Review article

Dermatological Manifestations in Diabetes

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Abstract

Diabetes mellitus (DM) is a very common and debilitating chronic disease that affects almost all organs of the body including the skin. Between thirty and seventy percent of patients with DM, both type 1 and type 2, will present with a cutaneous complication of DM at some point during their lifetime. A wide array of dermatologic manifestations has been described in DM and these conditions vary in severity. But these skin changes can offer insight into patients' glycemic control status and may be the first sign of metabolic derangement in undiagnosed patients with DM in many instances. Early diagnosis and appropriate management of these conditions are important in maximizing the quality of life and in avoiding serious adverse effects in patients with DM.

Key words: Diabetes mellitus, Skin disease.

Introduction

Chronic hyperglycemia in DM causes changes in several organ systems of the patients. Dermatologic manifestations of DM have various health implications ranging from those that are aesthetically concerning to those that may be life-threatening. Awareness of cutaneous manifestations of DM can provide insight into the present or prior metabolic status of patients. The recognition of such findings may aid in the diagnosis of DM or may be followed as a marker of glycemic control. The text that follows describes the relationship between DM and the skin,
more specifically: (1) skin manifestations strongly DM, (3) dermatologic diseases associated with DM, (4) common skin infections in DM, and (5) cutaneous changes associated with DM medications.

Skin Changes Strongly Associated with DM

Acanthosis nigricans:

Epidemiology

Acanthosisnigricans (AN) is a classic dermatologic manifestation of DM that affects men and women of all ages. AN is more common in type 2 DM and is more prevalent in those with darker skin colour.[1-2] AN is disproportionately represented in African Americans, Hispanics, Native Americans and Asians.[3] AN is observed in a variety of endocrinopathies associated with resistance to insulin such as acromegaly, Cushing syndrome, obesity, polycystic ovarian syndrome, and thyroid dysfunction. Unrelated to insulin resistance, AN can also be associated with malignancies such as gastric adenocarcinomas and other carcinomas.[4]

Presentation

AN usually presents as multiple poorly demarcated plaques with grey to dark-brown hyperpigmentation and a thickened velvety to verrucous texture over months or years. In classical cases, AN has a symmetrical distribution and is located in intertriginous or flexural surfaces such as the back of

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the neck, axilla, elbows, palmer hands (tripe palms), inframammary folds, umbilicus, or groin and so on. The changes occur gradually, and the person is generally initially asymptomatic; however, extensive involvement may cause discomfort or fetor. Microscopic findings reveal hyperkeratosis and epidermal papillomatosis
with acanthosis. The skin changes are primarily a consequence of hyperkeratosis, not changes in melanin. In many cases, AN can present before to the clinical diagnosis of DM; the presence 4 of AN should be promptly evaluated for DM and other signs of insulin resistance.

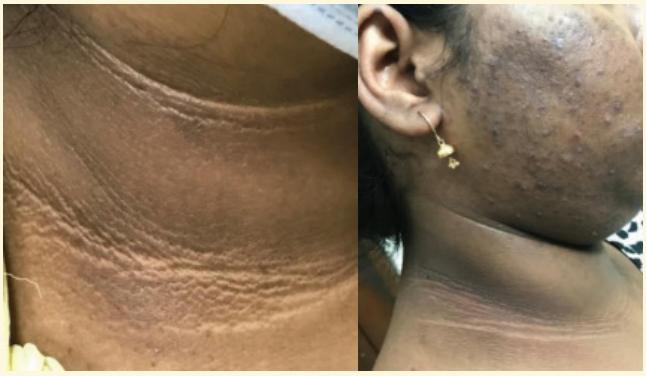

Figure 1: Acanthosis nigricans.

Pathogenesis:

The pathogenesis of AN is not determined yet. The most commonly accepted theory is that a hyperinsulinemic state activates insulin growth factor receptors (IGF), specifically IGF-1, on keratinocytes and fibroblasts, provoking cellular proliferation, resulting in the cutaneous manifestations in different parts of the body.[5-6]

Treatment:

AN is managed with lifestyle modifications such as dietary modifications, increased physical activity, and weight reduction. In patients with DM, pharmacologic adjuvants, such as metformin, that improve glycemic control and reduce insulin resistance are also beneficial.[7] But, primary dermatologic therapies are usually ineffective especially in patients with generalized involvement. However, in those with thickened or macerated areas of skin, oral retinoids or topical keratolytics such as ammonium lactate, retinoic acid, or salicylic acid can be used to alleviate symptoms.[8-10]

Diabetic dermopathy:

Epidemiology

Diabetic dermopathy (DD) which is also known as pigmented pretibial patches or diabetic shin spots, is the most common dermatologic manifestation of DM, presenting in as many as one-half of those with DM.[11] Some consider the presence of DD to be pathognomonic for DM though some do not. DD has a strong predilection for men and those older than 50 years of age.[12] Although DD may antecede the onset of DM, it occurs more frequently as a late complication of DM and in those with microvascular disease. Nephropathy, neuropathy, retinopathy and other microvascular complications of DM are regularly present in patients with DD.[13]

Presentation:

DD presents initially with rounded, dull, papules of red colour that progressively evolve over one-to-two weeks into well-circumscribed, atrophic, brown macules with a fine scale. Normally after about 18 to 24 months, lesions dissipate and leave behind an area of concavity and hyperpigmentation. At any time, different lesions can present at different stages of evolution. The lesions are normally distributed over both the limbs and localized over bony prominences. Although other bony prominences such as the forearms, lateral malleoli or thighs may also be involved, the pretibial area is most commonly involved in DD. Aside from the aforementioned changes, patients are otherwise asymptomatic. DD is a clinical diagnosis that should not require a skin biopsy. DD is rather nonspecific histologically; it is characterized by lymphocytic infiltrates surrounding vasculature, engorged blood vessels in the papillary dermis, and dispersed hemosiderin deposits. Moreover, the histology varies based on the stage of the lesion. Immature lesions present with epidermal edema as opposed to epidermal atrophy which isrepresentative of older lesions.[14]

Pathogenesis:

The origin of DD remains unclear, however, mild trauma to affected areas, hemosiderin and melanin deposition, microangiopathic changes, and destruction of subcutaneous nerves have all been suggested.[15-18]

Treatment:

Treatment is typically avoided given the asymptomatic and self-resolving nature of DD as well as the ineffectiveness of available treatments. However, DD often occurs in the context of

microvascular complications and neuropathies.[12] Hence, patients need to be examined and followed more rigorously for these complications. Although it is important to manage DM and its complications accordingly, there is no evidence that improved glycemic control alters the development of DD.

