I. INTRODUCTION

The incidence of diabetes mellitus (DM) is dramatically increasing worldwide. \(^1\) Thirty percent of patients with DM will present a disease-related dermatological problems during the course of their disease. \(^2\) Furthermore, dermatological conditions occur with increased frequency in individuals with DM, especially on the lower limbs. Some morbidities are strongly associated with DM (eg, granuloma anulare, diabetic dermopathy, scleredema, and granuloma anulare). The purpose of this review is to describe the molecular and anatomopathological alterations occurring at the skin during DM, and to illustrate the most important and common clinical skin manifestations in patients with DM.

II. HISTOLOGY OF SKIN

A. PHYSIOLOGY

1. Vascularization

Vessels from the skeletal muscles and the connective tissue of the subcutaneous fat septa deliver blood to the skin, where they give origin to two separate microvasculature plexuses: a ramifying arteriole and a venule network. The subpapillary plexus lies between the papillary and the reticular dermis and delimitates them. The subcutaneous plexus is located between the dermis and the subcutaneous fat. A rich network of reticular dermal vessels connects the two plexuses. The capillary loops extend from the superficial
plexus into the dermal papillae and the return loop is the post-capillary venule. Other plexuses are localized in the surrounding dermal tissue and in the hair follicles.

Lymph vessels are located around the subpapillary layer. They originate as lymphatic capillaries and extend through the postcapillary lymph vessels to the dermal and subcutaneous lymph vessels. The lymph vessels follow the course of veins and arteries. The papillary dermis is a single anatomical-pathological unit where the vessels are terminal arterioles, arterial and venous capillaries, and lymphatic capillaries. Capillaries consist of a single layer of endothelial cells, a basement membrane, and asent pericytes. In arterial and venous capillaries the basement membrane is different, since in the former it is solitary and homogeneous, while in the venous it is multilayered.

From the lumen outward, arterioles consist of a thin intima, an internal elastic lamina, the media, and the adventitia. In the venules, the endothelial cells are surrounded from the basement membrane and pericytes; those in the lymph vessels by elastic fibers, and a lax basement membrane.

2. Nervous System

The skin is innervated by two systems: an efferent non-myelinated, and an afferent myelinated and non-myelinated. The former is responsible for the function of cutaneous vasculature and skin appendages, the latter for the detection of cutaneous sensation. Skin nerves derive from musculocutaneous nerves that arise from the spinal nerves; they follow the main routes of the vascular plexuses and present a microanatomy similar to the vascular plexus. Autonomic nerves are subdivided in adrenergic and cholinergic systems, according to their function. The adrenergic sympathetic nerves innervate the arrector pili muscles, blood vessels, and glomus apparatus. Conversely, the cholinergic non-myelinated sympathetic nerves are distributed to the eccrine and apocrine sweat glands.

The scientific community believed that the sebaceous glands were not innervated and that in normal skin the peripheral nervous system had no effect on their activity. However, small fibers have been recently detected around sebaceous glands, indicating they are subject to neuronal control. Sensory innervation plays an important role in the physiological protection of the skin from thermal and noxious injuries. A 3-dimensional network of A-delta and C unmyelinated fibers, along with their free nerve endings that are connected to special neurogenic structures and individual cells, are distributed subepidermally in the papillary dermis and into the epidermis. The neurogenic specialized structures in the skin include the Merkel cells and the Meissner corpuscles, responsible for the detection of light touch; the Pacini corpuscles, which specialize in detecting pressure and are distributed deeply in the dermis and in the subcutaneous tissue; the Krause bulbs and the Meffini corpuscles are thermal sensors, activated by cold and heat, respectively. Naked nerve endings are responsible for transmission of pain and are localized in the basal layer of the epidermis.

Collectively, these structures work as a unique system in a suitable hormonal milieu where neurotransmitters and various inflammatory factors are fundamental for retrieving external stimuli.

