and planetary viability are the biggest family medicine issues globally ... page 78

Editorial

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In this issue a number of papers from the region and an opinion section that addresses the atrocity of the various wars in the Region and Ukrainian.

Tabain et al., presented a case on Diagnosis of Colorectal Carcinoma in the Younger Population Amidst Mental Health Challenges. This case report goes through the journey of a 42 year old female patient getting diagnosed with colorectal carcinoma. They stressed that
Bowel cancer is a common type of cancer in both men and women - it is the 4th most common cancer in the UK, with over 42,000 people diagnosed every year. About 1 in 20 people will get it during their lifetime. Most people diagnosed with Colorectal cancer are over the age of 60. The diagnosis of Colorectal cancer is being made in the younger populations more frequently, and this case is an example of it. The chief complaint in this case has been a history of having intermittent loose stools for around 9 months on the background of always having a 'sensitive stomach'. Sometimes there has been mucus present. At times, there has been a feeling of being constipated. There has also been cramping abdominal pain which is relieved by opening your bowels and an on and off feeling of bloating. There has not been any weight loss, nor any blood in the stool and no meleana present throughout. No opening of bowels at night disturbing sleep. There has also not been any upper gastrointestinal symptoms throughout. No foreign travel prior. No patterns related to food. The symptoms did seem to follow a pattern of getting worse when there was undue stress/anxiety. There has been a past medical history of anxiety and more recently in the last few months of Irritable Bowel Syndrome (IBS). There is no significant family history apart from a cousin who has been diagnosed with Crohn's Disease. The patient was taking Sertraline for anxiety, and was also trialled on Mebeverine for a month for her IBS symptoms, to no success.

Dr Elghblawi, discussed Inflammoscopy and Stethoscopic of inflammatory skin lesions. The term Inflammoscopy merely implies trichoscopic distinctive features of inflammatory skin conditions; the commonest ones along with some rare ones, to demonstrate the usefulness, and to ease our understanding and help conclude, if possible, in aiding and supporting the diagnosis when it is equivocal. Previously, dermoscopy, an optical device that is used to detect skin malignancy, but promptly, it is also used to analyse inflammatory skin disorders as a supportive tool in various non-neoplastic dermatoses such as inflammatory, infiltrative, and infectious diseases, however; it doesn't follow a standardised approach. It is non-invasive, easy to apply, and allows visualization of the epidermis, dermo-epidermal junction, and papillary dermis, in vivo magnification of the skin which cannot be seen with the naked eye. Dermoscopy employs a ×10 to ×100 microscopic visualisation with a light source to magnify the structures under the skin's surface. There are three kinds of dermoscopy: namely, conventional nonpolarized dermoscopy, nonpolarized contact dermoscopy, and polarized contact dermoscopy. Many dermoscopic structures have a high degree of correspondence with pathognomonic histopathologic features. It's considered the dermatologist's stethoscope as it's an economic tool, yet data on the skill of colour is still limited and is a challenge. Histology is the cutting edge to learn about the underlying issues, but that needs a biopsy. Thus, applying trichoscopy features with the clinical findings can be sufficient to establish the right

diagnosis without the need for a biopsy. Nonetheless, dermoscopy requires special training and experience.

Helvaci, et al., looked at Metformin in the treatment of chronic obstructive pulmonary disease even in cases with normal weight. All patients with the SCD were studied. They included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused RBC in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly. SCD are prototypes of an accelerated atherosclerotic process all over the body. On the other hand, the role of excess fat tissue on the systemic atherosclerosis, the efficacy of metformin in loss of appetite, and atherosclerotic background of COPD are obvious in the literature. Since metformin is a safe, cheap, oral, long term used, and effective drug for the treatment of excess weight, it should be prescribed in COPD even in patients with the normal weight to minimise the adverse effects of excess fat tissue on the lungs since there are approximately 20 kg of excess fat tissue between the upper and lower borders of the normal weight in adults.

Helvaci*, et al., looked at Metformin in the treatment of cirrhosis. All patients with the SCD were included. They studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused RBC in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males. SCD terminate with an accelerated atherosclerotic process in whole body, and cirrhosis may just be one of the several consequences of systemic atherosclerosis. Excess fat tissue may be much more important than alcohol and smoking for the development of cirrhosis all over the world at the moment. The efficacy of metformin in loss of appetite is well known in the literature. Since metformin is a safe, cheap, orally used, and effective drug for the treatment of excess weight, it should be advised in cirrhosis even in patients with the normal weight since there are approximately 20 kg of excess fat tissue even between the upper and lower borders of normal weight in adults.

Metformin in the treatment of cirrhosis

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Abstract

Background: Hardened red blood cells (RBC)-induced capillary endothelial damage initiating at birth terminates with atherosclerotic end-organ failures in much earlier ages of life in sickle cell diseases (SCD).

Methods: All patients with the SCD were included.

Results: We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused RBC in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males.

Conclusion: SCD terminate with an accelerated atherosclerotic process in whole body, and cirrhosis may just be one of the several consequences of systemic atherosclerosis. Excess fat tissue may be much more important than alcohol and smoking for the development of cirrhosis all over the world at the moment. The efficacy of metformin in loss of appetite is well known in the literature. Since metformin is a safe, cheap, orally used, and effective drug for the treatment of excess weight, it should be advised in cirrhosis even in patients with the normal weight since there are approximately 20 kg of excess fat tissue even between the upper and lower borders of normal weight in adults.

Key words: Sickle cell diseases, cirrhosis, excess fat tissue, alcohol, smoking, vascular endothelial inflammation, systemic atherosclerosis

Introduction

Chronic endothelial damage may be the major cause of aging and death by causing end-organ failures in human being (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, and dementia-like end-organ insufficiencies and aging, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the vascular process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the cases with associated thalassemia minors (TM), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened RBC into the tissues. The hardened RBC-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in the SCD (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, since the SCD with associated TM show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with

with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively), and there was no patient above the age of 59 years in both genders. Prevalences of associated TM were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes (Table 2). On the other hand, mean ages of the other atherosclerotic consequences in the SCD were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Excess weight may be the most common cause of disseminated vasculitis all over the world at the moment, and it may be one of the terminal endpoints of the metabolic syndrome, since after development of excess weight, nonpharmaceutical approaches provide limited benefit either to improve excess weight or to prevent its complications. Excess fat tissue may lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Excess fat tissue is associated with many coagulation and fibrinolytic abnormalities suggesting that it causes a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22, 23). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (24, 25). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (26, 27). On the other hand, individuals with excess fat tissue will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excess fat tissue. In addition to the common comorbidity of atherosclerosis and HT, the prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased with increased body mass index (BMI) (28). Similarly, the prevalences of CHD and stroke, particularly ischemic stroke, increased parallel with the elevated BMI values in another study (29). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess fat tissue for both genders in all age groups (30). The excess fat tissue may be the most common cause of accelerated atherosclerotic process all over the body at the moment, the individuals with underweight may even have lower biological ages (30). Similarly, calorie restriction extends lifespan and retards age-related chronic diseases (31).

Smoking may be the second most common cause of disseminated vasculitis all over the world at the moment. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in whole body (32). Its atherosclerotic effect is the most obvious in the COPD and Buerger's disease (33). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic findings are acute inflammation, stenoses and occlusions of arteries and veins, and involvements of hands and feet. It is usually seen in young males between the ages of 20 and 40 years. Claudication may be the most common initial symptom in Buerger's disease. It is an intense pain caused by insufficient blood flow during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness or tingling of the limbs is also common. Raynaud's phenomenon may also be seen in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers or toes are the final consequences. Gangrene of fingertips may even need amputation. Unlike many other forms of vasculitis, Buerger's disease does not keep other organs with unknown reasons, yet. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buerger's disease. In angiogram, stenoses and occlusions in multiple areas of arms and legs are seen. In order to rule out some other forms of vasculitis by excluding involvement of vascular regions atypical for Buerger's disease, it is sometimes necessary to perform angiograms of other body regions. Skin biopsies are rarely required, since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use, particularly cigarette smoking is clear. Although most patients are heavy smokers, some cases with limited smoking history have also been reported. The disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed stenoses and occlusions are irreversible. Due to the clear evidence of inflammation in this disorder, anti-inflammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in fingers or toes at the moment. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (34). Similarly, it is not an unexpected result that smoking was associated with the lower values of BMI due to the systemic inflammatory effects on vascular endothelium (35). In another definition, smoking causes a chronic inflammation in human body (36). Additionally, some evidences revealed an increased heart rate just after smoking even at rest (37). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (38). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (39). Smoking may be associated with a postcessation weight gain, but the

risk is the highest during the first year, and decreases with the following years (40). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher prevalences of white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (41). Beside that the prevalence of myocardial infarction is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (42). In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (43). There may be several underlying mechanisms to explain these associations (44). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (45). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (43).

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess fat tissue all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (46). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (46). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (47). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (48). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (49). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (39). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (50). For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (50, 51). As a result, cirrhosis may also be another atherosclerotic consequence of the SCD.

Acute painful crises are the most disabling symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (52). The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (53, 54). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (53, 54). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (55, 56). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during the crises (57). Actually, the decreased severity of pain by transfusions also indicates the decreased severity

of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, white blood cells (WBC), platelets (PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (58), and it was associated with the risk of stroke in a cohort of Jamaican patients (59). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (60), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (61, 62). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (63). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (64). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (65). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (65). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (65). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (65). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) in the previous study (53). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (66). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (66). The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (67). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PG) and thromboxanes (TX) is due to its irreversible inactivation of the COX enzyme required for PG and TX synthesis. PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (68). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (69). According to the literature, aspirin may also be effective in prevention of colorectal cancers (70). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome,

the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 12 years (71). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (72). Reye syndrome is a rapidly worsening brain disease (72). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (73). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (73). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (72). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (72). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (72). The cause of Reye syndrome is unknown (73). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (73, 74). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (72). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (73). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (73). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (75).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (76). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (77). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (78). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (79). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (78). The risk is particularly increased once the INR exceeds 4.5 (79). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (80). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (81). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (81). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (82). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (82). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (82). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (82). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTE), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTE in patients with CVT (83). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although

rectal bleeding occurs more frequently in those men who report this symptom (84). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (85). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (85). The mortality was markedly lower in the warfarin group, too (p= 0.005) (85). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (85). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (86). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (86). The average daily dose was 2.6 mg, and the mean INR was 1.5 (86). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (87). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (88). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (89). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCD (90). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (91).

COPD is the third leading cause of death with various underlying etiologies in whole world (92, 93). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the most significant cause of COPD all over the world due to the excess fat tissue-induced systemic atherosclerotic process in whole body. After smoking and excess fat tissue, regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (94). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (95). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (25, 96). For example, there may be close relationships between COPD, CHD, PAD, and stroke (97). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (98). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (98). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (99). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (92).

Leg ulcers are seen in 10% to 20% of the SCD (100), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (101). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (100). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (100). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (101). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities, again. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (102). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (103). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems in the SCD. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (64). Prolonged resolution of leg

ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema instead of the terminal fibrosis alone.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (104). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (105). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional role of male gender in the systemic atherosclerotic process.

CRD is also increasing all over the world that can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (106). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (107). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (108). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (106). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (109). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (109). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (110). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess fat tissue, CRD progresses much more easily (109). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (111). Although some authors reported that alcohol was not related with the CRD (111), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (110). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (112, 113). For example, the most common cause of death was the cardiovascular diseases in the CRD again (114). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (115).

Stroke is an important cause of death, and develops as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, and excess fat tissue may be the major underlying causes. Stroke is also a common complication of the SCD (116). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (117). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (118). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation, edema, and fibrosis (119).

As a conclusion, SCD terminate with an accelerated atherosclerotic process in whole body, and cirrhosis may just be one of the several consequences of systemic atherosclerosis. Excess fat tissue may be much more important than alcohol and smoking for the development of cirrhosis all over the world at the moment. The efficacy of metformin in loss of appetite is well known in the literature. Since metformin is a safe, cheap, orally used, and effective drug for the treatment of excess weight, it should be advised in cirrhosis even in patients with the normal weight since there are approximately 20 kg of excess fat tissue even between the upper and lower borders of normal weight in adults.

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Metformin in the treatment of chronic obstructive pulmonary disease even in cases with normal weight

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Abstract

Background: Hardened red blood cells (RBC)-induced capillary endothelial damage initiates at birth, and terminates with atherosclerotic end-organ insufficiencies in early years of life in the sickle cell diseases (SCD).

Methods: All patients with the SCD were studied.

Results: We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused RBC in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly.
Conclusion: SCD are prototypes of an accelerated atherosclerotic process all over the body. On the other hand, the role of excess fat tissue on the systemic atherosclerosis, the efficacy of metformin in loss of appetite, and atherosclerotic background of COPD are obvious in the literature. Since metformin is a safe, cheap, oral, long term used, and effective drug for the treatment of excess weight, it should be prescribed in COPD even in patients with the normal weight to minimise the adverse effects of excess fat tissue on the lungs since there are approximately 20 kg of excess fat tissue between the upper and lower borders of the normal weight in adults.

Key words: Sickle cell diseases, chronic obstructive pulmonary disease, smoking, excess fat tissue, vascular endothelial inflammation, systemic atherosclerosis, end-organ insufficiency

Introduction

Chronic endothelial damage may be the major cause of aging and death by causing end-organ failures in human being (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, and dementia-like end-organ insufficiencies and aging, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the vascular process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the cases with associated thalassemia minors (TM), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened RBC into the tissues. The hardened RBC-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in the SCD (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, since the SCD with associated TM show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the

cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively), and there was no patient above the age of 59 years in both genders. Prevalences of associated TM were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes (Table 2). On the other hand, mean ages of the other atherosclerotic consequences in the SCD were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	*48.1 ± 61.8 (0-434)*	*0.000*	*28.5 ± 35.8 (0-206)*
Disseminated teeth losses (<20 teeth present)	*5.4% (12)*	*<0.001*	*1.4% (3)*
COPD§	*25.2% (56)*	*<0.001*	*7.0% (15)*
Ileus	*7.2% (16)*	*<0.001*	*1.4% (3)*
Cirrhosis	*8.1% (18)*	*<0.001*	*1.8% (4)*
Leg ulcers	*19.8% (44)*	*<0.001*	*7.0% (15)*
Digital clubbing	*14.8% (33)*	*<0.001*	*6.6% (14)*
CHD¶	*18.0% (40)*	*<0.05*	*13.2% (28)*
*CRD***	*9.9% (22)*	*<0.05*	*6.1% (13)*
Stroke	*12.1% (27)*	*<0.05*	*7.5% (16)*
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Obesity may be one of the major terminal endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to improve obesity or to prevent its complications. Excess fat tissue probably leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Excess fat tissue is associated with many coagulation and fibrinolytic abnormalities suggesting that it causes a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22, 23). For instance, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (24, 25). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (26, 27). On the other hand, individuals with excess fat tissue will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excess fat tissue. The prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of atherosclerosis and HT. In addition to systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased with increased body mass index (BMI) (28). Similarly, the prevalences of CHD and stroke, particularly ischemic stroke, increased parallel with the elevated BMI values in another study (29). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess fat tissue for both genders in all age groups (30). The excess fat tissue may be the most common cause of accelerated atherosclerotic process all over the body at the moment, the individuals with underweight may even have lower biological ages (30). Similarly, calorie restriction extends lifespan and retards age-related chronic diseases (31).

After excess fat tissue, smoking may be the second most common cause of disseminated vasculitis all over the world. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in whole body (32). Its atherosclerotic effect is the most obvious in the COPD and Buerger's disease (33). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic findings are acute inflammation, stenoses and occlusions of arteries and veins, and involvements of hands and feet. It is usually seen in young males between the ages of 20 and 40 years. Claudication may be the most common initial symptom in Buerger's disease. It is an intense pain caused by insufficient blood flow during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness or tingling of the limbs is also common. Raynaud's phenomenon may also be seen in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers or toes are the final consequences. Gangrene of fingertips may even need amputation. Unlike many other forms of vasculitis, Buerger's disease does not keep other organs with unknown reasons, yet. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buerger's disease. In angiogram, stenoses and occlusions in multiple areas of arms and legs are seen. In order to rule out some other forms of vasculitis by excluding involvement of vascular regions atypical for Buerger's disease, it is sometimes necessary to perform angiograms of other body regions. Skin biopsies are rarely required, since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use, particularly cigarette smoking is clear. Although most patients are heavy smokers, some cases with limited smoking history have also been reported. The disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed stenoses and occlusions are irreversible. Due to the clear evidence of inflammation in this disorder, anti-inflammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in fingers or toes at the moment. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (34). Similarly, it is not an unexpected result that smoking was associated with the lower values of BMI due to the systemic inflammatory effects on vascular endothelium (35). In another definition, smoking causes a chronic inflammation in human body (36). Additionally, some evidences revealed an increased heart rate just after smoking even at rest (37). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (38). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (39). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (40).

Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher prevalences of white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (41). Beside that the prevalence of myocardial infarction is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (42). In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (43). There may be several underlying mechanisms to explain these associations (44). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (45). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (43).

COPD is the third leading cause of death with various underlying etiologies in whole world (46, 47). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the most significant cause of COPD all over the world due to the excess fat tissue-induced systemic atherosclerotic process in whole body. After smoking and excess fat tissue, regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (48). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (49). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (25, 50). For example, there may be close relationships between COPD, CHD, PAD, and stroke (51). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (52). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (52). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (53). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (46).

Acute painful crises are the most disabling symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (54). The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (55, 56). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (55, 56). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (57, 58). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since

RBC transfusions probably have the strongest analgesic effects during the crises (59). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, white blood cells (WBC), platelets (PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (60), and it was associated with the risk of stroke in a cohort of Jamaican patients (61). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (62), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (63, 64). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (65). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (66). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (67). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (67). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (67). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (67). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) in the previous study (55). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (68). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (68). The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (69). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PG) and thromboxanes (TX) is due to its irreversible inactivation of the COX enzyme required for PG and TX synthesis. PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (70). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (71). According to the literature, aspirin may also be effective in prevention

of colorectal cancers (72). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 12 years (73). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (74). Reye syndrome is a rapidly worsening brain disease (74). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (75). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (75). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (74). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (74). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (74). The cause of Reye syndrome is unknown (75). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (75, 76). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (74). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (75). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (75). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (77).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (78). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (79). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (80). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (81). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (80). The risk is particularly increased once the INR exceeds 4.5 (81). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (82). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (83). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) (83). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (84). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) (84). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin ($p= 0.002$) (84). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between ($p>0.05$) (84). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTE), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran

are safe and effective for preventing recurrent VTE in patients with CVT (85). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (86). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (87). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (87). The mortality was markedly lower in the warfarin group, too (p= 0.005) (87). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (87). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (88). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (88). The average daily dose was 2.6 mg, and the mean INR was 1.5 (88). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (89). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (90). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (91). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCD (92). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (93).

Leg ulcers are seen in 10% to 20% of the SCD (94), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (95). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (94). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (94). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (95). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities, again. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (96). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (97). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems in the SCD. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (66). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema instead of the fibrosis alone.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (98). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (99). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, p<0.001) may also show some additional role of male gender in the systemic atherosclerotic process.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess fat tissue all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (100). NAFLD is a

marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (100). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (101). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (102). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (103). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (39). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (104). For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (104, 105). As a result, cirrhosis may also be another atherosclerotic consequence of the SCD.

CRD is also increasing all over the world that can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (106). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (107). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (108). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (106). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (109). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (109). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (110). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess fat tissue, CRD progresses much more easily (109). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (111). Although some authors reported that alcohol was not related with the CRD (111), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (104). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (112, 113). For example, the most common cause of death was the cardiovascular diseases in the CRD again (114). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (115).

Stroke is an important cause of death, and develops as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, and excess fat tissue may be the major underlying causes. Stroke is also a common complication of the SCD (116). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (117). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (118). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation, edema, and fibrosis (119).

As a conclusion, SCD are prototypes of an accelerated atherosclerotic process all over the body. On the other hand, the role of excess fat tissue on the systemic atherosclerosis, the efficacy of metformin in loss of appetite, and atherosclerotic background of COPD are obvious in the literature. Since metformin is a safe, cheap, oral, long term used, and effective drug for the treatment of excess weight, it should be prescribed in COPD even in patients with the normal weight to minimise the adverse effects of excess fat tissue on the lungs since there are approximately 20 kg of excess fat tissue between the upper and lower borders of the normal weight in adults.

