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EDITORIAL

Cutaneous markers of coronary artery disease

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Abstract

Coronary artery disease (CAD) is rapidly increasing in prevalence across the world and particularly in south Asians at a relatively younger age. As atherosclerosis starts in early childhood, the process of risk evaluation must start quite early. The present review addresses the issue of cutaneous markers associated with atherosclerosis, and the strengths and weaknesses of the markers in identifying early coronary atherosclerosis. A diligent search for such clinical markers, namely xanthelasma, xanthoma, arcus juvenilis, acanthosis nigricans, skin tags, ear lobe crease, nicotine stains, premature graying in smokers, hyperpigmented hands in betel quid sellers, central obesity, and signs of peripheral vascular disease may prove to be a rewarding exercise in identifying asymptomatic CAD in high risk individuals.

Key words: Cutaneous markers; Coronary artery disease; Xanthoma; Arcus juvenilis; Acanthosis nigricans; Nicotine

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INTRODUCTION

Coronary artery disease (CAD) is rapidly increasing in prevalence across the world and particularly in south Asians at a relatively younger age, with severe and diffuse forms of lesions. The subject of CAD in Indians (referred to as immigrants or Asian Indians, or south Asians when outside India) has become an interesting and challenging issue for research worldwide[1,2]. The prevalence of CAD has progressively increased in India during the latter half of the last century[3]. The risk of CAD in Indians is considered to be 3-4 times higher than in white Americans, 6 times higher than in the Chinese, and 20 times higher than in the Japanese[1,4]. Indians as a community are prone to CAD at a much younger age[5,6]. As atherosclerosis starts in early childhood, the process of risk evaluation must start quite early. Identifying subtle cutaneous clinical markers suggesting atherosclerosis at a young age may prove to be helpful in early diagnosis and prevention of CAD. It costs little to look for various cutaneous signs which may suggest subclinical or obvious atherosclerosis and/or other vascular diseases, such as diabetes, hypertension, peripheral arterial diseases *etc*. Judicious appraisal of various cutaneous markers linked to CAD would help clinicians to suspect disease in the subclinical phase, and thus make it easier to decide who is likely to need further detailed cardiovascular investigation. A diligent search for the following cutaneous markers relevant to CAD may prove to be a rewarding exercise in identifying asymptomatic CAD in high risk individuals (Table 1).

XANTHELASMA/XANTHOMA

The term xanthelasma is derived from the Greek *xanthos* (yellow) and *elasma* (beaten metal plate). These are yellow

Table 1 Clinical markers of atherosclerosis[7]

1	Xanthelasma, xanthoma/giant gluteal xanthoma
2	Arcus juvenilis
3	Acanthosis nigricans
4	Skin tags
5	Premature graying and balding in smokers
6	Ear lobe crease
7	Nicotine stains
8	Betel quid seller syndrome
9	Central obesity-flabs and folds
10	Signs of peripheral vascular disease
11	Gouty arthritis
12	Rheumatoid arthritis
13	Psoriasis

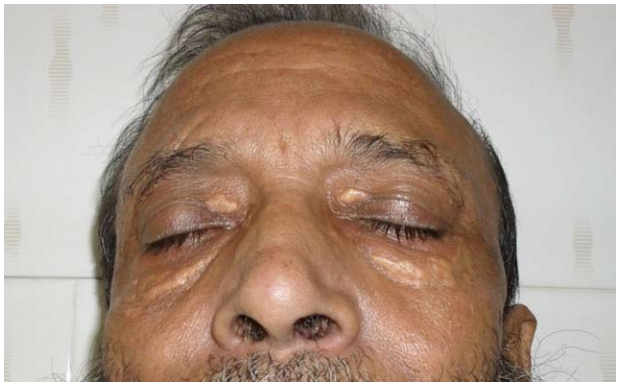

Figure 1 Symmetrical xanthelasma in all four lids.

plaques that occur most commonly near the inner canthus of the eyelid, more often on the upper lid than the lower lid. Xanthelasma palpebrarum is the most common cutaneous xanthoma. Xanthelasma can be soft, semisolid, or calcareous. Frequently, they are symmetrical; often, all four lids are involved (Figure 1). Xanthelasma have a tendency to progress, coalesce, and become permanent.