Diabetic Foot Syndrome:

Epidemiology

Diabetic Foot Syndrome (DFS) encompasses the neuropathic and vasculopathic complications that develop in the feet of patients with DM. Although potentially preventable, DFS is a significant cause of morbidity, mortality, hospitalization, and reduction in quality of life of patients with DM. The incidence and prevalence of DFS in patients with DM is 1% to 4% and 4% to 10%, respectively.[19] DFS is slightly more prevalent in tT1DM compared with T2DM.[20]

Clinical features:

DFS usually presents with callosities and dry skin related to diabetic neuropathy. Subsequently, chronic ulcers and a variety of other malformations of the feet develop. About 20% (15% - 25% of patients with DM will develop ulcers.[21]These ulcers may be neuropathic, ischemic or mixed. The most common type of ulcer is neuropathic ulcer, painless ulceration resulting from peripheral neuropathy. Ulcers associated with peripheral vascular ischemia are less common but often painful. Ulcers tend to occur in areas prone to trauma, classically presenting at the site of calluses or over bony prominences. It is common for ulcers to occur on the toes, forefoot, and ankles. Untreated ulcers usually heal within one year, however, fifty percent of patients with DM will have a recurrence of the ulcer within three years.[22] The skin of affected patients, especially in those with type 2 DM, is more prone to fungal infection and the toe webs are a common port of entry for fungi which can then infect and complicate ulcers.[23] Secondary infection of ulcers is 7 a serious complication that can result in gangrenous necrosis, osteomyelitis and may even require lower extremity amputation. Another complication, diabetic neuro-osteoarthropathy (charcot foot), is an irreversible, debilitating and deforming condition involving progressive destruction of weight-bearing bones and joints. Diabetic neuro-osteoarthropathy occurs most frequently in the feet and can result in collapse of the midfoot, referred to as “rocker-bottom foot.” Moreover, a reduction of the intrinsic muscle volume and thickening of the plantar aponeurosis can cause imbalance of the muscles that produces a clawing deformation of the toes. Furthermore, a complication of DM and neuropathy involving the feet is erythromelalgia. Erythromelalgia presents with redness, warmth, and a burning pain involving the lower extremities, most often the feet. Symptoms may worsen in patients with erythromelalgia with exercise or heat exposure and may improve with cooling.[24]

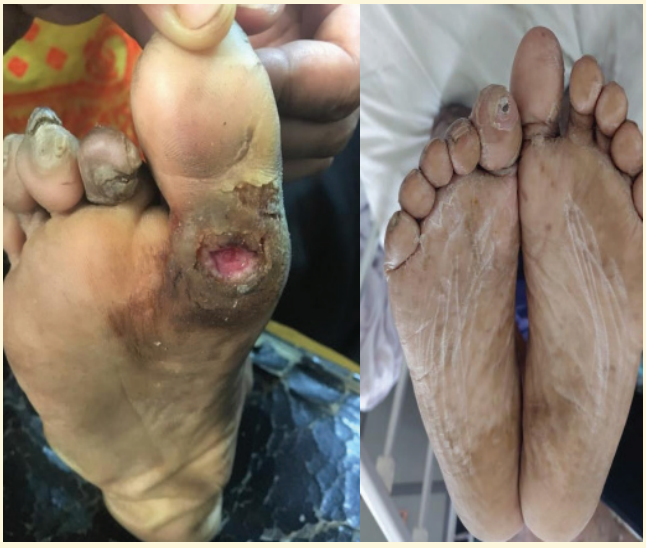

Figure 2: Diabetic foot (Photograph : Dr. Mohammad Jamal Uddin and Dr. Khandaker Snigdha Malabika)

Pathogenesis:

A combination of inciting factors that coexist together: neuropathy, atherosclerosis, and impaired wound healing is involved in the pathogenesis of DFS.[25-26] In the setting of long-standing hyperglycemia, there is an increase in advanced glycosylation end products, proinflammatory factors, and oxidative stress which results in the demyelination of nerves and subsequent neuropathy.[27-28] The effect on sensory and motor nerves, can blunt the perception of adverse stimuli and produce an altered gait, increasing the likelihood of developing foot ulcers and malformations. Also, damage to autonomic nerve fibres causes a reduction in sweating which may leave skin in the lower extremity dehydrated and prone to fissures and secondary infection.[29] In addition to neuropathy, accelerated arterial atherosclerosis can lead to peripheral ischemia and ulceration.[30] Finally, hyperglycemia impairs macrophage functionality as well as increases and prolongs the inflammatory response, slowing the healing of ulcers.[31]

Management:

Treatment should involve an interdisciplinary team-based approach with a focus on the prevention and management of current ulcers. Prevention entails daily surveillance, appropriate foot hygiene, and proper footwear, walkers, or other devices to minimize and distribute pressure. An appropriate wound care program should be used to care for ongoing ulcers. Different classes of wound dressing should be considered based on the wound type. Hydrogels, hyperbaric oxygen therapy, topical growth factors, and biofabricated skin grafts are also available.[19] The clinical presentation should indicate whether antibiotic therapy or wound debridement is necessary.[19] In patients with chronic treatment-resistant ulcers, underlying ischemia should be considered; these patients may require surgical revascularization or bypass.

Diabetic thick skin:

Thickening of skin is frequently observed in patients with DM. Affected skin areas can appear thickened, waxy, or edematous. These patients are often asymptomatic but can have a reduction in sensation and pain. Although different parts of the body can be involved, the hands and feet are most frequently involved. Ultrasound evaluation of the skin can be diagnostic and exhibit thickened skin. Subclinical generalized skin thickening is the most common type of skin thickening. Diabetic thick skin may represent another manifestation of scleroderma-like skin change or limited joint mobility, which are each described in more detail below

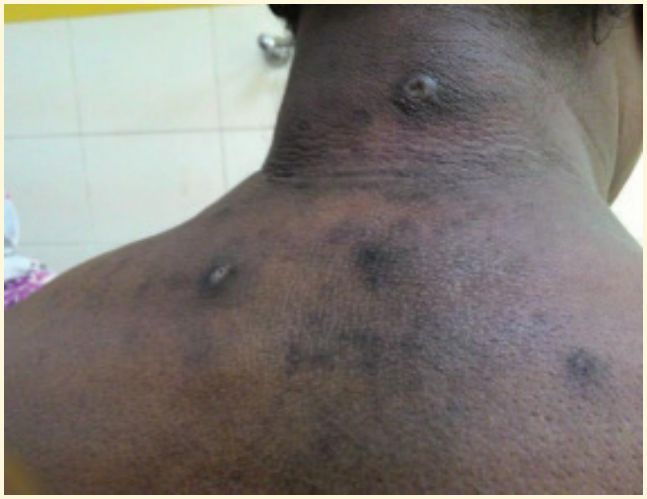

Figure 3: Diabetic thick skin. (Photograph: Dr. Towhida Noor)

Scleroderma-Like Skin Changes (SLSC):

Epidemiology

SLSC are a distinct and easily overlooked group of findings that are commonly observed in patients with DM. Ten to 50% of patients with DM present with the associated skin findings.[32] SLSC occurs more commonly in those with T1DM and those with longstanding disease.[33] There is no known variation in prevalence between males and females, or between racial groups.