B. DIABETES MELLITUS (DM)

1. Microcirculation

a. Structural Changes

The most striking structural changes in diabetic microcirculation are represented by thickening of the basement membrane and by reduction of the dimensions of capillaries.3,4 The capillarity density in diabetic skin is not affected compared to healthy subjects.5 On the contrary, the basement membrane has been shown to be thicker in poorly controlled diabetes.6

The mechanism by which the basement membrane thickens begins with an increase in the microcirculatory hydrostatic pressure and shear force. This initial phenomena triggers an endothelial cell response that leads to the release of extravascular matrix proteins, and thus, thickening of the basement membrane associated with arteriolar hyalinosis.7

It is significant to note that basement membrane thickening does not lead to a decrease in the diameter of the capillary lumen; these structural modifications determine important alterations of cellular functions, such as vascular permeability, cellular adhesion, proliferation, differentiation, and gene expression.

b. Functional Changes

Microcirculation functional changes include reduced vasodilating capacity through reduced elasticity of capillaries,7 altered cellular migration, and impaired exchanges of nutrients. These alterations are secondary to endothelial dysfunction, smooth muscle cell alterations, and deficient nerve axon reflex and cause diminished parophysiological hyperemic response, also called functional ischemia.10

The microcirculatory functional impairment has been
attributed to changes in the expression of endothelial nitric oxide synthetase (eNOS) and poly adenosine diphosphate (ADP) polymerase (PARP). The relationship between neuropathy and endothelial dysfunction was suggested by the observation that in peripheral neuropathy eNOS expression is significantly reduced. Under conditions of stress, such as pain and trauma, the C-nociceptive nerve fibers are activated and antidromically stimulate the adjacent C fibers to secrete Substance P, Neuropeptide Y, Neurotensin, Calcitonin gene-related peptide, and Histamine. These peptides in turn exert vasodilation and increase vessel permeability. This paraphysiologic protective hyperemic response, also known as Lewis’s triple flare response or Nerve-Axon Reflex, depends on the existence of an intact neurogenic vascular response and is equal to one-third of the maximal vasodilatory capacity. It has been demonstrated that nerve dysfunction contributes to the diminished vasodilatory response observed in diabetic patients with and without neuropathy with the largest reduction observed in neuropathic feet. Thus, the involvement of the C-nociceptive fibers in diabetes not only leads to the well-known impaired pain perception, but also to diminished vasodilation under stressful conditions.

An infected or injured foot will fail to respond in the usual manner in a diabetic neuropathic patient because of hyperemia deficiency due to Nerve-Axon Reflex impairment. Thus, diabetic neuropathy renders the diabetic foot functionally ischemic, as blood flow does not increase under stress.

### 2. Skin Collagen

The dermis consists of a thin superficial portion, known as the papillary dermis, and a wider, deeper area known as the reticular dermis. The epidermis binds the papillary dermis superiorly, the epidermal ridges laterally, and inferiorly by the superficial vascular plexus and the reticular dermis, which lies between the papillary dermis and the subcutaneous fat.

The papillary and reticular dermis contain collagen, reticulin, and elastic fibers embedded in a ground substance, also called dermal matrix. The dermal matrix fills the spaces between the fibers and contains mainly glycoproteins, water, electrolytes, and plasma proteins (Figure 1).

The pilosebaceous units and the eccrine and apocrine glands have a similar meshwork of collagen fibers to the one present in the papillary dermis. This meshwork is regarded as an anatomic unit called the adventitial dermis. Collagen provides the skin with tensile strength. Twenty-nine types of different collagen have been described in humans; however, more than 90% of the body’s collagen is represented by types I, II, III, IV, and V. Type I accounts for approximately 80% of the total amount of dermal collagen and is found in the large fiber bundles of the reticular dermis. Type II collagen is recognized in the cartilage. Type III, also known as fetal collagen or reticulum fibers, represents up to 10% of dermal collagen. This type of collagen is prevalent during fetal life; however, in post fetal life it is limited to the papillary and adventitial dermis. Furthermore, it serves as a framework on which type I collagen is synthesized. Type IV collagen is present mainly in the lamina densa of the basement membrane at the dermo-epidermal junction. Finally, type V is found in fetal membranes, blood vessels, and in the lamina lucida of the base membrane.