Pathophysiology

Xanthomas usually are associated with a disturbance of lipid metabolism[8]. The mechanism of accumulation of lipids in skin lesions is similar to the development of atheroma, especially when considering the role of modified low density lipoprotein (LDL) and the method of accumulation of lipids in macrophages. One half of these lesions are associated with elevated plasma lipid levels. Some occur with altered lipoprotein composition or structure, such as low high density lipoprotein (HDL) levels. They frequently occur in patients with type Ⅱ and type Ⅳ hyperlipidemia. In some cases, xanthoma may be seen in many members of the same family with pleomorphic presentation in individual members. We came across a 40-year-old female presenting with acute coronary syndrome and peripheral vascular disease (PVD) and having manifest bilateral xanthelasma. Both her parents had suffered CAD and one of her three brothers had a past history of a cerebrovascular accident. Interestingly both parents and two siblings had some form of xanthoma.

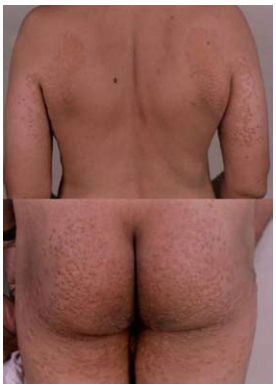

Figure 2 Xanthomas spread over the back and gluteal region.

The elder brother who had suffered a stroke was found to have both xanthelasma palpebrarum and extensive xanthomas spread over the back of his shoulders and gluteal region as well as dyslipidemia (Figure 2).

Types and causes

Xanthomas are of many types including xanthelasma palpebrum, tuberous xanthomas, tendinous xanthomas, eruptive xanthomas, plane xanthomas, diffuse plane xanthomatosis, xanthoma disseminatum and giant gluteal xanthoma. Tuberous and tendinous xanthomas are typical of familial hypercholesterolemia and are common symptoms of homozygous familial hypercholesterolemia.

Small and quickly developing eruptive xanthomas are typical of mixed hyperlipoproteinemia. Eruptive xanthomas can be seen in primary and secondary causes of hyperlipidemia. Examples of primary genetic causes include familial dyslipoproteinemia, familial hypertriglyceridemia, and familial lipoprotein lipase deficiency. Uncontrolled diabetes is a common cause of secondary hyperlipidemia. However, most xanthelasmas occur in normolipemic persons who may have low HDL cholesterol levels or other lipoprotein abnormalities.

Gluteal xanthomas warrant special mention because of their peculiar location in the gluteal region and are likely to be missed completely if not looked for diligently. In a recent case report[9], it was found that a 27-year-old male who was being investigated for a possible diagnosis of familial hypercholesterolemia (total cholesterol: 480 mg/dL; LDL: 440 mg/dL; HDL: 25 mg/dL and triglyceride: 76 mg/dL on treatment) had acute myocardial infarction and extensive triple vessel disease at age 24 years. He was found to have extensive tendon and gluteal xanthomas. There were 13 xanthomatous swellings of various sizes measuring 14 cm × 8 cm to 2 cm × 2 cm in the gluteal region alone. Besides gluteal xanthomas, there were xanthomatous lesions in bilateral elbows, knees, and Achilles tendons. On family screening, all his family members (i.e. parents and three siblings) were found to have CAD. Notably neither the patient nor any of his family members were smokers or diabetic, but all had clinical clues to suggest dyslipidemia.

