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Case report

A case of multiple autoimmune syndrome comprising autoimmune thyroid disease, vitiligo, morphea, and lichen sclerosus

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Abstract

Multiple autoimmune syndrome is a manifestation of polyautoimmunity with the co-occurrence of three or more autoimmune diseases in a single patient. We report a unique case of a 55-year-old female patient that presented with four autoimmune diseases: autoimmune thyroid disease, vitiligo, morphea, and lichen sclerosus. She was evaluated for progression of morphea and lichen sclerosus, and we confirmed histopathological overlapping of these two diseases in the same lesion. We discuss the increasing prevalence of autoimmune diseases and similar case reports on dermatological polyautoimmunity.

Keywords: multiple autoimmune syndrome, polyautoimmunity, vitiligo, lichen sclerosus, morphea

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Introduction

Autoimmune diseases (ADs) are a heterogeneous pathology characterized by abnormalities in both humoral and cell-mediated immunity, resulting in their assault on normal bodily constituents, which leads to inflammation, cell injury, or a dysfunction with clinical manifestations in specific target organs (1). Historically perceived as rare, epidemiological revelations over the last two decades, particularly in Western countries, show a rise in the global prevalence of ADs (2–4). A recently published British population–based study highlights this trend, indicating that ADs afflict nearly 10% of the population, with an average age of onset at 54 years and a female predilection (2:1) (5). Predominant among these diseases are autoimmune thyroid disorders and type 1 diabetes, followed by systemic lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis, celiac disease, and inflammatory bowel diseases (3, 6). Globally, Graves' disease, celiac disease, and rheumatic disorders have witnessed the most substantial increases in incidence (5). Autoimmune skin disorders, comprising vitiligo, psoriasis, alopecia areata, bullous diseases, and systemic lupus erythematosus, have similarly experienced an escalating path (7). With genetic factors remaining constant, detailed scrutiny has shifted toward exploring environmental influences as potential contributors to the increasing prevalence of ADs. Ongoing evidence points to significant alterations in diet, xenobiotics, air quality, infections, personal lifestyles, stress, and climate change as factors precipitating the surge in AD incidence (8).

Polyautoimmunity (PAI) is defined as the presence of more than one AD in an individual. PAI can be overt (fulfilling clinical criteria) or latent (presence of unrelated autoantibodies without clinical criteria fulfilment of the AD), and it can affect one or more organ systems. Various ADs tend to cluster together in specific patterns, suggesting shared genetic susceptibility traits (5). However, the clinical relevance within these clusters of ADs remains unclear (particularly in terms of management and outcome). PAI occurs in 25% to 34% of individuals with ADs, and familial autoimmunity, especially in females, is a predisposing factor for PAI. The observed female predilection is attributed to hormonal fluctuations and genetic disparities—both

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direct (i.e., influence of genes on sex chromosomes) and indirect, such as microchimerism—alongside sex-specific lifestyle distinctions (9, 10).

When three or more ADs coexist, the condition is called multiple autoimmune syndrome (MAS), categorizable into three types according to the prevalence of their associations with one another. This classification proves helpful, particularly when signs of a third disorder emerge. Individuals with MAS often have multiple autoantibodies, some of which are organ-reactive. Although the pathogenesis remains elusive, genetic, infectious, immunologic, and psychological factors are implicated, leading to theorizing that environmental triggers in genetically susceptible individuals precipitate dysregulation of immune processes (9). Of particular interest is the observation that patients manifesting MAS frequently exhibit at least one dermatological condition, typically comprising vitiligo, alopecia areata, psoriasis, or morphea. In many reported cases of MAS, vitiligo is the first AD to be diagnosed, demonstrating a bilateral and symmetrical presentation. Concurrently, autoimmune thyroid disease tends to coexist in these instances. The manifestation of one AD often serves as a sign, guiding the discovery of additional autoimmune conditions. Research also highlights the occurrence of overlap syndromes in varied combinations, although the simultaneous coexistence of five or more ADs proves exceedingly rare (9).

Case report

A 55-year-old female with a longstanding medical history of autoimmune thyroid disease (15 years), chronic gastritis (9 years), symmetric vitiligo (5 years), and morphea (2 years) presented to our dermatology clinic due to the progression of her morphea on the abdomen and the emergence of depressed brownish macules on her right upper arm and right calf, as well as a burning whitish patch over her right scapula. Her regular therapeutic regimen consisted of systemic sodium levothyroxine and esomeprazole. It is noteworthy that her mother also experienced autoimmune thyroid disease.