Collagen is mainly synthesized by fibroblasts, and less extensively by epithelial cells, smooth muscle cells, myofibroblasts, and endothelial cells. Collagen has a characteristic amino acid composition and sequence; glycine is present at every third position, proline, and lysine are repeated with a regular pattern. The two latter amino acids are post-translationally modified into hydroxyproline and hydroxylysine. Furthermore, the glycosylation of the hydroxylysine residues plays an important role in determining the final molecular structure of collagen.

Collagen is initially synthesized as proprocollagen. Alpha-1 and alpha-2 peptide chains are assembled into the rough endoplasmic reticulum (RER). Subsequently, they pass into the RER’s lumen where lysine and proline are hydroxylated and hydroxylysine is glycosylated. The
newly formed molecules are named procollagen, which form disulfide (S-S) bonds and acquire a triple helical configuration. Procollagen then migrates to the Golgi apparatus, where it is packaged and secreted in vesicles into the intercellular fluid. The final step of collagen synthesis is the chain cleavage catalyzed by peptidases.

Elastic fibers are fundamental for maintenance of cutaneous elasticity and they consist of two components: microfibrillar and matrix elastin. The former accounts for 15% of the elastic fibers and are composed of elastic tissue microfibrillar proteins. The latter accounts for the remaining 85% of the elastic fibers and is composed of an amorphous electron-dense compound consisting of a complex protein called elastin.

Elastic fibers in the papillary dermis are thin and oriented perpendicularly to the skin surface, while in the reticular dermis they are thicker and parallel to the skin surface. Elaunin and oxytalan fibers are names for the elastic fibers in the papillary dermis. Elaunin fibers are bundles of microfibrils that form a plexus oriented parallel to the dermal-epidermal junction. From this plexus, cross-linked elastic fibers called oxytalan run upward and terminate at the basement membrane (Figure 2).

Fibrocytes and muscle cells synthesize elastic fibers. In hematoxylin and eosin (H&E) stained sections, elastic fibers are inconspicuous and difficult to interpret. They are visualized with special histochemical stains, such as orcein and Verhoeff-Van Gieson. Elastic fibers undergo changes during life, mainly as a result of chronic sun exposure, and decrease in number, become thicker, fragmented, and nearly disappear in elderly subjects.

III. CUTANEOUS MANIFESTATIONS OF DIABETES MELLITUS

Cutaneous infections are more common in type 2 diabetes, whereas autoimmune-related lesions are more common in type 1. Importantly, diabetes-related cutaneous lesions may also serve as a port of entry for secondary infection; however, that is a topic beyond the scope of this review.

1. Acanthosis nigricans

Acanthosis nigricans (AN) is a symmetric eruption characterized by a hyperpigmented, velvety, cutaneous thickening that characteristically affects the intertriginous areas, such as axillae, neck, and submammary areas, but can occur on any part of the body. The lesions are generally asymptomatic, but sometimes can be painful, malodorous, or macerated. Typically, the dermal papillae are projected upward, and the valleys in between them show mild to moderate acanthosis and are filled with keratotic material. The epidermis at the top and at the sides of the papillae appears thinned and the brown color of the lesions is due to the thickening of keratin-containing superficial epithelium (Figure 3). The histologic differential diagnosis for AN includes seborrheic keratosis, linear epidermal nevi, and confluent reticulated papillomatosis. Seborrheic keratosis has numerous horn cysts into a hyperplastic, papillomatous, or reticulated epidermis with lamellar hyperkeratosis. In linear epidermal nevi there is more compact orthokeratosis and marked acanthosis than AN. According to some authors, reticulated and confluent papillomatosis is a variant of AN. However,
the clinical picture is typical with verrucoid papules confluent at the center and peripherally reticulated, and usually located at the upper part of the chest.\textsuperscript{19-21}

There are eight types of acanthosis nigricans: benign inherited (autosomal dominant trait), obesity-associated, syndromic, malignant (particularly gastric carcinoma), acral, unilateral acanthosis nigricans, drug-induced (nicotinic acid and corticosteroids), and mixed. The pathogenesis is related to high levels of circulating insulin, which binds to insulin-like growth factor receptors to stimulate keratinocyte and dermal fibroblast growth. Skin biopsy from the groin of a 45-year-old woman with T2DM is shown in Figure 3. Hematoxylin and eosin shows hyperkeratosis, papillomatosis and mild acanthosis and intervening valleys between the papillary projections. The treatment of AN is based on the management of its underlying disorder; however, topical treatment with tretinoin and calcipotriol has been shown to be somewhat successful. Other treatment options include both laser-therapy and surgical excision.

2. Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica diabeticorum (NLD) is an idiopathic disorder characterized by red, nonscaling patches or plaques. The edges are elevated, erythematous, and slightly indurated; the center of the lesion is atrophic, yellow-brownish, and may ulcerate (Figure 4).\textsuperscript{18} NLD lesions are generally bilateral and are more frequently found in the pretibial area, but may be also localized at the trunk, penis, or diffusely on the body. The cause of NLD is unknown; however, it is more common in women than in men, and two-thirds of patients have diabetes mellitus at the time of diagnosis.\textsuperscript{22} NLD raises diagnostic dilemmas most often of histological rather than clinical nature. Histological differential diagnosis includes palisaded granulomatous dermatitis among them being granuloma annulare, rheumatoid nodule, and necrobiotic xanthogranuloma (NX). In NLD the degenerated collagen is pale, acellular, and horizontal in its distribution (Figure 5). Plasma cells into lymphoid nodules are a common finding in deep dermis (Figure 6). Rheumatoid nodule granulomas are larger, located in the deep dermis, or in subcutis surrounding a central area with fibrinoid material. NX has more typical clinical findings with a peribulbar predilection. Histological findings for NX includes an inflammatory mixed cellular population with massive cells, foamy histiocytes, and necrotic areas with neutrophilic debris involving the dermis and subcutaneous tissue.\textsuperscript{19,24} It is remarkable that improvement in glycemic

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{NLD in a 16-year-old girl with T1DM and a patch on the leg with an atrophic, depressed, slightly yellow center, and well-defined raised purple edge.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{figure5.png}
\caption{H&E stain (x100) shows extensive incomplete necrobiotic area in dermis surrounded by few histiocytes (arrows).}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{figure6.png}
\caption{Patchy lymphoplasmacytic infiltration around blood vessels (arrows point to plasma cells). (H&E x200).}
\end{figure}
control does not improve these cutaneous lesions. Treatment of NLD includes corticosteroids (topical, intralesional, or systemic), antiplatelet drugs (eg, aspirin or ticlopidine), and anti-rheologic agents (eg, pentoxifylline). Other drugs have been shown to be effective in the treatment of NLD, such as retinoin (the acid form of vitamin A), mycophenolate mofetil, cyclosporin A, anti-TNF-α, thalidomide, psoralen-ultraviolet A (P-UVA), and topical tacrolimus.

3. Palmar fibromatosis (Dupuytren’s disease)

Dupuytren’s disease (DD) is a benign and progressive disorder of pathologic collagen production and deposition. It is characterized by the thickening of the palmar fascia that initiates with palpable nodules in the palm, and is frequently complicated by cord-like structures that extend from the palm into the affected fingers. The nodules are composed of uniform, spindled fibroblasts and myofibroblasts that are oriented parallel to each other in a dense, collagenous background. Effectually, no other lesion arises precisely within the palmar fascia, and the lesion rarely creates diagnostic problems. DD is commonly bilateral and causes progressive, permanent, and symptomatic flexion contracture of the digits, therefore deforming the affected hand, limiting hand function, and diminishing the patient’s quality of life. The incidence of DD increases with age, and several environmental factors have been proposed to contribute to its development, such as hyperglycemia, smoking, alcohol intake, use of anticonvulsant drugs, and manual labor or exposure to vibrations. DD has a strong genetic component and aggregates in families and individuals with a family history of DD. Surgical intervention is the current mainstay of treatment for DD and consists of open fasciectomy (most common), percutaneous or open fasciotomy, needle fasciotomy, or dermofasciectomy (procedure with lowest recurrence rate). However, surgical treatment of DD, aside from being invasive and involving a long recovery period, is also associated with a significant rate of recurrence, and several nonsurgical interventions have been evaluated in clinical trials. These therapies include Clostridium histolyticum collagenase injection, radiotherapy, interferon-γ injection, and steroids.

