**JID VisualDx QUIZ: MECHANISM OF FIBROSIS IN SCLERODERMA**

**QUESTIONS**

1. **What is the diagnosis for this patient?**
   a. Eosinophilic fasciitis.
   b. Scleroderma.
   c. Scleredema.
   d. Nephrogenic systemic fibrosis.
   e. Graft-versus-host disease.

2. **Which of the following names is associated with a scoring system for scleroderma?**
   a. Rodnan.
   b. Wagner.
   c. Hanifin.
   d. Margolis.

3. **Which of the following is consistent with the role of p300 in promoting fibrosis in scleroderma?**
   a. It is downregulated by TGF-β.
   b. It has increased expression in cytoplasm of fibroblasts of patients with scleroderma.
   c. It is dependent on Smads.
   d. It is dependent on acetyltransferase activity to exert TGF-β’s effect.
   e. All of the above.

**ANSWERS**

1. b. Scleroderma.

Scleroderma (systemic sclerosis, SSc) is a multisystem autoimmune connective-tissue disease that affects the skin, blood vessels, and internal organs. SSc’s etiology is unknown, and its pathogenesis is characterized by the activation of cellular and humoral immunity, including autoantibody production (anticentromere, antitopoisomerase I) (Steen, 2005; Cepeda and Reveille, 2004), chronic inflammation, microvascular as well as large-vessel damage with fibrotic obliteratorive vasculopathy, and widespread tissue fibrosis. This results in tissue deposition of collagen and other extracellular matrix proteins such as
proteoglycans, fibronectin, fibrillins, and adhesion molecules. These changes are promoted by Th2 and Th17 profibrotic cytokines including IL-4, IL-13, and IL-17, interferon, transforming growth factor β (TGF-β), and connective-tissue growth factor (CTGF) (Topal and Dhurat, 2013; Gabrielli et al., 2009).

Fibrotic changes often are initially observed in the hands and fingers, with spreading to forearms, arms, trunk, face, and lower extremities. Skin features include finger swelling, Raynaud’s phenomenon, nail fold capillary changes, telangiectasias, pitted scars on the tips of the fingers, skin hardening, calcinosis, hyperpigmentation in sun-exposed areas, depigmentation in sclerotic areas, and depigmentation with sparing of perifollicular areas (salt-and-pepper sign). One variant (CREST syndrome: calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, and telangiectasias) involves primarily the hands, fingers, face, and esophagus. Late manifestations include skin atrophy, contractures and flexion of the fingers, beaked nose, microstomia, skin ulcers, osteomyelitis, and the need for amputation. Extracutaneous manifestations cause severe morbidity and mortality; they include interstitial lung disease, pulmonary fibrosis, pulmonary arterial hypertension, and cardiac (congestive heart failure), renal (scleroderma crisis), and gastrointestinal symptoms (dyspepsia, dysphagia, constipation, diarrhea, malnutrition) (Katsumoto et al., 2011).

Clinical diagnosis is supported by serologic determination of autoantibodies (ANA with nucleolar and discrete speckled pattern; antitopoisozeromer I Abs (Scl70) for diffuse disease, and anticentromere Abs for CREST syndrome). In contrast, eosinophilic fasciitis typically lacks face or hand involvement and develops acutely (days to weeks), often after intense exercise, with erythema and edema. It may be associated with inflammatory arthritis, joint contractures, and the so-called “Grove sign”—venous furrowing around muscles. Scleredema also occurs rapidly because it is at times associated with febrile illness such as upper respiratory infection, diabetes mellitus, or blood dyscrasia (such as monoclonal gammopathy). Clinically, the face may have extensive involvement, as may the neck, trunk, and extremities; however, hands and feet are typically spared. Nephrogenic systemic fibrosis occurs in patients with renal insufficiency undergoing imaging studies with the contrast agent gadolinium. Involvement of the extremities is common, and papules and subcutaneous nodules can develop; however, the face is rarely involved. Yellow palmar papules and yellow scleral plaques are also common. Graft-versus-host disease may also present, with fibrotic changes seen in chronic disease. Sclerodactyly, however, is not common.