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Inflammoscopy and Stethoscopic view of inflammatory skin lesions

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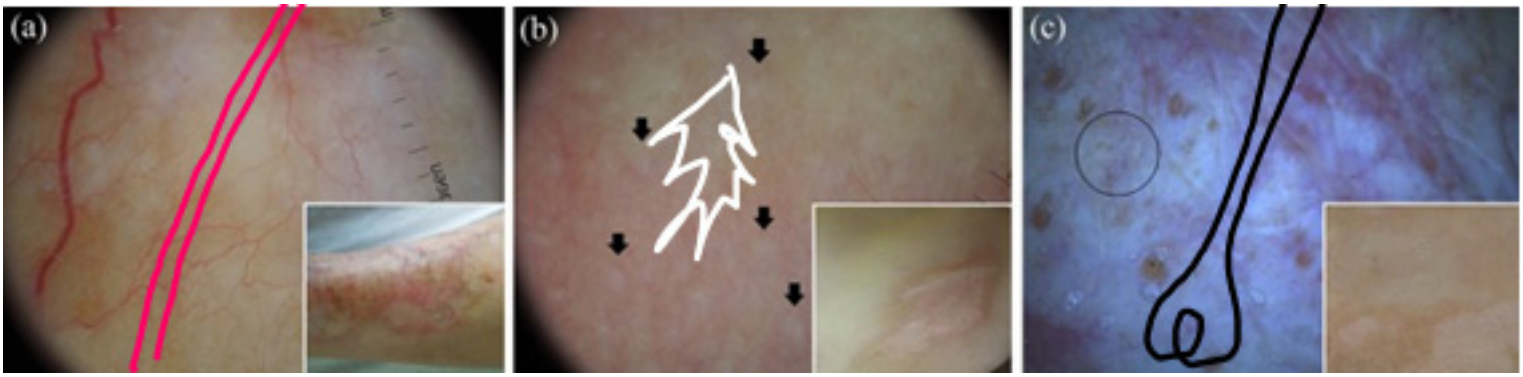
Abstract

The term inflammoscopy merely implies trichoscopic distinctive features of inflammatory skin conditions; the common ones along with some rare ones, to demonstrate the usefulness, and to ease our understanding and help conclude if possible, aiding and supporting the diagnosis when it is equivocal. Previously, it was termed dermoscopy. It entailed an optical device that is used to detect skin malignancy promptly. It is also used to analyse inflammatory skin disorders and as a supportive tool in various non-neoplastic dermatoses such as inflammatory, infiltrative, and infectious diseases, however; it doesn't follow a standardised approach. It is non-invasive, easy to apply, and allows visualization of the epidermis, dermo-epidermal junction, and papillary dermis, in vivo magnification of the skin which cannot be seen with the naked eye.

Dermoscopy employs a ×10 to ×100 microscopic visualisation with a light source to magnify the structures under the skin's surface. There are three kinds of dermoscopy: namely, conventional nonpolarized dermoscopy, nonpolarized contact dermoscopy, and polarized contact dermoscopy. Many dermoscopic structures have a high degree of correspondence with pathognomonic histopathologic features.

The dermatoscope is considered the dermatologist's stethoscope and is an economic tool, yet data on the skill of colour is still limited and is a challenge. Histology is the cutting edge method to learn about the underlying issues, but requires a biopsy. Thus, applying trichoscopy features with the clinical findings can be sufficient to establish the right diagnosis without the need for a biopsy. Nonetheless, dermoscopy requires special training and experience.

Keywords:
Dermoscopy, trichoscopy, inflammoscopy, inflammation, skin.



Most common structures: vessels, scales, hair follicles.

Introduction

The most common structures seen in any inflammatory skin diseases are mainly blood vessels (a), scales or crusts (b), and hair follicle changes (c). Thus, the International Dermoscopy Society came up with a consensus for dermatoscopic parameters to be applied to the skin in general dermatology usage; namely,

1. blood vessels morphology and distribution,
2. scales colour and distribution,
3. follicular findings and their disturbances,
4. other specific clues like in lichen planus (Wickham striae) and porokeratosis (peripheral collarette which coincides with coronoid lamella histologically).

In any inflammatory skin condition, the main thing to consider is the vascular structure along the scales. Applying a noncontact polarising dermatoscope is recommended, in some cases along with an interface fluid such as oil or gel to enhance visualization over scales.

Common inflammatory scalp diseases, such as psoriasis, seborrheic dermatitis, lichen planopilaris, discoid lupus erythematosus, contact dermatitis, syphilis, or pemphigus may share similar clinical features. Thus, trichoscopy may offer a quick, non-invasive, cost-effective, and in-office diagnostic method of significant value in clinical practice, with a microstructure view.

The vessel morphology can be:
Dotted, as rounded vessels of any size, and is seen in most skin inflammatory conditions including dermatitis, lichen planus, pityriasis rosea, and porokeratosis. However, **linear** vessels without branching or **curving** can be seen in sun-damaged skin, steroids-treated areas for a long time, and rosacea which displays a polygonal vessel morphology. On the other hand, any **linear branching** vessels are distinctively associated with basal cell carcinoma, granuloma (tuberculosis and sarcoidosis), and advanced lupus. Besides **linear curved** vessels (comma vessels) are linked to dermal nevi, lichen planus, and mycosis fungoides(1).

Vessels can be distributed in a distinctive **regular** manner all over the lesion surface which is typified in psoriasis, or seen at the peripheral as in lichen planus. It can be **patchy**, that is randomly arranged without a specific pattern as seen in dermatitis and pityriasis rosea or network (plexus) like in psoriasis (dotted) and rosacea (linear)(1-4).

Scales play a role as well as colour and their distribution can aid in diagnosis as well. **Whitish** is seen in psoriasis mainly and lichen planus, while **yellowish** is linked to serum extravasation and keratin which is seen in all dermatitis coinciding with spongiosis, histologically. Also, scale distribution can aid as well, for example, if diffusely covering the lesion surface, which is visualised in several hyperkeratotic dermatoses, while central scales are seen mostly in psoriasis though it is not specific. Peripheral scales can be seen in pityriasis rosea and tinea, while patchy can be seen in several diseases (1-4).

Hair follicle distribution and its disturbance can aid in diagnosis as well. If it has follicular plugs, this can denote mostly discoid lupus. Additionally, it can show peri-follicular halo or pigmentation like in alopecia and re-pigmentation in vitiligo.

Specific clues can suggest a strong association with specific skin conditions, like the white crossing lines of Wickham striae in lichen planus and the peripheral keratotic rim of porokeratosis.

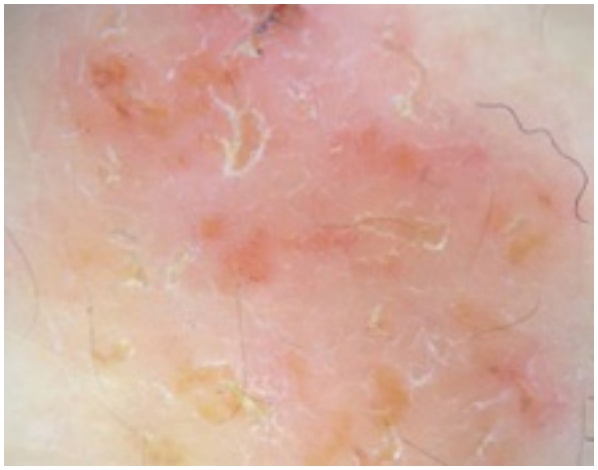
Psoriasis:
Psoriasis is a chronic and commonly encountered relapsing skin condition in the clinical setting that is characterised by thick silvery scales mostly in the scalp, and extensor parts of the body including the flexures and nails. Psoriasis is a multisystem disease.

The trichoscopic features can be: diffuse scaling, simple and twisted red loops, loads of red dots evenly distributed, globules, perifollicular scales, and glomerular vessels in the regular distribution along dry regular white scales observed (bushy pattern). Additionally, hidden hair and signet ring vessels have been reported recently. The uniformly distributed dotted vessels correspond histologically to dilated capillaries in regularly elongated dermal papillae over a dull red background along diffuse scaling which corresponds histologically to parakeratosis. The vessels are uniform in size and shape and on scale removal, red dots are noted that correspond to Auspitz sign (5).

Psoriasis, regular distribution (5).

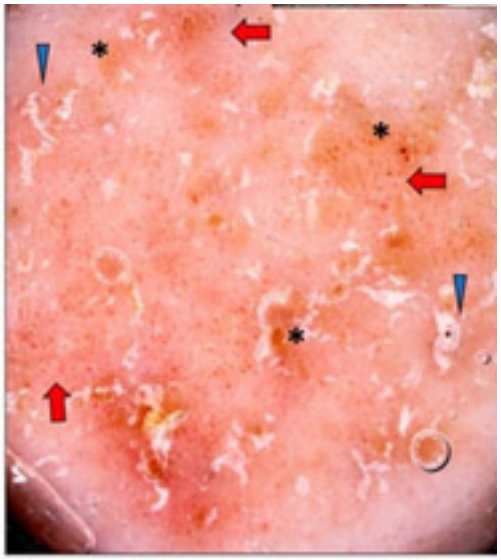
Psoriasis: thick white scales (5).

Eczema/dermatitis:
Eczema/dermatitis is a commonly encountered relapsing skin condition in the clinical setting that is characterised by itching, and dermatoscopic features are yellow scales/crusts which coincide with spongiosis /exocytosis in patchy/ clustered distribution, serocrusts, resulting from hyperkeratosis with some red dots but not linear, and white halo in chronic phases (lichenification) (1).



Dermatitis: dotted vessels in clusters with yellow scales (1).

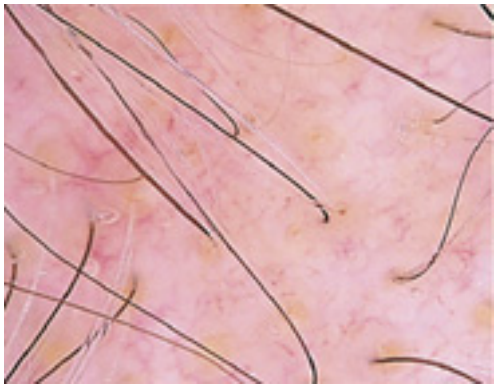
Discoid eczema, nummular eczema:
The predominant dermoscopy feature noted is dotted vessels in irregular distributions along white scales over yellowish scales with yellow structureless areas and “sticky fiber” sign with erosions(59).



Discoid eczema: dotted vessels in irregular distributions along white scales over yellowish scales (59).

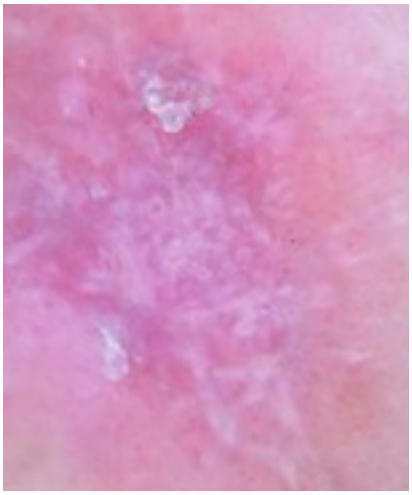
Seborrheic dermatitis:
Seborrheic dermatitis is a commonly encountered relapsing skin condition in the clinical setting that is characterised by scales in the oily based area of the face and anterior chest.

The trichoscope highlights some features, namely; atypical red vessels, twisted red loops, glomerular vessels, thin arborizing red vessels lines, glomerular vessels, structureless red areas, adherent yellowish scales, yellow dots between the follicular opening, perifollicular scales, and dandelion sign which denotes a yellow dot surrounded by glomerular and comma vessels which have the shape described and cherry blossom sign which means arborising vessels with glomerular and comma vessels around them (5-6).



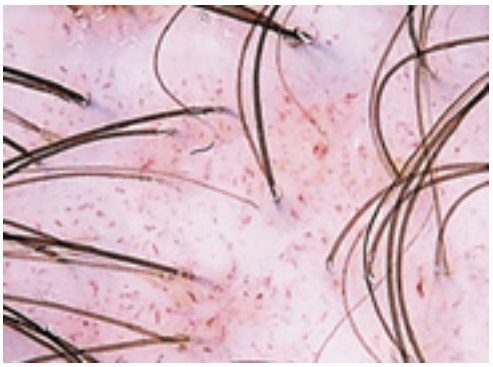
Seborrheic dermatitis: yellow scales (5-6).

Stasis dermatitis:
Stasis dermatitis exhibits glomerular vessels distributed in clusters or throughout the lesion (41). It also, displays superficial scales, white shiny structures, multiple rosette signs, white circles and generalized and homogeneous dotted vessels.



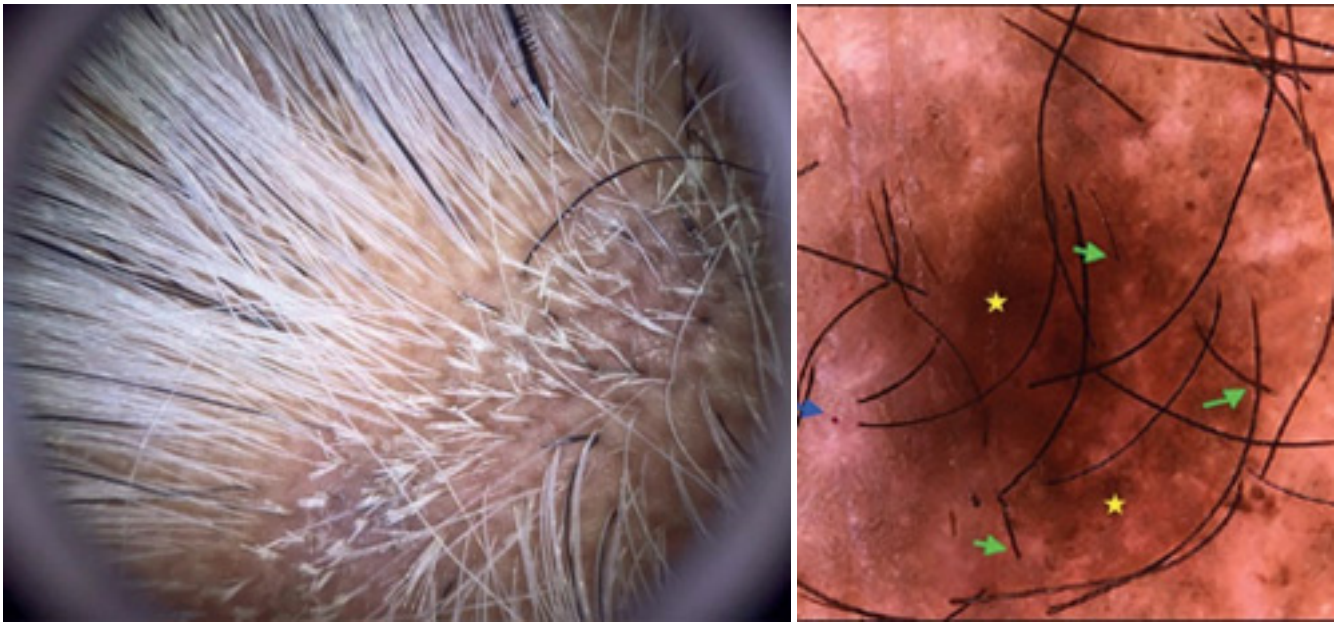
Stasis dermatitis: shows glomerular vessels distributed in clusters or throughout the lesion (41).

Contact dermatitis:
Contact dermatitis will show twisted red loops along arborising red lines (5-6).



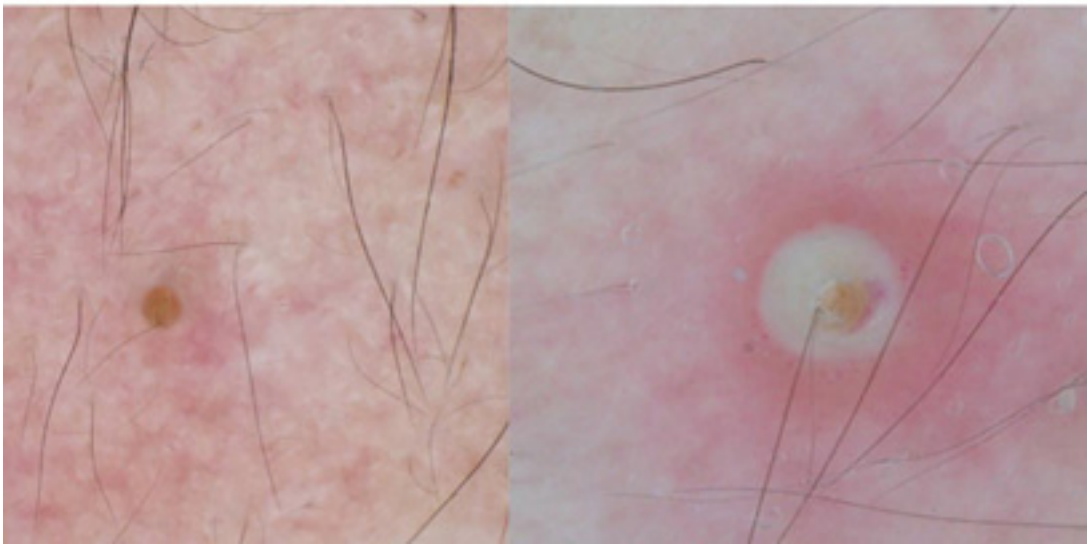
Contact dermatitis: irregular distribution (5-6).

Neurodermatitis/Lichen simplex chronicus:
It can show erythema, perifollicular scaling associated with hair shaft breakage in a chronic state. Also, on the scalp, an important dermoscopic feature of the disease is the 'broom fibers' which denote a well-delimited hair rarefaction area that displays a tonsure pattern (multiple hair emerging from the same follicle break at the same level distally) (43,57).



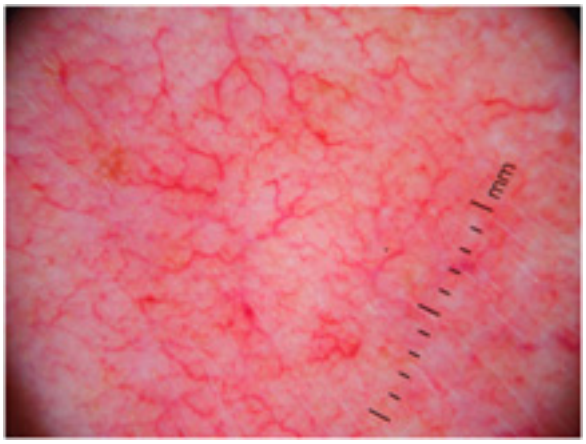
Lichen simplex chronicus: Shows erythema, perifollicular desquamation and tonsure pattern (43,57).

Acne vulgaris:
The main elementary findings are comedos that appear as dilated follicles filled with a white yellow circle or a brown pus that coincides with oxidised keratin, papules that appear as reddish rounded lesions due to the local inflammation and pustules due to collected purulent material inside the lesion cavity (64).



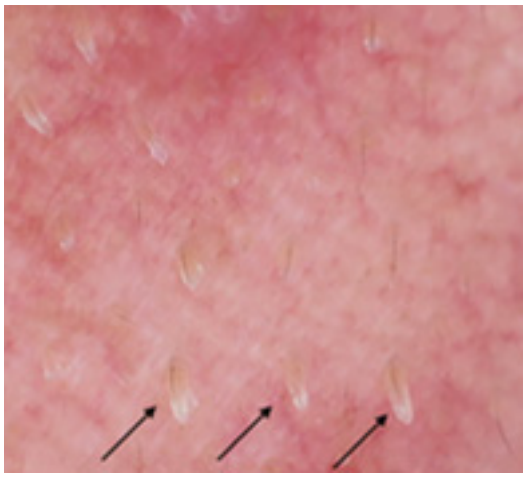
Acne vulgaris: papule and pustule consecutively (64).

Rosacea:
Dermatoscopic sensitive features comprise linear polygonal/arborising vessels (vascular polygons), orange yellowish areas along follicular plugs, dilated follicles, pigmented areas of white scales which are features of the presence of demodex tails(11-12).