Upon physical examination, we observed symmetrical vitiligo on her face, arms, and knees, affecting approximately 5% of the body surface area (Fig. 1). Sclerotic plaques, characteristic of morphea, were observed on her abdomen, accompanied by purplish red halos (Fig. 2). In addition, two suspicious brownish depressed macules, indicative of deep morphea, were identified on her right upper arm and right calf (Fig. 3). Above her right scapula, a well-defined whitish atrophic patch measuring approximately 6 × 4 cm was observed (Fig. 4). Laboratory testing, including a complete blood count, urea, creatinine, liver tests, urine C-reactive protein, thyroid-stimulating hormone, thyroid hormones (T3 and T4), and thyroglobulin, were all within normal ranges. However, her anti-thyroid peroxidase antibodies were found to be elevated at 185 IU/ml (normal value < 35 IU/ml). Antinuclear antibodies and antibodies against *Borrelia burgdorferi* (IgG and IgM) were negative.

Further histopathological examination of the depressed lesion located on her right upper arm confirmed the diagnosis of morphea through the presence of a perivascular infiltrate comprising lymphocytes and plasma cells, dermal sclerosis, and collagen homogenization. In addition, examination of the skin lesion above her right scapula revealed concurrent occurrence of morphea and lichen sclerosus within the same lesion (Fig. 5). Lichen sclerosus was characterized by the thickening and homogenization of collagen bundles in the papillary and reticular dermis, along with follicular plugging, hyperkeratosis, epidermal atrophy, and basal cell hydropic degeneration.

We initiated treatment with daily application of topical betamethasone ointment for a duration of 3 months. Given the progression of the conditions, we subsequently injected intralesional triamcinolone acetonide into the edges of the morphea and lichen sclerosus lesions, administering 40 mg per session thrice, with a 1-month interval between sessions. Afterward, we commenced narrowband UVB phototherapy at a frequency of three times weekly, spanning 30 sessions. Remarkably, this comprehensive therapeutic approach resulted in the stagnation of her morphea, lichen sclerosus, and vitiligo.

Discussion

ADs may frequently evolve from a single diagnosis and over the years develop into PAI and even MAS in the same patient because new clinical symptoms and laboratory findings emerge over time (11). MAS best illustrates that PAI is more than a coincidence, emphasizing the shared pathogenesis of several ADs, including similar clinical signs and symptoms, pathophysiological mechanisms, and genetic factors within AD and aggregation of diverse ADs within families (autoimmune tautology). Conflicting perspectives exist on whether the coexistence of ADs contributes to a more severe disease course (12).

We present what we believe is an extraordinary case of a patient with MAS, initially diagnosed with autoimmune thyroid disease, which later developed into a spectrum of three dermatological ADs (vitiligo, morphea, and lichen sclerosus). Autoimmune thyroid disease, being the first manifested AD in our patient, is the most prevalent AD globally, affecting 4.8% to 25.8% of women and 0.9% to 7.9% of men (13). According to a meta-analysis by Botello et al., overt PAI was found in 13.5% of patients with autoimmune thyroid disease, whereas latent PAI was present in 17.5% of these patients, mainly involving type 1 diabetes, autoimmune gastritis, pernicious anemia, celiac disease, rheumatoid arthritis, and vitiligo (14). A study by Gupta et al. described 10 MAS cases involving multiple dermatological autoimmune disorders. These cases included individuals with three, four, or even five coexisting autoimmune diseases, such as alopecia areata, vitiligo, lichen planus, type 1 diabetes mellitus, and autoimmune thyroid disease. Among these cases, autoimmune thyroid disease was the most commonly observed (15).

Over a decade, our patient's autoimmune thyroid disease progressed to vitiligo, a disorder frequently associated with both cutaneous (alopecia areata, morphea, and pyoderma gangrenosum) and non-cutaneous ADs (type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroiditis), especially in females and older patients (16). The peak incidence of vitiligo seems to be in the second and third decade, but it can appear at any age. The approximate prevalence is 0.1% to 2% of the population (17). A recent study by Rios-Duarte et al. reveals that 17.7% of vitiligo patients have at least one AD comorbidity, with 0.69% of patients having MAS. The most prevalent autoimmune comorbidities in vitiligo cases include type 1 diabetes (4.5%), rheumatoid arthritis (2.8%), and systemic lupus erythematosus (2.5%) (16).

