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CLINICAL VIGNETTE

A False Positive Scl-70 Lead to a Diagnosis of Pulmonary Arterial Hypertension

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Case

A 60-year-old female presented to her primary care doctor with intermittent joint pains and cold distal extremities with associated skin tightness. Her past medical history includes mood disorder, hypothyroidism, prior 22-year tobacco use, breast cancer, hypertension, hyperlipidemia, and diabetes. Physical exam was remarkable for thickening of the skin overlying the middle phalanges of several fingers. There was also two telangiectasias, on her hands, at the base of the 4th right finger and the left palm. The spots blanched with pressure with prompt return of normal color. No subcutaneous nodularity was present in the hands, elbows or ankles.

She denied any oral lesions, photosensitivity, fevers, night sweats, weight loss, nor muscle weakness. Her lab evaluation was significant for high titer scleroderma Scl-70 and negative ANA. She described changes in temperature and numbness in distal extremities without any change in skin color. She reported fatigue with minimal physical activity but denied shortness of breath at rest or swelling in her lower extremities. She had no heartburn or dysphagia but reported hives with spicy foods. Chest x-ray six months prior noted only pleural thickening. Echocardiogram 1 year prior showed normal ejection fraction and normal pulmonary arterial pressures. She also has a history of recurrent asymptomatic microscopic hematuria with stage 2 chronic kidney disease with normal kidney ultrasound and CT Urogram.

Rheumatology consult recommended additional testing for possible CREST syndrome or mixed connective tissue disease. This included CBC, CMP, centromere antibody, repeat inflammatory markers, a new transthoracic ECHO, and a high-resolution CT scan to assess for interstitial lung disease. Based on her history of breast cancer and possible diagnosis of scleroderma, the patient was thought at increased risk for recurrent malignancy. Her oncologist obtained SPEP, ESR, CBC, a RNA-polymerase III antibody along with a PET scan. Urinalysis was repeated.

Repeat Scl-70 remained positive along with a positive anti-histone AB 5.1 which raised concerns for drug induced lupus. Although she displayed no clinical manifestations of lupus, hydrochlorothiazide and amlodipine were stopped due to reports of association with cutaneous lupus.[1] She was seen by dermatology who did not identify significant skin lesions or indication for skin biopsy. The nailfold capillary loops appeared normal and there was no evidence of sclerodactyly.

High resolution CT scan noted no evidence of interstitial lung disease. The rheumatologist ordered another scleroderma panel from a different specialty laboratory which found SCL70 ab by EIA of 24 (normal less than 20). However, the confirmatory Scl-70 by immunodiffusion was negative. Thus, her Scl70 antibody was thought to be a false positive. Echocardiogram found pulmonary artery pressure of 30 mmHg at rest which increased to 57 mmHg with exercise. Stress echocardiogram also raised concern for exercise induced pulmonary hypertension. Some air trapping was present on HRCT. To definitively assess her pulmonary arterial pressures right heart cardiac catheterization was scheduled.

At this point there was no strong evidence for systemic scleroderma. Repeat scleroderma panel noted positive ANA 1:40 speckled at RDL, weak positive Ku, positive histone ab without clinical manifestations of drug induced lupus with only intermittent joint pains. There remained concern for possible systemic connective tissue disease due to the presence of the Ku antibody and exercise induced pulmonary hypertension. She declined starting immunomodulator therapy with plaquenil. Repeat urinalysis was clear of protein, and she will continue to follow up with nephrology for surveillance for underlying vasculitis. No clear explanation was found for the microscopic hematuria. PET scan was negative for malignancy and RNA-polymerase III ab, (associated with malignancy) was also negative.

Patient was restarted on amlodipine for hypertension but remained off of hydrochlorothiazide. She is tolerating the PCSK-9 inhibitor, repatha.

While the pulmonary function tests were within normal limits, cardiac catheterization confirmed pulmonary arterial hypertension. The patient was initiated on dual therapy of Tadalafil (ADCIRCA) and Macitentan (OPSUMIT).[2] He will be followed with periodic echocardiograms, pulmonary function tests, and routine rheumatologic antibody screening given the potential for Limited Systemic Sclerosis (SSc) or Undifferentiated Connective Tissue Disease (UCTD).

