A Case of Unilateral Dermopathy Possibly Related to Graves' Disease

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What Is Known about this Topic?

- Thyroid dermopathy is a rare extrathyroidal manifestation of Graves' disease (GD). It is usually bilateral, but monolateral variants can be observed. As for Graves' orbitopathy, the most common extrathyroidal manifestation of GD, the pathogenesis is believed to reflect autoimmunity against antigens constitutively expressed by the thyroid and by the extrathyroidal affected tissues. According to another hypothesis, soluble antigens released from the thyroid would reach the affected tissues, thereby becoming the target of an autoimmune reaction. In the latter case, gravity may play a role in the deposition of these antigens.

What Does This Case Report Add?

- The observation of a patient with GD with a monolateral dermopathy affecting the ipsilateral leg and hand on the side of his body he preferentially slept laying on supports the hypothesis that soluble antigens released from the thyroid may possibly be responsible for this extrathyroidal manifestation of GD, at least in this particular patient, provided dermopathy is actually related to GD. Whether or not this were the case, our observation would increase our knowledge on the pathogenesis of the extrathyroidal manifestations of GD.

Keywords

Graves' dermopathy · Pretibial myxoedema · Graves' orbitopathy · Graves' disease · Thyroid · Autoimmunity

Abstract

Background: The pathogenesis of the extrathyroidal manifestations of Graves' disease (GD) is not fully clarified. According to the most common hypothesis, they would reflect

an autoimmune reaction against antigens constitutively expressed by the thyroid and by the extrathyroidal affected tissues. According to another hypothesis, the so-called Kriss' hypothesis, soluble autoantigens released from the thyroid would reach the affected tissues, where they would become the target of the immune system. In this regard, a shift in gravity during sleep may favour antigen deposition. **Case Report:** A 59-year old man with GD came to our observation because of a dermopathy. He had been treated with radioac-

tive iodine for Graves' hyperthyroidism and with glucocorticoids and orbital decompression for a bilateral Graves' orbitopathy (GO). The patient complained of a monolateral, untreated dermatopathy, affecting the left leg and hand. At physical examination the skin of the left pretibial area and of the dorsal surface of the left hand appeared red and thickened, with an orange peel aspect. Interestingly, the patient reported that he usually slept laying on the left side of his body. **Discussion:** The observation of a patient with a monolateral dermatopathy somehow reports to the Kriss' hypothesis, especially in view of the patient's habit of sleeping on the same side as dermatopathy was present. Of course, this does not represent a proof that the Kriss' hypothesis is correct, but it carries an element in favour of it. The fact that GO was bilateral is somehow against it, but does not exclude this possibility.

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Introduction

Extrathyroidal manifestations of Graves' disease (GD) include Graves' orbitopathy (GO), which is observed in approximately 30% of patients [1, 2], and more rarely a localized dermatopathy called Graves' dermatopathy or pretibial myxoedema [3, 4]. Even more rarely, a condition known as Graves' acropachy can be present [3, 4]. Der-

mopathy is characterized by one or more restricted and delimited areas of skin thickening, with a coloration from red to brown [3]. Patients may complain of pruritus and rarely with pain. In most cases, Graves' dermatopathy is localized in the pretibial area, but skin lesions can be less commonly observed also on the feet, toes and upper extremities, as well as in the forehead and ear [3]. In the most severe, proliferative forms, the skin can assume an elephantiasic appearance. Treatment of Graves' dermatopathy is based on the use of local steroids. Whereas the non-proliferative, fortunately most common, variants respond successfully, the proliferative variants respond poorly [3]. Systemic steroids or other immunosuppressive medications, as well as surgery, have also been used, but no clear data on the outcomes are available.

The pathogenesis of the extrathyroidal manifestation of GD is not fully clarified. According to the most common hypothesis, they would be the consequence of an autoimmune reaction against antigens constitutively expressed by the thyroid and by the extrathyroidal affected tissues, with the TSH receptor being the most suitable candidate [5]. According to another hypothesis concerning GO, also known as the Kriss' hypothesis, soluble autoantigens released from the thyroid would reach the orbit through a retrograde route, where they would become the target of the immune system, thereby eliciting the development of GO [6]. A similar mechanism may in theory also account for Graves' dermatopathy.

Fig. 1. **a** Picture of the legs of a 59-year-old man with a monolateral Graves' dermatopathy. The skin of the right leg is normal. The pretibial skin of the left leg is red and thickened. **b** Picture of the hands of the same patient. The skin and the dorsal surface of the left hand are red and thickened with an orange peel aspect. The right hand is normal.

Fig. 2. **a** Alcian blue staining of a tissue specimen taken at surgery from a 59-year-old man with a monolateral dermopathy. No mucin deposition between collagen bundles can be observed. **b** Hematoxylin and eosin staining. Fibroadipose tissue is present, with a moderate, focal, inflammatory infiltrate, predominantly composed of lymphocytes. CD20 (**c**) and CD3 (**d**) immunostaining showing that the lymphocytic infiltrate is composed of both B cells (CD20-positive) and T cells (CD3-positive), with a predominance of B cells and a few scattered T cells. **a–d** Original magnification $\times 100$.