Xanthomas and xanthelasmas are also indicators of other complicating diseases such as development of acute pancreatitis during a hyperlipoproteinemic crisis, aggrava-

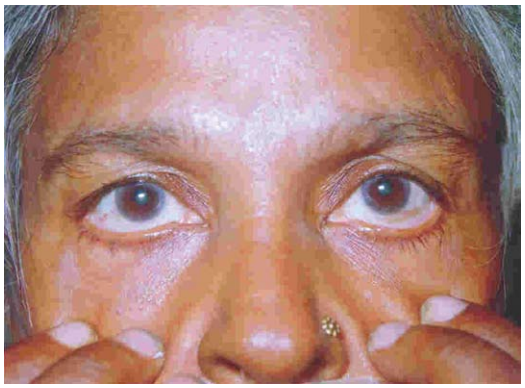

Figure 3 A female smoker with manifest arcus senilis and early graying.

Figure 4 A 25-year-old male showing acanthosis nigricans over the nose bridge.

tion of insulin resistance, and decompensation of type 2 diabetes mellitus, in addition to atherosclerotic coronary diseases[10].

Treatment

Therapy focuses on adjustment of diet (elimination of dietary fat and concentrated saccharides); in the long run patients have to strictly observe their dietary regime based on the type of hyperlipoproteinemia. As regards drug therapy, fibrates and atorvastatin are the drugs of choice. It is very important not to focus on symptoms, i.e. xanthoma or xanthelasma, but to correct the associated dyslipidemia or the disease that underlies hyperlipoproteinemia (e.g. type 2 diabetes mellitus or metabolic syndrome). Unfortunately, it is still the practice for dermatologists, ophthalmologists or plastic surgeons to remove extensive xanthelasmas, while the underlying cause such as diabetes, CAD and dyslipidemia is not investigated diagnostically or adequately addressed.

ARCUS JUVENILIS

A corneal arcus is a lipid-rich and predominantly extracellular deposit that forms at the corneoscleral limbus (Figure 3). It represents the most common peripheral corneal opacity and is not associated with tissue breakdown but rather with the deposition of lipids. Rudolf Virchow, who is credited with the hypothesis that atherosclerosis reflects insudation of pathogenic agents into tissue, also noted, in 1852, the association of corneal arcus with atherosclerosis, and hypothesized a similar mechanism for its formation[11]. However, the attempt to correlate corneal lipid deposits and vascular lipid deposits has been and remains controversial, despite continued interest[12,13]. It has been associated with hypercholesterolemia, xanthelasmas, alcohol, blood pressure, cigarette smoking, diabetes, age, and coronary heart disease (CHD)[14].

In a cross-sectional study by Zech *et al*[15] of 17 patients homozygous for familial hypercholesterolemia presented to the Clinical Center of the National Institutes of Health; plasma lipoproteins, circumferential extent of the corneal arcus and thoracic aorta, coronary calcific atherosclerosis score, and Achilles tendon width were measured. Corneal arcus and Achilles tendon width were strongly correlated and predictive of each other. Although the corneal arcus was correlated with calcific atherosclerosis ($r = 0.67$, $P = 0.004$), it was not as highly correlated as was the Achilles tendon width ($r = 0.855$, $P < 0.001$). Thus it was concluded that the corneal arcus reflects widespread tissue lipid deposition and is correlated with both calcific atherosclerosis and xanthomatosis in these patients. Patients with a more severe arcus tend to have more severe calcific atherosclerosis.

In a systematic review to examine the relationship of a corneal arcus and CHD to determine if a corneal arcus is an independent CHD risk factor, it was concluded that there was no consensus that a corneal arcus is an independent risk factor, but the presence of a corneal arcus in a young person should prompt a search for lipid abnormalities[12]. Also, because a corneal arcus represents physical evidence of early lipid deposition, its presence suggests the need for aggressive lipid therapy[12].

ACANTHOSIS NIGRICANS

Acanthosis nigricans (AN) is a skin disorder characterized by darkening (hyperpigmentation) and thickening (hyperkeratosis) of the skin, occurring mainly in the folds of the skin, back of the neck, the axilla and/or groin. Rarely it may be observed in some regions of the face (Figure 4). AN is not a skin disease *per se* but is a cutaneous sign indicating insulin resistance, diabetes, metabolic syndrome, Cushing's syndrome, internal malignancy, polycystic ovarian syndrome, *etc*.