Discussion

Systemic sclerosis or scleroderma (SSc) is a connective tissue disorder of unknown origin with significant mortality. Early diagnosis and timely management are critical to delay progress-

sion. However, due to the diverse and heterogeneous presentation of SSc, there are unique challenges in diagnosis with ongoing efforts to develop a single test for diagnosis.[3] Diagnosing patients in the early stages of SSc is much more difficult because their clinical presentations vary immensely and are difficult to distinguish from other connective tissue disorders. Although historic classification criteria for SSc have been developed based on data from patients with long-standing SSc, these may miss patients who present with early or subtle SSc symptoms.[3] The 2013 classification criterion from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) attempted to encompass patients both in the early and late stages of SSc.[4]

SSc can present with several different subtypes: limited scleroderma (lcSSc), diffuse scleroderma (dcSSc), or scleroderma without skin involvement (ssSSc).[4] lcSSc is classically associated with CREST syndrome (calcinosis, Raynaud phenomenon (RP), esophageal dysmotility, sclerodactyly, and telangiectasia) and can lead to pulmonary arterial hypertension (PAH).[5] Conversely, dcSSc and ssSSc with no skin involvement follow a more aggressive course, with variable involvement of internal organs. Long-term clinical sequelae include fibrosis of multiple organs including interstitial lung disease, myocardial fibrosis, and renal crisis which are associated with significant mortality.[5] For our patient, we were particularly concerned about the development of dcSSc based on elevated Scl-70 with symptoms including intermittent joint pain, change in temperature of distal extremities, mild tightening of skin distal to DIPs, and persistent hematuria.

The 2013 ACR/EULAR classification system for SSc ranges from 0 to 19 points, containing items of varying weight on the scoring scale. Any patient who scores $\geq$9 points meets the criteria for SSc. The strongest predictor for SSc on the scale is the clinical symptom of skin thickening of fingers on both hands (extending proximal to the MCP joint), which is automatically given 9 points.[4] Other factors on the scale include fingertip lesions (2-3 points), telangiectasia (2 points), abnormal nailfold capillaries (2 points), pulmonary hypertension/interstitial lung disease (2 points), Raynauds (3 points), and SSc related antibodies (3 points).[4] The approximate specificity and sensitivity of this criteria for all SSs patients are reported as 0.95 and 0.93, respectively, much better than all previous criteria.[3,4]

As our patient exhibits mild Raynaud-like symptoms, pulmonary arterial hypertension, positive Scl-70 antibody, and possible telangiectasia, had an aggregate score of 7 points. Given the false positive Scl-70 antibody, her score drops to 4. Based on the 2013 ACR/EULAR there is not enough evidence for a definitive diagnosis of SSc. However, concerns have been raised about strict application of the 2013 guidelines, as this may miss a subset of people with SSc. Our patient, who presents with Raynauds-like symptoms and mild tightening of skin distal to DIPs, there remains concern for future development of SSc or other connective tissue diseases. Sensitivity for mixed connective tissue disorders using the ACR/EULAR criteria has been reported to be low. Mixed connective tissue disorders generally have gradual onset, and Raynauds-like symptoms may precede other symptoms for several months to years.[6] The possibility of a mixed connective tissue disorder is further supported by weakly positive ku antibody, which has been correlated to a wide variety of mixed connective tissue diseases such as SSc and myositis.[7]

Because of future SSc or other mixed connective tissue disorders she will be followed closely to allow for early intervention and treatment. As pulmonary hypertension is a major risk factor in SSc, yearly echocardiograms are recommended for SSc patients yearly, with confirmatory right heart catheterization.[8,9] However, the clinical manifestations of PH are highly variable due to the numerous phenotypes of SSc. The most common PH etiology for patients with SSc has been found to be type 1 PAH.[10] Similarly, as deterioration of the lung can also lead to mortality in SSc patients, periodic pulmonary function testing is advised. Our patient will receive ongoing treatment for PAH and will undergo 6 month pulmonary function testing with spirometry and DLCO diffusing capacity. Treatment for PAH associated with SSc involves combination therapy with PDE-5 inhibitors and endothelial receptor agonists such as macitentan.[11]

SSc has been associated with an increased risk for cancer, particularly the lungs and breast.[12] With her past history of breast cancer, ongoing screening is recommended. The RNA Polymerase III antibody (Anti-RNA3) is associated with malignancies, and our patient has tested negative.[13] She also has mildly positive ANA and positive anti-histone without any clinical manifestations of drug induced lupus. The clinical significance is uncertain, as there is no set criteria for the diagnosis of drug induced lupus. Our patient may have developed systemic drug induced lupus, in which arthralgia may be the only characteristic symptom.[14] On the other hand, some patients with SSc may present with positive anti-histone antibodies.

This case represents the difficulty of diagnosing SSc and the complexities involved in interpreting autoimmune antibody results. While the 2013 ACR/EULAR guidelines do not classify this patient with SSc, there is still a possibility that this patient has early SSc or another mixed connective tissue disorder further complicated by her new diagnosis of pulmonary arterial hypertension.

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