4. Granuloma anulare

Granuloma anulare is an idiopathic, benign, and asymptomatic granulomatous condition that is more frequently seen in women than in men. The classic variant presents with small, firm, flesh colored (or pale red) papules,
generally localized on arms, legs, hands, and feet (Figure 7). Generally, the lesions are multiple, grouped in an anular or circinate fashion, and are sub-chronic and self-limiting. The histopathologic findings in each of the possible clinical expression of this granulomatous process have subtle features that reflect the clinical form. However, the essential changes include epithelioid histiocytes that are arranged either in a palisaded or interstitial fashion that deposit variable amounts of mucin (Figures 8, 9).

There are four other rare forms of disease: generalized, perforating, erythematous, and subcutaneous/deep. Besides DM, Granuloma anulare is associated with human immunodeficiency virus (HIV) infection, herpes zoster, NLD, and sarcoidosis. The main differential diagnosis, both from a clinical and histological perspective, is with NLD. Treatment is similar to NLD.

5. Bullosis diabeticorum

Bullosis diabeticorum is the sudden and spontaneous (or in response to minor shearing stress) presence of blisters on the distal extremities (legs and arms). The blisters have a non-inflammatory nature and heal in several weeks without scarring. The histologic presentation is heterogeneous, as the blister may appear in a subcorneal, intraepidermal, or subepidermal location. Spongiosis of epidermis may be present. The blister contains fibrin and a few inflammatory cells. The differential diagnoses include bullous diseases, porphyria, and pseudo-porphyria. Immunofluorescence studies are regularly negative or non-specific. The lesions arise more frequently in patients with diabetes complicated by neuropathy, vascular disease, or both. Their cause is unknown and the treatment is both symptomatic and conservative.

6. Diabetic dermopathy

Diabetic dermopathy (DD), also known as spotted leg syndrome, is the most common cutaneous manifestation in DM. However, DD is not pathognomonic of DM since 20% of patients with these lesions are not affected by DM. The lesions present as multiple brown atrophic spots, are asymptomatic, and may persist indefinitely or resolve spontaneously without treatment. Treatment of DD is neither recommended nor effective. The histologic findings at the onset of the disease are non-specific; while the well-developed lesions show epidermal atrophy with slight perivascular infiltration of lymphocytes and plasma cells. Differential diagnoses include stasis dermatitis and purpura pigmentosa chronica. The etiology is unknown, although trauma has been reported as a contributor factor. Interestingly, a correlation of the microcirculatory changes of diabetic dermopathy and the presence of retinopathy, neuropathy, and nephropathy has been reported.

7. Lichen planus

Lichen planus is a subacute or chronic dermatosis that may involve skin, mucous membranes, and skin adnexa. Lichen planus has a predilection for the flexor surfaces of forearm, legs, and the penis glans. Oral manifestations—generally white coalescent papules in the buccal and glossal mucosa—may be associated to cutaneous lesions or can be solitary. There are many morphologic manifestations, the most important of which are hypertrophic, atrophic, and bullous. The stereotypical histological features are irrespective of the clinical features and are represented by band-like lymphohistiocytic infiltration at the upper dermis with vacuolar alteration of the basal membrane, squamotization of the basal layer, irregular acanthosis with necrotic keratinocytes, and wedge shaped hypergranulosis (Figure 10). The etiology of lichen planus is idiopathic; however, the predominance of T helper cells in the dermal infiltrate strongly suggests an immunologic basis for this disease. Numerous reports have studied the association of diabetes and lichen planus, but few have examined the frequency of clinical and histological evidence of lichen planus in known diabetics (highest rate 5.76%). Treatment consists of topical corticosteroids, topical cyclosporine, or both.

