Systemic Sclerosis: A Prickly Issue

Marina Pekar[1], Gilad Twig MD[1,2], Alex Levin MD[1] and Howard Amital MD MHA[1]

[1]Department of Medicine B and [2]Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: systemic sclerosis (SSc), palm tree thorns, autoimmunity, arthritis

IMAJ 2014; 16: 257–258

Systemic sclerosis is a rare autoimmune disease; its incidence in the United States is 9–19 cases per million per year. There is a female predominance with an onset age of 30–50 years. SSc is characterized by extensive vasculopathy, inflammation and fibrosis. It can involve the skin (scleroderma) and almost any organ or system [1].

The pathophysiology of the disease is not fully understood and several mechanisms have been proposed. Genetic factors seem to play a role in induction of the disease, and infectious causes have also been suggested to have a role in mechanisms of molecular mimicry, endothelial cell damage, superantigen immune activation, and microchimerism [2]. Various environmental exposures to viruses such as cytomegalovirus and Parvo virus B19 have also been implicated in the pathogenesis of SSc [2]. Furthermore, environmental exposure to contaminated rapeseed oil in Spain in the 1980s caused an outbreak of SSc-like disease, which was termed "toxic oil syndrome." Similarly, eosinophilia-myalgia syndrome, characterized by scleroderma-like chronic thickening skin lesions, was also reported following the consumption of L-tryptophan. These two syndromes present with skin changes resembling scleroderma, but pathologic and laboratory features clearly distinguish them from SSc. Several occupational chemicals such as silicates, polyvinyl chloride and epoxy resins are known as occupational exposure hazards that might be implicated in the pathogenesis of scleroderma and Raynaud's syndrome.

SSc = systemic sclerosis

We describe here a patient who was pricked extensively by palm tree thorns and subsequently developed a severe case of SSc.

PATIENT DESCRIPTION

A 53 year old man of Yemenite descent, previously healthy, and now retired from his occupation as a land surveyor, presented to our rheumatology clinic with progressively hardening and thickening skin on his palms and fingers. His personal and familial medical history was unremarkable. The serology panel for autoimmune diseases was negative and his blood and chemistry laboratory test results were normal. The only significant finding was an incident of dozens of thorn pricks of the Sago palm (*Cycas revoluta*) that occurred while working in the garden 2 months prior to this presentation. An ultrasound examination did not detect thorn remnants within the skin of his hands. Due to the more proximal spread of the skin involvement, a nail bed capillaroscopy was performed, which revealed typical giant widening of the arterioles consistent with the diagnosis of SSc. Several months after his initial visit, severe Raynaud's phenomenon, elevated blood pressure of 180/100 mmHg, dyspnea, and an increase in serum creatinine up to 1.8 mg/dl (from 0.7 mg/dl baseline) were observed. During that period the patient also reported a 15 kg weight loss without any overt digestive complaints.

The patient was hospitalized, and severe proximal and distal cutaneous thickening of the upper limbs, chest and abdomen with the development of typical SSc joint involvement, and severe Raynaud's phenomenon with several digital pitting scars were noted. The fibrosis was prominent in his right dominant hand.

A lung computed tomography scan showed peripheral mild interstitial pulmonary fibrosis, and an abdominal skin biopsy confirmed the diagnosis of SSc. The patient's hypertension was successfully treated with captopril 50 mg three times a day and lercanidipine 10 mg twice daily, and his creatinine decreased to 1.45 mg/dl. He also developed an antinuclear antibody titer of 1:160 with a fine speckled pattern but no other measurable autoantibodies. Currently the patient is on the above described medical regimen to control his hypertension; he is also receiving bosentan, an anti-endothelin receptor blocker, to treat his severe Raynaud's syndrome and prevent additional digital ulcers. Unfortunately, he is becoming progressively disabled due to severe extensive palmar and digital joint fibrosis with flexion contractures. His renal and pulmonary status remains stable with the described therapeutic regimen.

COMMENT

A literature review indicates that thorn-prick may elicit rheumatic conditions [3]. In most of the reported cases of thorn-prick injury, synovitis represented an aseptic immunologic reaction to the foreign body that was retained. Most reports end with the conclusion that a high index of suspicion should be exercised, including the search for retained plant material that cannot be evidenced in plain radiographs and necessitate ultrasound visualization. Several reports have linked palm thorn-pricks with consequent septic synovitis primarily due to *Pantoea/Enterobacter*

agglomerans infections [3,4]. Our patient had no evidence of arthritis apart from minor initial tenosynovitis, and his entire clinical presentation seemed aseptic with no discharge to be cultured and with no thorn remnants detected by comprehensive ultrasonographic evaluation.