Case Report

An otherwise healthy, 59-year-old man came to our observation because of a possible Graves' dermopathy. He had been affected with Graves' hyperthyroidism since 1988, for which he had been treated with methimazole for 8 years, and then with radioactive iodine (in 1996), with consequent hypothyroidism, for which he was on L-thyroxine 150 $\mu\text{g}/\text{day}$. He reported the appearance of bilateral eye symptoms simultaneously with Graves' hyperthyroidism, for which he had been treated with oral glucocorticoids (given as coverage at the time of radioiodine treatment), and then with intravenous methylprednisolone pulse therapy, given in three separate cycles (1988, total dose 6 g; 2010, total dose 3 g; 2017, total dose 1 g). In addition, he had been

treated with orbital decompression on two occasions: the right eye was operated in 2008, whereas the left eye was operated in 2014. The reason for the different timing of orbital decompression in the two eyes was unclear. In 2011, the patient noticed the appearance of a dermopathy in the left leg and hand, for which he had not received any treatments, and that was still present when he came to our observation in February 2018. At physical examination the skin of the left pretibial area (Fig. 1a) and of the dorsal surface of the left hand (Fig. 1b) appeared red and thickened with an orange peel aspect. Interestingly, the patient reported that he usually, if not exclusively, slept laying on the left side of his body. We prescribed topical therapy with beclomethasone dipropionate and recommended him to undergo a follow-up visit 3 months later. However, the patient did not come for

the follow-up visit, and when we contacted him by phone, approximately 4 months after our first observation, he reported that he had undergone hand surgery somewhere else. We therefore asked him to send us the histological specimens removed at surgery, including slides already stained with hematoxylin and eosin. Then, further examinations were performed by our pathologists, including Alcian blue staining and immunohistochemistry for CD3 (a T-cell marker) and CD20 (a B-cell marker). As shown in Figure 2a, Alcian blue staining failed to demonstrate the presence of mucin deposition between collagen bundles, which is somehow against a diagnosis of thyroid dermopathy, in which the presence of glycosaminoglycans is expected [3, 4]. On the other hand, there was a focal lymphocytic infiltration (Fig. 2b), comprising both CD20-positive cells (Fig. 2c) and CD3-positive cells (Fig. 2d) within fibroadipose tissue, a picture quite similar to the one reported in GO [7]. Overall, the findings seem to indicate the presence of an autoimmune dermopathy, possibly related to GD.

One interesting feature in our patient was the relatively long interval (approx. 23 years) that elapsed between the occurrence of Graves' hyperthyroidism and the appearance of the dermopathy. We postulated that the late appearance of the dermopathy could be the consequence of a rise in autoimmunity against the responsible autoantigens, possibly the TSH receptor. To investigate this possibility, we collected all the measurements of serum autoantibodies against the TSH receptor (TRAb) performed over the years. As shown in Figure 3, only 4 measurements were available. Whereas in the period between 1997 and 1998, namely 1 and 2 years after radioiodine, serum TRAb were undetectable, TRAb levels were relatively high in 2017, approximately 6 years after the appearance of the dermopathy and approximately 1 year before our observation. If this surge in autoimmunity against the TSH receptor had initiated a few years before, it could explain the late appearance and then the persistence of the dermopathy, provided the dermopathy was actually related to GD.

Discussion

In the early 1970s Joseph P. Kriss formulated one of the most intriguing hypotheses to explain the pathogenesis of GO [6]. He postulated that the initiating event would be the deposition and accumulation in the orbit of one or more soluble antigens constitutively expressed in the thyroid gland, following their massive release, as occurs during thyrotoxicosis or after radioiodine treatment [6]. According to this hypothesis, once in the orbit, the above-mentioned antigen/s would trigger an autoimmune reaction. Because of its abundance within the thyroid and its solubility, the most suitable candidate was thyroglobulin (Tg), and a few studies showed its presence in orbital tissues from GO patients, although no pathogenetic role of Tg was demonstrated [6, 8, 9]. Interestingly, Kriss was convinced that the shift in gravity between the thyroid and the orbit during sleep

Fig. 3. Serum antibodies against TRAb measured over the years in a 59-year-old man with a monolateral dermopathy.

might have favoured a retrograde flow of lymph and, therefore, of thyroid antigens [10]. On the other hand, Wiersinga et al. [11] failed to demonstrate that GO is related to the sleeping position. Our observation of a patient with a monolateral dermopathy, possibly related to GD, somehow reminds of the hypothesis of Kriss, especially in view of the patient's habit of preferentially sleeping on the same side where dermopathy was present. Of course, this does not represent a proof that the Kriss' hypothesis is correct, but it certainly carries an element in favour of it. The fact that GO was not monolateral is somehow against it, but does not exclude this possibility.

Whether dermopathy in our patient is to be considered part of GD is somehow questionable. Thus, Alcian blue staining did not show the presence of mucin, which is typical of thyroid dermopathy [3, 4]. On the other hand, the presence of a focal lymphocytic infiltration comprising both B and T cells militates in favour of a diagnosis of an autoimmune dermopathy, which, in view of its association with Graves' hyperthyroidism and GO, was in our opinion likely to be related to GD.

A peculiar feature of our patient is the long interval between the occurrence of Graves' hyperthyroidism and the appearance of the dermopathy. A surge in autoimmunity against the TSH receptor, testified by a possible late increase and then a persistence of high levels of serum TRAb, may be an explanation for this observation, provided the dermopathy was actually related to GD.

Statement of Ethics

All diagnostic and therapeutic procedures were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the individual participant included in the study.

Disclosure Statement

The authors have no conflicts of interest.

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