Clinical and Histopathological Features of Scleroderma-like Disorders

Subjects: Allergy

Contributor: Alice Ramondetta

Scleroderma-like disorders include a set of entities involving cutis, subcutis and, sometimes, even muscular tissue, caused by several pathogenetic mechanisms responsible for different clinical–pathological pictures. The absence of antinuclear antibodies (ANA), Raynaud's phenomenon and capillaroscopic anomalies constitutes an important element of differential diagnosis with systemic sclerosis.

scleroderma-like scleredema

1. Introduction

Scleroderma-like disorders (SLDs) include various diseases in which sclerosis-like changes occur in the dermis and subcutaneous tissue, sometimes with extension to the deeper planes, involving the underlying muscles and bones. Each entity is distinguished from systemic sclerosis by the different distribution pattern of sclerosis and the lack of other peculiar features, such as Raynaud's phenomenon, capillaroscopic abnormalities or scleroderma-specific autoantibodies. The major histologic feature, although non-specific in most cases, is an excessive local accumulation of collagen and other extracellular matrix components, such as mucin and glycosaminoglycans [1]. These entities are divided into groups (**Table 1**) based on the underlying pathogenetic mechanisms to better define the specific clinical and histopathological characteristics.

Table 1. Classification of scleroderma-like disorders.

Classification of Scleroderma-like Disorders	
Inflammatory	Morphea, atrophoderma of Pasini and Pierini, eosinophilic fasciitis, graft-versus-host disease
Sclerodermiform mucinoses	Scleromyxedema, Buschke scleredema, nefrogenic systemic fibrosis, cutaneous amyloidosis
Genetic	Werner's syndrome, scleroatrophic Huriez syndrome, stiff-skin syndrome, melhoreostosis
Drug-induced	Pentazocine, bleomycin, vitamin K, interferon-β1a, peplomycin, cocaine, D-penicillamine, vitamin B12, uracil–tegafur, methysergide, gemcitabine, paclitaxel
Toxic	Toxic-oil syndrome, eosinophilia–myalgia syndrome, vinyl-chloride syndrome

Classification of Scleroderma-like Disorders	
Metabolic	Porphyria cutanea tarda, diabetes mellitus, phenylketonuria
Paraneoplastic	POEMS syndrome, myeloma with scleroderma-like changes, carcinoid syndrome, scleroderma-like manifestations in myeloproliferative hypereosinophilic syndrome

Chronic GVHD can manifest as scleroderma or lichenoid variant [2]. In the first case, the sclerosis appears to depend on excessive tissue repair, caused by immunologic injury induced by lymphocytic hyperactivity. Clinically, circumscribed sclerotic plaques, often localized in the lower part of the trunk with a tendency to spread, are observed. Sclerodermoid GVHD can occasionally mimic eosinophilic fasciitis or deep morphea [2]. Dystrophic alterations of the nails such as onycholysis and telangiectasias of the proximal nailfold may occur [3]. Specific autoantibodies, such as anti-Scl-70, anti-PM-Scl, aCL or ANCA, can be found in this form of GVHD, although their significance and clinical utility are unclear [4]. Histological specimens show a thin epidermis, hyperkeratosis with follicular obstruction, dermatitis of the focal interface, the homogenization of collagen with a loss of elastic fibers in the papillary dermis, thickened collagen bundles and perivascular lymphocytic infiltrates in the deep reticular dermis.

3. Sclerodermiform Mucinoses

Scleromyxedema, commonly known as lichen myxedematosus, or papular mucinosis, is a rare chronic disease of unknown etiology characterized by the presence of infiltrative and confluent skin papules until induration, due to an increased deposition of glycosaminoglycans within the dermis [5][6]. Clinically, it manifests with the gradual appearance of papular flesh-colored lesions over the back of the hands, distal forearms and face (specifically glabella), which, over time, tend to merge into hardened plaques. The mucin deposition in this site is responsible for the so-called leonine facies. A very particular and typical localization is the ear and the retro-auricular region, although skin involvement in advanced stages is widespread, with no spared areas (unlike in scleroderma, which typically spares the central part of the back). The progressive thickening and hardening of the skin can limit the mobility of the hands and wrists and reduce the opening of the mouth. The diagnostic criteria are as follows: a papular rash; evidence of mucin in the dermis and the proliferation of fusiform fibroblasts with increased collagen; monoclonal gammopathy in the peripheral blood; normal thyroid function. [7] According to the histology, it was found that the fibroblasts synthesize a greater amount of hyaluronic acid and mucin than normal fibroblasts. In fact, stains with colloidal iron, toluidine blue or Alcian blue allow the identification of diffuse mucin depositions within the upper and middle reticular dermis [8][5][9]. It is also known that scleromyxedema is almost always associated with a benign gammopathy, mainly of the lambda IgG type [9]. There may be manifestations of systemic involvement responsible for dysphagia due to impaired esophageal motility, myopathy and cardiopulmonary or central nervous system disorders due to mucin deposition (**Figure 1**).