Figure 10. Lichen planus. Skin punch biopsy from the penis shaft of a 42-year-old man with T1DM. H&E (x100) reveals a band-like lymphocytic infiltration in the upper dermis involving the basal layer that has microvascular degeneration.
8. Acquired perforating dermatosis

The term “acquired perforating dermatoses” (APD) defines a group of disorders characterized by a common phenomenon called transepithelial elimination.\(^{50}\) Classically, APD has been divided into four types: 1) elastosis perforans serpiginosa, 2) reactive perforating collagenosis, 3) Kyrle’s disease, and 4) perforating folliculitis. The pathogenesis of APD is represented by minor trauma, microangiopathy, subcutaneous deposition of calcium, and genetic predisposition.\(^ {51}\) APD is seen in patients with diabetes mellitus or kidney failure, and 10% of patients undergoing hemodialysis present with APD.\(^ {52}\) Clinically, the lesions vary from hyperkeratotic papules to erythematous, follicular papules and nodules; they are generally pruritic and occur mainly on the extensor surface of the limbs, but also on the trunk, hands, and face. Histologically, transepidermal channels traverse an acanthotic epidermis and are filled with keratin, pyknotic nuclear debris, inflammatory cells, elastin, and collagen. They all share a common microscopic finding, which is transepidermal elimination of these substances. In elastosis perforans, serpiginosa altered elastic fibers pass through channels from dermis to epidermis (Figures 11, 12). In Kyrle’s disease and perforating folliculitis, the content of the follicular and perifollicular infundibulum is usually suppurative, mixed with keratin and degenerated collagen. This suppurative material moves away from the dermis and penetrates into the epidermis. In perforating collagenosis, which is not considered a disease per se but a trauma-related condition (except for the rare inherited child form), the altered dermal collagen appears through the epidermis. Histochemical stains for collagen and elastic fibers, such as Masson’s trichrome stain and van Gieson’s stain, play an important role in the differential diagnosis. In elastosis perforans serpiginosa, the elastic fiber’s staining shows coarse elastic fibers in the dermis, which progressively lose their staining properties as they enter into the epidermis. When the histochemical staining of both collagen and elastic fibers is positive in the follicles, then the findings are consistent with perforating folliculitis. In Kyrle’s disease, due to the degeneration of collagen and elastic fibers, histochemical staining is negative. In contrast, in perforating collagenosis, the collagen bundles appear oriented vertically.\(^ {19,24,53,54}\) Lesions are chronic but may heal if trauma and scratching are avoided. Further treatments include topical keratolytics, PUVA (psoralen-ultraviolet A), UVB, topical and systemic retinoids, topical and intralesional steroids, oral antihistamines, and cryotherapy.\(^ {49}\)

9. Diabetic thick skin

Patients with diabetes often present with thickening of the skin caused by excessive accumulation of abnormal collagen. Glycosylation end products lead to
increased cross-linking of collagen fibers that become resistant to degradation by collagenase, which in turn leads to abnormal collagen. Other pathophysiological mechanisms have been proposed: overproduction of collagen secondary to insulin acting as a growth factor; increase of collagen and fibroblasts synthesis of glycosaminoglycan secondary to decreased local oxygen pressure caused by microangiopathy; and polyol accumulation caused collagen hydration. There are three forms of clinical diabetic thick skin: 1) asymptomatic but measurable increase in skin thickness; 2) sclerodermalike skin changes in the fingers with limited joint mobility, also known as diabetic hand syndrome or limited joint mobility syndrome; 3) diabetic scleredema.

Diabetic hand syndrome begins with stiffness of the metacarpophalangeal and proximal interphalangeal joints, generally, but not necessarily the fifth, and subsequently progresses to the other fingers. Although there is not any direct joint involvement, the abnormal stiffening of collagen in the periarticular tissue frequently leads to joint limitations that can be demonstrated by failure of palmar approximation and an inability to flatten the hand on a tabletop. The literature suggests that diabetic hand syndrome is related to the development of diabetes-related microvascular complications more so than to disease duration or control.