Presentation

SLSC develop slowly and present with painless, indurated, occasionally waxy appearing, thickened skin. These changes occur symmetrically and bilaterally in acral areas. In patients with scleroderma-like skin changes the acral areas are involved, specifically the dorsum of the fingers (sclerodactyly), proximal interphalangeal, and metacarpophalangeal joints. Severe disease may extend centrally from the hands to the arms or back. A small number of patients with DM may develop more extensive disease, which presents earlier and with truncal involvement. The risk of developing nephropathy and retinopathy is increased in those with SLSC who also have T1DM.[33-34] The aforementioned symptoms are also associated with diabetic hand syndrome which may present with limited joint mobility, palmar fibromatosis (Dupuytren's contracture), and stenosing tenosynovitis ("trigger finger").[35] The physical finding known as the "prayer sign" (inability to flatty press palmar surfaces on each hand together) may be present in patients with diabetic hand syndrome and scleroderma-like skin changes.[36] SLSC reveal thickening of the dermis on histology, minimal-to-absent mucin, and increased interlinking of collagen. Although on physical exam scleroderma may be difficult to distinguish from these skin changes, SLSC is not associated with atrophy of the dermis, Raynaud's syndrome, pain, or telangiectasias

Pathogenesis

Though not fully revealed, the pathogenesis is believed to involve the strengthening of collagen as a result of reactions associated with advanced glycosylation end products or a buildup of sugar alcohols in the upper dermis.[37-38]

Treatment

Scleroderma-like skin changes is a chronic condition that is also associated with joint and microvascular complication. Therapeutic options are extremely limited. One observational report has suggested that very tight blood sugar control may result in the narrowing of thickened skin.[39] In addition, aldose reductase inhibitors, which limit increases in sugar alcohols, may be efficacious.[38] In patients with restricted ranges of motions, physical therapy can help to maintain and improve joint mobility.

Limited Joint Mobility:

Limited Joint Mobility (LJM), also known as diabetic cheiroart flush press arthropathy, is a relatively common complication of long-standing DM. The majority of patients with LJM also present with scleroderma-like skin changes.[38,40] The prevalence of LJM is 4% to 26% in patients without DM and 8% to 58% in patients with DM.[41] LJM disorders present with progressive flexed contractures and restricted joint extension, most commonly involving the metacarpophalangeal and interphalangeal joints of the hand. The initial changes often begin in the joints of the fifth finger before then spreading to involve the other joints of the hand.[38] Patients may present with an inability to flushly press the palmar surfaces of each of their hands together ("prayer sign") or against the surface of a table when their forearms are perpendicular to the surface of the table ("tabletop sign").[42] These changes occur as a result of periarticular enlargement of connective tissue. The pathogenesis likely involves hyperglycemia-induced formation of advanced glycation end-products, which accumulate to promote inflammation and the formation of stiffening cross-links between collagen.[43] LJM is strongly associated with microvascular and macrovascular changes and diagnosis of LJM should prompt a workup for the related sequel.[44] Patients with LJM may also be at increased risk for falls.[45] Currently there are no curative treatments for the condition. Symptomatic patients may benefit from non-steroidal anti-inflammatory drugs or targeted injection of corticosteroids.[43] LJM is best managed with improved glycemic control as well as, regular stretching to maintain and minimize further limitations in joint mobility.[46]

Scleredema diabeticorum:

Epidemiology

Scleredema diabeticorum is a chronic and slowly progressive sclerotic skin disorder that is oftenseen in the context of DM. Whereas, 2.5% to 14% of all patients with DM have scleredema, over 50% of those with scleredema present with concomitant DM.[47] Scleredema has a proclivity for those with a long history of DM. It remains unclear whether there is a predilection for scleredema in those with T1DMs compared to those with T2DM.[48] Women are affected more often than men.[49] Although all ages are affected, scleredema occurs more frequently in those over the age of twenty.[48- 49]

Presentation

Scleredema presents with gradual worsening indurated and thickened skin changes occurring symmetrically and diffusely. The most commonly involved areas are the upper back, shoulders, and back of the neck. The face, chest, abdomen, buttocks, and thighs may also be involved; however, the distal extremities are classically spared. The affected areas are normally asymptomatic but there can be reduced sensation. Patients with severe longstanding disease may develop a reduced range of motion, most often affecting the trunk. In extreme cases, this can lead to restrictive respiratory problems. A full-thickness skin biopsy may be useful in supporting a clinical presentation. The histology of scleredema displays increased collagen and a thickened reticular dermis, with a surrounding mucinous infiltrate, without edema or sclerosis.

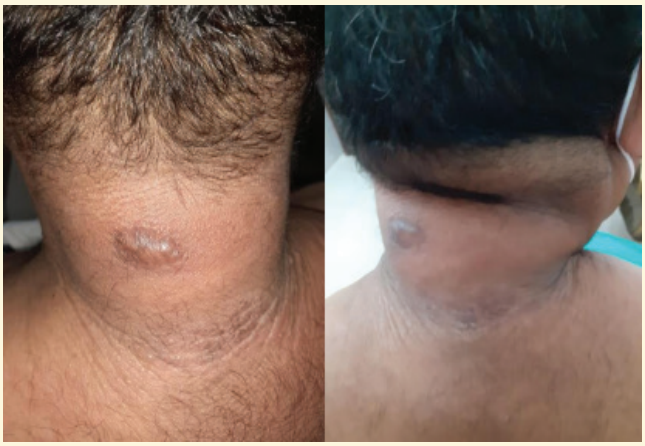

Figure 4: Scleredema diabeticorum (Photograph : Dr. Marshad Hossain)

Pathogenesis

Although many theories focus on abnormalities in collagen, there is no consensus regarding the pathogenesis of scleredema. The pathogenesis of scleredema may involve an interplay between non-enzymatic glycosylation of collagen, increased

fibroblast production of collagen, or decreases in collagen breakdown.[50-51]

Treatment

Scleredema diabeticorum is generally unresolving and slowly progressive over years. Optimum glycemic control may be an important means of prevention, but evidence shown no clinical improvements in those already affected by scleredemadiabeticorum. A variety of therapeutic options have been proposed with variable efficacy. Some of these therapies include immunosuppressants, corticosteroids, intravenous immunoglobulin and electron-beam therapy.[52] Phototherapy with UVA1 or PUVA may be effective in those that are severely affected.[52] Independent of other treatments, physical therapy is an important therapeutic modality for patients with scleredema and reduced mobility.[53]

Necrobiosis Lipoidica:

Epidemiology

Necrobiosislipoidica (NL) is a rare chronic granulomatous dermatologic disease that is seen most frequently in patients with DM as well as in others. Although nearly 25% of patients presenting with NL also have DM, less than 1% of patients with DM develop NL.[54] NL expresses a strong predilection for women compared to men, but the reason is unclear still.[55] NL generally occurs in type 1 DM during the third decade of life, whereas, in type 2 DM it commonly presents in the fourth or fifth decades of life.[54] Frequently NL presents years after a diagnosis of DM; however, about 20% (14% to 24%) of cases of NL may occur before or at the time of diagnosis.[56]

Presentation

NL usually begins as a single or group of firm well-demarcated rounded erythematous papules.The papules then expand and aggregate into plaques characterized by circumferential red-brown borders and a firm yellow-brown waxen atrophic centre containing telangiectasias. NL usually occurs symmetrically and exhibits Koebnerization. The lesions are almost always found on the pretibial areas of the lower extremities. The forearm scalp, distal upper extremities, face,or abdomen may be affected occasionally, and the heel of the foot or glans penis even more infrequently. About 15% of lesions will resolve within twelve years if left untreated. Despite the pronounced appearance of the lesions, NL is often remaining unnoticed over years. However, there may be pruritus and hypoesthesia of affected areas, and pain may be present in the areas of ulceration. Ulceration occurs in about 31% of lesions and has been associated with secondary infections and squamous cell carcinoma. The histopathology of NL primarily involves the dermis and is marked by palisading granulomatous inflammation, necrobiotic collagen, a mixed inflammatory infiltrate, blood vessel wall thickening, and reduced mucin.

