CLINICAL IMAGE

Successful treatment of systemic sclerosis coexisting with smoldering myeloma

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In 2016, a 65-year-old woman presenting with skin thickening and Raynaud phenomenon was referred to a rheumatologist with a suspicion of systemic sclerosis (SSc). Her modified Rodnan skin score was 18, capillaroscopy showed active alternations of scleroderma pattern, serological testing revealed a significant titer of antinuclear antibodies, anti-topoisomerase I, and antineutrophil cytoplasmic antibodies, both antimyeloperoxidase and anti-proteinase 3. Apart from an elevated C-reactive protein level and sedimentation rate, no abnormalities were found on biochemical parameters, peripheral blood smear, proteinogram, chest and abdomen computed tomography, or pulmonary function tests. Echocardiography revealed normal biventricular systolic function, mild left ventricular diastolic dysfunction, and aortic valve stenosis. The patient was diagnosed with the diffuse type of SSc and therapy with mycophenolate mofetil was started. Because of negative prognostic factors, the patient remained under close surveillance. One month later, IgG kappa monoclonal gammopathy in serum (κ/λ index, 2.08) and Bence Jones protein in the urine were found. The first bone marrow biopsy with immunophenotyping showed an elevated percentage of plasma cells (4%) without clonal growth. Seven months later, the second biopsy revealed a significant increase of plasma cells (14.6%); 1.64% were clonal. The concentration of free light chains kept increasing (up to 3-fold normal range for free κ light chains); however, the patient did not meet the criteria for multiple myeloma (MM) and was diagnosed with smoldering myeloma (SMM). Meanwhile, the symptoms of SSc were aggravating rapidly. Skin changes advanced to 29 points in the modified Rodnan skin score and were followed by telangiectasia, digital ulcers, tendon friction rubs, and dysphagia. Cardiac magnetic resonance imaging presented features of active inflammatory injury (FIGURE 1A–1C). Troponin levels were normal but creatine kinase MB mass was slightly elevated (10.7 ng/ml; reference range, 0.0–6.6 ng/ml) and active myocarditis was diagnosed. Rapid progression prompted therapy escalation to corticosteroids and cyclophosphamide. Unfortunately, while on this treatment, in November 2017, the patient developed interstitial lung disease. Therefore, other therapeutic options, including hematopoietic stem cell transplantation, were considered. The interleukin 6 (IL-6) concentration was elevated, an experimental therapy with tocilizumab was introduced (first, 480 mg/mo intravenously, then 162 mg/wk subcutaneously). This therapy quickly led to improvement. At the time of writing, the patient presented a remarkable remission on physical examination with 6 points in the modified Rodnan skin score, no digital ulcers, telangiectasia, nor tendon friction rubs. Radiological imaging showed satisfactory control of interstitial lung disease and heart involvement (FIGURE 1D–1F). Laboratory tests showed a significant decrease in monoclonal immunoglobulins, absence of Bence Jones protein, normalization of creatine kinase MB mass, and a significant decrease in the antineutrophil cytoplasmic antibodies titer. Consequently, the patient continues the anti–IL-6 treatment.

Systemic sclerosis is a severe autoimmune disease of connective tissue presenting skin fibrosis and multisystem involvement. An increased prevalence of hematologic malignancies in patients with SSc is observed and it correlates with a worse course of the disease.[1] However, few cases of SSc coexistence with SMM were described in the literature. SMM itself does not require treatment and no specific guidelines for patients with SSc and SMM have been proposed,[2] although it was observed that treatment of hematologic disorders may lead to SSc remission.[3] Therefore, we share with the medical community our experience of treatment of aggressive diffuse SSc with tocilizumab. To our best knowledge, this is

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Received: August 29, 2021.
Revision accepted: October 11, 2021.
Published online: October 26, 2021.
Pol Arch Intern Med. 2021; 131 (12): 16133
doi:10.20452/pamw.16133