The cause of AN is still not clearly defined but it appears to be related to insulin resistance. It has been associated with various benign and malignant conditions. Based on the pre-disposing conditions, AN has been divided into seven subtypes (Table 2).

In the cross-sectional study by Kumar *et al*[16] to determine the prevalence of AN in a south Indian population and to evaluate its correlations with diabetes, obesity, insulin levels and other factors, it was shown that 16.1% of the population had AN and it was significantly higher among females (19.6%) than males (11.4%). The prevalence of

Table 2 Types of acanthosis nigricans

Type	Characteristics
Obesity-associated AN	Most common type of AN May occur at any age but more common in adulthood Obesity often caused by insulin resistance
Syndromic AN	Defined as AN that is associated with a syndrome, e.g. hyperinsulinemia, Cushing's syndrome, polycystic ovary syndrome, total lipodystrophy
Benign AN	Also referred to as acral acanthotic anomaly Thick velvety lesion most prominent over the upper surface of hands and feet in patients who are in otherwise good health Most common in dark-skinned people, especially those of African American descent
Drug-induced AN	Uncommon, but AN may be induced by several medications, including nicotinic acid, insulin, systemic corticosteroids and hormone treatments
Hereditary benign AN	AN inherited as an autosomal dominant trait Lesions may manifest at any age, infancy, childhood or adulthood
Malignant AN	AN associated with internal malignancy Most common underlying cancer is tumor of the gut (90%) especially stomach cancer In 25%-50% of cases, lesions are present in the mouth on the tongue and lips
Mixed-type AN	Patients with one type of AN who also develop new lesions of a different type, e.g. overweight patient with obesity-associated AN who then develops malignant AN

AN: Acanthosis nigricans.

AN was highest in the 30-40 years age group and it decreased with the age. The prevalence of AN correlated positively with female gender, obesity, high triglyceride levels and presence of diabetes. The presence of AN was significantly associated with higher fasting insulin levels. Males with AN had significantly higher insulin levels than females with AN. The authors concluded that AN has stronger clinical relevance among males than females and it can be used as a marker of insulin resistance in the south Indian population especially if obesity and a family history of diabetes are also present. It is therefore suggested that patients with AN should be evaluated for underlying insulin resistance and CAD.

SKIN TAGS

Skin tags are thought to be relatively common skin lesions. However it has been reported that they might reflect insulin resistance states[17,18]. In a large study of patients with skin tags, over 25% of individuals had diabetes mellitus and a further 8% had impaired glucose tolerance, although there was no association with the number or localization of the skin tags in that study[19]. There are reports describing an association between skin tags and an atherogenic lipid profile. This lipid profile is thought to be strongly associated with atherosclerosis and cardiovascular disease[20].

In a study by Erdoğan *et al*[21], comprising 36 patients with skin tags and 22 healthy controls, it was found that the mean body mass index (BMI), homeostasis model assessment of insulin resistance, and total cholesterol were significantly higher in patients showing skin tags than in controls. It was concluded that skin tags may not be innocent tumoral proliferations; instead, follow-up of such patients with regard to the development of diseases associated with atherosclerosis may be beneficial. Furthermore, skin tags associated with AN carry more sinister significance than skin tags alone.

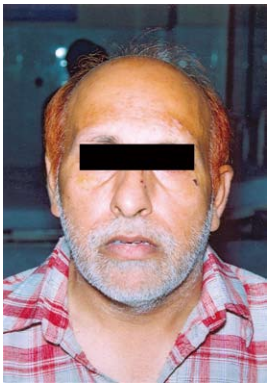

Figure 5 A male, who had a stroke at 27 years of age, continued to smoke, and developed an acute myocardial infarction at 44 years old. Note premature graying and balding.

PREMATURE GRAYING AND BALDING

Smoking has been considered to be the most important preventable risk factor responsible for premature CAD[22]. Coupled with this fact, it has been observed that young CAD patients who are heavy smokers develop premature graying and balding (Figure 5). Thus, the presence of premature graying in chronic smokers indicates higher-than-normal risk for CAD[7]. Also, early-onset androgenic alopecia, in particular, is somehow related to CAD. Besides premature graying, premature balding has also been suspected to be associated with CAD in smokers.