Figure 1. A 65-year-old male patient with IgGk monoclonal gammopathy. Presence of confluent erythematous brown papules distributed on the back (**a**) and extensor surfaces of the limbs (**b**,**c**). Leonine facies caused by mucin deposition in the forehead and glabella (**d**). H&E (original magnification: 50×)—epidermis and full-thickness dermis (**e**); H&E (original magnification: 200×)—wide magnification with evidence of a significant number of eosinophils (**f**); Alcian–Pas (original magnification: 200×)—superficial dermis with dermal mucinosis (accumulation of acid mucopolysaccharides (light blue in the photo)), mainly in the superficial dermis (**g**) and between the collagen bands (**h**).

4. Genetic

Werner's syndrome (WS) is a rare autosomal recessive disease caused by null mutations in the WRN gene, which affects connective tissue and is characterized by premature aging and various endocrine disorders [9][10]. The diagnostic criteria, detailed by the International Registry of Werner Syndrome, include bilateral cataracts (present in 99% of WS cases), premature graying and/or thinning of the scalp hair (100%), characteristic dermatological changes (96%) and short stature (95%) [11][12]. Skin lesions, in particular, consist of skin atrophy and sclerosis most evident in the distal extremities, especially in the legs and feet [9]. In addition to these main elements, there are other peculiar manifestations, such as bird-like facies, soft tissue calcifications, a cushingoid appearance, intractable skin ulcers, hoarseness-like voice abnormalities and disproportion between the patient's real age and physical appearance [13]. Diagnostic confirmation requires WRN gene testing. The histological features of the skin

and subcutaneous tissue of the extremities show epidermal thinning and dermal fibrosis; the newly synthesized hyalinized collagen tends to replace subcutaneous fat. No inflammatory infiltrates are usually evident.

Scleroatrophic Huriez syndrome, also called palmoplantar keratoderma with sclerodactyly, is a rare congenital genodermatosis with autosomal dominant transmission, characterized by palmoplantar keratoderma, scleroatrophy of the hands and feet, hyperhidrosis and hypoplasia of the nails [14]. The specific gene involved has not yet been identified, but it seems to be located on chromosome 4q23k [15]. Around the third or fourth decade, 15% of subjects are at risk of developing aggressive forms of squamous cell carcinomas of the skin, with high metastatic potential [14]. Histopathological specimens show hyper- and parakeratosis, hypergranulosis, irregular acanthosis and mild papillomatosis. Immunohistochemical analysis shows a marked reduction in the epidermal cells of Langerhans' CD1a, Lag + and S-100 expression [16].

5. Drug-Induced Scleroderma-like Illnesses

In some rare cases, a scleroderma-like disease has been described as a consequence of the administration of drugs such as bleomycin, pentazocine, cocaine, D-penicillamine, vitamin K [9], vitamin B12 [17], peplomycin [18], interferon-β1a [19], uracil–tegafur [20], paclitaxel [21][22], methysergide [22] and gemcitabine [23]. The cutaneous manifestations, variable in shape and extension, include Raynaud's phenomenon, edema and thickening of the skin of both the hands and forearms, microstomy, facial telangiectasias and flexion contractures of the distal interphalangeal joints. Capillaroscopic examination may show an active pattern characterized by numerous megacapillaries, limited areas of capillary desertification and disorganization of the capillary architecture. Clinical manifestations of visceral involvement, such as gastroesophageal reflux and myositis, can sometimes be detected [24]. The histopathological examination of the skin shows a prevalent diffuse cutaneous fibrosis with vascular ectasias, loss of the adnexa and a slight lymphocytic perivascular infiltrate in the absence of mucin deposits. What distinguishes these forms of SLD from systemic sclerosis is the absence of specific scleroderma autoantibodies.

6. Conclusions

Scleroderma-like disorders are a large group of diseases mainly characterized by skin thickening with specific clinical, histopathological and topographical features. This last criterion, in particular, in addition to the absence of ANA, Raynaud's phenomenon and capillaroscopic anomalies, constitutes an important element of differential diagnosis with systemic sclerosis. For a correct diagnosis, it is therefore necessary to take into account the distribution of skin thickening, the histological characteristics of the biopsy sample (which, in most cases, must include skin, subcutis and muscle fascia), any changes in laboratory parameters and possible related pathologies.