2. a. Rodnan.

The modified Rodnan skin score (mRSS) is a validated (gold standard), reproducible technique to evaluate the degree of skin involvement, skin thickness, and induration in scleroderma through palpation (Czirja’k et al., 2008). It is an easy tool to use to evaluate and document the progress of the disease, as
well as to evaluate treatment response; however, it requires training and experience, fails to detect small (but perhaps relevant) changes, and involves a degree of subjectivity. Particularly useful in early disease, it has been found to predict the outcome in scleroderma and correlates well with internal organ disease (Czirja’k et al., 2008; Clements et al., 2000). The mRSS assesses skin thickness clinically in each of 17 body surface areas on a 0–3 scale: 0 = normal, 1 = mild thickness, 2 = moderate thickness, 3 = severe thickness (with a maximum score of 51) (see Figure 1) (Clements et al., 2000; Avouac et al., 2010).

As a predictor of clinical outcome, a score ≥20, together with lung involvement, is the most important identifiable risk factor for early mortality. Overall, higher skin scores (≥20) have been related to higher rates of mortality, scleroderma renal crisis, heart involvement, and disability (Clements et al., 2000). In addition, the risk of 5- and 10-year mortality has been reported to decrease significantly in patients with diffuse scleroderma whose skin scores decreased over a 2-year period compared with patients whose skin scores did not improve (Clements et al., 2000). The Wagner classification classifies diabetic foot ulcers based on wound depth and presence of infection or gangrene (Sun, 2012). Grade 0–2 grades depth from no ulcer to a deep ulcer, penetrating down to ligaments, and muscle. Grade 3–5 adds the presence of localized infection, localized gangrene, or extensive gangrene involving the whole foot. The Hanifin or Hanifin and Radjka diagnostic criteria are used for atopic dermatitis (Hanifin et al., 1980). Major criteria include pruritus, typical morphology and distribution, chronic or chronically relapsing dermatitis, and personal or family history of atopy. Minor criteria include xerosis, ichthyosis, palmar hyperlinearity, keratosis pilaris, immediate (type I) skin test reactivity, and raised serum IgE, among others. Margolis score refers to a 2-point scoring system for venous ulcer where size (>5cm²) and duration (presence >6 months) predict likelihood of healing with standard care (Margolis et al., 2000).

3. **d.** It is dependent on acetyltransferase activity to exert TGF-β’s effect.

p300 is a ubiquitous nuclear phosphoprotein with important roles in embryogenesis, extracellular matrix homeostasis regulation, myofibroblast transformation, and epithelial–mesenchymal transition. In addition, it is a component of the chromatin remodeling and transcriptional complex that modulates the expression of genes involved in cell cycle regulation, apoptosis, growth, and development. Through its histone acetyltransferase (HAT) domain, p300 serves to augment activator-dependent transcription (Kraus and Kadonaga, 1998; Vo and Goodman, 2001), and its interaction with activated Smads is essential for transforming growth factor β (TGF-β)-induced profibrotic signaling. p300 can also catalyze acetylation of early growth response-1 (Egr-1) and other transcription factors.

p300 has been linked to the pathogenesis of scleroderma because it has been found to be significantly elevated in explanted scleroderma fibroblasts (Bhattacharyya et al., 2005) and other fibrotic conditions.
such as chronic graft-versus-host disease and pulmonary fibrosis. In this issue, Ghosh et al. (2013) report that p300 expression is increased with stimulation by TGF-β by a Smad-independent pathway, associated with p300 accumulation on target gene promoters, histone H4 acetylation, and elevated Type I collagen transcriptional activity. In summary, the link between TGF-β signaling, excessive collagen gene expression, and fibrosis in scleroderma appears mediated by induction of p300 and via histone acetylation, which promotes collagen gene expression. Pharmacological inhibition of HAT activity markedly nullified the stimulation of collagen expression induced by TGF-β, making p300 a possible target in future therapies to control the progression of fibrosis in scleroderma.

Figure 1. Modified from Avouac et al. (1010).
REFERENCES