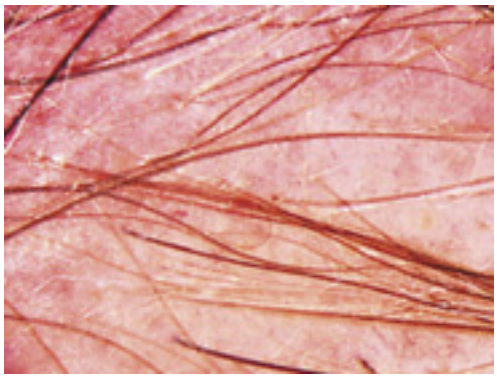
Rosacea: polygon vessels (11-12).

Demodicosis:
Its clinical findings can mimic several dermatoses like rosacea and seborrheic dermatitis. Its dermatoscopic distinctive finding is demodex tails which are white yellow protruding follicular keratotic plugs due to the presence of keratotic material and mites in the follicles (5-7,11).



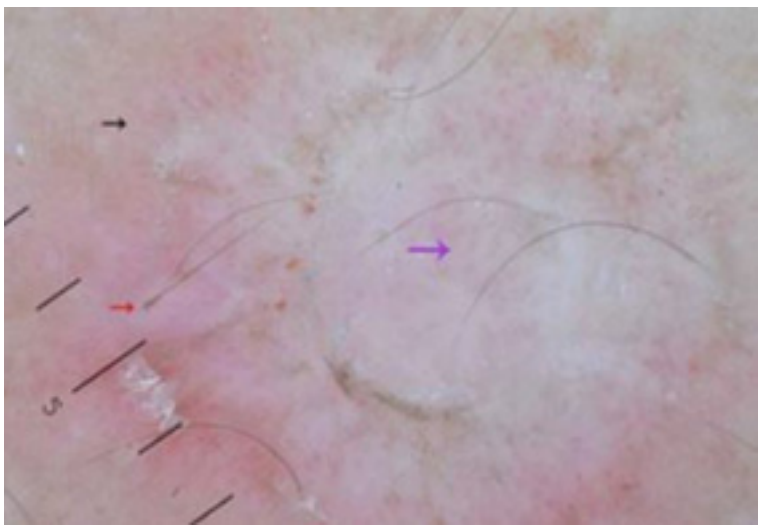
Demodicosis: Demodex tail (5-7).

Discoid lupus erythematosus:
The early stage will show follicular plugs, linear vessels, erythema around follicles, perifollicular white halo, white patches/scales, honeycomb or brownish pigmentation, structureless brownish areas, red, yellow, and white dots, arborising red lines, loss of follicular units, loss of follicular ostia and perifollicular scaling and pigmentation along telangiectasis at later stages (5-7).



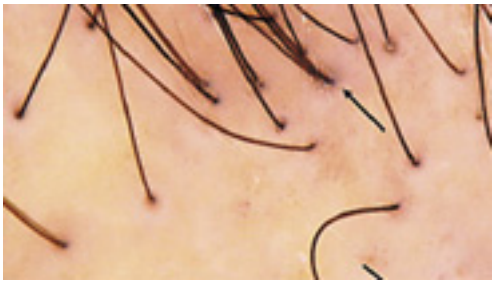
Discoid lupus erythematosus: red brown skin discolouration (5-7).

Subacute lupus erythematosus:
It shows white scales and mixed vascular patterns of linear, linear irregular, branching, and sparsely distributed dotted vessels along pinkish-red background due to hemosiderin deposits, and brown to blue-grey dots/peppering (5-7,13).



Subacute lupus erythematosus: red-white background, scales, and mixed vascular pattern (5-7).

Lichen planopilaris:
It will show milky red areas or fibrotic patches, perifollicular erythema, pigmented halo in targetoid pattern, loss of vellus hair, perifollicular vessels, black dots, pigmented network, tubular casts, loss of follicular units, white dots, and perifollicular scales (5-7).

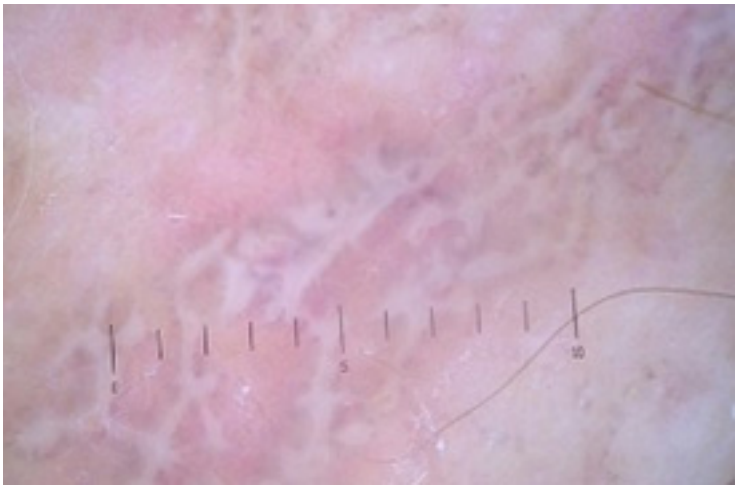


Lichen planopilaris: pigmented halo (5-7).

Lichen planopilaris: perifollicular scaling with scales entangling hair shafts (5-7).

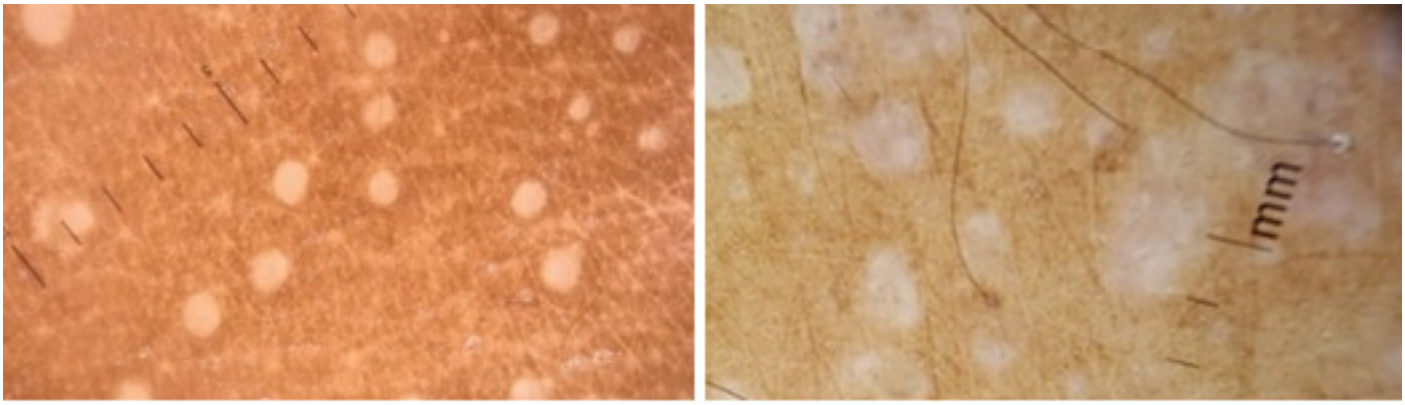
Lichen planus:
The main distinctive hallmark is white crossing streaks (Wickham striae) which coincide histologically with hypergranulosis (14). However, in scarring and resolving dermatosis lesions, a pseudo-Wickham stria can be mimicked in discoid lupus erythematosus, nodular scabies, and prurigo nodularis due to dermal fibrosis, along dotted/linear vessels, but can be quite dilated, more than those seen in Wickham striae. However, findings can vary according to lichen planus's variants (5-7).

Also, perifollicular erythema and white halo, interfollicular area blue-grey dots, white dots, and reduced follicular ostia can be seen in follicular lichen planus.



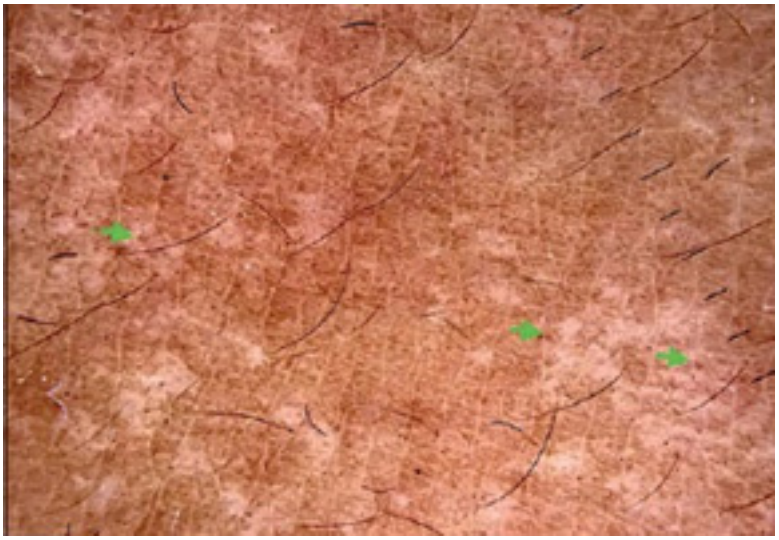
Lichen planus: Wickham striae (14).

Lichen nitidus:
Dermatoscope shows a distinctive round well-defined white area with indistinct brown shadow reflected through each of these white circles (corresponds to epidermal acanthosis) devoid of skin markings due to flattening of the epidermis overlying the inflammatory infiltrate, but on the penis, it retains the skin marking in a pronounced manner (8,51-52).



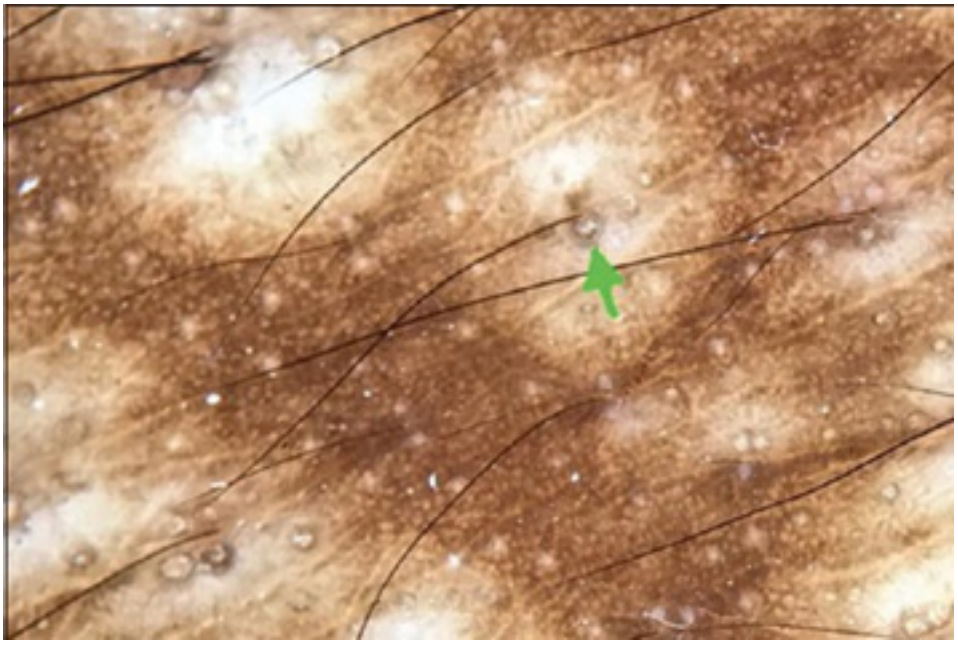
Lichen nitidus: rounded well-defined area with indistinct brown shadow was reflected through each of these white circles (14,51-52).

Lichen striatus:
Displays brownish to greyish granular pigmentation, dotted vessels, and white scales (57).



Lichen striatus: brownish to greyish granular pigmentation (57).

Lichen sclerosus et atrophicus (LSA):
Features keratotic follicular plugs and white structureless areas, corresponding to follicular hyperkeratosis and superficial fibrosis, however, dotted vessels, haemorrhagic dots, erythematous areas, and pigmented dots and networks can be seen in dark skin (57).

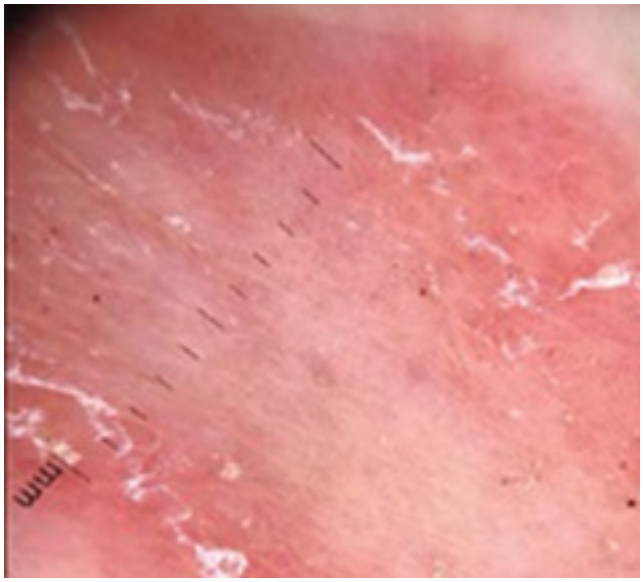


Lichen sclerosus et atrophicus (LSA): keratotic follicular plugs and white structureless areas (57).

Zoon's balanitis (plasma cell balanitis):
Shows homogenous orange structureless areas, corresponding to hemosiderin deposition, and the curved or serpiginous vessels, representing vascular proliferation (57).

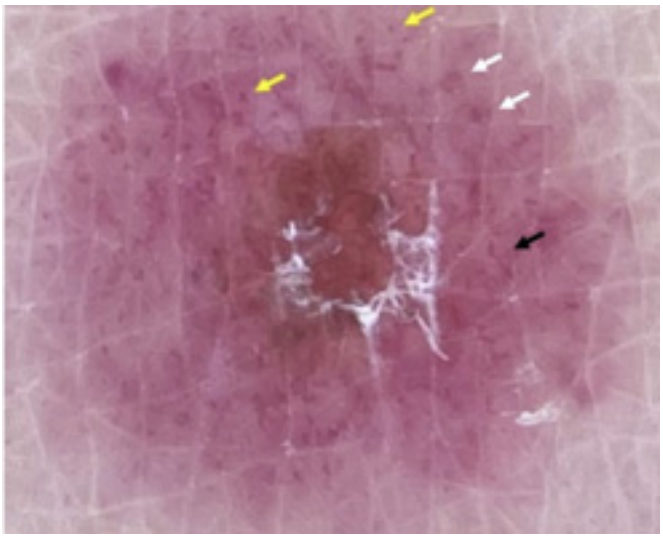
Zoon's balanitis (plasma cell balanitis): homogenous orange structureless areas and curved vessels (57).

Pityriasis rosea:
It displays a yellowish-red background with peripheral white scales (herald collarette sign), along dotted vessels in an irregular patchy manner (7-8).



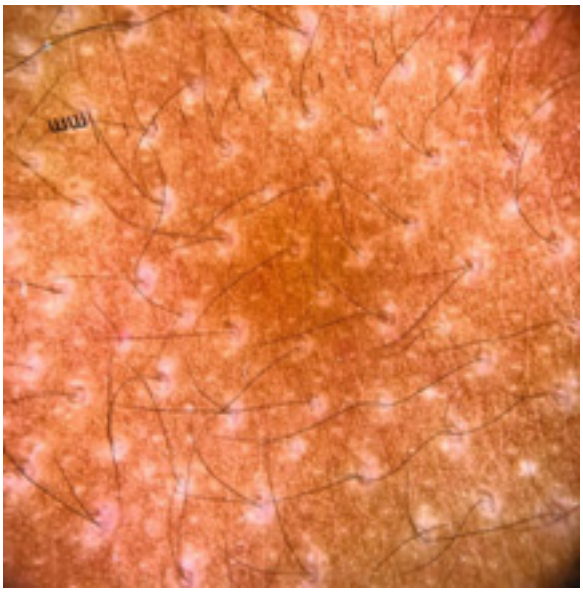
Pityriasis rosea: collarette (peripheral white scales), and dotted vessels (15).

Pityriasis lichenoides:
This encompasses two diseases' spectrum; pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica. The latter display orange yellowish structureless areas due to dermal erythrocyte extravasation and non-dotted vessels along the hypopigmented area in long-standing condition, while PLEVA varies according to the lesion age where an early one shows purpuric area and a mature lesion shows a central amorphous brown crust due to epidermal necrosis and in the centre, a white area can be seen in a healing lesion (7-8).



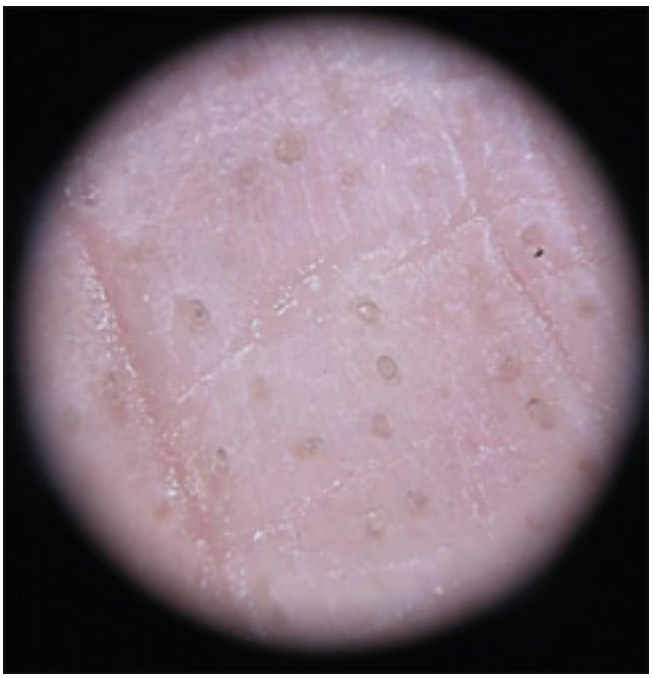
PLEVA; dotted vessels (yellow arrows), glomerular vessels (white arrows), and linear irregular vessels (black arrows) (7-8).

Pityriasis rubra pilaris (PRP):
Yellow area with dotted and linear vessels, with patchy white scales along central follicular keratin plugs, along perifollicular yellow/orange halos, and central hair (18).



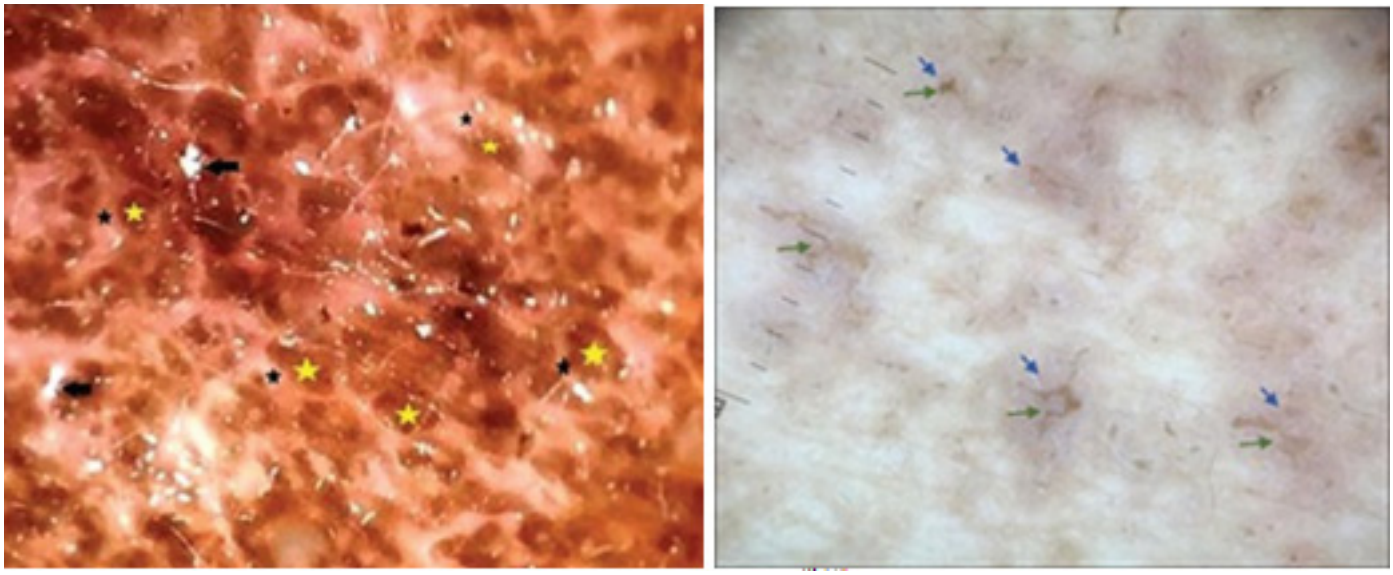
Pityriasis rubra pilaris: keratotic follicular plugs surrounded with erythema and presence of central hair (18).