The concurrence of autoimmune thyroid disease and vitiligo is explained by a hypothesis linking excessive reactive oxygen species to the destruction of melanocytes and thyrocytes. About 34% of vitiligo patients exhibit positive thyroid antibodies, indicative of latent PAI (18). This discovery bears clinical significance for practitioners engaged in surveillance of these patients (19).

Subsequently, after a span of 13 years from the initial diagnosis of autoimmune thyroid disease, morphea emerged as the third AD in our patient's clinical profile. This is an uncommon fibrotic disorder, primarily affecting the dermis with possible spread to underlying tissues. Two incidence peaks are noticed: between 2 and 14 years and in the fifth decade of life, primarily in women (female-to-male ratio 4:1). Total annual incidence ranges from four to 27 new cases per million people. Certain stimuli may trigger vascular and immune dysregulations in genetically predisposed individuals. A rare combination of plaque and the deep type of morphea, which was observed in our patient, is strongly associated with familial ADs (20). Furthermore, the coexistence of morphea and segmental vitiligo within the framework of PAI has been documented, especially in the pediatric population. Notably, these lesions often follow a Blaschko linear distribution, suggesting genetic mosaicism (21). Dervis et al. reported another instance of MAS characterized by the combination of morphea, vitiligo, and autoimmune thyroid disease (22). We observed a similar combination of autoimmune disorders in our patient, along with the additional presence of lichen sclerosus, and we classified this case as overlapping type 2 and 3 MAS (9).

Of particular interest in our patient's clinical case is the manifestation of a whitish atrophic patch on the scapula, histopathologically exhibiting features characteristic of both morphea and lichen sclerosus. Distinguishing between the two can be difficult, but elucidating the clinical nuances of the biopsy site (distinguishing an inflammatory border from a sclerotic center) offers valuable insights to pathologists, providing an optimal clinicopathological correlation (23). The literature highlights the convergence of clinical and histopathological attributes between morphea and lichen sclerosus, speculating they may represent different features along a shared disease spectrum (24). PAI comprising morphea and lichen sclerosus has been well documented in numerous clinical instances, presenting a formidable challenge in clinical and dermoscopic differential diagnoses of lichen sclerosus (25). Although the etiology of both conditions remains

largely unknown, some cases show differentiation based on genetic predispositions (particularly involving predisposing HLA alleles) and environmental triggers (i.e., infection with *Borrelia burgdorferi*). The prevalence of genital lichen sclerosus is higher in patients afflicted with morphea, leading some scholars to consider lichen sclerosus to be the genital manifestation of morphea (26). However, our patient denied any symptoms or lesions of the anogenital region.

Lichen sclerosus, which was the final AD observed in our patient, is an inflammatory mucocutaneous condition predominantly affecting anogenital areas; however, the extragenital type can affect any site on the skin and mucosa, especially the neck, shoulders, thighs, and oral cavity. Two incidence peaks are characteristic, correlating with hormonal status (in premenarchal girls and menopausal women, both linked to a low estrogen status). Consequently, women are most commonly affected (female-to-male ratio 3:1 to 10:1). The estimated incidence of lichen sclerosus in both sexes is 0.1% to 0.3%. The underestimation of prevalence and incidence highlights the challenges in recognizing and diagnosing this AD, often leading to the condition being misdiagnosed or overlooked (27). Similar MAS comprising lichen sclerosus, vitiligo, and autoimmune thyroid disease has been discussed by Kim et al. It has been observed that both nonsegmental vitiligo and lichen sclerosus can exhibit the Koebner phenomenon, wherein mechanical stimulation can induce symptoms in genetically susceptible individuals (28).

Although patients with MAS often exhibit multiple autoantibodies (9), antinuclear antibodies in our patient were absent, and this led us to forgo broader serological screening for potential latent autoimmune diseases. We deemed it questionable to attribute clinical significance to positive autoantibodies in the absence of symptoms or signs of associated disorders.

