CASE REPORT

Limited cutaneous systemic sclerosis arising in a patient with Graves' disease

Marc Gregory Yu,¹ John Paul Montinola Quisumbing^{1,2}

¹Department of Medicine, University of the Philippines—Philippine General Hospital, Manila, Philippines

²Section of Endocrinology, Diabetes and Metabolism, University of the Philippines—Philippine General Hospital, Manila, Philippines

Correspondence to

Dr Marc Gregory Yu, marcgreggy@yahoo.com

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SUMMARY

Although Graves' disease and systemic sclerosis are both autoimmune disorders, their relationship is rarely reported. We present the case of a Filipino woman with goitre and thyrotoxic signs and symptoms. Diagnosed with Graves' disease at the outpatient clinic, she took antithyroid medications and underwent radioactive iodine ablation with resultant hypothyroidism after 6 months, during which she began to experience skin tightness over the face, neck and fingers. Workup revealed limited cutaneous systemic sclerosis, and the patient improved with methotrexate. This case highlights the increased prevalence of coincident autoimmune disorders in Graves' disease.

BACKGROUND

Autoimmune thyroid diseases can be associated with other systemic autoimmune disorders. While the association of systemic sclerosis (SSc) with Hashimoto's thyroiditis has been well documented, its association with Graves' disease is rarely reported.¹ We describe the case of a Filipino woman who developed limited cutaneous systemic sclerosis (lcSSc) after undergoing radioactive iodine (RAI) ablation for Graves' disease.

CASE PRESENTATION

A 40-year-old Filipino woman presented at the outpatient clinic with a 5-year history of diffuse goitre, palpitations, heat intolerance, fine tremors and undocumented weight loss. Free thyroxine levels were high at 58.1 pmol/L (normal 11–24 pmol/L), while thyroid-stimulating hormone levels were low at 0.19 μ IU/mL (normal 0.3–3.8 μ IU/mL). Antithyroid peroxidase (anti-TPO) antibodies were positive. Thyroid scintigraphy and uptake studies showed a diffuse goitre with uniformly avid 2-hour and 24 hour uptake (31%, normal 5–12% and 49%, normal 20–45%, respectively). She was diagnosed as a case of Graves' disease and was started on methimazole 20 mg/day with improvement of symptoms. She subsequently underwent RAI ablation with a calculated activity of 9.9 mCi as definitive treatment.

Six months after RAI, the patient became hypothyroid and was prescribed levothyroxine replacement therapy with eventual restoration of euthyroidism. Around this time, she also began to have symptoms of skin tightening of the face and neck rendering limitation of movement. On physical examination, reduced facial mobility was demonstrated together with thinning of the upper lip and accentuation of central incisor teeth

(figure 1). A distinct salt-and-pepper pattern was observed at the neck area (figure 2). Taut skin was also observed at the pinnae and fingers of both hands, giving the latter a puffy appearance. Further examination did not reveal sclerodactyly, calcinosis, telangiectasia or Raynaud's phenomenon. The patient was referred to rheumatology with the consideration of SSc.

INVESTIGATIONS

The Modified Rodnan Skin Score (MRSS), a measure of skin thickening, was 16 on initial examination. Autoantibody testing revealed negative results for antinuclear antibodies (ANA) and anti-Scl 70; however, anticentromere antibodies were positive. Age-adjusted erythrocyte sedimentation rate (ESR) was slightly elevated at 27 mm/h (normal 0–25 mm/h). Although nailfold capillaroscopy was unremarkable, skin biopsy of the finger revealed excessive collagen deposition, deep fibrosis and perivascular lymphohistiocytic infiltration consistent with SSc. Further workup for target organ damage showed a normal haemogram, urinalysis, chest and hand radiograph, serum creatinine and fasting blood sugar (FBS) level. A two-dimensional echocardiogram with Doppler study did not show pulmonary hypertension, while spirometry and high-resolution chest CT with contrast did not detect interstitial lung disease. An oesophageal evaluation was also performed, revealing normal results.

TREATMENT AND OUTCOME

The patient was diagnosed with lcSSc and was started on methotrexate 7.5 mg weekly. After 10 months of treatment, she noted a subjective improvement in skin symptoms. The MRSS

Figure 1 Reduced facial mobility with thinning of the patient's upper lip and accentuation of central incisor teeth.

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Figure 2 Salt-and-pepper appearance of the neck.

decreased to 8 and the ESR decreased to 15 mm/h. She is currently on regular follow-up at the endocrinology and rheumatology outpatient clinics. An ophthalmological evaluation also ruled out the presence of concomitant Sjogren's syndrome.