Porokeratosis:
Coronoid lamella which is the hallmark of porokeratosis histologically, with dermatoscopic finding of well-defined white-yellow annular structure peripherally (white track outlining volcanic crater). In the centre, brown pigmentation, and dotted or linear vessels (17).



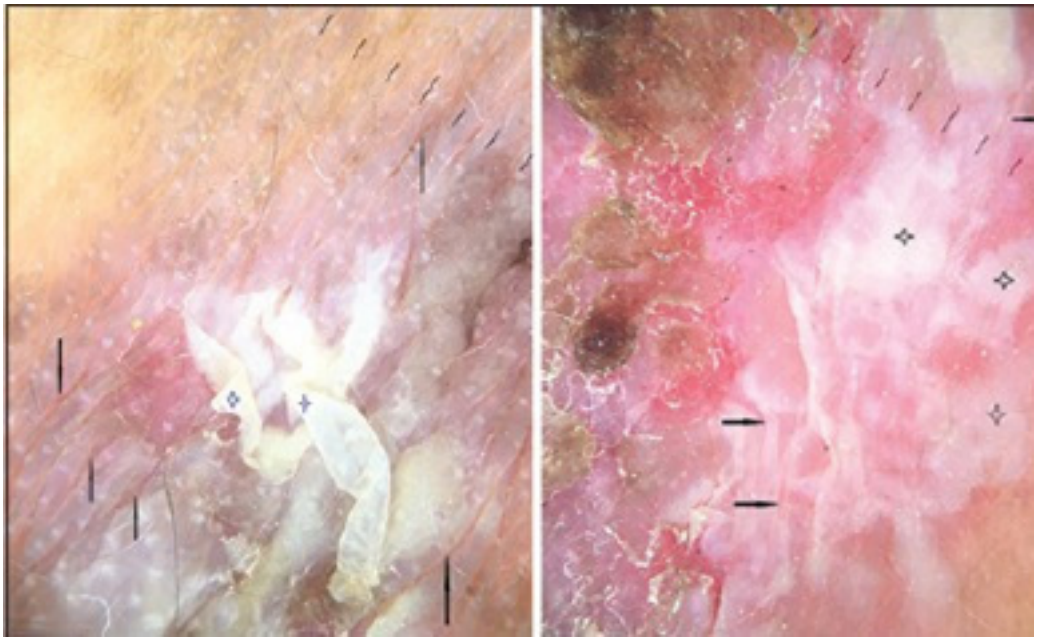
Porokeratosis: the periphery of each lesion shows a white track structure (17).

Darier disease and Grover disease:
Both have similar histology and thus they share similar dermatoscope findings.
Both show central yellow-brown area with star-like branched polygonal or round oval shape due to hyperkeratosis and exocytosis (acantholysis) and peripheral white halo coincides with acanthosis-pseudocomedones, erythema, dotted or linear vessels (8-9,21,57).



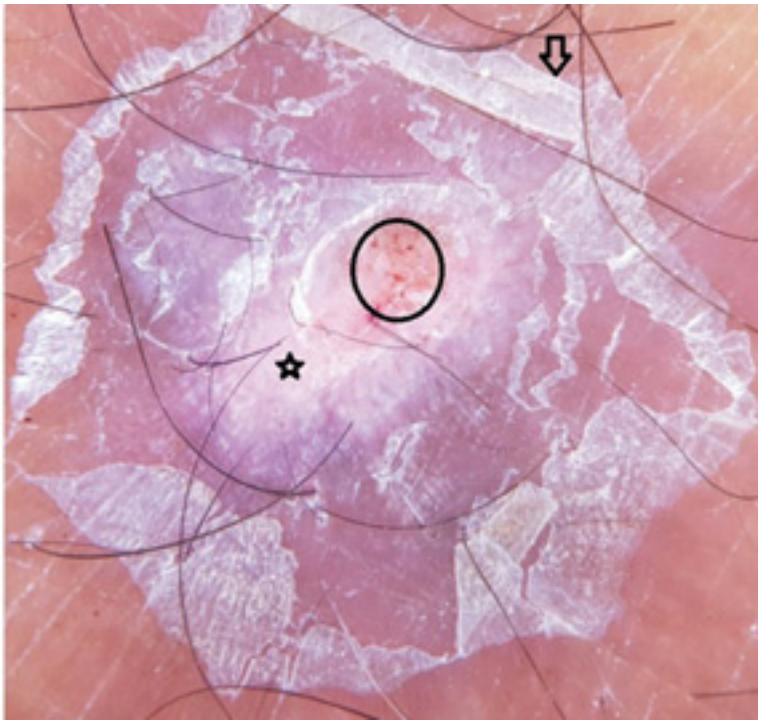
Darier disease and Grover disease: polygonal or round oval shape (21,57)

Hailey-Hailey disease:
Can reveal irregular pinkish-white areas separated by pink furrows along with whitish areas in a cloud-like arrangement or as irregularly raised wavy folds giving a crumpled fabric pattern. Erosions with a few dotted vessels and crusted areas can be seen (57-58).

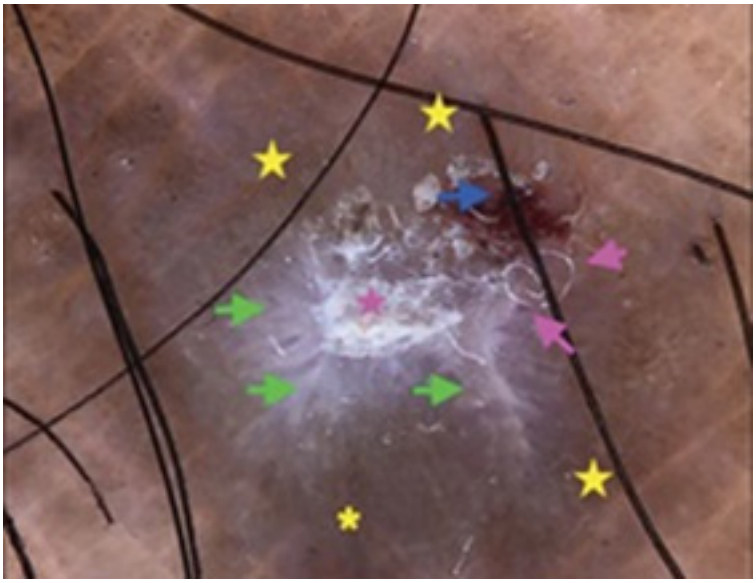


Hailey-Hailey disease: irregular pinkish-white areas separated by pink furrows along with whitish areas (57-58).

Prurigo nodularis:
It shows central erosion, crusting, radially arranged white lines with scales or peripheral white halo with coarse projections on brown-red background (white starburst pattern of pearly white areas with peripheral pigmented dots (57), haemorrhagic spots, red dots, and globules in excoriated lesions (22).

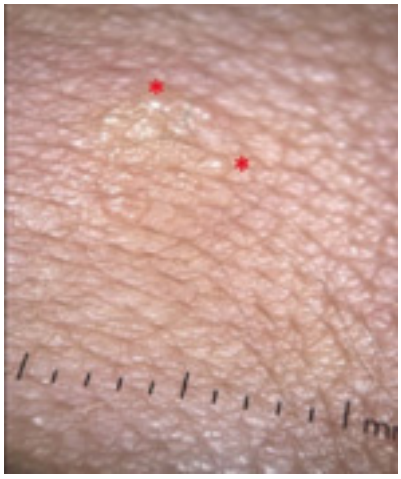


Prurigo nodularis: pearly white areas, peripheral striations with scaling in the hyperkeratotic lesion (22).



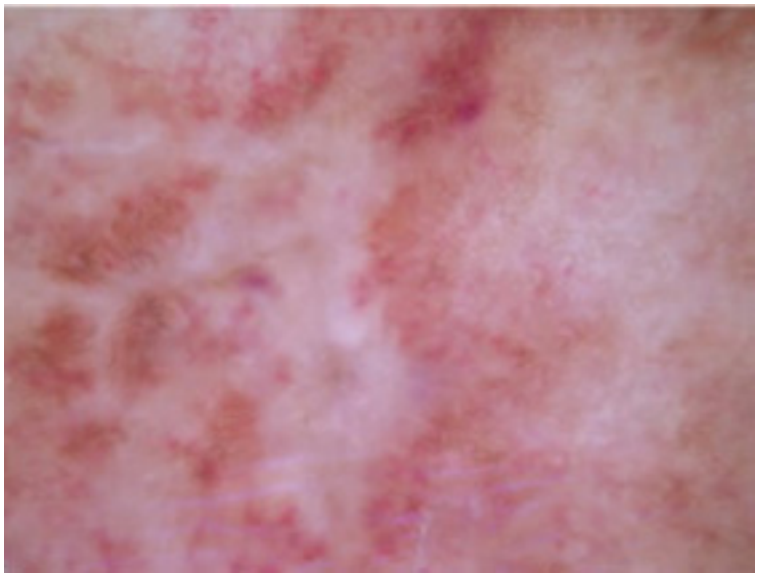
Prurigo nodularis (PN): central erosion, crusting surrounded by a white starburst pattern of pearly white areas (57).

Mastocytosis:
Light brown blot, pigment network, reticular vascular pattern, or yellow orange blot (4-7).



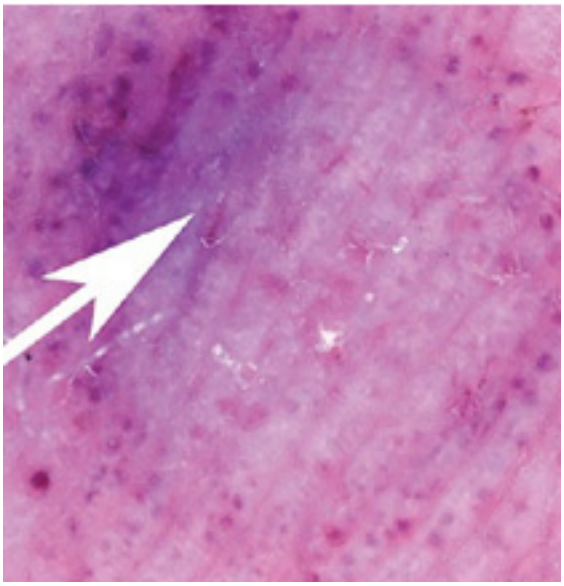
Mastocytosis: diffuse yellowish thickening of the skin giving a “leathery pattern” (4-7).

Livedo recticularis:
Linear vessels with a regular distribution, central crusted ulcer, or ivory-white atrophic scar-like areas (corresponding to dermal fibrosis), along the periphery featured hyperpigmentation in a reticular pattern (corresponding to basal layer of the epidermis or melanin within melanophages in dermal papillae), with increased vascular pattern in the periphery including linear telangiectatic vessels and glomerular vessels (correspond to proliferated capillaries in upper dermis) (20).



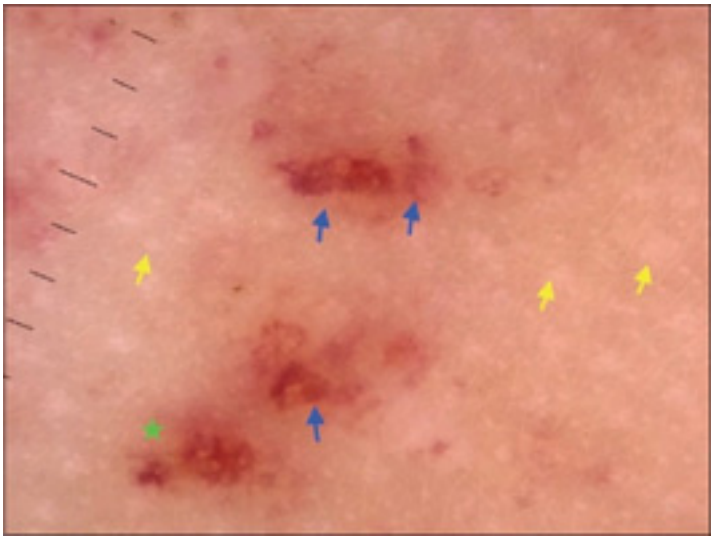
Livedo recticularis: central crusted ulcer/white scar-like area with peripheral pigmentation and increased vascularity (20).

Erythema multiform:
The typical target or iris lesions are portrayed by three circular zones of a central dusky zone, surrounded by a ring of pale oedema and a peripheral red rim. Dermascopy shows Linear vessels peripherally, and bluish patches centrally (25).



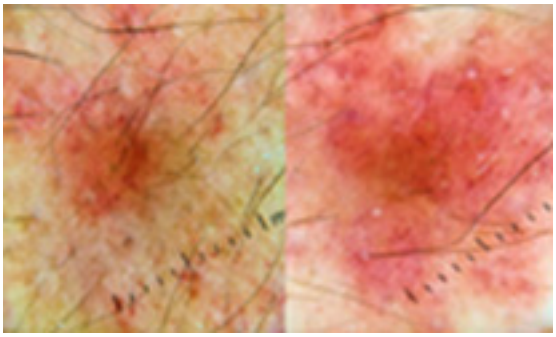
Erythema multiform: shows a central dusky zone of various colours, red/blue/purple and black (25).

Langerhans cell histiocytosis (LCH):
Shows reddish purple areas, brown dots, and central white area with telangiectasia (57). The presence of vascular blotch corresponds to dermal haemorrhage, white homogeneous areas to dermal Langerhans cell infiltration without epidermal involvement and brown dots or structureless area or crust to epidermal infiltration and necrosis by Langerhans cells.



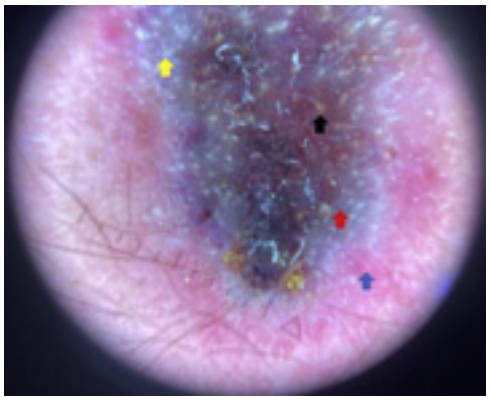
Langerhans cell histiocytosis (LCH): vascular blotches, brown globules, and white structureless area (57).

Sweet syndrome:
Dermoscopy shows structureless bluish patches, with a focal arrangement of red clods vessels (26).



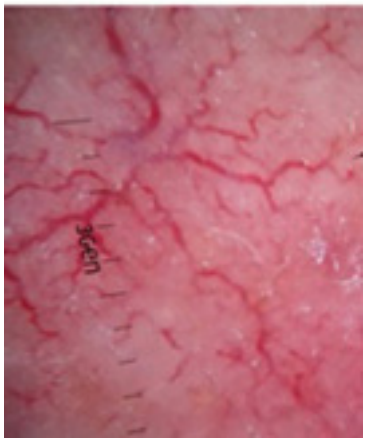
Sweet syndrome: shows red clods over patchy pinkish background with pale areas (26).

Granuloma;
Dermatoscopic features comprise mainly translucent orange-yellowish globular-like or structureless areas possibly corresponding to the well-defined sarcoid granulomas predominately which imply dermal change with histocyte and lymphocyte density, along linear or branching vessels and this could fall under sarcoidosis, tuberculosis, lupus vulgaris and lymphoma (4-7).



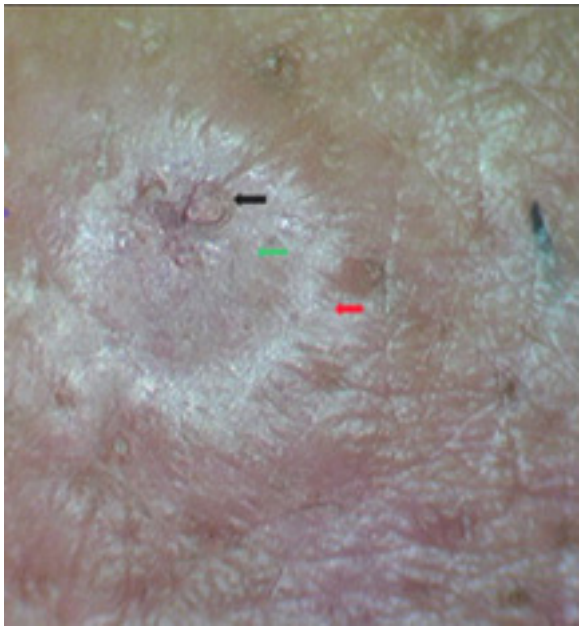
Granuloma: translucent orange-yellowish structures area (4-7).

Sarcoidosis:
Shows orange yellow globules or areas along linear vessels (27).



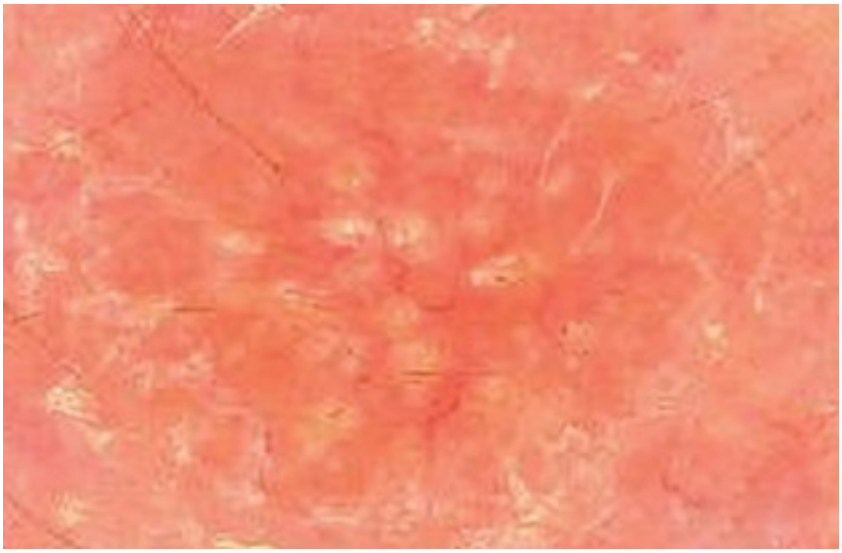
Sarcoidosis: translucent orange yellowish globular-like or structureless areas with linear or branching vessels (27).

Granuloma faciale:
It's not granuloma as the name implies, however it's chronic leukocytoclastic vasculitis, characteristic by the presence of dilated follicular openings, perifollicular white halo, follicular keratotic plugs, linear branching vessels with purpuric spots due to erythrocyte extravasation and hemosiderin dermal deposits(19).



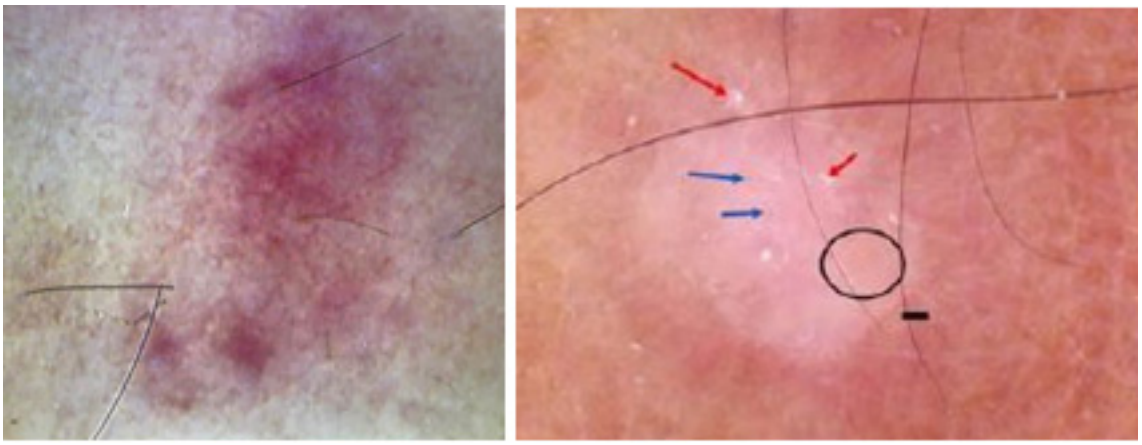
Granuloma faciale: pink background (blue arrow), with aggregates of brown dots/globules (green arrow), white striations in different directions (red arrow), and prominent follicular orifices (black arrow) (19).