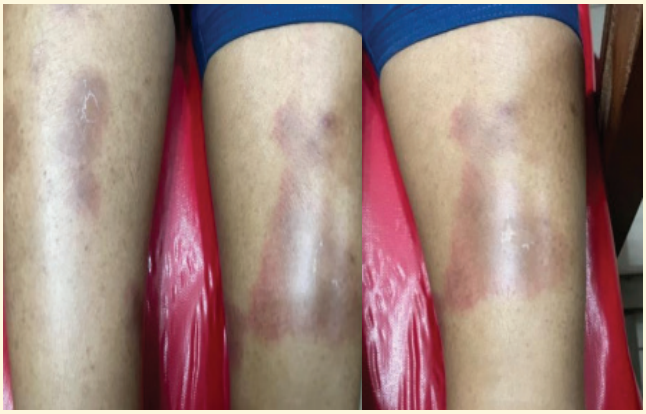

Figure 5: Necrobiosis lipoidica

Pathogenesis

The pathogenesis of NL is not well understood yet. The relationship between DM and NL has led some to theorize that DM-related microangiopathy is related to the development of NL.[54] Other theories focus on irregularities in collagen, autoimmune disease, neutrophil chemotaxis, or blood vessels.[57]

Treatment

NL is a chronic, disfiguring condition that can be debilitating for patients and difficult for clinicians to manage. Differing degrees of success have been reported with a variety of treatments; however, the majority of such reports are limited by inconsistent treatment responses in patients and a lack of large controlled studies. Corticosteroids are often used in the management of NL and may be administered topically, intralesionally, or orally. Corticosteroids can be used to manage active lesion, but is best not used in atrophic areas. Success has also been reported with calcineurin inhibitors (e.g. cyclosporine), anti-tumor necrosis factor inhibitors (e.g. infliximab), pentoxifylline, antimalarials (e.g. hydroxychloroquine), PUVA, granulocyte colony stimulating factor, dipyridamole and low-dose aspirin.[54] Appropriate wound care is important for ulcerated lesions; this often includes topical

antibiotics, protecting areas vulnerable to injury, emollients and compression bandaging. Surgical excision of ulcers typically has poor results. Some ulcerated lesions may improve with split-skin grafting. Although still recommended, improved control of DM has not been found to lead to an improvement in skin lesions.

Bullosis diabeticorum:

Epidemiology

Bullosis diabeticorum (BD) is an uncommon eruptive blistering disorder that presents in patients with DM. Although BD can occasionally present in early-DM.[58] It often occurs in long-standing DM along with other complications such as neuropathy, nephropathy, and retinopathy. In the United States, the prevalence of BD is around 0.5% amongst patients with DM and is believed to be higher in those with type 1 DM.[13] BD is significantly more common in male patients than in female patients.[59] The average age of onset is between 50 and 70 years of age.[59]

Presentation

BD presents at sites of previously healthy-appearing skin with the abrupt onset of one or more non-erythematous, firm, sterile bullae. Shortly after forming, bullae increase in size and become more flaccid, ranging in size from about 0.5 cm to 5 cm. Bullae frequently present bilaterally involving the acral areas of the lower extremities. However, involvement of the upper extremities and even more rarely the trunk can be seen. The bullae and the adjacent areas are nontender. BD often presents acutely, classically overnight, with no history of trauma to the affected area. Generally, the bullae heal within two to six weeks, but then commonly reoccur. Histological findings are often non-specific but are useful in distinguishing BD from other bullous diseases. Histology, typically shows an intraepidermal or subepidermal blister, spongiosis, no acantholysis, minimal inflammatory infiltrate, and normal immunofluorescence.

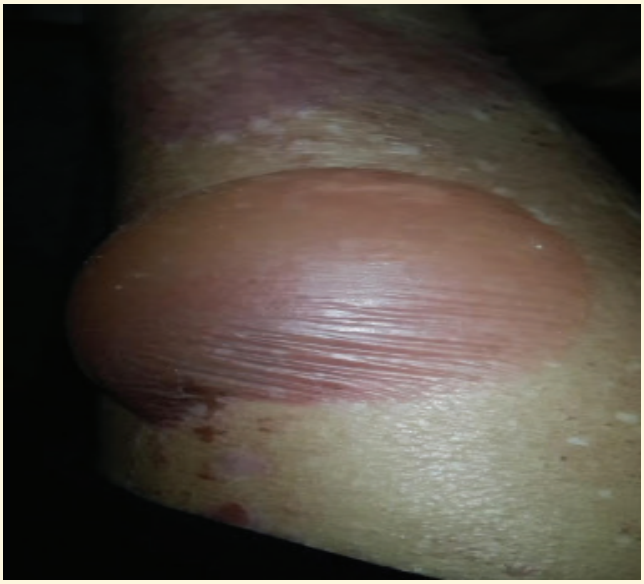

Figure 6: Bullosis Diabeticorum (Photograph : Dr. Mohammed Jamal Uddin)

Pathogenesis

There is an incomplete understanding of the underlying pathogenesis of BD and no consensus regarding a leading theory. Various mechanisms have been proposed, some of which focus on autoimmune processes, exposure to ultraviolet light, variations in blood glucose, neuropathy, or changes in microvasculature.[60]

Treatment

BD resolve without treatment and are therefore managed by avoiding secondary infection and the corresponding sequelae (e.g. necrosis, osteomyelitis). This involves protection of the affected skin, leaving blisters intact (except for large blisters, which may be aspirated to prevent rupture), and monitoring for infection. Topical antibiotics are not necessary unless specifically indicated, such as with secondary infection or positive culture.