In a review of 24 articles by Rebora[23], it was concluded that baldness did not coincide with androgenic alopecia. However, it was observed that subjects who developed baldness before their 30s may have a higher risk for CAD than other men, and they may be the individuals with early-onset androgenic alopecia who also present with particularly elevated dihydrotestosterone:testosterone ratios. Based on this, it is suggested that the baldness theory should be included as a secondary hypothesis in large epidemiological studies of CAD.

A case-control study[24] examined the association of dermatological signs, such as baldness, thoracic hairiness,

hair graying, and diagonal ear lobe crease (ELC), with the risk of myocardial infarction in male subjects younger than 60 years, and concluded that baldness, thoracic hairiness and diagonal earlobe crease indicate an additional risk of myocardial infarction in men under the age of 60 years, independent of age and other established coronary risk factors.

In a report by Matilainen *et al*[25], the presence of insulin resistance that increases coronary disease risk has been shown to be associated with an early onset of male-pattern baldness or alopecia. This may represent a common pathogenetic mechanism for baldness and coronary atherosclerosis.

EAR LOBE CREASE

The ear lobes of children and young adults are normally smooth. The presence of an ELC and its association with CAD was first described in 1973[26]. Blodgett *et al*[27] found that 75% of CAD cases had an ELC as compared to 35% of the controls (age and gender matched). Afterwards, many studies presented ELC as a marker for CAD[28,29].

In addition, a diagonal ELC has also been suggested as a marker of vascular disease in a population with diabetes (population with increased risk of microangiopathy); but only limited data are available[30]. The Fremantle Diabetes Study reported the prevalence of ELC to be 55% in the western Australian population[30]. In an Indian study, data suggested that the ELC was present in 59.7% of the diabetic population > 40 years in the urban south Indian population[31]. The above study showed that the subjects in the ELC group were older, had longer duration of diabetes and had poor glycemic control. These observations were in agreement with the Fremantle study[30]. Subjects with ELC had a higher socioeconomic status as compared to the group without ELC; this could be an indirect measure of the population at a greater risk of CAD.

With regard to the association between ELC and diabetic retinopathy, the Indian study noted that increasing age, poor glycemic control and increasing duration of diabetes were significant variables in both univariate and multivariate models[30]. Similar observations were made in other population-based studies on diabetic retinopathy[32,33]. However some other studies have found no such associations and have concluded that the prevalence of earlobe creases probably increases with age, as does heart diseases[34,35].

Taking into consideration the above points, it appears prudent to examine the earlobes in a suspected case of CAD as additional indirect evidence.

NICOTINE STAINING

Nicotine is a naturally-occurring alkaloid found primarily in tobacco. It is most commonly absorbed from cigarette smoke, with each puff containing approximately 50 μg of nicotine. The adverse effects of smoking on the cardiovascular system are known to all.

There are certain cutaneous markers which indicate that a person is a smoker, thus indirectly pointing towards a cardiovascular risk. The most evident and enduring signs of smoking are the tar and nicotine stains found on hands, fingers, lips and on the skin in addition to the teeth. The discolorations more often than not develop on the lips and on the nails of the fingers. Black stained nails, dark brownish crusts below the fingernails, blackened lips, dark gums and stained enamel of the teeth point towards chronic heavy smoking and the likely possibility of coexisting CAD and/or other smoking-associated diseases[36].