As mentioned previously, some reports have proposed a possible link between infections and the development of SSc [2,5]. DNA and RNA of organisms such as Parvo viruses (B19), Epstein-Barr virus, cytomegalovirus andToxoplasma isolated from the blood and tissues of patients with SSc might be implicated in the pathogenesis and were proposed as possible causes of SSc [2,5]. Higher rates of *Helicobacter pylori* and chlamydial infections in SSc patients might also suggest a relationship between infection and development of the disease [2]. Additionally, it was postulated that viral products might synergize with other factors in the microenvironment, predisposing exposed patients to the development of SSc by other mechanisms. However, the specific connection is yet to be elucidated since homology between viruses and autoantibody targets has not been confirmed.

The ultrasonographic scan of our patient, involving both the right and left arm, did not yield any evidence of a foreign body. Based on this temporary association it was suspected that the thorn-prick injury was the cause of the development of SSc in our patient. In addition, connective tissue fibrosis of the skin of his right hand was more prominent than that of his left non-dominant hand, which had sustained fewer thorn-pricks.

In conclusion, we postulate that in this patient an immunological response to a massive injury from *Cycas revoluta* palm thorns enhanced the pathological process, culminating in the emergence of SSc.

Corresponding author:
Dr. H. Amital
Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2661, **Fax:** (972-3) 530-4796
email: Howard.amital@sheba.health.gov.il

References

1. Mehra S, Walker J, Patterson K, Fritzler MJ. Autoantibodies in systemic sclerosis. *Autoimmun Rev* 2013; 12: 340-54.
2. Grossman C, Dovrish Z, Shoenfeld Y, Amital H. Do infections facilitate the emergence of systemic sclerosis? *Autoimmun Rev* 2011; 10: 244-7.
3. Taskiran E, Toros T. Chronic synovitis caused by a date palm thorn: an unusual clinical picture. *Arthroscopy* 2002; 18: E7.
4. Rave O, Assous MV, Hashkes PJ, Lebel E, Hadas-Halpern I, Megged O. Pantoea agglomerans foreign body-induced septic arthritis. *Pediatr Infect Dis J* 2012; 31: 1311-12.
5. Randone SB, Guiducci S, Cerinic MM. Systemic sclerosis and infections. *Autoimmun Rev* 2008; 8: 36-40.

Capsule

Negative reinforcement in cancer

About 15% to 20% of breast cancers are classified as "triple negative," so called because these tumors do not express three key proteins that are biomarkers and/or drug targets for breast cancer: the estrogen receptor, the progesterone receptor, and HER2 (a member of the epidermal growth factor receptor family). Triple-negative tumors are aggressive and more likely to metastasize than other breast cancers, and there is no effective treatment. To acquire new insights into the biology and possible therapy of these tumors, Feigin et al. looked for aberrant expression of G protein-coupled receptors, cell signaling proteins that have been successfully targeted for treatment of other disorders such as depression. An orphan receptor called GPR161 was found to be overexpressed in triple-negative but not in other breast cancer types. In cell culture, high expression levels of GPR161 induced proliferation of mammary epithelial cells, disrupted the acinar structures formed by these cells, and enhanced their invasive capacity. GPR161 was shown to activate the mTORC1/S6K signaling pathway. These observations suggest that GPR161 dysfunction contributes to the development of triple-negative breast cancers.

Proc Natl Acad Sci USA 2014; 10.1073/pnas.1320239111

Eitan Israeli

Capsule

Misfolded proteins can be targets for autoantibodies

MHC class II molecules can rescue endoplasmic reticulum-localized misfolded proteins from protein degradation and transport them to the cell surface intact by associating with the misfolded protein. MHC class II allelic polymorphisms are associated with susceptibility to many autoimmune diseases. Jin et al. now found that cellular misfolded autoantigens rescued and complexed with MHC class II molecules can become targets for autoantibodies in patients with rheumatoid arthritis (RA). By analyzing sera from some RA patients in which autoantibodies against correctly folded intact proteins were not detectable, autoantibodies specific to misfolded proteins complexed with MHC class II molecules of disease-susceptible alleles but not disease-resistant MHC class II alleles were observed. This suggested that misfolded proteins complexed with MHC class II molecules are natural autoantigens for autoantibodies. Autoantibody binding to misfolded proteins transported by MHC class II molecules was strongly correlated with susceptibility to RA. Thus, misfolded proteins, which normally would not be exposed to the immune system, can be targets for autoantibodies when they avoid protein degradation.

Proc Natl Acad Sci USA 2014; 111: 3787

Eitan Israeli