Nonspecific signs and Symptoms of Skin:

Ichthyosiform changes of the shins

Ichthyosiform changes of the shins presents with large bilateral areas of dryness and scaling (sometimes described as “fish scale” skin). Although cutaneous changes may occur on the hands or feet, the anterior shin is most classically involved. These cutaneous changes are related to rapid skin aging and adhesion defects in the stratum corneum.[61] The prevalence of ichthyosiform changes of the shins in

those with type 1 DM has been reported to be between 22% to 48%.[62, 33] These changes present relatively early in the disease course of DM. There is no known difference in prevalence between males and females.[33] The development of ichthyosiform changes of the shins is related to the production of advanced glycosylation end products and microangiopathic changes. Treatment is limited but topical emollients or keratolytic agents may be beneficial.[61]

Xerosis

Xerosis is one of the most common skin presentations in patients with DM and has been reported to be present in as many as 40% of patients with DM.[63] Xerosis refers to abnormally dry skin. Affected skin may present with scaling, cracks or a rough texture. These skin changes are most frequently located on the feet of patients with DM. In patients with DM, xerosis occurs often in the context of microvascular complications.[40] To avoid complications such as fissures and secondary infections, xerosis can be managed with emollients like ammonium lactate.[64]

Acquired perforating dermatosis:

Epidemiology

Perforating dermatoses refers to a broad group of chronic skin disorders characterized by a loss of dermal connective tissue. A subset of perforating dermatoses, known as acquired perforating dermatoses (APD), encompasses those perforating dermatoses that are associated with systemic diseases. Although APD may be seen with any systemic diseases, it is classically observed in patients with chronic renal failure or long-standing DM.[65] APD occurs most often in adulthood in patients between the ages of 30 and 90 years of age.[65-66] The prevalence of APD is unknown. It is estimated that of those diagnosed with APD about 15% also have DM.[67] In a review, 4.5% to 10% of patients with chronic renal failure presented with concurrent APD.[68-69]

Presentation

APD presents as groups of hyperkeratotic umbilicated nodules and papules with centralized keratin plugs. The lesions undergo koebnerization and hence the extensor surfaces of the arms and more commonly the legs are often involved; eruptions also occur frequently on the trunk. However, lesions can develop anywhere on the body. Lesions are extremely pruritic and are aggravated by excoriation. Eruptions may improve after a few months but an area of hyperpigmentation typically remains. Histologically, perforating dermatoses are characterized by a lymphocytic infiltrate, an absence or degeneration of dermal connective tissue components (e.g. collagen, elastic fibres), and transepidermal extrusion of keratotic material.

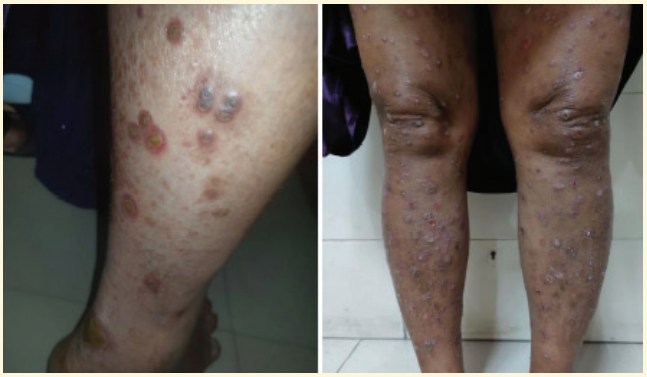

Figure 7-a & 7-b: Acquired perforating dermatoses (Photograph : a. Dr. Tauhidur Rahman; b. Dr. Afrina Jahan)

Pathogenesis

The underlying pathogenesis is disputed and not fully understood. It has been suggested that repetitive superficial trauma from chronic scratching may induce epidermal or dermal derangements.[70] The glycosylation of microvasculature or dermal components has been suggested as well. Other hypotheses have implicated additional metabolic disturbance or the accumulation of unknown immunogenic substances that are not eliminated by dialysis.[65]

Treatment

APD can be challenging to treat and many of the interventions have variable efficacy. Minimizing scratching and other traumas to involved areas can allow lesions to resolve over months. This is best achieved with symptomatic relief of pruritus. Individual lesions can be managed with topical agents such as keratolytics (e.g. 5% to 7% salicylic acid), retinoids (e.g. 0.01% to 0.1% tretinoin), or high-potency steroids.[71] Refractory lesions may respond to intralesional steroid injections or cryotherapy.[71] A common initial approach is a topical steroid in combination with emollients and an oral antihistamine. Generalized symptoms may improve with systemic therapy with oral retinoids, psoralen

plus UVA light (PUVA), allopurinol (100 mg daily for 2 to 4 months), or oral antibiotics (doxycycline or clindamycin).[72] Nevertheless, effective management of the underlying systemic disease is fundamental to the treatment of APD. In those with DM, APD is unlikely to improve without improved blood sugar control. Moreover, dialysis does not reduce symptoms; however, renal transplantation can result in the improvement and resolution of cutaneous lesions.

Eruptive xanthomas:

Epidemiology

Eruptive xanthomas (EX) is a clinical presentation of hypertriglyceridemia, generally associated with serum triglycerides above 2,000 mg/dL.[73] However, in patients with DM, lower levels of triglycerides may be associated with EX. The prevalence of EX is around one percent in type 1 DM and two percent in type 2 DM.[74-75] Serum lipid abnormalities are present in about seventy-five percent of patients with DM.[76]

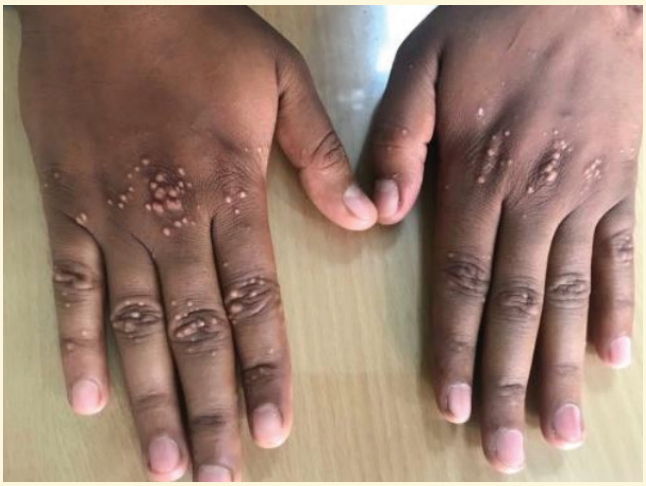

Figure 8: Eruptive Xanthomas

Presentation

EX has been reported as the first presenting sign of DM, granting it can present at any time in the disease course. EX presents as eruptions of clusters of glossy pink-to-yellow papules, ranging in diameter from 1 mm to 4 mm, overlying an erythematous area. The lesions can be found on extensor surfaces of the extremities, the buttocks, and in areas susceptible to koebnerization. EX is usually asymptomatic but may be pruritic or tender. The histology reveals a mixed inflammatory infiltrate of the dermis which includes triglyceride containing macrophages, also referred to as foam cells.

Pathogenesis

Lipoprotein lipase, a key enzyme in the metabolism of triglyceride rich-lipoproteins, is stimulated by insulin. In an insulin-deficient state, such as poorly controlled DM, there is decreased lipoprotein lipase activity resulting in the accumulation of chylomicrons and other triglyceride-rich lipoproteins.[77] Increased levels of these substances are scavenged by macrophages.[78] These lipid-laden macrophages then collect in the dermis of the skin where they can lead to eruptive xanthomas.