Cutaneous leishmaniasis:
An erythema, yellow tear (follicular plugs), hyperkeratosis with central erosion/ulceration/crust, with vascular morphology of linear irregular, dotted, hairpin, arborizing, and comma-shaped patterns are mostly appreciated peripherally (38).



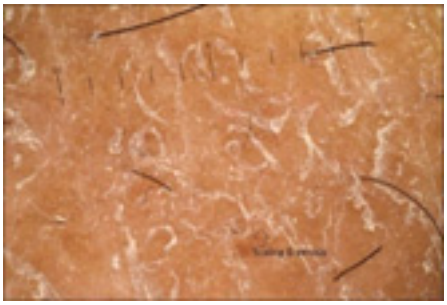
Cutaneous leishmaniasis: showing yellow tears with central crust (38).

Erythema nodosum:
Shows erythematous lobules, shiny white scaling, red dots, hypopigmented structureless areas and vascular dilatation. These lobules substantiated the presence of lobular panniculitides (46,54).



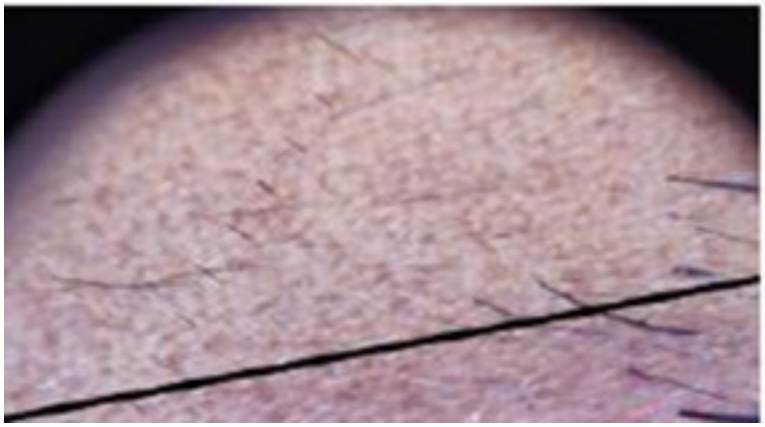
Erythema nodosum: showing erythematous lobules (46,54).

Leprosy:
Tuberculoid/ lepromatous leprosy: shows xerosis, white scaling, and absence of pigment as well as white dots as sweat glands (42).



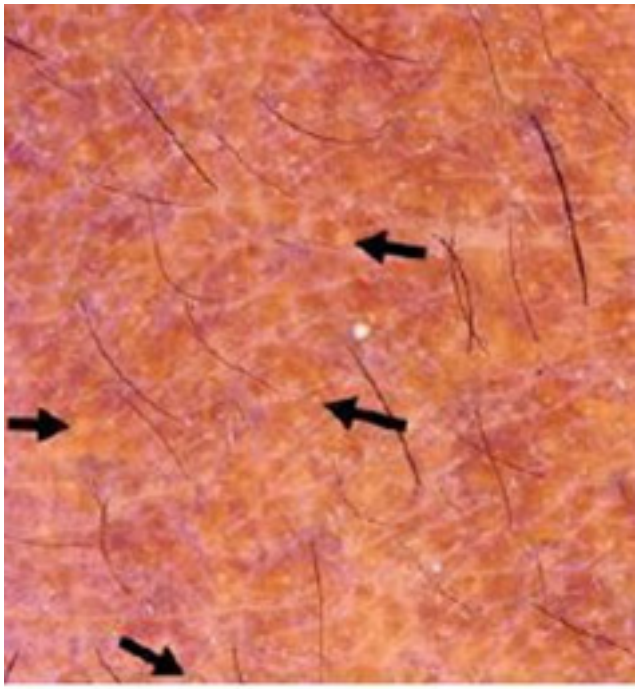
lepromatous leprosy: shows xerosis and scaling (42).

Tuberculoid leprosy: shows orange yellowish structureless areas, white structureless areas, peripheral erythema, relative vellus hair sparing and extensive loss of pigment network (54).



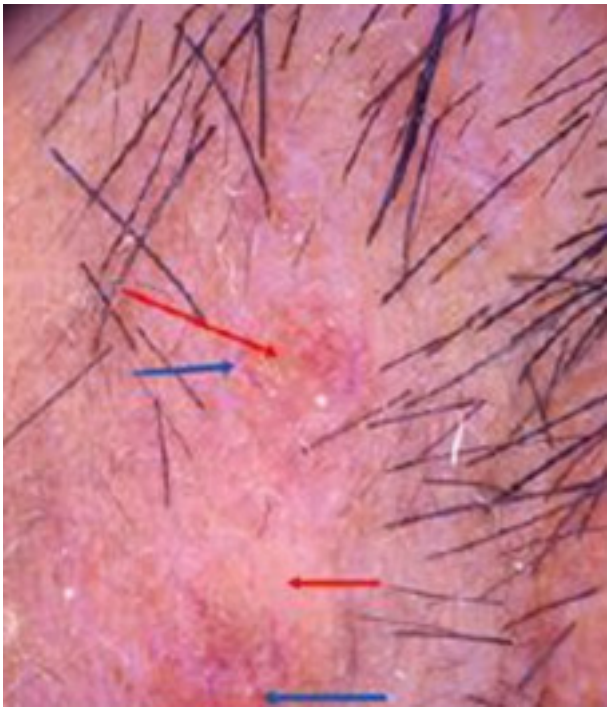
Tuberculoid leprosy: orange yellowish structureless areas, and extensive loss of pigment network (54).

Borderline Tuberculoid leprosy: shows yellowish orange structureless areas surmounted by branching vessels with violaceous hue in the background, with patchy loss of the pigment network, diminished hair follicles, and sweat glands along with yellow dots and globules (54).



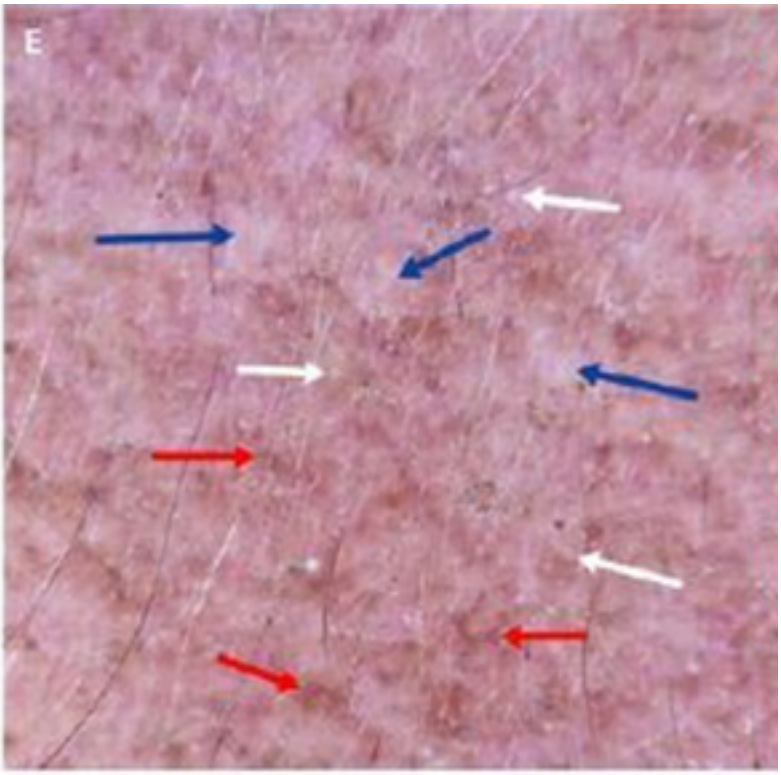
Borderline Tuberculoid leprosy: shows yellowish orange structureless areas with violaceous hue in the background (54).

Lepromatous leprosy:
Yellowish orange and structureless areas with yellow globules, shiny skin, telangiectatic vessels and sparse appendages along attenuation of normal reticular pigment network (54).



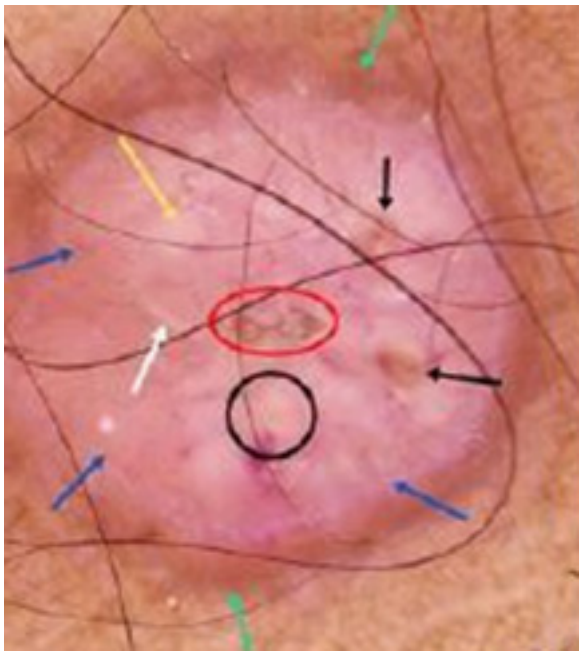
Lepromatous leprosy: Yellowish orange and structureless areas with yellow globules (54).

Borderline Lepromatous leprosy:
Shows loss of pigment networks with focal areas of hyperpigmentation. Other dermoscopic features included white, shiny streaks with relative sparing of appendages and hair follicles with no branching vessel (54).



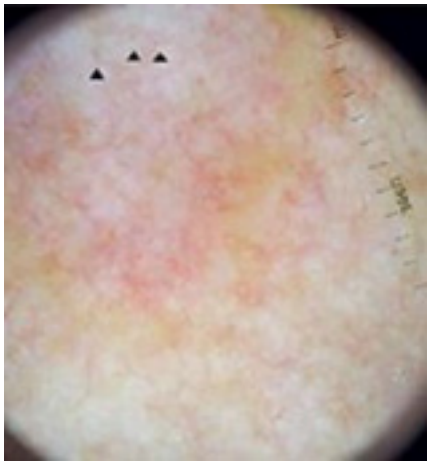
Borderline Lepromatous leprosy: loss of pigment networks with focal areas of hyperpigmentation with relative sparing of appendages and hair follicles (54).

Histoid leprosy:
Exhibited a distinctive dermoscopic appearance, which encompassed crown vessels with central hypopigmented and blanchable dome-shaped structures along with crystalline lines. Additionally, central umbilication displayed central white dots and keratotic plugs along with pseudokoebnerization (54).



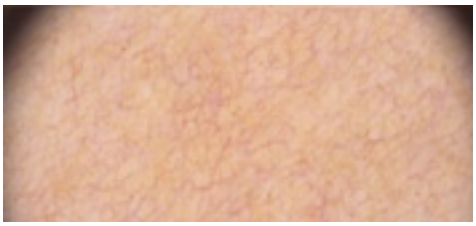
Histoid leprosy: crown vessels, central hypopigmented and blanchable dome-shaped structures along with crystalline lines and central umbilication of keratotic plug (54).

Granuloma annulare:
Hazy vessels having variable appearance (dotted, linear short-irregular, and branching) with background of either red, yellow or white area, and other findings could be rosettes, crystalline structures, and whitish scaling (34).



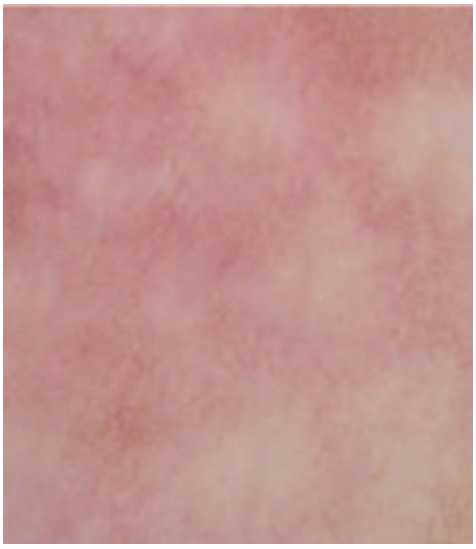
Granuloma annulare: red, yellow or white area (34).

Cutaneous lichen sclerosis and morphoea:
Mostly characterized by bright white yellowish patches/structureless area with linear vessels with yellowish keratotic plugs surrounded by red halo which marks the disease activity. In morphoea, pigmentary structures were mostly significant along white clouds which is ill defined dull white areas due to deep dermal fibrosis (white fibrotic beams), linear vessels within lilac ring are typical finding (36).



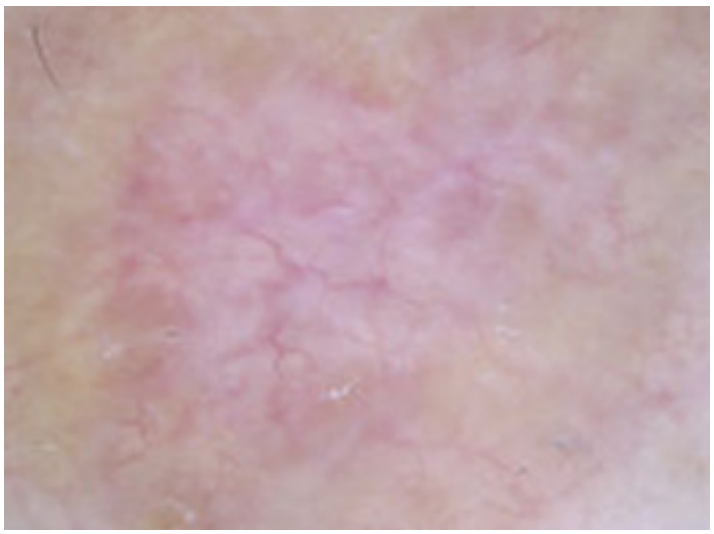
Active cutaneous lichen sclerosis: shows linear branching vessels throughout (36).

Inactive cutaneous lichen sclerosis: shows reticulated brown areas (36).



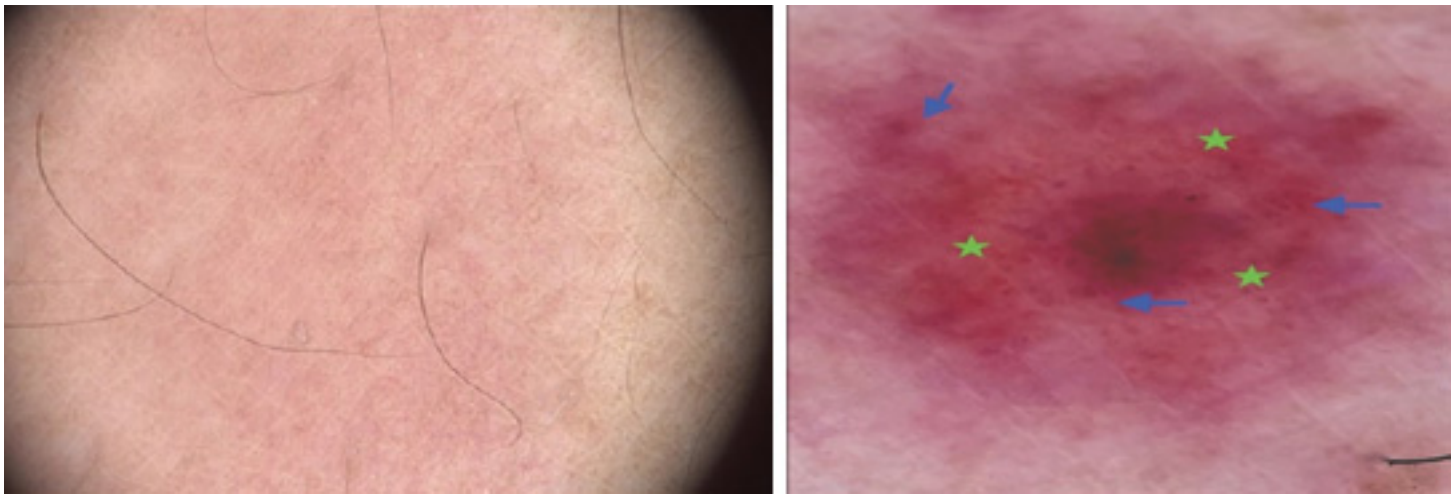
Morphea: multiple white clouds with pigmentary structure (37).

Necrobiosis lipoidica:
It shows yellowish orange structureless areas due to granuloma inflammatory infiltrate and lipid deposit in the dermis with well-focused vascular structure, along comma-shaped vessels, dotted vessels, globular, comma-shaped and glomerular vessels in earlier lesions stage and hairpin, linear and network like at mature stages or active lesions, or branching serpentine like in advanced stages with attenuation at periphery due to epidermal atrophy of the centre (32).



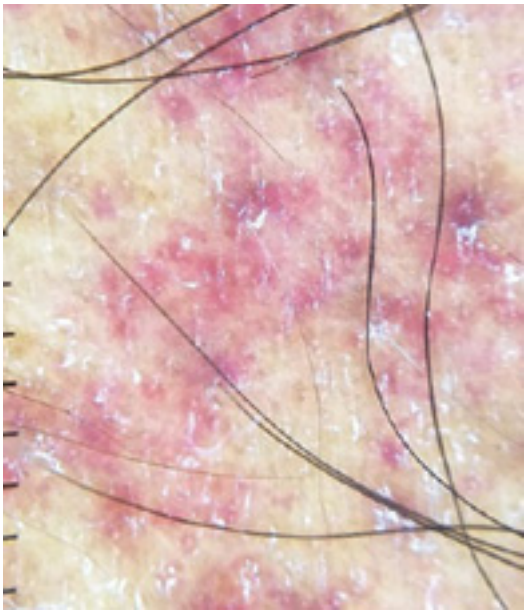
Necrobiosis lipoidica: irregular arborizing vessels on a light brown background, whitish structures, patchy pigmented reticulum (32).

Urticaria:
Dermoscopy will show enhanced visualization of subclinical red/purpuric patches of a network of linear vessels surrounding avascular erythematous areas that correspond to dermal oedema (39).



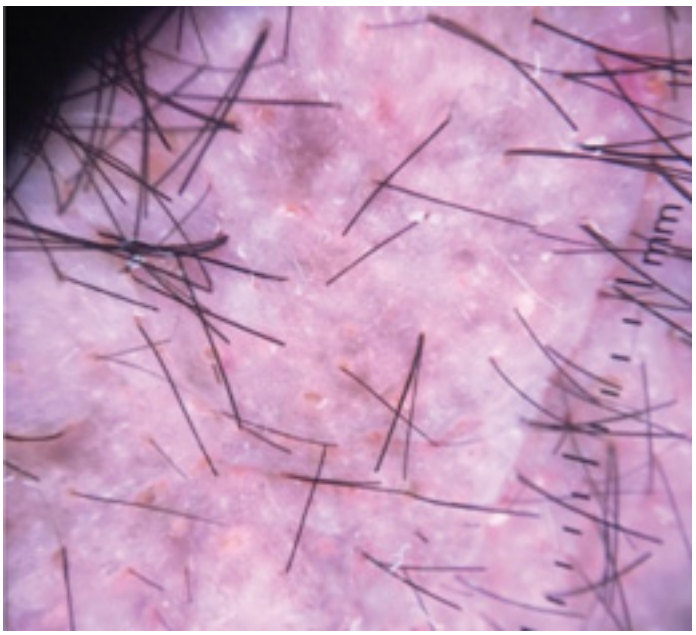
Urticaria: shows red, reticular network of linear vessels, surrounded by an area devoid of vessels (39).

Urticarial vasculitis:
Purpuric dots or globules, orange-brown background, a network of linear vessels (39).



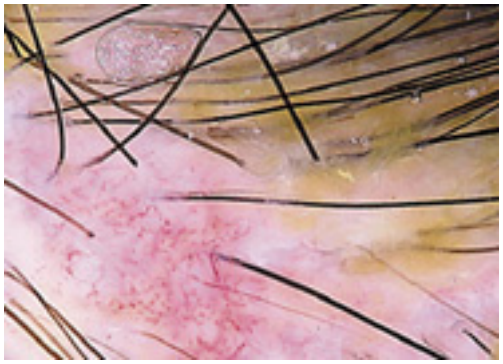
Urticarial vasculitis: shows purpuric globules (39).

Mycosis fungoid, CTCL:
Classic MF shows characteristic flat macular itchy skin lesions that show dermatoscopically broken, small short vessels, dot vessels with yellow crust scales, orange-yellow areas, and spermatozoa-like structures with a striking pigmentary change, thick black lines, white rosettes, and geometric white lines (35).