Scleredema diabeticorum is one of three known forms of scleredema adultorum (the other two are the abrupt onset and insidious onset scleredema). Diabetic scleredema consists of a dramatic increase in the thickness of the skin, initially on the face, and extends to the posterior neck and upper back. It is usually asymptomatic, but neck discomfort and back pain may be present, especially in more severe cases. Clinically, a peau d’orange appearance of the skin can occur often with decreased sensitivity to pain and touch. Histologically, the dermis is thickened (three times more than normal), mast cells are increased, collagen presents fenestrations because the bundles are thickened and separated by clear spaces, hyaluronic acid is accumulated between the collagen bundles, and there is no sign of edema nor sclerosis. In the early stages of the disease mucin histochemical staining easily reveals the presence of mucin between thickened collagen bundles. In later stages of the disease frozen sections stained with Alcian blue (pH 2.5) or toluidine blue (pH 7.00) are needed. Histologically, the differential diagnoses include other forms of dermal mucinosis and scleroderma. In mucinosis, the mucin deposition has a more widespread or focal pattern accompanied by a fibroblastic and mild inflammatory reaction. In scleroderma, inflammatory perivasculare infiltration is seen at the early stage, and thick, hypertrophic collagen bundles without fenestration at the later stage. Seventy-five percent of cases show complete resolution within a few months, and in the remaining 25% of patients, the disease persists and no effective treatment is known.

10. Soft fibroma

Soft fibroma, or fibroepithelial polyps and acrochordons, may occur in three different forms: 1) multiple furrowed papules, 2) single or multiple filiform, and 3) solitary pedunculated. The histologic features include a collagenous core, which may vary from loose edematous to sclerotic, and contains thin wall blood vessels and fibroblasts. The epidermis may be thin or hyperplastic with a lichenoid pattern (Figure 13). The differential diagnosis includes seborrheic keratosis and HPV related lesions. In seborrheic keratosis, small horn cysts are found inside a hyperplastic epidermis. HPV-related lesions usually contain koilocytes specifically distributed between epidermal cells and atypical parakeratotic cells into the horn layer. The association of soft fibroma with DM and acromegaly is well established; the one with colonic polyps is controversial. Treatment of soft fibroma consists of its removal. However, it is not necessary unless the lesions become frequently irritated or present a cosmetic concern for the patient. Removal of these lesions can be achieved via cauterization, cryosurgery, surgical ligation, or excision.

Figure 13. Soft fibroma from the shoulder of a 45-year-old woman with T2DM. H&E (x100) stain shows broad projections of loose connective tissue stroma covered by thin epidermis.
11. Periungual telangiectasia

Periungual telangiectasia involves venous capillary dilatation in the nail folds. It appear as red, dilated, capillary veins and is visible to the naked eye. These alterations are secondary to the loss of capillary loops and dilatation of the remaining capillaries, and appear to be an excellent indicator of functional microcirculatory impairment. In DM, periungual telangiectasia is frequently associated with erythema of the nail fold accompanied by tenderness of the fingertip and "ragged" cuticles.

12. Vitiligo vulgaris

Vitiligo is the disfiguring and patchy complete loss of skin pigment. One percent to 7% of all patients with DM have vitiligo, and it occurs more often in type 1 DM. The most prominent feature of this lesion is the alteration of melanocytes at the dermal-epidermal junction. Histologic examination of the involved skin shows total absence of melanocytes and epidermal pigmentation. However, this effect cannot be detected by routine histochemical stains, such as Masson-Fontana. Conversely, immunohistochemical stains with specific antibodies for tyrosinase pathway, such as HMB-45 and Melan-A, fail to reveal melanocytes. Electron microscopy does not demonstrate neither quantitative nor qualitative forms of melanosomes. Vitiligo is most likely an autoimmune disorder with genetic predisposition. Antibodies against melanocytes have been found in the serum of patients with vitiligo. Treatment of vitiligo is generally unsatisfactory; patients should avoid exposure to the sun and use broad-spectrum sunscreens. Topical corticosteroids are the first choice therapy for localized Vitiligo; treatment with ultraviolet light (UVB) is preferred for generalized vitiligo.

References