Treatment

EX can resolve with improved glycemic control and a reduction in serum triglyceride levels.[79] This may be achieved with fibrates or omega-3-fatty acids in addition to an appropriate insulin regimen.[80]

Acrochordons

Acrochordons (also known as soft benign fibromas, fibroepithlial polyps, or skin tags) are benign, soft, pedunculated growths that vary in size and can occur singularly or in groups. The neck, axilla, and periorbital area are most frequently involved, although other intertriginous areas can also be affected. Skin tags are common in the general population but are more prevalent in those with increased weight or age, and in women. It has been reported that as many as three out of four patients presenting with acrochordons also have DM.[81] Patients with acanthosis nigricans may have acrochordons overlying the affected areas of skin. Although disputed, some studies have suggested that the number of skin tags on an individual may correspond with an individual's risk of DM or insulin resistance.[82] Excision or cryotherapy is not medically indicated but may be considered in those with symptomatic or cosmetically displeasing lesions.

DM-Associated pruritus

DM can be associated with pruritus, more often localized than generalized. Affected areas can include the scalp, ankles, feet, trunk, or genitalia.[83-84] Pruritus is more likely in patients with DM who have dry skin or diabetic neuropathy. Involvement of the genitalia or intertriginous areas may occur in the setting of infection (e.g. candidiasis). Treatments include topical capsaicin, topical ketamine-amitriptyline-lidocaine, oral anticonvulsants (e.g. gabapentin or pregabalin), and, in the case of candida infection, antifungals.

Huntley's papules (Finger pebbles)

Huntley's papules, also known as finger pebbles, are a benign cutaneous finding affecting the hands. Patients present with clusters of non-erythematous, asymptomatic, small papules on the dorsal surface of the hand, specifically affecting the metacarpophalangeal joints and periungual areas. The clusters of small papules can develop into coalescent plaques. Other associated cutaneous findings include hypopigmentation and induration of the skin. Huntley's papules are strongly associated with type 2 DM and may be an early sign of diabetic thick skin.[85-86] Topical therapies are usually ineffective; however, patients suffering from excessive dryness of the skinmay benefit from 12% ammonium lactate cream.[87]

Keratosis pilaris

Keratosis pilaris is a very common benign keratotic disorder. Patients with keratosis pilaris classically present with areas of keratotic perifollicular papules with surrounding erythema or hyperpigmentation. The posterior surfaces of the upper arms are often affected but the involvement of the thighs, face and buttocks can also be seen. Compared to the general population, keratosis pilaris occurs more frequently and with more extensive involvement of the skin in those with DM.[33, 62] Keratosis pilaris can be treated with various topical therapies, including salicylic acid, moisturizers, and emollients.

Pigmented purpuric dermatoses

Pigmented purpuric dermatoses (also known as pigmented purpura) is associated with DM, more often in the elderly, and frequently coexists with diabetic dermopathy.[88-89] Pigmented purpura presents with non-blanching copper-colorued patches involving the pretibial areas of the legs or the dorsum of the feet. The lesions are usually asymptomatic but may be pruritic. Pigmented purpuric dermatoses occur more often in late-stage DM in patients with nephropathy and retinopathy as a result of microangiopathic damage to capillaries and sequential erythrocyte deposition.[90]

Palmar erythema

Palmar erythema is a benign finding that presents with symmetric redness and warmth involving the palms. The erythema is asymptomatic and often most heavily affects the hypothenar and thenar eminences of the palms. The microvascular complications of DM are thought to be involved in the pathogenesis of palmar erythema.[91] Although DM associated palmar erythema is distinct from physiologic mottled skin, it is similar to other types of palmar erythema such as those related to pregnancy and rheumatoid arthritis.

Periungual telangiectasias

As many as one in every two patients with DM are affected by periungual telangiectasias.[92] Periungualtelangiectasias presents asymptomatically with erythema and telangiectasias surrounding the proximal nail folds.[71] Such findings may occur in association with "ragged" cuticles and fingertip tenderness. The cutaneous findings are due to venous capillary dilatation that occurs secondary to diabetic microangiopathy. Capillary abnormalities, such as venous capillary tortuosity, may differ and can represent an early manifestation of DM-related microangiopathy.[93]

Rubeosis faciei

Rubeosis faciei is a benign finding present in about 7% of patients with DM; however, in hospitalized patients, the prevalence may exceed 50%.[94] Rubeosisfaciei presents with chronic erythema of the face or neck. Telangiectasias may also be visible. The flushed appearance is often more prominent in those with lighter colored skin. The flushed appearance is thought to occur secondary to small vessel dilation and microangiopathic changes. Complications of DM, such as retinopathy, neuropathy, and nephropathy are also associated with rubeosis faciei.[90] Facial erythema may improve with better glycemic control and reduction of caffeine or alcohol intake.

Yellow skin and nails

It is common for patients with DM, particularly elderly patients with T2DM, to present with asymptomatic yellow discolourations of their skin or fingernails. These benign changes commonly involve the palms, soles, face, or the distal nail of the first toe. The accumulation of various substances (e.g. carotene, glycosylated proteins) in patients with DM may be responsible for the changes in complexion; however, the pathogenesis remains controversial.[95]

Dermatological Diseases Associated with DM:

Generalized granuloma annulare

Epidemiology

Although various forms of granuloma annulare exist, only generalized granuloma annulare (GGA) is

thought to be associated with DM. It is estimated that between ten and fifteen percent of cases of GGA occur in patients with DM.[96] Meanwhile, less than one percent of patients with DM present with GGA. GGA occurs around the average age of 50 years. It occurs more frequently in women than in men, and in those with T2DM.[97]

Presentation

GGA initially presents with groups of skin-coloured or reddish, firm papules which slowly grow and centrally involute to then form hypo- or hyper-pigmented annular rings with elevated circumferential borders. The lesions can range in size from 0.5 cm to 5.0 cm. The trunk and extremities are classically involved in a bilateral distribution. GGA is normally asymptomatic but can present with pruritus. The histology shows dermal granulomatous inflammation surrounding foci of necrotic collagen and mucin. Necrobiosislipoidica can present similarly to GGA; GGA is distinguished from necrobiosis lipoidica by its red color, the absence of an atrophic epidermis, and on histopathology: the presence of mucin and lack of plasma cells.

