Autoimmune Tautology in a Complex Case of Poly-Autoimmunity: Systemic Sclerosis, Autoimmune Liver Involvement, Antiphospholipid Syndrome and Hashimoto's Thyroiditis

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KEY WORDS: autoimmunity, systemic sclerosis (SSc), liver, Raynaud's phenomenon, Hashimoto's thyroiditis

IMAJ 2017; 19: 193–195

For Editorial see page 186

Systemic sclerosis (SSc) is a chronic multisystem disorder characterized by autoantibody production, inflammation, microvascular abnormalities and connective tissue fibrosis [1]. The skin involvement may be minimal or absent in some cases. In a very small percentage of SSc patients it is possible to detect antiphospholipid antibodies (APA) that are more often found in other autoimmune diseases (ADs), such as rheumatoid arthritis, Sjögren´s syndrome and autoimmune hepatitis (AIH).

Antiphospholipid antibody syndrome (APS) is defined by the persistent presence of APA in individuals with recurrent venous or arterial thromboembolism or pregnancy morbidity [2]. The coexistence of SSc/APS is therefore a rare overlapping syndrome. When these two conditions are associated, more severe manifestations can be observed, such as pulmonary hypertension and gangrene of the extremities [2].

AIH is an autoimmune disease characterized by chronic liver inflammation of unknown cause. Its diagnostic criteria are in accordance with the International Autoimmune Hepatitis Group and the simplified criteria are based on the elevation of immunoglobulin G (IgG), the demonstration of characteristic autoantibodies, and histological evidence of interface hepatitis in the absence of viral disease [3]. Although AIH can be characterized by the simultaneous occurrence of other ADs, the co-occurrence of AIH and SSc remains to be defined. In fact, gastrointestinal involvement has been reported in as many as 90% of patients with SSc, yet the frequency of liver involvement remains low and there have been only sporadic reports of SSc with AIH. Another feature of SSc is the overlap with thyroid disorders. Discordant results on the association between thyroid autoimmunity and SSc have been reported; yet a high incidence of thyroid dysfunction has been shown [4].

Interestingly, to the best of our knowledge the co-occurrence of SSc, AIH, APS and Hashimoto's thyroiditis in a single patient has never been described. We present such a case here.

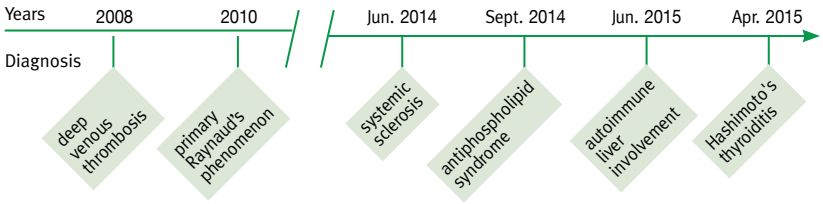
PATIENT DESCRIPTION

Our patient was a 34 year old male, non-smoker, with a history of recurrent deep venous thrombosis and dysphagia to both solids and liquids. He had a previous diagnosis (in 2010) of primary Raynaud's phenomenon for which he was treated with acetylsalicylic acid and nifedipine. In June 2014, he came to our attention complaining of arthralgia, asthenia, dyspepsia, dysphagia and worsening of Raynaud's phenomenon.

The laboratory investigation showed positive antinuclear antibodies (ANA) at high titer (640 UA/ml), anti-centromere antibodies (640 UA/ml) and anti-b2-glycoprotein I antibodies (25.4 U/ml), as well as erythrocyte sedimentation rate (ESR) (28 mm/hr) and a slightly reduced complement (C3 0.79 g/L, C4 0.13 g/L). Other autoantibodies (anti-Jo-1, anti-Sm, anti-SSb, anti-SSb, anti-Scl70, anticardiolipin antibodies and lupus anticoagulant) were negative. Nailfold capillaroscopy showed a scleroderma pattern. Esophagogastroduodenoscopy demonstrated a lower esophageal sphincter dysfunction with grade 2 esophagitis, and high resolution esophagus manometry detected a marked reduction of peristaltic pressures in the distal two-thirds of the esophagus. There was no evidence of pulmonary involvement on high resolution computed tomography (HRCT) and pulmonary function tests were normal. The echocardiogram systolic pulmonary pressure (sPAP) was 20 mmHg. No evidence of skin thickening was observed but facial telangiectasia was present. According to the 2013 American College

