Giant cell arteritis and systemic sclerosis: a rare overlap syndrome

Antonios Psarras, Konstantinos Tselios, Ioannis Gkougkourelas, Alexandros Sarantopoulos, Panagiota Boura

Clinical Immunology Unit, Second Department of Internal Medicine, Hippokration General Hospital, Aristotle University of Thessaloniki, Greece

Abstract

Systemic sclerosis (SSc) is a connective tissue disease which is characterized by endothelium dysfunction, inflammation and fibrosis. Although scleroderma is often presented as an overlap syndrome with other autoimmune rheumatic diseases, the development of large vessel vasculitis in patients with SSc is considered extremely rare, since only three case reports have thus far been reported in English literature. Herein, we report a 65-year-old woman with a long-standing history of systemic sclerosis who developed giant cell arteritis, eight years after initial diagnosis.

Introduction

Overlap syndromes describe the incidence of two or more autoimmune diseases in a single patient. Patients with systemic sclerosis (SSc) often present clinical features commonly seen in other connective tissue diseases, such systemic lupus erythematosus, polymyositis, dermatomyositis or rheumatoid arthritis. However, the co-existence of SSc and primary vasculitis is thought to be very uncommon. Our patient developed symptoms and signs typical of giant cell arteritis (GCA), such as headache, tenderness of the right temporal artery and elevated erythrocyte sedimentation rate (ESR), which were similarly present in past case reports.[1,2] Digital ulcers as a result not of microvascular occlusion, but of GCA, have also been described in one case report.[3]

The pathogenesis of SSc is characterized by immune dysfunction, endothelial dysregulation and fibrosis. It is believed that the failure of immune system to resolve the inflammation caused by repeated vascular injury is the main key for fibroblast activation.[4] In the site of inflammation, both monocytes and T cells are recruited to secrete profibrotic cytokines, while B-cells are derived to plasma cells producing autoantibodies (anti-topoisomerase I, anti-centromere) highly specific of the disease. All these mechanisms cause further differentiation of fibroblasts, continuous production of extracellular matrix leading to extensive fibrosis of visceral organs and microangiopathy.[5]

On the other hand, the pathogenesis of GCA reflects a dysregulation of immune system that affects predominantly large or medium-sized arteries, such as the temporal artery and its branches, the thoracic aorta and branches of the external carotid arteries. Histologic findings show that arteries are mainly infiltrated by T lymphocytes and macrophages, whilst the characteristic giant cells are found only in 50% of temporal artery biopsies. Activated by unidentified causes monocytes infiltrate the media or the internal elastic membrane of the arteries and consequently, the recruitment of macrophages and lymphocytes leads to the progression of inflammation and tissue injury. Remodeling of blood vessels results to narrowing and finally, occlusion of the affected arteries.[6]

Case Report

The patient was admitted in December 2005 because of exertional dyspnea, Raynaud's phenomenon, a localized morphea on the left arm and symptoms of gastroesophageal reflux disease for 10 months. High resolution computed tomography (HRCT) of the thorax revealed bilateral basal ground glass opacities, while diffusing capacity of the lung for carbon monoxide (DLCO) was significantly impaired. Heart ultrasound was normal without evidence of pulmonary hypertension. Esophagoscopy showed lower esophageal sphincter dysfunction and grade 2 esophagitis. Biopsy of the morphea was compatible with SSc, as well as nailfold capillaroscopy. Immunological screening (including antinuclear, anti-Scl-70, anti-centromere and anti-U1-RNP antibodies) was negative, whereas ESR and C3/C4d complement fragments were normal.

The patient was initially treated with cyclophosphamide pulse therapy (500 mg/m^2 per month for 6 months) for lung disease and D-penicillamine as an antifibrotic agent with satisfactory response; the cutaneous lesions were limited during this period. Thereafter, she was on standard treatment with D-penicillamine, azathioprine, nifedipine and pantoprazole. Disease course was uneventful during the following years, since the patient was closely monitored. After 12 months from initial diagnosis, HRCT was performed showing that the extension of interstitial lung disease had no significant changes, while there was no further reduction in DLCO. The follow-up of the lung disease, including heart ultrasound, was suggested every 24 months. Regarding the gastrointestinal involvement, esophagoscopy was performed every 12 months revealing no alterations in mucosal abnormalities, although the patient was under treatment with proton pump inhibitors. Full blood count and immunology screening, which remained negative, were checked annually. Even though the patient had no arterial hypertension, she was recommended to monitor her blood pressure every 6 months.

In September 2013, the patient developed right temporal headache with tenderness of the right temporal artery and an elevated ESR. Doppler ultrasound revealed total occlusion of the right temporal artery; biopsy revealed lymphocytic infiltration of the media layer and giant cell formation. A diagnosis of GCA was made and the patient was administered methylprednisolone (32 mg/day, slow tapering), which led to symptom resolution.

Discussion

Although large artery involvement in SSc is unexpected, since disease pathogenesis is characterized by microangiopathy and fibrosis, current reports support that macrovascular disease and accelerated atherosclerosis may be present in a significant proportion of patients.[4] Apart from that, macroangiopathy

Correspondence: Antonios Psarras, Clinical Immunology Unit, 2nd Department of Internal Medicine, Hippokration General Hospital, Aristotle University of Thessaloniki, Konstantinoupoleos St. 49, 54642 Thessaloniki, Greece.
Tel.:+30.2310.892.239 - Fax: +30.2310.992.794.
E-mail: antonios.psarras@gmail.com

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may be associated with the extent of skin involvement in SSc and certain autoantibodies such as anti-topoisomerase I (Scl-70).[7] However, the presence of typical GCA in this patient may suggest a rare overlap syndrome since the pathogenetic mechanisms of these diseases differ considerably.[8]

The use of glucocorticoids is considered to be the gold standard in treatment of GCA. Especially patients at high risk of visual loss or other macrovascular complications should start therapy with prednisone or equivalent as soon as possible. However, glucocorticoids in high doses have been associated with an increase at risk of renal crisis in SSc.[9] There are several studies indicating that more than one-half of patients with scleroderma renal crisis had an exposure to moderate or high doses of glucocorticoids.[10,11] To eliminate the possibility of renal involvement or other adverse reactions by the use of glucocorticoids, it has been suggested methotrexate to be moderately effective as a glucocorticoid-sparing agent.[12] Other agents, such as cyclophosphamide or tocilizumab (monoclonal antibody against IL-6R), have been introduced as possible alternatives, but their definite effectiveness is yet to be proven.[13,14] It is worth mentioning that one clinical trial proved anti-TNF agents to be unable to induce remission.[15] Due to the fact that our patient had no evidence of renal involvement in the previous years, she was introduced under standard treatment with methylprednisolone and no adverse complications have been developed so far.

Conclusions

The presence of suggestive symptoms, which can not be attributed to the primary disease, and/or abnormal physical signs in an elderly patient with diffuse SSc should alert the clinician to consider the possibility of large vessel involvement. Thus, the required screening for confirmation of GCA's diagnosis is recommended in highly suspected patients with other connective tissue diseases.

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