Pathogenesis

The pathogenesis of GGA is incompletely understood. It is believed to involve an unknown stimulus that leads to the activation of lymphocytes through a delayed-type hypersensitivity reaction, ultimately initiating a pro-inflammatory cascade and granuloma formation.[98]

Treatment

GGA has a prolonged often unresolving disease course and multiple treatments have been suggested to better manage GGA. However, much of the support stems from small studies and case reports. Antimalarials, retinoids, corticosteroids, dapsone, cyclosporine, PUVA, and calcineurin inhibitors have been suggested as therapies.[98]

Psoriasis

Psoriasis is a chronic immune-mediated inflammatory disorder that may present with a variety of symptoms, including erythematous, indurated, and scaly areas of the skin. Psoriasis is associated with a variety of risk factors, such as hypertension and metabolic syndrome, that increase the likelihood of cardiovascular disease. The development of DM, an additional cardiovascular risk factor, has been strongly associated with psoriasis.[99] In particular, younger patients and those with severe psoriasis may be more likely to develop DM in the future.[99]

Lichen planus

Lichen planus is a mucocutaneous inflammatory disorder characterized by firm, erythematous, polygonal, pruritic, papules. These papules classically involve the wrists or ankles, although the trunk, back and thighs can also be affected. Many studies have cited an association between lichen planus and abnormalities in glucose tolerance testing. Approximately one in four patients with lichen planus have DM.[100] Although the association is contested, it has been reported that patients with DM may also be more likely to develop oral lichen planus.[101]

Vitiligo

Vitiligo is an acquired autoimmune disorder involving melanocyte destruction. Patients with vitiligo present with scattered well-demarcated areas of depigmentation that can occur anywhere on the body, but frequently involves the acral surfaces and the face. Whereas about 1% of the general population is affected by vitiligo, vitiligo is much more prevalent in those with DM. Vitiligo occurs more frequently in women and is also more common in type 1 than in T2DM.[96,98] Coinciding vitiligo and T2DM may be associated with endocrine autoimmune abnormalities of the gastric parietal cells, adrenal, or thyroid.[102]

Hidradenitis suppurativa

Hidradenitis Suppurativa (HS) is a chronic inflammatory condition characterized by nodules and abscesses located in intreginious areas such as the axilla or groin. These lesions are often painful and malodorous. HS is frequently complicated by sinus formation and the development of disfiguring scars. HS occurs more often in women than men and usually presents in patients beginning in their twenties.[103] Compared to the general population, DM is three times more common in patients with HS.[104] Patients with HS be screened for DM. There is no standardized approach to the treatment of HS, although some benefits have been reported with the use of antibiotics, retinoids, antiandrogens, or immunomodulators such as tumor necrosis factor (TNF) inhibitors.[105]

Glucagonoma

Glucagonoma is a rare neuroendocrine tumor that most frequently affects patients in their sixth decade of life.[106] Patients with glucagonoma may present with a variety of non-specific symptoms. However, necrolytic migratory erythema (NME) is classically associated with glucagonoma and presents in 70% to 83% of patients.[106-107] NME is characterized by erythematous erosive crusted or vesicular eruptions of papules or plaques with irregular borders. The lesions may become bullous or blistered and may be painful or pruritic. The abdomen, groin, genitals, or buttocks are frequently involved, although cheilitis or glossitis may also be present. Biopsy at the edge of the lesion may demonstrate epidermal pallor, necrolytic edema and perivascular inflammatory infiltrate.[108] Patients with glucagonoma may also present with DM. In patients with glucagonoma, DM frequently presents before NME.[107] Approximately 20% to 40% of patients will present with DM before the diagnosis of glucagonoma.[107,109] Of those patients diagnosed with glucagonoma but not DM, 76% to 94% will eventually develop DM.[110]

Skin Infections

The prevalence of cutaneous infections in patients with DM is about 1 in every 5 patients.[111] Compared with the general population, patients with DM are more susceptible to infections and more prone to repeated infections. A variety of factors are believed to be involved in the vulnerability to infection in patients with uncontrolled DM, some of these factors include: angiopathy, neuropathy, hindrance of the anti-oxidant system, abnormalities in leukocyte adherence, chemotaxis, and phagocytosis, as well as, a glucose-rich environment facilitates the growth of pathogens

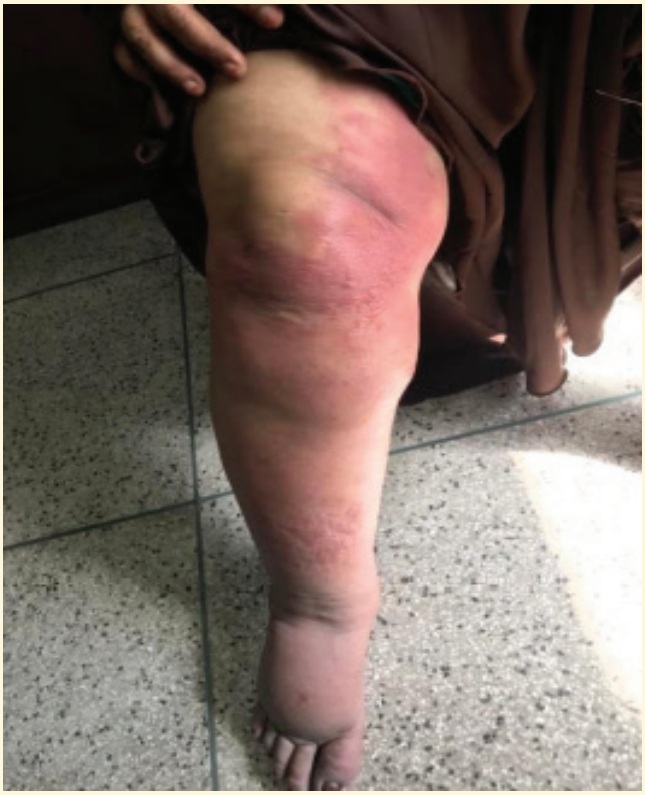

Figure 9: Cellulitis and erysipelas.

Bacterial

Erysipelas and cellulitis are cutaneous infections that occur frequently in patients with DM. Erysipelas presents with pain and well-demarcated superficial erythema. Cellulitis is a deeper cutaneous infection that presents with pain and poorly-demarcated erythema. Folliculitis is common among patients with DM and is characterized by inflamed, perifollicular, papules and pustules. Treatment for the aforementioned conditions depends on the severity of the infection. Uncomplicated cellulitis and erysipelas are typically treated empirically with oral antibiotics, whereas uncomplicated folliculitis may be managed with topical antibiotics. Colonization with methicillin-resistant Staphylococcus aureus (MRSA) is not uncommon among patients with DM.[112] However, it is debated as to whether or not colonized patients are predisposed to increased complications; such as bullous erysipelas, carbuncles, or perifollicular abscesses.[113] Regardless, it is important that appropriate precautions are taken in these patients and that antibiotics are selected that account for antimicrobial resistance.

Infection of the foot is the most common type of soft tissue infection in patients with DM. If not managed

properly, diabetic foot infections can become severe, possibly leading to sepsis, amputation, or even death. Although less severe, the areas between the toes and the toenails are also frequently infected in patients with DM. Infections can stem from monomicrobial or polymicrobial etiologies. Staphylococcal infections are very common and complications with infection by Pseudomonas aeruginosa are also frequent.[114-115] Pseudomonal infection of the toenail may present with a green discolouration, which may become more pronounced with the use of a Wood's light. Treatment frequently requires coordination of care from multiple medical providers. Topical or oral antibiotics and surgical debridement may be indicated depending on the severity of the infection.