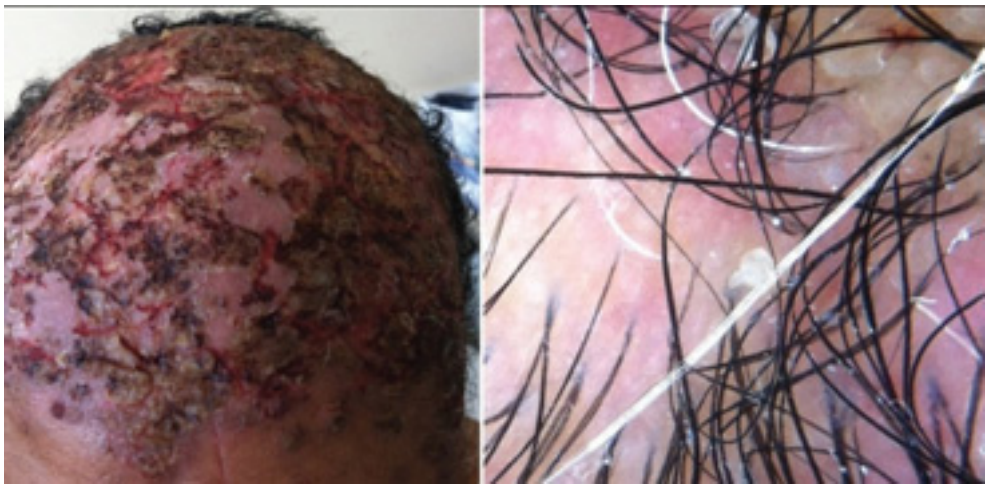
Mycosis fungoid: pigmentary change (35).

Pemphigus foliaceous:
It will show white polygonal structures along linear serpentine vessels, dotted and arborising vessels, linear helical vessels, glomerular vessels, scaling, fried egg sign, yellow haemorrhagic crusts, yellow scaling, tubular casts, haemorrhage, and white perifollicular scaling (4-7).



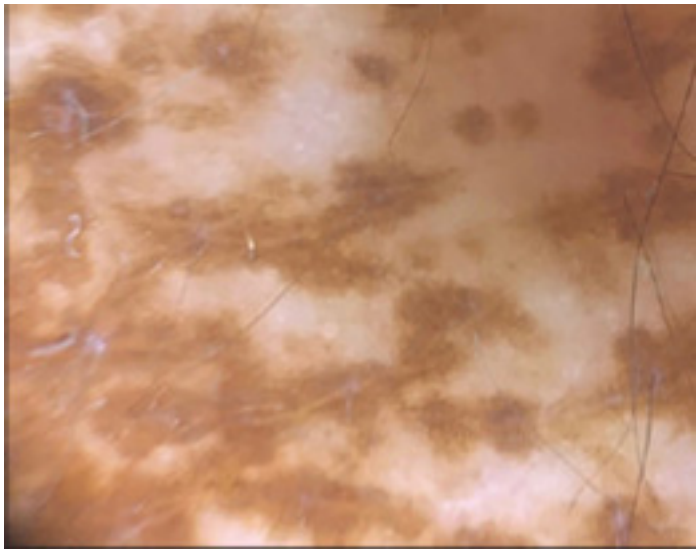
Pemphigus foliaceus: helical and linear serpentine vessels (4-7).

Pemphigus vulgaris:
It will show red dots with white halo and lace-like vessels, fried egg sign, linear serpentine, lace-like glomerular and arborising vessels, yellow scale, hemorrhage, dots, and globules (33).



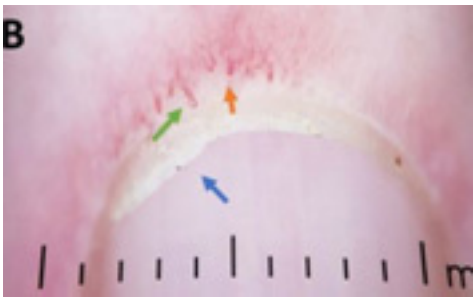
Pemphigus vulgaris: perilesional area reveals hair casts encircling hair shafts (33).

Systemic sclerosis:
It's an autoimmune connective tissue disease that is characterised by: polymorphic vessels, telangiectasia, along salt and pepper signs(28). Loss of follicular openings, broken hairs, black dots, and pili torti.



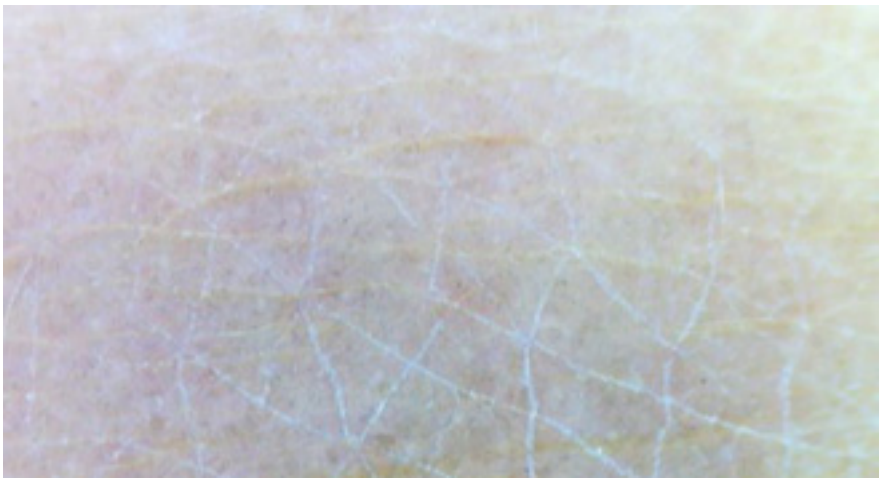
Systemic sclerosis: white homogenous areas with perifollicular pigment. Salt and pepper pigmentation clinically manifests as vitiligo-like depigmentation with perifollicular pigmentary retention (28).

Dermatomyositis:
It's a chronic skin condition with multisystem involvement and some distinctive skin features. Dermsocopy detected advanced nail fold giant capillaries, micro hemorrhages, and avascular areas (29). The trichoscopic features are; erythematous violaceous areas with enlarged tortuous capillaries or lake-like vascular structures, serpentine vessels, interfollicular scales, peripilar casts, tubular casts, and perifollicular and interfollicular pigmentation, along scalp atrophy, and tufting of hair where three or more emerging together with peripilar cast (9).



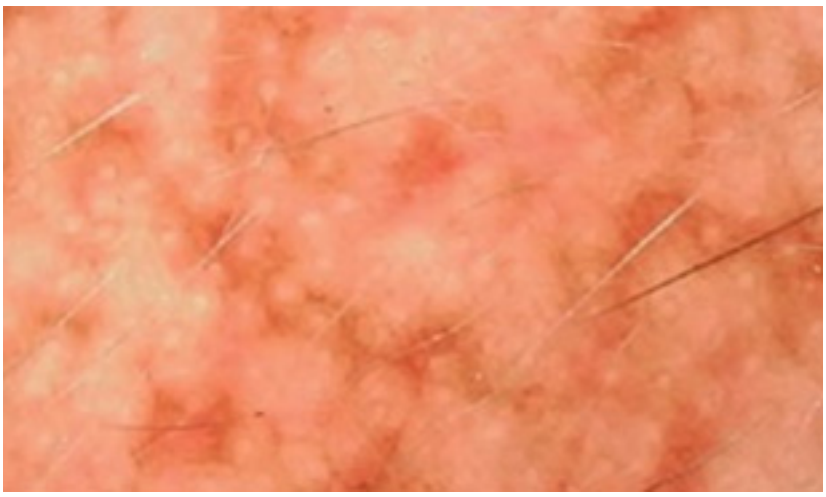
Dermatomyositis: giant nail capillaries (30).

Syphilis:
Dilated capillary vessels, reduced number of terminal hair shafts, broken hairs, thin white scales, perifollicular hyperkeratosis, hemorrhage, yellow dots, pigmented network, white scaling, loss of follicular units and perifollicular scaling (24).



Syphilis: scaling with skin furrows (24).

Melasma:
It shows a pseudoreticular pigment network, diffuse light-to-dark brown background with sparing of the periappendageal region (follicular and sweat gland openings), brown granules, and globules, including arcuate and annular structures, sometimes with increased vascularises and telangiectasia (31).

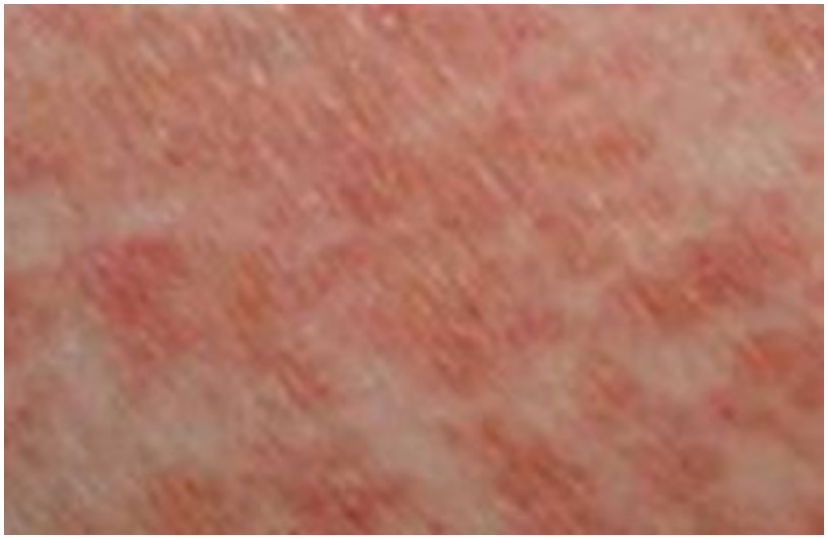


Melasma: diffuse light-to-dark brown pseudoreticular network, multiple brown dots, globules, globule and increased vascularises (red line) (31).

Argyria:
Shows an area comprising blue-grey structures uniformly distributed across a yellow background (53).

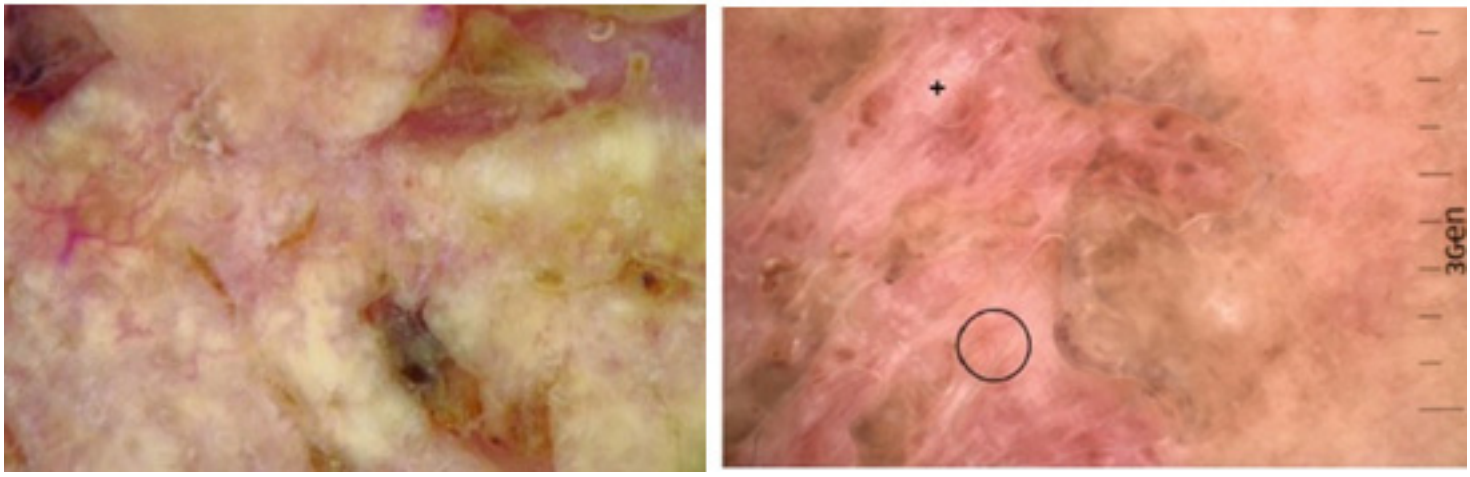
Argyria: blue-grey structures uniformly distributed across a yellow background (53).

Pigmented purpuric dermatoses (PPDs):
are a group of inflammatory skin diseases that may be mistaken as vasculitides. Dermoscopic features show a copper-red background, rounded to oval dots, grey dots, and a network of brownish-to-grey linked lines, purpuric dots, and an orange-brown area of pigmentation (44).



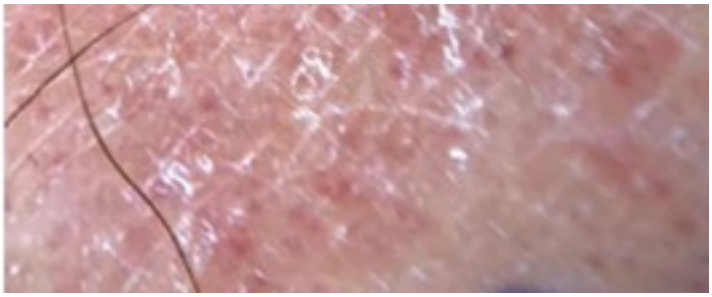
Pigmented purpuric dermatoses (PPDs): shows discrete yellow red patches with superimposed Petechiae (44).

Favre-Racouchot syndrome (FRD):
Shows yellowish lobular-like structures with rare peripheral telangiectasia (55). Though rare it can display an erythematous background, scar-like depigmentation areas, chrysalides and fine linear irregular vessels. In the central area, small islands of normal skin can be visualized, while at the periphery of the plaques there are milia cysts and comedones (56).



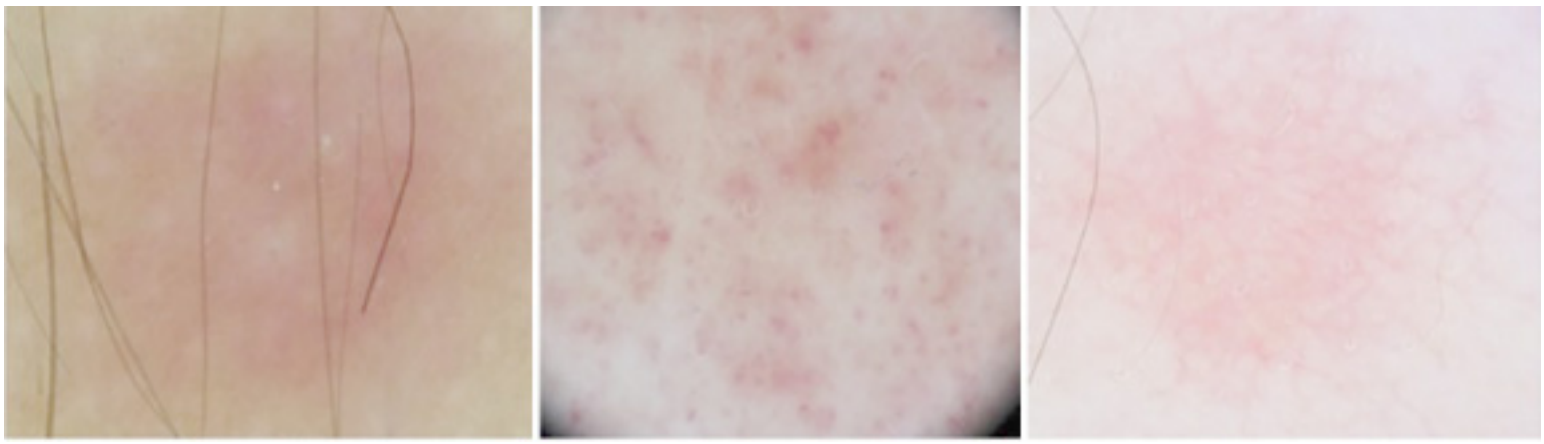
Favre-Racouchot syndrome (FRD): yellowish lobular-like structures (55-56).

Capillaritis:
Is a variant of PPDs and characteristic by extravasation of erythrocytes in the skin (petechia) with hemosiderin deposition over brownish coppery background like in the subgroups of PPDs; Schaumberg disease (progressive pigmentary dermatosis), Doucas-Kapetanakis disease, Majocchi disease, Gougerot–Blum syndrome, and lichen aureus (45).



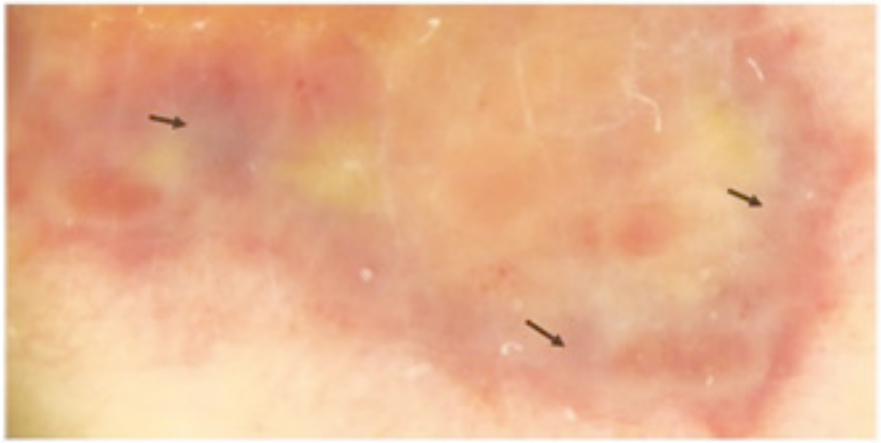
Capillaritis: shows red globules, brown dots and scaling with coppery red background (45).

Cutaneous vasculitis
Three patterns are observed: homogeneous pattern, mottled pattern, and meshy pattern (23).



Cutaneous vasculitis: homogeneous pattern, mottled pattern, and meshy pattern (23).

Henoch Schonlein purpura (IgA vasculitis):
Irregular shaped red patches with blurred borders (23).

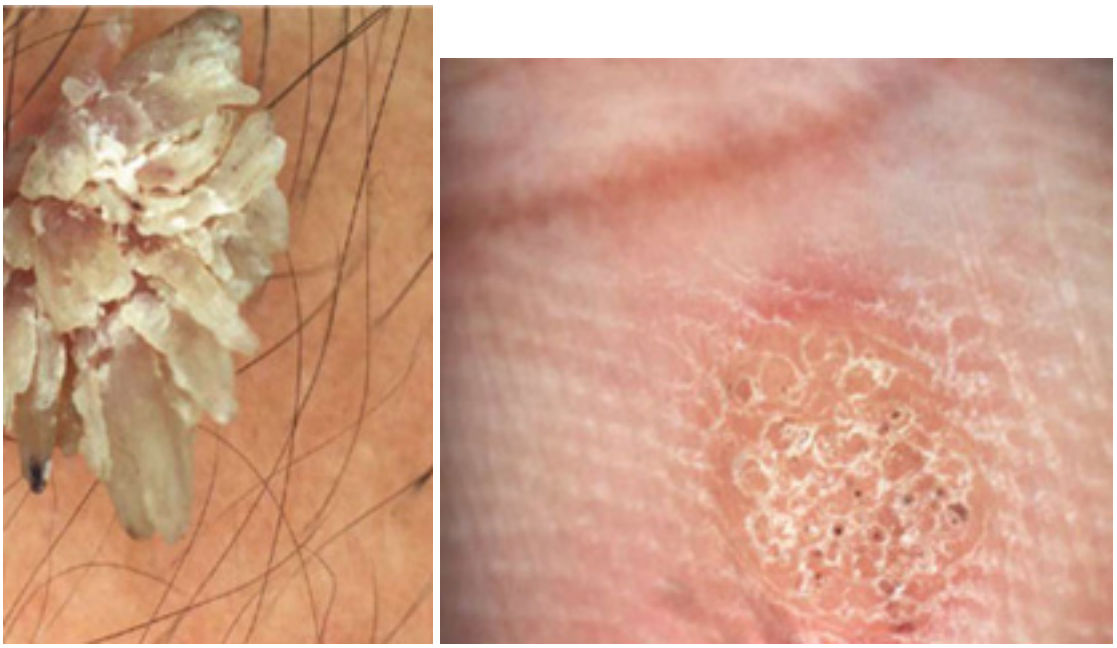


Henoch Schonlein purpura: shows red patches with blurred borders (23).