BETEL QUID SELLER SYNDROME

This syndrome, first described by Dwivedi *et al*[37] is characterized by central obesity, brick-brownish lips and palms of the hands and denuded skin over the tips of the fingers, as observed in betel quid sellers in south Asian countries, primarily India, Pakistan, Bangladesh and Nepal. People who sell betel quid in south Asia also sell smokeless, non-perishable and dried tobacco preparations like 'gutkha' and 'pan masala' and over the years they develop a characteristic body habitus comprising central obesity because of long hours of sitting, and have discolored tips and palms of the hands as they are constantly exposed to betel quid, containing resinous extract of *Acacia catechu*, baked shell lime, betel nut (*Areca catechu* containing arecoline) and tobacco[37]. In the process of preparing quid they apply baked lime and liquefied *Acacia catechu* paste to the betel leaf, varying from 100 to 1000 times a day. The overlying skin surface that comes into direct contact with the shell lime and *Areca catechu* becomes roughened, denuded and brick-red colored. It is speculated that the denuded epithelium may be the source of absorption of nicotine and arecoline in the betel quid sellers. They are also prone to consume betel quid, gutkha and paan masala containing betel nut and sweetening agents[38]. The sedentary nature of their occupation combined with their daily intake of tobacco and betel nut leads to early development of diabetes, hypertension and dyslipidemia[39-41]. In addition, keeping quid in the space between the buccal mucosa and lower teeth results in the coloring of saliva due to interaction of *Acacia catechu* with alkaline shell lime, and damage to teeth. It is considered that features of 'betel quid seller syndrome' are a harbinger of diabetes, hypertension and/or CAD.

Interestingly, people who consume surti, a form of saltless tobacco (SLT) much used in south Asia, develop a patch of white discoloration on their palm due to constant rubbing of liquefied calcium carbonate and meshed tobacco leaves before putting it in oral cavity (Figure 6). This may provide evidence of SLT being associated with an increased risk of CAD.

CENTRAL OBESITY - FLABS AND FOLDS

Obesity is defined as a state of excessive adipose tissue mass. Although not a direct measure of adiposity, the most widely used method to gauge obesity is the BMI, which is equal to weight/height^2 in kg/m^2 with BMI > 25 taken as obesity in South Asian countries[42]. The vast majority of urban people currently have excess abdomi-

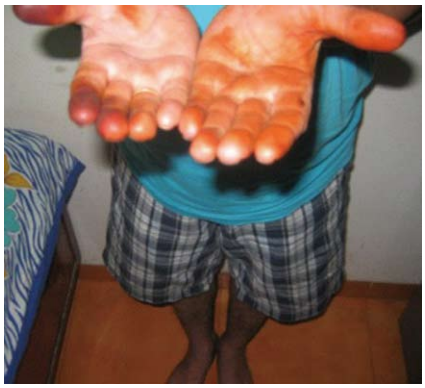

Figure 6 Betel Quid Seller Syndrome[37].

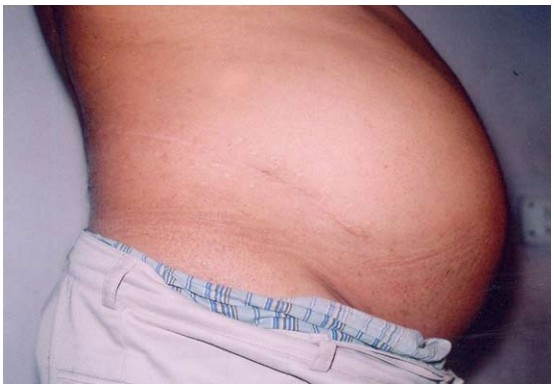

Figure 7 A beer belly in a patient with coronary artery disease.

nal fat. The excess belly fat is not just an esthetic issue alone, but is also a risk factor to health. There is a large amount of convincing scientific data which confirms it is unhealthy in general to have excess body fat throughout the body, particularly so in the abdomen. A large belly objectively measured as waist circumference is clinically known as central obesity (Figure 7). This is due to an increased amount of visceral fat. Visceral fat lies deeper in the abdomen beneath the muscles and the surrounding organs. Visceral fat also plays a role in giving certain men that "beer belly" appearance where their abdomen protrudes excessively but at the same time, also feels hard if prodded. Excessive visceral fat is more dangerous than subcutaneous fat. Central obesity increases the risk of developing diabetes, heart disease, high blood pressure, stroke, sleep apnea, various forms of cancer, and other degenerative diseases[43]. Thus excessive fat and flabs, particularly abdominal obesity, can indicate underlying CHD. According to the current guidelines a waist circumference of > 90 cm in south Asian men and > 80 cm in south Asian women are indicative of central obesity[42].