Necrotizing fasciitis is an acute life-threatening infection of the skin and the underlying tissue.Those with poorly controlled DM are at an increased risk for necrotizing fasciitis. Necrotizing fasciitis presents early with erythema, induration, and tenderness which may then progress within days to hemorrhagic bullous. Patients will classically present with severe pain out of proportion to their presentation on physical exam. Palpation of the affected area often illicit crepitus. Involvement can occur on any part of the body but normally occurs in a single area, most commonly affecting the lower extremities. Fournier's gangrene refers to necrotizing fasciitis of the perineum or genitals, often involving the scrotum and spreading rapidly to adjacent tissues. The infection in patients with DM is most often polymicrobial. Complications of it include thrombosis, gangrenous necrosis, sepsis, and organ failure. Necrotizing fasciitis has a mortality rate of around twenty percent.[116] In addition, those patients with DM and necrotizing fasciitis are more likely to require amputation during their treatment.[117] Treatment warrants promptness and includes extensive surgical debridement and broad-spectrum antibiotics. Erythrasma is a chronic cutaneous infection, usually asymptomatic, most often attributed to *Corynebacteriumminutissiumum.* DM, as well as obesity and older age are associated with erythrasma. Erythrasma presents with non-pruritic non-tender clearly demarcated red-brown finely scaled patches or plaques. These lesions are commonly located in the axilla or groin (in intriginuous areas). Due to similarity of appearance and location, erythrasma is commonlymistaken for dermatophytosis or Candidial infection; in such cases, the presence of coral-red fluorescence under a Wood's light can confirm the diagnosis of erythrasma. Treatment options include topical erythromycin or clindamycin, Whitfield's ointment, and sodium fusidate ointment. More generalized erythrasma may respond better to oral erythromycin.

Malignant otitis externa is a rare but serious infection of the external auditory canal that occurs most often in those with a suppressed immune system, DM, or of older age. Malignant otitis externa develops as a complication of otitis externa and is associated with infection by *Pseudomonas aeruginosa*. Patients with malignant otitis externa present with severe otalgia and purulent otorrhea. The infection can spread to nearby structures and cause complications such as chondritis, osteomyelitis, meningitis, or cerebritis. If untreated, malignant otitis externa has a mortality rate of about 50%; however, with an aggressive treatment, the mortality rate can be reduced to 10% to 20%.[118] Treatment involves long-term systemic antibiotics with appropriate pseudomonal coverage, hyperbaric oxygen, and possibly surgical debridement.

Fungal Candidiasis is a frequent presentation in patients with DM. Moreover, asymptomatic patients presenting with recurrent candidiasis should be evaluated for DM. Elevated salivary glucose concentrations and elevated skin surface pH in the intertriginious regions of patients with DM may promote an environment in which candida can thrive.[119-120] Candida infection can involve the mucosa (e.g. thrush, vulvovaginitis), intertriginuous areas (e.g. intertrigo, Erosio interdigitalis blastomycetica, balanitis), or nails (e.g. paronychia). Mucosal involvement presents with pruritus, erythema, and white plaques which can be removed when scraped. Intertriginous Candida infections may be pruritic or painful and present with red macerated, fissured plaques with satellite vesciulopustules. Involvement of the nails may present with periungual inflammation or superficial white spots. Onychomycosis may be due to dermatophytes (discussed below) or Candidal infection. Onychomycosis, characterized by subungual hyperkeratosis and onycholysis, is present in nearly one in two patients with T2DM. Candidiasis is treated with topical or oral antifungal agents. Patients also benefit from improved glycemic control and by keeping the affected areas dry.

Although it remains controversial, dermatophyte

infections appear to be more prevalent among patients with DM.[121- 123] Various regions of the body may be affected but tinea pedis (foot) is the most common dermatophyte infection affecting patients; it presents with pruritus or pain and erythematous keratotic or bullous lesions. Relatively benign dermatophyte infections like tinea pedis can lead to serious sequelae, such as secondary bacterial infection, fungemia, or sepsis, in patients with DM if not treated hastily. Patients with diabetic neuropathy may be especially vulnerable.[124] Treatment may include topical or systemic antifungal medications depending on the severity.

Mucormycosis is a serious infection that is associated with T1DM, particularly common in those who develop diabetic ketoacidosis. A variety of factors including hyperglycemia and a lower pH, create an environment in which *Rhizopus oryzae*, a common pathogen responsible for mucormycosis, can prosper. Mucormycosis may present in different ways. Rhino-orbital-cerebral mucormycosis is the most common presentation; it develops quickly and presents with acute sinusitis, headache, facial edema, and tissue necrosis. The infection may worsen to cause extensive necrosis and thrombosis of nearby structures such as the eye. Mucormycosis should be treated urgently with surgical debridement and intravenous amphotericin B.

Lastly, abnormal toe web findings (e.g. maceration, scale, or erythema) may be an early marker of irregularities in glucose metabolism and of undiagnosed DM.[125]Additionally, such findings may be a sign of epidermal barrier disruption, a precursor of infection.[125]

Cutaneous changes associated with DM

Insulin

Subcutaneous injection of insulin is associated with many localized changes. The most common local adverse effect is lipohypertrophy, which affects less than thirty percent of patients with DM that use insulin.[126-127] Lipohypertrophy is characterized by localized adipocyte hypertrophy and presents with soft dermal nodules at injection sites. Continued injection of insulin at sites of lipohypertrophy can result in delayed systemic insulin absorption and capricious glycemic control. With the avoidance of subcutaneous insulin at affected sites, lipohypertrophy normally improves over a few months. Furthermore, lipoatrophy is an uncommon cutaneous finding which occurred more frequently before the introduction of modern purified forms of insulin. Lipoatrophy presents at insulin injection sites over a period of months with round concave areas of adipose tissue atrophy. Allergic reactions to the injection of insulin may be immediate (within one hour) or delayed (within one day) and can present with localized or systemic symptoms. These reactions may be due to a type one hypersensitivity reaction to insulin or certain additives. However, allergic reactions to subcutaneous insulin are rare, with systemic allergic reactions occurring in only 0.01% of patients.[126] Other cutaneous changes at areas of injection include the development of pruritus, induration, erythema, nodular amyloidosis, or calcification.

Oral Medications

Oral hypoglycemic agents may cause many cutaneous adverse effects such as erythema multiforme or urticaria. DPP-IV inhibitors, such as vildagliptin, can be associated with inflamed blistering skin lesions, including bullous pemphigoid and Stevens-Johnson syndrome, as well as, angioedema.128, 129 Allergic skin and photosensitivity reactions may occur with sulfonylureas.[130] The sulfonylureas, chlorpropamide and tolbutamide, are associated with the development of a maculopapular rash during the initial two months of treatment; the rash quickly improves with stoppage of the medication.[131-132] In certain patients with genetic predispositions,[32] chlorpropamide may also cause acute facial flushing following alcohol consumption.133Canagliflozin, as SGLT-2 inhibitor, has been associated with an increased risk of genital fungal infections.[134]

Conclusion

DM is associated with a wide array of dermatologic disorders. Many of the sources describing dermatologic changes associated with DM are antiquated; larger research studies utilizing modern analytic tools are needed to better understand the underlying pathophysiology and treatment efficacy. Although each condition may respond to a variety of specific treatments, many will improve with improved glycemic control. Hence, patient education and lifestyle changes are key in improving the health and quality of life of patients with DM.

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