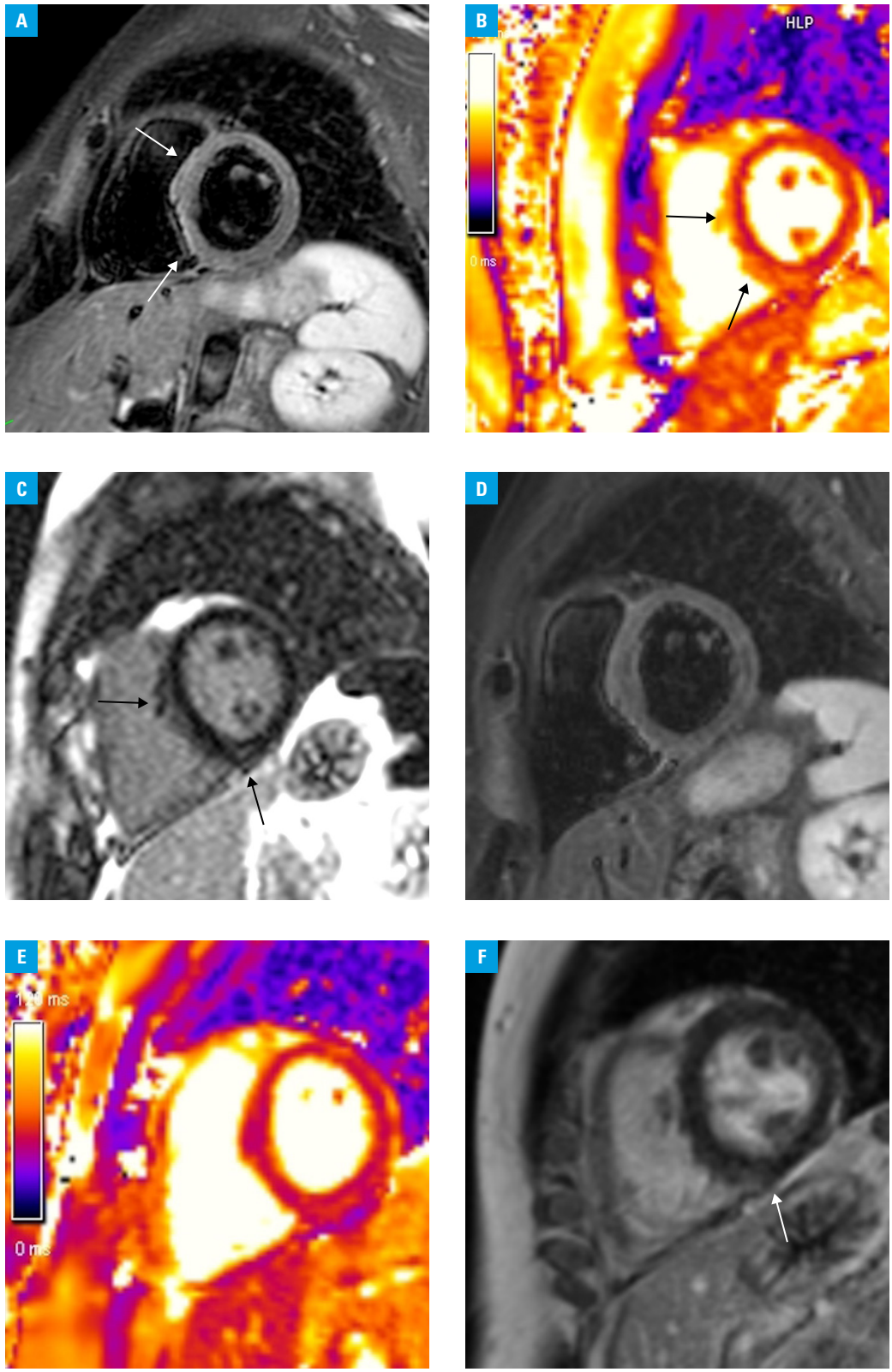

FIGURE 1 **A–C** – baseline (2016) and early follow-up (2018) cardiac magnetic resonance imaging; **A** – T2-weighted short-tau inversion recovery (T2STIR) sequence showing increased signal of the myocardium (arrows) consistent with myocardial edema (baseline, 2016); **B** – elevated global T2 relaxation time (54 ms; institutional reference range, 39–49 ms) with local (arrows) increase of the T2 relaxation time (segmental region of interest average T2, 59 ms) in the basal inferoseptal segment consistent with acute injury/ongoing inflammation (early follow-up, 2018), paralleled by subtle intramyocardial areas of irreversible damage (inflammatory necrosis/fibrosis) as shown by late gadolinium enhancement (**C**, arrows); **D–F** – follow-up cardiac magnetic resonance imaging (2020); **D** – T2STIR sequence showing normalized signal of the myocardium with no features of myocardial edema; **E** – normalized T2 relaxation time—no unequivocal features of acute injury/ongoing inflammation (global T2 relaxation time, 49 ms); **F** – subtle intramyocardial areas of irreversible damage (inflammatory necrosis/fibrosis) can still be noticed on late gadolinium enhancement imaging (arrow).

the first case report of anti–IL-6 treatment of coexisting SSc and SMM. Based on our experience, those entities progress on standard treatment. The decision to introduce tocilizumab, an antibody against an IL-6 receptor, was supported by a report of successful management of SMM coexisting with RA[4] and by studies showing that IL-6 stimulates the survival of plasma cells and activation of osteoclast, which presumably is crucial for MM development, although MM cell lines quickly become independent.[5] It is worth mentioning that tocilizumab has already gained its registration for SSc with interstitial lung disease treatment in the United States and we do believe that anti–IL-6 treatment might become a promising remedy for patients with SSc coexisting with SMM and also for those with SSc-related myocarditis as we observed in this case. A significant decrease of serum free light chains may correspond to a lower plasma cell activity, but its influence on progression to MM is difficult to assess as there are no indications for further bone marrow biopsies in this patient.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Smoleńska Ż, Gogulska Z, Dorniak K, Zdrojewski Z. Successful treatment of systemic sclerosis coexisting with smoldering myeloma. Pol Arch Intern Med. 2021; 131: 16133. doi:10.20452/pamw.16133

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