In recent decades, there have been significant changes in the treatment of ADs. Previously, corticosteroids and conventional immunosuppressant drugs such as methotrexate and azathioprine were used to alleviate symptoms of ADs. The exact mechanisms behind ADs are not fully understood, but knowledge about B-cell and T-cell subsets and cytokine environments provides promising treatment prospects. The field of drugs targeting immune-mediated diseases is rapidly evolving, including various biologic agents, and many drugs in development and clinical trials (29, 30). Our patient's autoimmune thyroid disease was being managed through thyroid hormone replacement therapy, while her vitiligo remained stable and relatively non-disturbing. Our primary therapeutic goal was to halt the progression of symptomatic lichen sclerosus and morphea. To achieve this, we employed a combination of intralesional triamcinolone and narrowband phototherapy. This therapeutic approach managed to achieve stagnation of the lesions, but not regression. In the event of significant deterioration in any of the cutaneous ADs, systemic corticosteroids and methotrexate would be considered as treatment options.

Conclusions

We present a compelling case of a patient diagnosed with MAS, primarily exhibiting cutaneous ADs. Considering the escalating global incidence of ADs, it is plausible that we will encounter a surging prevalence of MAS and PAI in clinical practice. In light of this prediction, we emphasize the importance of long-term clinical surveillance for patients affected by PAI because it allows the ongoing monitoring of existing ADs and facilitates the prompt identification of any newly emerging ones based on clinical, serological, and relevant auxiliary diagnostic measures as well as incorporation of multidisciplinary management.

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Figure 1. Symmetrical, sharply defined depigmented macules present on the hands, knees, and face: vitiligo.

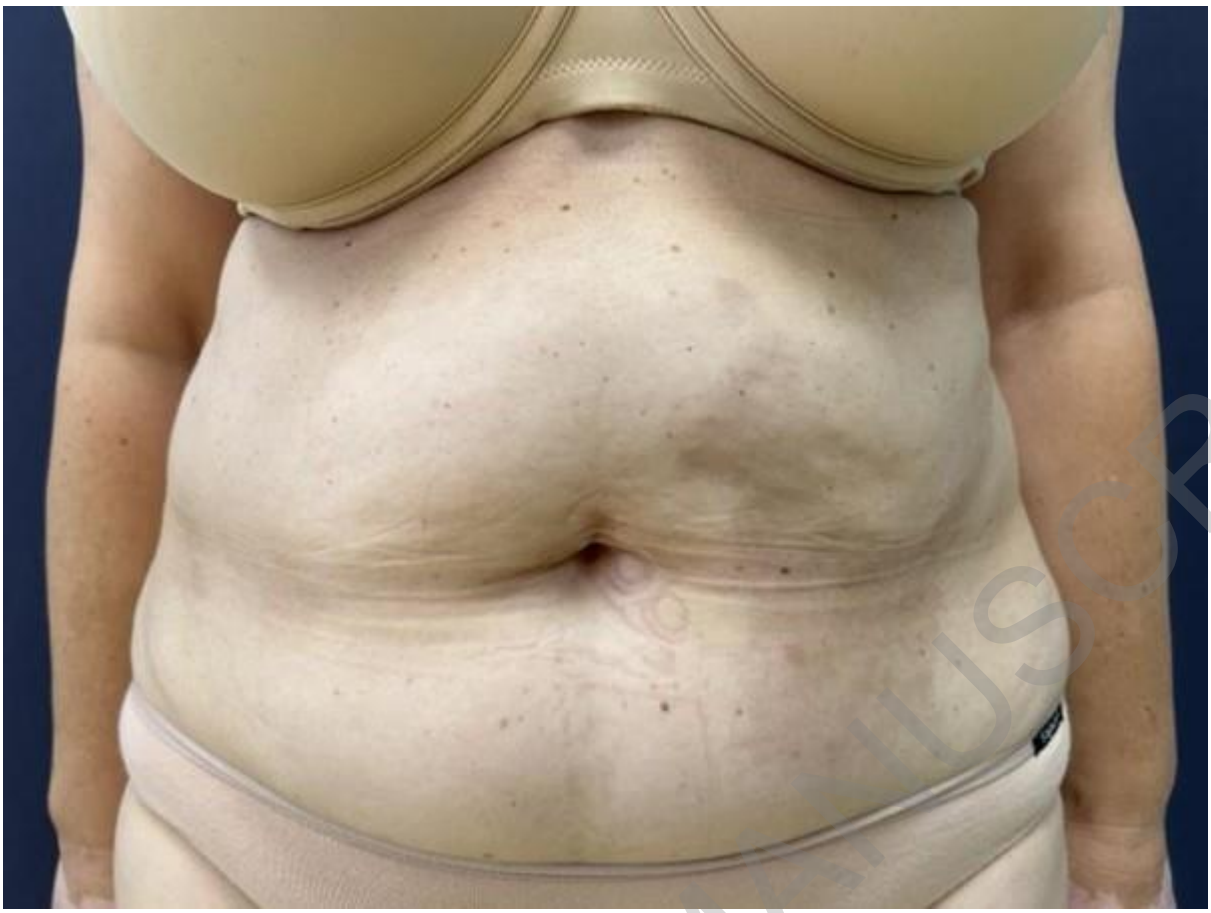

Figure 2. Sclerotic plaques surrounded by lilac halos on the abdomen: plaque morphea.

