Three cases of systemic sclerosis with different antibodies and clinical features within one family

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Introduction

Systemic sclerosis (SSc) is a polygenic disorder and both genetic and environmental factors play a role in the pathogenesis of the disease.[1] Familial occurrence of SSc is uncommon and accounts for less than 2% of cases.[2,3] In previous reports familial cases tend to have similar autoantibodies and disease features.[4] HLA studies suggest that major histocompatibility complex (MHC) genes exert their influence primarily on autoantibody expression in SSc.[5] In addition, skin biology differences to anti-RNA polymerase III (ARA) and anti-topoisomerase antibodies (ATA) were studied suggesting both shared and antinuclear antibody (ANA) specific molecular drivers.[6] We hypothesize that the predisposition to develop SSc is hereditary, yet the phenotype and antibodies can vary. We present three cases of SSc within one family with different antibodies but with a typical antibody-associated phenotype to illustrate this.

Case 1

A Caucasian, 68-year old female was referred to our clinics with Raynaud's, arthralgia and skin thickening since one year. Her symptoms had progressed over time despite hydroxychloroquine and were accompanied with breathlessness, sicca symptoms, constipation, oesophageal reflux and weight loss. Her medical history included hypothyroidism and coronary artery disease. She was a retired hairdresser and former smoker. On examination she had diffusely distributed skin thickening (modified Rodnan skin score, mRSS of 26/51) and hyperpigmentation. She tested positive for ATA. Her lung function was deteriorated compared to 6 months earlier (FVC -18% and DLco -20%) and interstitial lung disease was confirmed on HRCT showing subpleural reticulation in the lower lobes and mild traction bronchiectasis. Vasoactive medication was optimised and mycophenolate mofetil (MMF) which was started two months earlier, was continued. After 9 months she presented with shortness of breath, atrial flutter and raised troponins (332ng/L). Cardiac MRI showed diffuse inflammatory non-ischemic myocardial changes with severe right and left ventricular dysfunction. A cardiac biopsy confirmed fibrosis and vasculopathy consistent with cardiac involvement. She was treated with two pulses of monthly intravenous cyclophosphamide, but sadly died of heart failure three months later.

Case 2

Her 48-year old daughter, also ex-smoker and hairdresser, presented simultaneously with widespread skin thickening (mRSS 28/51) and Raynaud's phenomenon. She also had a history of hypothyroidism. She had ARA and anti-Ro antibodies. Her lung function showed restrictive changes (FVC 108% and DLco of 68%) and an HRCT showed very mild lung fibrosis. She was started on MMF and vasoactive therapy including iloprost infusions for her Raynaud's with digital ulcers.Tocilizumab was added later in the context of a clinical trial, and was continued for two years. After trial completion she maintained on MMF. A year later she developed myositis (confirmed with EMG) for which she was treated with two doses of rituximab 1000mg intravenously. Five years after diagnosis she developed pulmonary arterial hypertension (mean pulmonary arterial pressure 35mmHg, pulmonary arterial wedge pressure 7mmHg, right arterial pressure 9mmHg) and was treated with tadalafil 40mg.

Case 3

Their 59-year old cousin also developed systemic sclerosis. She is an ex-smoker and had breast cancer 15 years ago, which was treated curatively. Her symptoms started 1.5 years ago with Raynaud's phenomenon followed by puffy fingers, sclerodactyly and dysphagia and esophageal reflex three months later. She was tested positive for anticentromere antibodies. She did not develop cardiopulmonary involvement and she is currently treated with calcium antagonists and a proton pump inhibitor.

Discussion

We describe three patients within one family who were diagnosed with SSc with different antibodies and clinical manifestations consistent with these antibody profiles (Table 1). Furthermore, the cases illustrate that both external factors i.e. exposure through occupation and smoking, as well as a genetic predisposition probably have played a role in the development of SSc.

In SSc, ANA subtypes have been demonstrated to be linked to clinical features as well as biologic pathways.[7,6] In literature most familial cases had similar clinical manifestations and autoantibodies. Also, the majority of these cases were ACA positive with limited cutaneous SSc.[4,8,9]

One report describes ATA positive dcSSc in a mother and daughter with similar clinical features and the HLA-DRB1*1104-DQA1*0501-DQB1*0301 haplotype, which is associated with ATA in Caucasians.[10] An American cohort of 18 multi-case families identified two families with two members with ATA positive dcSSc who had all similar disease manifestations related to ATA.[4] This study reported significant antibody concordance within each family. Six families had disconcordant autoantibodies, but only one family had both different antibodies (ACA and ATA) and matching subtypes (lcSSc and dcSSc, respectively) similar to our family.

HLA class II contributes strongly to SSc susceptibility, as was shown in a recent genome-wide genotyping study in 9095 SSc patients.[11] In this study a link between HLA class I and SSc was established as well, and associations between specific alleles, disease subsets (HLA-DQA1*02:01 with lcSSc, HLA-DQA1*05:01 with dcSSc) and antibodies were found, suggesting a different genetic basis for each autoantibody profile (HLA-DRB1*07:01 with ACA, HLA-DPA1*02:01 and HLA-DQB1*03:01 with ATA). The link between familial SSc and shared class II MHC antigens has been investigated in five Australian families with two affected members.[12] In this study, all patients had the same antibodies and identical HLA haplotypes and no common HLA haplotype between the different families was identified, which was confirmed in other reports.[13] This unique report of a multi-case family affecting three members with different autoantibodies and clinical features, supports the theory that the genetic background in SSc contributes to the risk of getting dcSSc but does not seem to define phenotype and related antibody profile.

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Table 1. Case characteristics

Case	Auto-antibodies	Clinical features	Environmental factors
1	ATA	RP, skin thickening (diffuse pattern), severe lung fibrosis, arthritis, cardiac disease	Smoking Hair dressing
2	ARA anti-Ro antibodies	RP, skin thickening (diffuse pattern), mild lung fibrosis, myositis, PAH	Smoking Hair dressing
3	ACA	RP, skin thickening (limited pattern), oesophageal reflux	Smoking

ACA: anticentromere antibodies, ARA: anti-polymerase III antibodies, ATA: anti-topoisomerase I antibodies, PAH: pulmonary arterial hypertension, RP: Raynaud's phenomenon.

Figure 1. Family tree with affected members.