SIGNS OF PVD

PVD, also known as arteriosclerosis obliterans, is primarily the result of atherosclerosis. The atheroma consists of a core of cholesterol attached to proteins with a fibrous intravascular covering. The atherosclerotic process may gradually progress to complete occlusion of medium and large arteries. Cutaneous signs of PVD are the classic "5 P's" namely pulselessness, paralysis, paresthesia, pain and pallor. The disease typically is segmental, with significant variation from patient to patient. Other maladies that often coexist with PVD are CAD, myocardial infarction, atrial fibrillation, transient ischemic attack, stroke, and renal disease. Studies have suggested that even asymptomatic peripheral arterial disease is associated with increased CAD mortality[44]. Features of PVD are thus helpful in predicting potential CAD.

GOUT AND SIGNS OF ARTHRITIS

Gout is a metabolic disease marked by acute arthritis and inflammation of the joints, usually beginning in the knee or foot and clinically characterized by acute mono or poly arthritis often involving the metatarso-phalangeal joint of the first toe, bursitis, tendonitis, enthesitis, tophaceous deposits, or synovial osteochondromatosis. It is caused by hyperuricemia. Gout often accompanies both risk factors for heart disease and heart disease itself. It is found in higher rates in people with obesity, high blood pressure, CAD, and congestive heart failure.

The relationship between gout, not associated with the use of diuretics, and the development of CAD was examined in 5209 subjects originally enrolled in the Framingham Study[45]. Based on 32 years of follow-up, it was concluded that gout, unrelated to the intake of diuretics, imparts an additional risk of CAD in men, unexplained by clinically measured risk factors, but in women there were no significant associations between gout and CAD. Therefore, looking for gouty inflamed joints can be a useful tool for the physicians to predict underlying heart disease.

PERIPHERAL AND CUTANEOUS SIGNS OF RHEUMATOID ARTHRITIS

Atherosclerosis is now considered as inflammatory disease[46]. As rheumatoid arthritis (RA) is considered a quintessential systemic disease that can manifest in most major organ systems, it also spreads to extra-articular sites, such as mid-size arteries and capillaries, and predisposes patients to accelerated atherosclerosis and CAD[47]. Several studies have documented an increased risk of atherosclerosis and myocardial infarction in patients with RA[48,49]. Therefore, it is prudent to look for CAD if a patient presents with chest pain and has evidence of peripheral/cutaneous signs of RA.

SIGNS OF PSORIASIS

Recently, much emphasis has being laid on a link between CAD and psoriasis in the medical literature[50,51]. Reports suggest that psoriasis increases the chance of acute coronary episodes and also psoriasis appears to play a bigger role in heart disease in young people[52]. It was reported that a 30-year-old with severe psoriasis is approximately three times (300%) more likely to suffer a heart attack

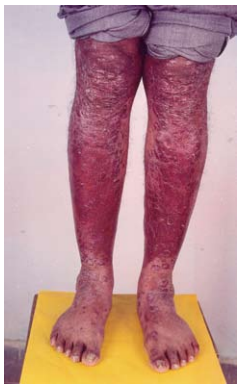

Figure 8 A patient with psoriasis and coronary artery disease.

than a 30-year-old from the general population, but a 60-year-old with severe psoriasis has only a 36% higher risk than his age-matched peers[52]. The above findings emphasize the need for psoriasis patients to monitor their cardiovascular health at an earlier age and to take measures to lessen their risks for heart attack, heart failure and other cardiovascular problems (Figure 8).

CONCLUSION

Judicious appraisal of the above cutaneous markers linked to CAD would help clinicians to recognize disease in the subclinical phase and thus make it easier to decide who is likely to need further detailed cardiovascular investigation. A diligent search for these cutaneous markers relevant to CAD may prove to be a rewarding exercise in unraveling asymptomatic CAD in high risk individuals at no extra cost.

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