Diabetic dermopathy:
Central or ring-like globular area surrounded by ill-defined brown peripheral rim along scarcely branching linear vessels that can look like dusky Wickham striae (40).

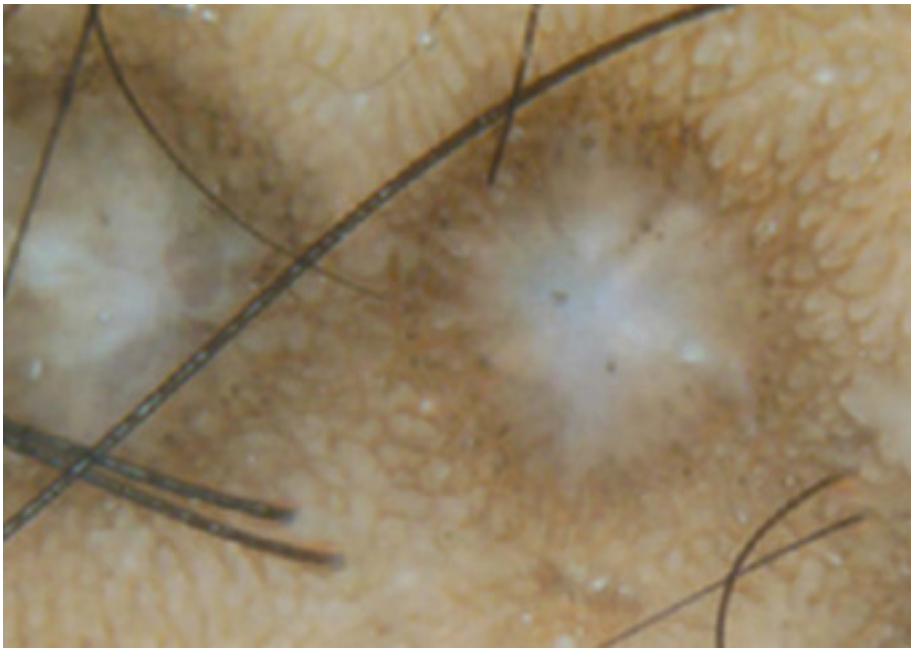
Diabetic dermopathy: ring-like globular structure surrounded by ill-defined brown peripheral rim (40).

Warts:
Different patterns of finger-like projections with bleeding spots, papillomatous lesions with bleeding spots, and hairpin-like vessels, surrounded with frogspawn appearance (47,51).



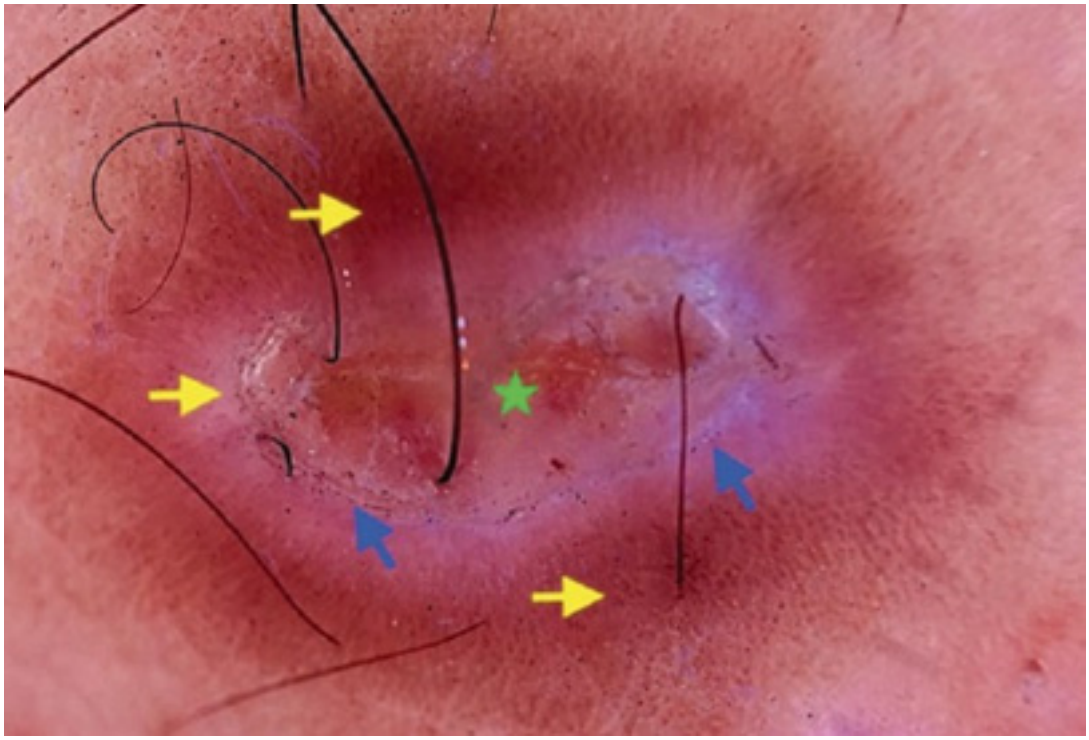
Warts: finger-like projections and frogspawn appearance (47).

Cutaneous Amyloidosis: can vary and show a central white core with peripheral rippled hyperpigmentation, brown dots, and spoke wheel pigmentation (48).



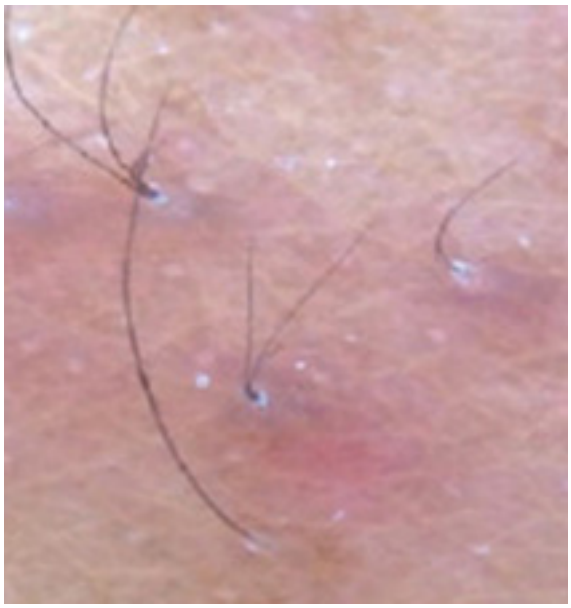
Cutaneous Amyloidosis: can display central white hub with peripheral hyperpigmentation, and spoke wheel pigmentation (48).

Reactive perforating collagenosis:
Shows central round yellowish-brown structureless area, corresponding to transepidermal elimination of collagen, surrounded by white keratotic collarette and erythematous halo- "trizonal concentric" pattern (57).



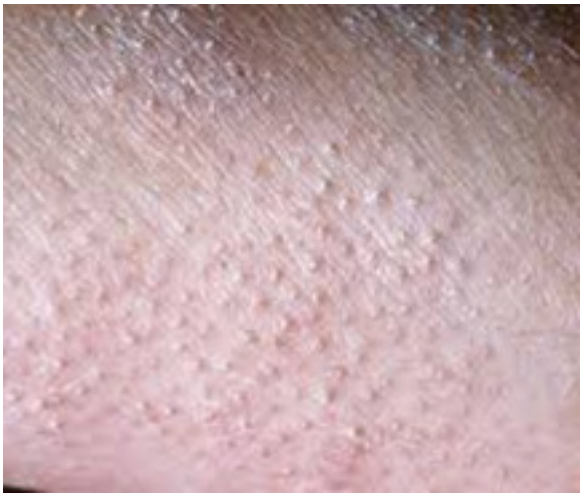
Reactive perforating collagenosis: central round yellowish-brown structureless area, surrounded by white keratotic collarette and erythematous halo (57).

Keratosis Pilaris:
Can show perifollicular papular erythema, vellus hairs frequently coiled and emerging in groups of 2–3, focal peripilar casts/scaling, keratotic plugs, white scales, and scattered pigmented globules (49-51).



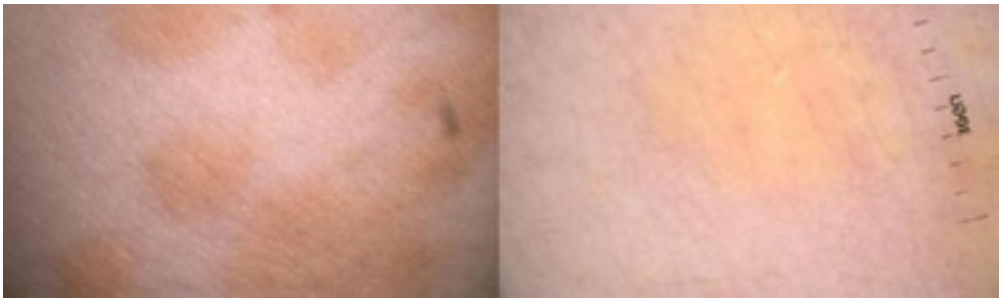
Keratosis Pilaris: shows perifollicular scaling and erythema (49-51).

Lichen spinulosus:
Features perifollicular white halo areas with normal interfollicular areas, perifollicular scaling, and follicular plug (51-52).



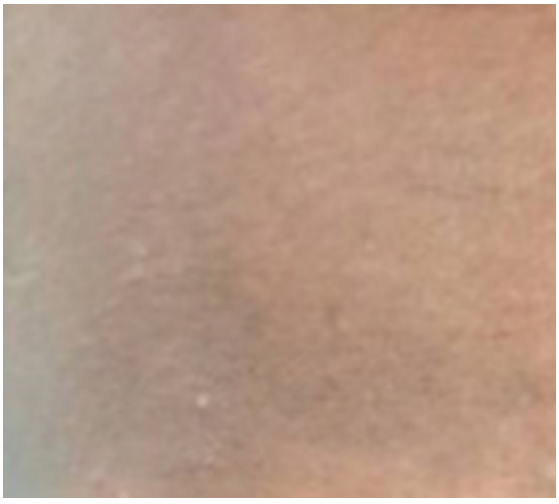
lichen spinulosus: perifollicular white halo areas with normal interfollicular areas, and follicular plug (51-52).

Eruptive xanthoma:
Dermoscopy with polarised mode shows structureless plaque without erythema or vascular proliferation (60).



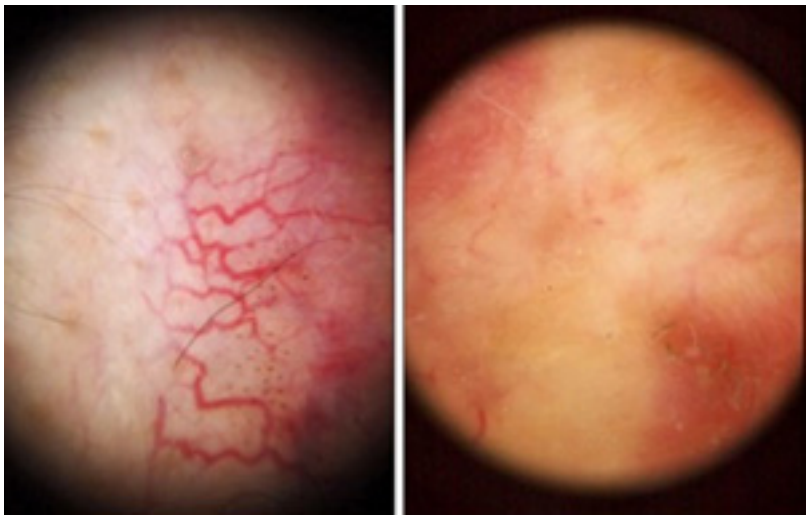
Eruptive xanthoma: shows structureless plaque (60).

Acanthosis nigricans (AN):
Milder cases show irregular brown globules with perifollicular pigmentation and mild hyperkeratosis and hypermelanization of the basal layer with minimal acanthosis and papillomatosis on histopathology. While facial AN on Dermoscopy shows linear crista cutis, sulcus cutis, and hyperpigmented dots in crista cutis (61).



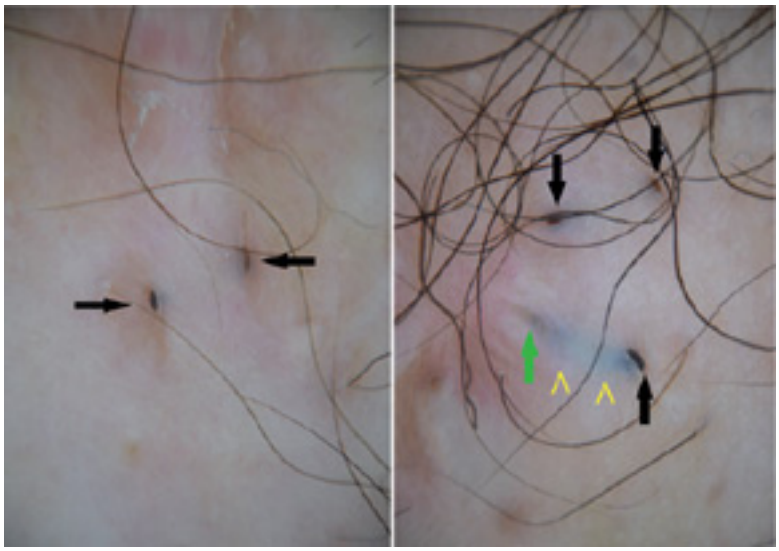
Acanthosis nigricans: shows hyperpigmented dots in crista cutis (61).

Keloid:
Dermoscopy provides a horizontal view of the upper dermis. The vascular structures of keloids appear linear and relatively parallel to the skin surface, whereas vascular structures are usually not apparent in hypertrophic scars which help distinguish keloids and hypertrophic scars even without biopsy (62).



Keloid: distinguish keloids and hypertrophic scars by the vascular structure (62).

Hidradenitis Suppurativa (HS):
Dermoscopy shows multiple keratin accumulation, with irregular openings, either superficially or deeply seated embedded in whitish cicatricial tissue and can be observed connected by blue tunnel (63).



Hidradenitis Suppurativa (HS): multiple keratin accumulation connected by blue tunnel (63).

Discussion

Trichoscopy can offer a non-invasive easier tool in the office for easier diagnosis. It is an important tool in a dermatologist's armamentarium as it can reduce the need for a biopsy in a wide array of conditions17. In psoriasis and seborrheic dermatitis, the distinctive scales colour is straightforward, whereas yellowish dominates in seborrheic dermatitis, and in psoriasis it is whitish (9).

Whereas, in discoid lupus erythematosus and lichen planpilaris, the presence of keratin plugs is the hallmark and specific for discoid lupus mostly (10).

Conclusion

Trichoscopy offers a high quality with huge accuracy in differential diagnosis in inflammatory skin conditions in the clinical setting.

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Diagnosis of Colorectal Carcinoma in the Younger Population Amidst Mental Health Challenges

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Abstract

This case report explores the diagnosis of colorectal carcinoma in a 42-year-old female with a history of anxiety and irritable bowel syndrome (IBS). Colorectal cancer, commonly diagnosed in individuals over 60, is increasingly being identified in younger populations. The patient presented with intermittent gastrointestinal symptoms, initially managed as IBS, and underwent stepwise investigations including blood tests, stool cultures, and imaging, all yielding non-concerning findings. However, a positive faecal immunochemical test (FIT) led to a colonoscopy, confirming colorectal carcinoma. The case highlights the complexities of diagnosing serious conditions in patients without obvious red flags, the importance of timely screening, and the impact of mental health on diagnostic delays. The report also discusses the challenges of primary care systems, such as continuity of care and the patient's mental health history, which potentially delayed diagnosis and treatment.

Keywords: Colorectal cancer, younger population, Irritable bowel syndrome (IBS) Faecal immunochemical test (FIT), Mental health, Diagnostic delays, Primary care Screening, anxiety, Multidisciplinary team (MDT)

Introduction

This case report goes through the journey of a 42 year old female patient getting diagnosed with colorectal carcinoma.

Bowel cancer is a common type of cancer in both men and women - it is the 4th most common cancer in the UK, with over 42,000 people diagnosed every year. About 1 in 20 people will get it during their lifetime.

Most people diagnosed with Colorectal cancer are over the age of 60. The diagnosis of Colorectal cancer is being made in the younger populations more frequently, and this case is an example of it.

Screening can help detect bowel cancer at an early stage, when it is easier to treat. Screening can also be used to help check for and remove polyps, which can turn into cancer over time.

Residents of the United Kingdom (UK) are automatically invited for screening using a home, stool testing kit. This is offered every 2 years to everyone aged 60 to 74. The programme is currently expanding to also include people aged 50 to 59 years. This will be happening gradually over 4 years and started in April 2021.

Case presentation

The chief complaint in this case has been a history of having intermittent loose stools for around 9 months on the background of always having a 'sensitive stomach'. Sometimes there has been mucus present. At times, there has been a feeling of being constipated. There has also been cramping abdominal pain which is relieved by opening their bowels and an on and off feeling of bloating.

There has not been any weight loss, nor any blood in the stool and no meleana present throughout. No opening of bowels at night disturbing sleep. There has also not been any upper gastrointestinal symptoms throughout. No foreign travel prior. No patterns related to food.

The symptoms did seem to follow a pattern of getting worse when there was undue stress/anxiety.

There has been a past medical history of anxiety and more recently in the last few months of Irritable Bowel Syndrome (IBS).

There is no significant family history apart from a cousin who has been diagnosed with Crohn's Disease.

The patient was taking Sertraline for anxiety, and was also trialled on Mebeverine for a month for her IBS symptoms, with no success.

Investigations:
As described above, the bowels began to worsen 9 months ago, with intermittent loose stools increasing in frequency. The patient had come 5 months ago to her primary care team to investigate this. Over the months, the patient would undergo the investigations needed in stepwise fashion for a patient with no red flags - routine blood tests, stool cultures, a blood test for CA125, abdominal ultrasound, as well as a faecal calprotectin test. All of these results did not yield any concerning findings. The patient was at this point trialled on a dose of Mebeverine and guided on lifestyle factors. The patient had multiple appointments - a blend of telephone and physical face to face appointments.

A referral was made to the secondary care team, along with an 'advice and guidance' letter asking what the next steps would be for the patient who is not finding any relief from her symptoms. The response from the secondary care team was to do a faecal immunochemical test **(FIT)** to complete the investigations fully prior to proceeding with endoscopy or further scanning. The FIT test is an invaluable tool when trying to establish significant bowel pathology.

FIT test was positive; the patient was referred on **an urgent basis (seen within 2 weeks)** to secondary care and proceeded with a colonoscopy to establish diagnosis.

Diagnosis:
The patient was referred to the lower gastroenterology team on an urgent basis - what is called a 'two week wait' referral in the UK.

A colonoscopy arranged with biopsies was done, which confirmed colorectal carcinoma via the biopsy results.

Management:
The patient was then promptly discussed at a multidisciplinary team (MDT) meeting to discuss the further steps in management.

Discussion

This case underscores many topics relating to the complexity of making such a diagnosis in the context of the unique patient clinical scenario, as well as the dynamics, relationships and structures of primary and secondary care.

On the surface, this looks like a case in which a patient with **no red flags** was ultimately diagnosed with cancer. Despite this, there are several learning points to address.

Gastrointestinal
This patient had been suffering for the past 9 months. The diagnosis of (IBS) Irritable Bowel Syndrome (symptoms must be present for at least 6 months) is classed as:

'abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form.'

+ 2 of:

- Bloating, distention, tension or hardness.
- Altered stool passage (straining, urgency, incomplete evacuation).
- Passage of mucus.
- Symptoms made worse by eating.

Extra features which make IBS more likely:

- Lethargy
- Nausea
- Backache
- Bladder symptoms

The case underscores the importance of scanning for **red flags:**

- Per rectum bleeding
- Family history of bowel or ovarian cancer
- Fever
- Rectal or abdominal mass
- Change in bowel habit
- Unintentional and unexplained weight loss
- Diarrhoea waking the patient from sleep
- Abnormal blood tests – anaemia, raised inflammatory markers or CA125 (Cancer Antigen 125)

Investigations to rule out **other causes**:

- FBC (suspicious if raised platelet count or anaemia), ESR and CRP (IBD),
- coeliac screen and consider CA 125 +/– pelvic USS if raised.
- If recent antibiotic use or long-term PPI use, consider a Clostridium difficile screen.