Figure 1. Laboratory features and onset of clinical manifestations

Investigation	Value	Reference range
AST	180 U/L	‹ 40 U/L
ALT	150 U/L	‹ 40 U/L
GGT	95 U/L	8-61 U/L
IgG	32 g/L	7.37-16.07 g/L
ANA	1:640 (centromeric pattern)	1:80
ACA	640 UA/ml	‹ 5 UA/ml
Anti-b2-GP1 IgM	25.4 U/ml	‹ 18 U/ml
Anti-thyroglobulin antibodies	434 IU/ml	0-115 IU/ml



AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase, ANA = antinuclear antibodies, ACA = anti-centromere antibodies, anti-β2-GP1 = anti-beta2-glycoprotein I antibodies

of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria, the patient was classified as SSc (score 10).

At follow-up, elevated liver function tests – aspartate aminotransferase (AST) 180 U/L and alanine aminotransferase (ALT) 150 U/L – were detected. No cholestasis was present, and serological tests for infectious diseases (including human immunodeficiency virus, hepatitis B and C, toxoplasmosis and cytomegalovirus) were all negative. Nevertheless, the positive ANA and the increased serum IgG (32 g/L) led us to suspect that an autoimmune hepatitis was developing. In order to confirm this diagnosis and evaluate the severity of liver damage, a liver biopsy was performed. Histology showed typical features of interface hepatitis with portal and periportal cellular inflammation characterized by an infiltrate of lymphocytes, monocytes/macrophages and plasma cells. The biliary system was spared. Within 4 weeks, treatment with prednisone (0.5 mg/kg/day) and azathioprine (100 mg/day) led to the rapid normalization of liver function tests.

The persistence of anti-b2-glycoprotein I antibodies after 12 weeks, and the recurrent deep vein thrombosis, led to the diagnosis of APS, according to the international consensus statement on APS [2]. Anti-thrombotic treatment (warfarin) was started. The follow-up at 24 months did not reveal any significant change in lung function or additional complications, such as any change in chest HRCT and pulmonary function tests. Treatment with proton pump inhibitors (PPIs) was beneficial for symptoms of gastroesophageal reflux disease, warfarin prevented the recurrence of thromboembolic events, and no modification of liver enzymes was observed. Finally, during the follow-up we detected increased levels of antibodies against thyroglobulin (434 IU/ml), with normal thyroid function and normal parenchymal aspect on thyroid echography. However, fine-needle aspiration cytology confirmed the diagnosis of Hashimoto's thyroiditis [Figure 1].

COMMENT

The evidence that ADs share several clinical signs and symptoms, physiopathological mechanisms, and genetic factors has been described as autoimmune tautology [4]. Although many cases of association between autoimmune diseases have been reported, to the best of our knowledge the co-occurrence of SSc, AIH, APS and Hashimoto's thyroiditis has never been described.

We report for the first time a case of SSc/APA overlap: rapidly developing features of AIH and Hashimoto's thyroiditis. Both genetic and epidemiologic studies have suggested that SSc shares a genetic background with other ADs and our case confirms the concept of the "mosaic of autoimmunity." It is clear that autoimmunity plays a pivotal role in the pathogenesis of SSc. However, the complex mechanism involved in the development of multiple ADs in one individual and the effect of poly-autoimmunity on the final clinical autoimmune phenotype are not well understood. Genes and environmental factors for many traits are connected in a close interaction that is genetically programmed or is purely stochastic. Recent evidence demonstrates that environment, more than genetics, shapes the immune system, conferring a higher risk of ADs developing. The study of interactions among individuals and the environment leading to ADs has been defined as autoimmune ecology (AE) [5]. AE is therefore a crucial component of the autoimmune tautology and reinforces the theory that ADs share several common mechanisms.

In our case, the patient shared signs and symptoms of different ADs and it is remarkable that none were of significant severity. In fact, patients with poly-autoimmunity frequently present milder clinical syndromes that can be controlled with medium-low intensity treatment, as in our case.

In conclusion, overlap syndromes comprise multiple individual ADs. Several individual cases of overlap have been reported in patients simultaneously suffering from up to three organ-specific ADs. While many studies in the previous decades were designed to investigate different multiple associations of autoimmune diseases, multicentric collaborations are needed to obtain definite results of the incidence of poly-autoimmunity [4]. Finally, better understanding of the complex gene-environment interactions involved in the development of ADs, together with the

study of epigenetics, are strongly suggested in order to personalize interventions for these severe conditions.

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