References

1. Chung, L.; Lin, J.; Furst, D.E.; Fiorentino, D. Systemic and localized scleroderma. Clin. Dermatol. Ottobre 2006, 24, 374–392.
2. Schaffer, J.V.; McNiff, J.M.; Seropian, S.; Cooper, D.L.; Bolognia, J.L. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease, expanding the sclerodermoid spectrum. J. Am. Acad. Dermatol. 2005, 53, 591–601.
3. Ratanatharathorn, V.; Ayash, L.; Lazarus, H.M.; Fu, J.; Uberti, J.P. Chronic graft-versus-host disease, clinical manifestation and therapy. Bone Marrow Transpl. 2001, 28, 121–129.
4. Cepeda, E.J.; Reveille, J.D. Autoantibodies in systemic sclerosis and fibrosing syndromes, clinical indications and relevance. Curr. Opin. Rheumatol. 2004, 16, 723–732.
5. Cokonis Georgakis, C.-D.; Falasca, G.; Georgakis, A.; Heymann, W.R. Scleromyxedema. Clin. Dermatol. 2006, 24, 493–497.
6. Dinneen, A.M.; Dicken, C.H. Scleromyxedema. J. Am. Acad. Dermatol. 1995, 33, 37–43.
7. Hummers, L.K. Scleromyxedema. Curr. Opin. Rheumatol. 2014, 26, 658–662.
8. Mori, Y.; Kahari, V.-M.; Varga, J. Scleroderma-like cutaneous syndromes. Curr. Rheumatol. Rep. 2002, 4, 113–122.
9. Jablonska, S.; Blaszczyk, M. Scleroderma-like disorders. Semin. Cutan. Med. Surg. 1998, 17, 65–76.
10. Keijzers, G.; Maynard, S.; Shamanna, R.A.; Rasmussen, L.J.; Croteau, D.L.; Bohr, V.A. The role of RecQ helicases in non-homologous end-joining. Crit. Rev. Biochem. Mol. Biol. 2014, 49, 463–472.
11. Oshima, J.; Sidorova, J.M.; Monnat, R.J. Werner syndrome, Clinical features, pathogenesis and potential therapeutic interventions. Ageing Res. Rev. 2017, 33, 105–114.
12. Huang, S.; Lee, L.; Hanson, N.B.; Lenaerts, C.; Hoehn, H.; Poot, M.; Rubin, C.D.; Chen, D.F.; Yang, C.C.; Juch, H.; et al. The spectrum of WRN mutations in Werner syndrome patients. Hum. Mutat. 2006, 27, 558–567.
13. Takemoto, M.; Mori, S.; Kuzuya, M.; Yoshimoto, S.; Shimamoto, A.; Igarashi, M.; Tanaka, Y.; Miki, T.; Yokote, K. Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr. Gerontol. Int. 2013, 13, 475–481.
14. Hamm, H.; Traupe, H.; Bröcker, E.B.; Schubert, H.; Kolde, G. The scleroatrophic syndrome of Huriez, a cancer-prone genodermatosis. Br. J. Dermatol. 1996, 134, 512–518.
15. Lee, Y.A.; Stevens, H.P.; Delaporte, E.; Wahn, U.; Reis, A. A gene for an autosomal dominant scleroatrophic syndrome predisposing to skin cancer (Huriez syndrome) maps to chromosome 4q23. Am. J. Hum. Genet. 2000, 66, 326–330.

16. Çelik, N.S.; Yaşar, Ş.; Aytekin, S.; Güneş, P. A Rare Syndrome Resembling Scleroderma, Huriez Syndrome. Ski. Appendage Disord. 2018, 4, 82–85.
17. Ho, J.; Rothchild, Y.H.; Sengelmann, R. Vitamin B12-associated localized scleroderma and its treatment. Dermatol. Surg. 2004, 30, 1252–1255.
18. Asano, Y.; Ihn, H.; Shikada, J.; Kadono, T.; Kikuchi, K.; Tamaki, K. A case of peplomycin-induced scleroderma. Br. J. Dermatol. 2004, 150, 1213–1214.
19. Ozden, M.G.; Erel, A.; Erdem, O.; Oztas, M.O. Dermal fibrosis and cutaneous necrosis after recombinant interferon-beta1a injection in a multiple sclerosis patient. J. Eur. Acad. Dermatol. Venereol. 2005, 19, 112–113.
20. Kono, T.; Ishii, M.; Negoro, N.; Taniguchi, S. Scleroderma-like reaction induced by uracil-tegafur (UFT), a second-generation anticancer agent. J. Am. Acad. Dermatol. 2000, 42, 519–520.
21. Kupfer, I.; Balguerie, X.; Courville, P.; Chinet, P.; Joly, P. Scleroderma-like cutaneous lesions induced by paclitaxel, a case study. J. Am. Acad. Dermatol. 2003, 48, 279–281.
22. Kluger, N.; Girard, C.; Bessis, D.; Guillot, B. Methysergide-induced scleroderma-like changes of the legs. Br. J. Dermatol. 2005, 153, 224–225.
23. Bessis, D.; Guillot, B.; Legouffe, E.; Guilhou, J.-J. Gemcitabine-associated scleroderma-like changes of the lower extremities. J. Am. Acad. Dermatol. 2004, 51, 73–76.
24. De Angelis, R.; Bugatti, L.; Cerioni, A.; Del Medico, P.; Filosa, G. Diffuse scleroderma occurring after the use of paclitaxel for ovarian cancer. Clin. Rheumatol. 2003, 22, 49–52.

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