Depending on the clinical presentation, there is also consideration for other investigations - ultrasound, sigmoidoscopy, colonoscopy, barium enema, TSH, faecal ova/parasites, hydrogen breath tests.

Frequently omitted information that is also important in the journey of the patient is a lifestyle and social history. These include mood, stress, travel history, alcohol use, smoking status, and overall diet history.

A diagnostic tool of importance is **faecal calprotection**. This is a protein secreted from inflammatory cells in the gut.

When to test? - After ruling out red flags, to differentiate between IBS and Inflammatory Bowel Disease (IBD), specialist assessment should be considered.

Mental Health

It must be added that Mental health plays a role here too. There was already underlying stress and anxiety in the clinical presentation and past medical history of the patient.

Open questions help the real problem to surface, and addressing the patients' ideas, concerns, and expectations is vital during a consultation; be it over the phone or in person. Red flags can then steer diagnosis. Risk assessments will then guide management. In this case, there were no red flags for lower GI symptoms, but her history of anxiety and ongoing stress, certainly needed to be acknowledged and resolved.

NICE Guidance points out the stepped care model for the management of generalised anxiety:

Step 1: 'Identification and assessment; education about GAD and treatment options; active monitoring.'
Step 2: 'Low-intensity psychological interventions: individual non-facilitated self-help, individual guided self-help and psychoeducational groups.'(1)
Step 3: 'High-intensity psychological intervention (CBT/ applied relaxation) or a drug treatment.'(1)

SSRIs. Side effects: upset stomach and may increase anxiety initially.

Propranolol may be required in addition. Care of contraindications, e.g. asthma.

Alternative drug treatments: SNRI and pregabalin.

Benzodiazepines may be used for crisis management only.

Step 4: 'Highly specialised treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care.'

A simplified version of the CBT model adapted from Williams et al. (2, 3) which can be used in whole or in part within the 10-minute consultation after excluding red flags for the physical causes. This can help patients visualise why their physical symptoms are linked to their anxiety and not be a sign of something sinister - unfortunately this was ultimately not the case on this occasion. This is a unique way of demonstrating to the patient that they have been listened to.

Cancer
Refer via 2WW Colorectal cancer pathway:
Aged ≥40 years with unexplained weight loss and abdominal pain.
Aged ≥50 years with unexplained rectal bleeding.
Aged ≥60 years with either: Iron deficiency anaemia or a change in bowel habit.
Positive Faecal Occult Blood test

Consider cancer pathway referral:
Rectal or abdominal mass
Anal mass or ulceration
<50 years and rectal bleeding with any of the following unexplained symptoms or findings: Abdominal pain, A change in bowel habit, Weight loss, Iron deficiency anaemia
Offer FOB testing in people without rectal bleeding:
Aged ≥50 years and have abdominal pain or weight loss
Aged <60 years and have change in bowel habit or iron deficiency anaemia
Aged ≥60 years and have anaemia without iron deficiency

It is important to note that this patient unfortunately had an ever present scenario in primary care in the UK that often delays and hampers diagnosis: this included; first telephone consultations before a face to face consultation; long waiting times for appointments, investigations and results; no per rectum examination being done; and seeing multiple different physicians and therefore hampering her continuity of care.

Should this patient have been seen sooner and had a per rectum examination or had consistently seen the same physician would her diagnosis have come sooner?

Despite this patient being at the age of 42 with no red flags, the decision to offer a faecal occult blood stool test (FIT) was there and up to the clinical judgement of the physician. However, the unique blend of her age, her mental health and perhaps, not establishing a proper doctor-patient relationship, had all, perhaps, delayed that step.

Outcome and Follow-up:
The outcome of this was that in the space of a few months, the patient had a diagnosis and was booked for treatment.

The patient had a colonoscopy as per protocol to establish diagnosis and was subsequently discussed at a multidisciplinary team meeting, with the decision for surgery being made.

Waiting times unfortunately are not in the power of the individual physician on the day, but the pathways in place can be. The method of communication between primary and secondary care was robust and quick, leading to the advice to do a FIT and move forward with an urgent referral.

In terms of what the primary care setting has incorporated:

It has taken the steps to review guidelines and make the FIT more of a routine investigation in such cases. The FIT will likely be more routine and widespread in use in the younger populations, as is highlighted by the screening plans already.

Another aspect that the primary care setting has made a point to address, is to do per rectum examination when indicated, as a matter of importance, and to explain this importance to patients.

Background:
The number of under-50s diagnosed with cancer in the UK increased by 24 per cent between 1995 and 2019, according to figures released by Cancer Research UK (CRUK). The incidence of these “early onset” cases is increasing faster than any other age group, with almost 35,000 British 25 to 49-year-olds receiving a diagnosis in 2019. While cases among over-75s in G20 countries peaked in 2005 and are now in decline, rates for the youngest adults — 20 to 34-year-olds — are at their highest in 30 years.

Health seeking behaviour, mental health, physical symptoms, continuity of care, access to healthcare, and clinical pathways all contribute to the daily challenges in primary care. This case illustrates these issues quite well. Despite experiencing symptoms for months, the patient avoided seeking timely medical intervention due to fear of diagnosis and the potential implications on her socioeconomic status and future. This avoidance behaviour is not uncommon among patients, especially in younger patients and where mental health is being impacted as well. Then, when the clinical process began, the challenges mentioned were prominent, leading to a slower diagnosis of a pathology that was not expected to be made for such a patient.

Patient Perspective:
This is a patient who enjoyed work and had good concentration and focus. She had exercised to keep healthy, while not drinking much alcohol and not consuming any drugs.

Her husband has a good relationship with her but does acknowledge her significant anxiety. There is one child aged 15.

The patient did not seek initial primary care input as she has been put under a lot of pressure recently at work. She had targets to meet all the time, and this has been difficult. She has had some time off recently with anxiety but went back to work. She does not get sick pay. The sertraline does seem to help but she does worry about her older parents, along with fears about what her symptoms could be due to. When she presented to see the physician, she was under the impression that simply, her Mebeverine would be restarted along with some more dietary advice.

The parents live locally. Her father encouraged her to 'get checked out' as her cousin has Crohn's disease. This ultimately exacerbated her concerns.

She had tried to manage her symptoms but sought help when they eventually worsened. She even mentioned to a physician that she was ashamed to say that on one occasion she was caught short and had some faecal incontinence.

Ultimately there is always more to the clinical picture than just ruling out pathology. Having a holistic approach to patient care is of utmost importance, especially in the challenging healthcare environments where continuity of care can be difficult.

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War and planetary viability are the biggest family medicine issues globally

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Abstract

The world is currently in a critical state under the fist of psychopathic dictators who are killing ordinary, innocent people in huge numbers and stealing their land and resources, and we are all facing a very real climate catastrophe. Additionally those with vested financial interests in the status quo are actively seeking to prevent change while they selfishly and maliciously grab the remaining global resources for themselves.

Their fake news and propaganda (endless lies) are the tools used to confuse and divert the minds of concerned citizens who are increasingly marginalised and robbed of the basics of life.

At the same time global human fertility rates have been declining since 1950 and while an overpopulated planet may benefit from this infertility, longterm, it will cause additional problems for the viability of the human race. Pharmaceuticals and chemicals are also contributing to the problem not just for humans but also our animal and plant food stocks are being chemically manipulated for maximum return which is not necessarily making them viable longterm.

Keywords: family medicine, war, dictatorships, genocide, planetary viability

Introduction

It is time for all decent thinking humans on the planet to involve themselves in what is happening in our world as humanity itself is under threat.

While humans generally have shown themselves unworthy of the position of top predator on the planet, most of the damage and injustice is committed by a few. I believe that humans en masse are capable of making unselfish decisions that benefit all – and not just benefit all humans but all life forms on the planet which are increasingly becoming extinct and/or their habitats and food sources destroyed. All other life forms can live without humans but humans cannot live without them.

Destroyed ecosystems, flood, famine, fire and drought and dictatorial warmongers are the greatest and increasing threat to the viability of life on earth. The situation is urgent as the world increasingly falls under cruel and ruthless autocracies with leaders either incapable of recognising their own evil and worthlessness or, one must assume, are quite consciously seeking to destroy the only known life in the universe and purely for self-serving psychotic reasons.

War and genocide

All the wars on the planet as I write, are being conducted by these megalomaniacs – spending their country's resources, and reputations on genocide. Look at all the dictators - those old, and those 'in-training'. They all murder and torture groups within their society and they all have no conscience about killing the innocent members of other society; they are deliberately targeting women and children, and even babies in humidicribs. Huge populations within and without their countries are deliberately starved, fleeing children are shot in the head, hospital patients are bombed and burned alive, citizens denied shelter, water and healthcare, and are marched from one end of the country while where they are coming from and where they are sent to, is razed to the ground.

Homes, schools, hospitals, water and food resources are destroyed by dictators' 'scorched earth policies'. Their crimes last for millennia.

We have to acknowledge the truth and address it if life itself is to survive on this planet.

No longer can we look aside or irresponsibly leave it to another generation – there will be no other generations.

Our planetary viability is caused by the same issues.

This is the truth. We need to address that truth and do whatever we can to get rid of the malfeasant and try to save the viability of life on the only living planet we know of.

Both climate inaction and poisonous dictators come down to political ineptitude and political corruption.

Democracies are the closest we have to good government but increasingly they are being taken over by the would be dictators in consort with the weakness of their fellow party members, the bigots and the racists, the haters and the hit men, the feeble minded and the easily excitable, as well as by the criminals. Their voters seem to be more driven by prejudice and revenge as politicians seek to encourage the worst behaviour of populations (let's laugh at the disabled person! - really?) and they deliberately divide society by playing to the mentality of the worst members of society. Politics has become a negative divisional tool of unfit men and if a good man or woman arises, politically or in society, they will not stop until that person is torn to shreds and tainted with ridicule and false accusations (like the late Navalny in Russia, and Greta Thunberg).

We give lip service to the lies of the murderous regimes on our nightly news. We should all be courageous enough to speak the truth and call out evil and ignorance as and when it appears.

Truth will counter the endless lies of monetary focused social media and the sponsored and/or national political liars.

Our task as responsible, professional, intelligent and fair minded people is to recognise the desperate reality of our times and collectively rescue the planet and its life forms from the evil and stupidity which abounds. Working with family doctors has shown them to be some of the most balanced and decent people among us. While we all have enough to do I am trying to make the argument for extending the reach of primary care to all the aspects of family life, including human and planetary viability and respect for all people, and to be advocates for peace.

War and peace

Currently there are terrible wars and ongoing conflict in many countries including but not limited to the Ukraine, the Sudan, Palestine, Myanmar, and provinces of China to name but a few. Most, if not all of these are manufactured wars to better the financial and political aims of the dictators or would be dictators of the aggressive countries involved. Lies and propaganda abound. Scorched earth policies and genocide are also being conducted by the aggressors to ensure no one rises to claim justice.

In all our wars not one life is more important than another. We need to change hearts and minds, not kill.

Looking at the regional conflicts in the Middle East there are many interwoven issues. In Palestine, for example, war did not 'start' with the Hamas attack on Israel - it goes way, way back. Hamas was born of and finally retaliated against the 70 or so years of disrespect, aggression, small murders and land stealing by Israeli settlers.

That however goes back to the end of World War 2 and the Nazi atrocities against the Jews. Basically 'Israel' was other people's land given to them by the colonisers of Middle East countries, (European countries). If there

was to be proper reparation Germany should have given the Jews a homeland after the murder of an estimated 6 million. Between 1896 and 1948, hundreds of thousands of Jews resettled from Europe to what was then British-controlled Palestine, including large numbers forced out of Europe during the Holocaust.

The Jewish residents accepted the deal. The Palestinians, who saw the plan as an extension of a long-running Jewish attempt to push them out of their land, fought it. The Arab states of Egypt, Jordan, Iraq, and Syria all later declared war on Israel, as well (albeit not to defend the Palestinians).

Israeli forces defeated the Palestinian militias and Arab armies in a vicious conflict that turned 700,000 Palestinian civilians into refugees. The UN partition promised 56 percent of British Palestine for the Jewish state; by the end of the war, Israel possessed 77 percent ; everything except the West Bank and the eastern quarter of Jerusalem (controlled by Jordan), as well as the Gaza Strip (controlled by Egypt).

Prior to that we have the Ottoman Empire, the 'Crusades' and the occupation of great swathes of the Middle East by the Holy Roman Empire.

The current appalling despots and dictators are part of ongoing conflicts across the globe starting long ago when one early man picked up a large rock and bashed it over the head of another man. We all have a cruel and aggressive history but it does not make serial genocide right.

Scorched earth policy

The scorched earth policy that Putin used to destroy elements of the Syrian people is now being echoed in the Ukraine and it is not the first time in history that Russia has committed genocide in Ukraine and starved the population to death.

There is nothing wise or glorious in these wars; they are wanton evil. Now with modern armaments it is not a matter of conquering land, it is a matter of destroying earthly places for all time. These are acts of insanity; blind acts by the mentality of dictators/the criminally insane, to make others suffer for their own perceived mental suffering or needs or losses.

Not all people are evil and brutal but we all seem to be disempowered in the face of unconscionable evil.

The corrupt politician is no different to the dictator – they all have the same common goal – personal wealth and power at any cost (to others and the land) and the spoils to be gained from their own planet in their own lifetime.

Greed

You would have thought that with the earth in a state of imminent collapse, with many humans now destined to becoming the fossils of millennia hence, that we would have a common interest in the viability of our species and earthly home.

The last decade has been very lucrative for the world's super-rich residents.

Wealth of global top 1% grew by $42 trillion over past decade. (Oxfam https://edition.cnn.com/2024/07/25/economy/wealth-tax-super-rich-oxfam-report/index.html)

The top 1% has seen its wealth soar by $42 trillion over the past decade, according to a new analysis by Oxfam International. That's nearly 34 times more than the bottom 50% of global population.

"Inequality has reached obscene levels, and until now governments have failed to protect people and the planet from its catastrophic effects," said Max Lawson, Oxfam International's head of inequality policy. "The richest one percent of humanity continues to fill their pockets while the rest are left to scrap for crumbs."

Additionally this same evil, greedy class are stifling change to practices that are destroying the planet itself. It is how wealthy people become wealthy; they capitalise on the misfortunes of others and they rape earthly resources that should be there for all human and other life forms forever.

Sadly the greedy are consolidating their wealth while the ordinary person is increasingly homeless and hungry, and they cannot let go of their spoils even in the face of mass death.

We must not forget the HUGE business of war itself – the biggest business on the planet. This is both a reason to START a war and NOT END a war and it is playing out in the current genocide of Palestinians.

There are victims in all camps of course – the soldiers used as pawns by the political leaders along with the total breakdown of human society, Aid workers, UN peacekeepers, doctors, journalists - all targeted. Schools, and hospitals are destroyed and fleeing children are deliberately shot. This is what humans have become.

Evil

Apart from defensive armies it is ordinary people who suffer the deliberate evil of war. They are those who evil leaders see as expendable and the despots' tools of genocide are just as evil– e.g. the forced sterilisation of the women of Tibet, and the Uighurs, the rape of women and children in conflicts, (rape is one of the 'spoils of war' handed out to soldiers). The survivors of wars are the future of any country, hence the primitive act of rape is not only to cause maximum degradation, but to spread the sperm of the invaders' society to ensure the invaded population cannot rise again. How low can we go? There seems to be no limit to the evil in the mad dictator rule book.

Currently humans are the lowest life forms in the known universe. We have all, in many ways, carelessly defiled our planet and seas with filth, faeces and poisons and caused extinction of other life forms. Those we don't eat and imprison without respect for their lives lived in factory farms, we hunt for sport - the thrill of the kill.

Killing people is murder - in every situation. Most of us are totally sick of these primitive, rubbish humans in our midst and their unenlightened responses to everything. The planet is dying in front of our eyes yet they are still throwing rocks at each other and castigating those who don't want to throw rocks at innocent people. It is the decent, the innocent and the powerless who die.

Our genetic heritage is filled with the worst of human traits.

Wars are started by evil men, not good men. Sometimes good men fight back if they have the capacity and mental resolve.

The other great killer that none bothers about is mass starvation and destitution. The Sudan is suffering massive famine and societal destruction – almost unnoticed. Perhaps someone can 'like' the Sudanese online and draw some attention away from their own vapid pursuits that those not under siege occupy themselves with. Cities around the world are filled with homeless people and homeless families. Refugees die in vain trying to find a home, land to stand upon...

I am writing this to appeal to the good and sane men and women in our midst and one such large group is family doctors – who can be found in every 'village' in our world. I also believe in the decency of ordinary humanity; that with the right education, people can rise above the selfishness and carelessness espoused by the evil classes. Young people want a planet to stay alive in; we all want to find fish in the seas and oceans of our world – not just to eat but because they belong there and have always belonged there. We want to see birds fly free in our skies, watch children pick flowers in Spring (and spread their seeds for them), as has always happened. We want to walk through mighty forests and see timid animals learn to trust us. We want this world to be with us forever, even if we are not here.

Those populations who have really suffered don't want innocent people slaughtered in their name - they don't want babies left decomposing in humidicribs - all they want is for such evil to never happen again to anyone. We are all guilty - those who start these wars for self-serving reasons and those who fail to stop them.

In man's war against man, it never ends. The winner will be the one who says enough innocent people have died, and I will not perpetuate this insanity.

War is the biggest family medicine issue on the globe. It not only causes mass deaths, permanent physical disability, interruption to public health measures eg vaccination of children, and trauma and mental health issues that continue for generations. Through mass destruction of homes, hospitals, schools and infrastructure it also affects quality of life of survivors for generations and leads to epochs of war when individuals try to seek justice.

Sadly we need at this time for all good men to fight for peace and justice, to fight for our right to live in a healthy and safe planet, with clean air, food and water. We need to dispense wisdom, advocate and fight back when and where we have to.

People are happy to follow true leaders in society; only ignorant brutes follow ignorant brutes.

The scale of the current swarm of brutal dictators is shocking and it has happened as they have no respect for human life and decency. Those not killed directly by them are being starved, suffering thirst and left to die of treatable disease. Journalists are being targeted and murdered for speaking the truth. These acts should belong to the primitive past of this world - rather the dictators develop more cruel ambitions every day. Not one of the aggressors is concerned about the needs of their own people either who are seen as 'cannon fodder' or collateral damage – it is personal ambition only and that entails a race to the moral bottom.

When young people speak about climate change across the world they are ridiculed by the right wing press who are financially benefiting from the destruction of the planet and they know the young are right but they don't care. Again evil rules and money rules. What great things these miscreants aspire to.

Every man, woman and child, every doctor and teacher, every non-corrupt politician has to now stand up for the very future of our species and all species and our planetary home. We have to come together as the dictatorial classes divide to rule, within and without 'their' countries. This is not an appeal – this is the truth that we all live. I still hold out hope that several of these dictators will find their humanity and become a great man instead.

The future of the planet needs to be taken out of the hands of mad men and indeed politicians and put in the hands of appropriate people who respect land, air and water, and the sanctity of each human being.

Peace and planetary respect is good 'preventive medicine' not just for humans but the entire planet.

Rather than the words of the dictators and dickheads I follow with words of decent and kind and wise humans from around our world:

The Revised (Modern) Hippocratic Oath
"I swear to fulfil, to the best of my ability and judgment, this covenant:

I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.

I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.
I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know.

Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty.

Above all, I must not play at God.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.

I will prevent disease whenever I can, for prevention is preferable to cure.

I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter.

May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help."

Words of philosophers and thinkers

"The only thing necessary for the triumph of evil is for good men to do nothing." – Edmund Burke

Noam Chomsky: 'Wanton killing of innocent civilians is terrorism, not a war against terrorism.'

"Peace cannot be kept by force; it can only be achieved by understanding." – Albert Einstein.

"I object to violence because when it appears to do good, the good is only temporary; the evil it does is permanent." – Mahatma Gandhi.

War is only a cowardly escape from the problems of peace." – Thomas Mann

War is over… if you want it." – John Lennon.

"War is a defeat for humanity." – Pope John Paul II.

"An eye for an eye only ends up making the whole world blind." – Mahatma Gandhi.

"Peace begins with a smile." – Mother Teresa

War what is it good for - absolutely nothing . Edwin Starr

Peace is not merely a distant goal that we seek, but a means by which we arrive at that goal." – Martin Luther King Jr. King

"If we don't end war, war will end us." – H.G. Wells.