DISCUSSION

Skin changes can occur in different endocrine diseases. Clinicians should be aware of these manifestations in order to distinguish them from other disease entities. In Graves' disease, the most prominent skin changes are non-pitting pretibial myxoedema ('dermopathy') and soft-tissue swelling of the hands and clubbing of the fingers ('acropachy'). These manifestations, however, are found in only 4–5% and 1% of patients, respectively, and were not observed in our patient during the course of her illness.^{2,3}

Our patient started to develop skin tightening of the face and neck—which is not typical of Graves' disease—6 months after she was already rendered hypothyroid from definitive RAI. The classic skin features, their persistence despite adequate levothyroxine replacement and the patient's autoimmune predisposition all led to the primary consideration of SSc. An important differential is scleredema. However, under this condition the hands and feet are spared; autoantibody titres are negative and the episode of skin tightness is usually preceded by an identifiable trigger such as diabetes (scleredema diabeticorum, ruled out by a normal FBS), or an acute infection (negative in the history and workup). Finally, skin biopsy presents a different picture of epidermal sparing, mucin deposition between collagen bundles in the dermis and the absence of a lymphohistiocytic infiltrate.⁴

While the literature regarding the association of autoimmune hypothyroidism and SSc has been robust, the association of Graves' disease with the latter has only been supported by a few reports. Most reported the occurrence of Graves' disease in patients with established SSc, with onset ranging from as short as 1 year to as long as 30 years.^{5–7} The first case of a Graves' disease patient developing SSc after RAI therapy was reported in the 1970s by Ward *et al*,⁸ who described a 45-year-old man developing diffuse systemic sclerosis (dcSSc) 5 months after RAI. A more recent report in 2009 described a 45-year-old woman also developing dcSSc 6 months after RAI.⁹ Both time frames were consistent with our patient.

Several studies further attempted to explain the association between the two conditions. One study comparing the thyroid

status of female patients with and without SSc found three cases of Graves' disease in those with SSc versus zero in controls, which was statistically significant.¹ Another study involving a cohort of more than 1000 patients with systemic autoimmune disease estimated the overlap between SSc and Graves' disease to be around 2%.¹⁰ Because our patient tested positive for anti-TPO (which is present in over 90% of Graves' disease cases), we also looked at the association between anti-TPO and autoimmune skin disorders.¹¹ Kasumagic-Halilovic *et al*¹² found a significantly higher frequency of anti-TPO in patients with vitiligo versus healthy persons. Similar findings were likewise observed in patients with alopecia areata compared to controls.¹³

The exact pathogenesis linking Graves' disease and SSc, however, remains unknown. A genetic basis has been suggested due to the observed familial clustering of autoimmune phenomena and the conferment of certain genes such as the HLA family to autoimmune susceptibility.¹⁴ Furthermore, the Th-1 lymphokine profile in patients with thyroid disease, under the combined action of genetic and environmental conditions, has been implicated in the involvement of multiple organs resulting to a wide spectrum of immune-mediated disorders.¹⁵

We also considered whether the occurrence of lcSSc in our patient could have been precipitated by RAI alone. Although no data exist regarding this possible association, a paradoxical worsening of thyrotoxicosis and autoimmunity has been reported after RAI in some patients, especially those with Graves' ophthalmopathy. This phenomenon has been explained by the release of preformed thyroid hormones and autoantibodies into the bloodstream following RAI-mediated destruction of the thyroid gland.¹ It has also been associated with increased levels of peripheral blood lymphocytes (CD3+, CD4+ and CD3+ HLA-DR+), which are instrumental in the pathogenesis of SSc.¹⁶ However, the absence of active eye disease in our patient plus the complete resolution of her hyperthyroid state after RAI both make this theory less likely.

The approach to SSc patients involves categorising whether they fall under lcSSc or dcSSc. The former is characterised by positive anticentromere antibodies, an indolent onset and a benign course and organ involvement generally limited to the skin. A special type of lcSSc is the calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia (CREST) syndrome, whose features were absent in the patient. Meanwhile, dcSSc is characterised by positive anti-Scl 70 antibodies, a rapid onset and multiorgan involvement, emphasising the importance of an exhaustive workup and prompt treatment.¹⁷ Having been diagnosed with lcSSc, our patient readily improved with methotrexate alone, as evidenced by improvement of skin symptoms and a decrease in the MRSS and ESR. This is consistent with the literature showing a general amelioration in the course of Graves' disease and SSc with treatment of either condition, which has been attributed to attenuated autoimmunity.^{8,9}

Given the rarity of the association between Graves' disease and SSc, the presence of both conditions in a single patient can still be due to chance alone. Even so, our case highlights the importance of a comprehensive workup for coincident autoimmune disorders in patients with Graves' disease. It is the first documented report in Southeast Asia, which is significant given the geographical differences in autoimmune characteristics and iodine intake.

Learning points

- ▶ Clinicians should be aware of the different skin manifestations in endocrine disease.
- ▶ There is an increased prevalence of coincident autoimmune disease in patients with Graves' disease.
- ▶ To date there is still limited knowledge on the association between Graves' disease and SSc, as well as between RAI and SSc.

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Contributors MGY and JPMQ were responsible for writing the manuscript draft.

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