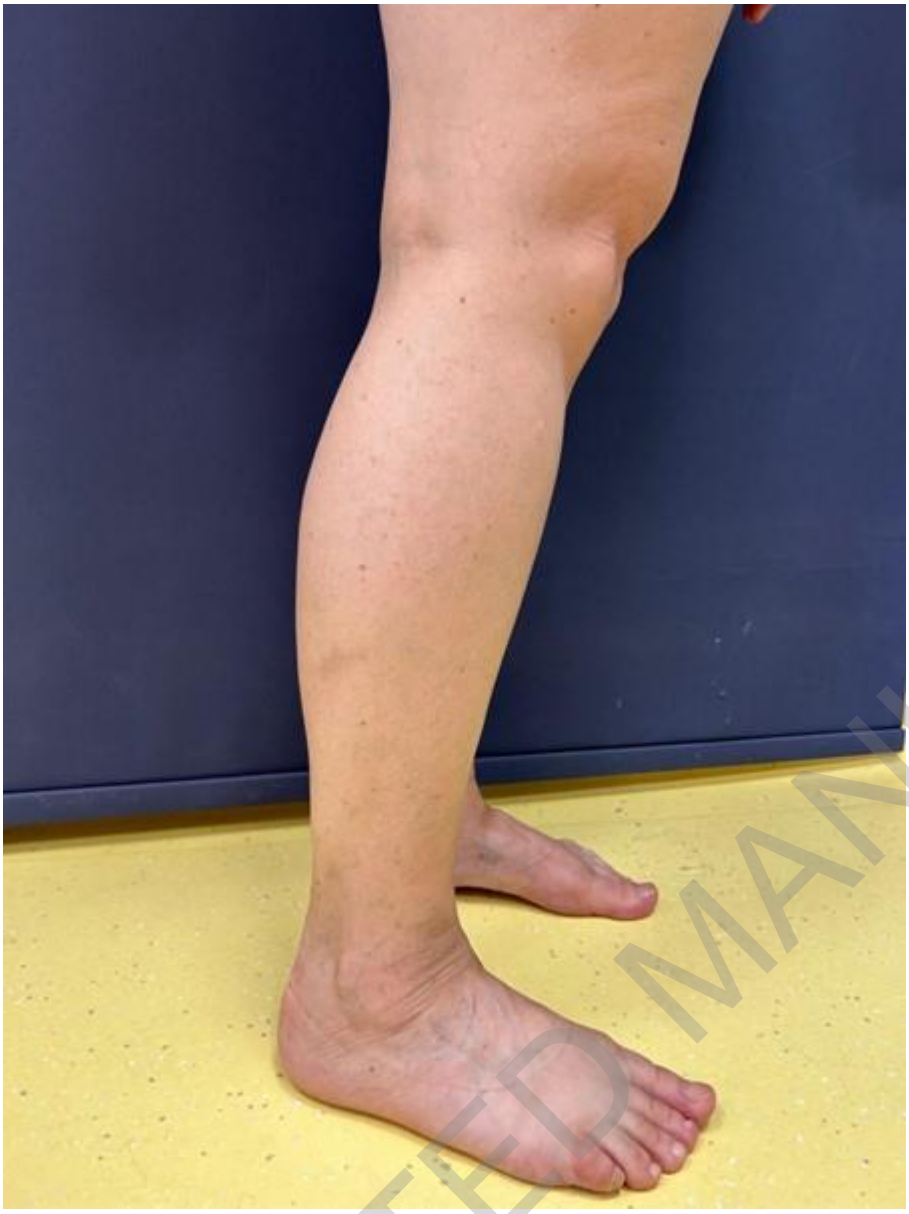

Figure 3. Depressed brownish macule on the patient's right calf: deep morphea.

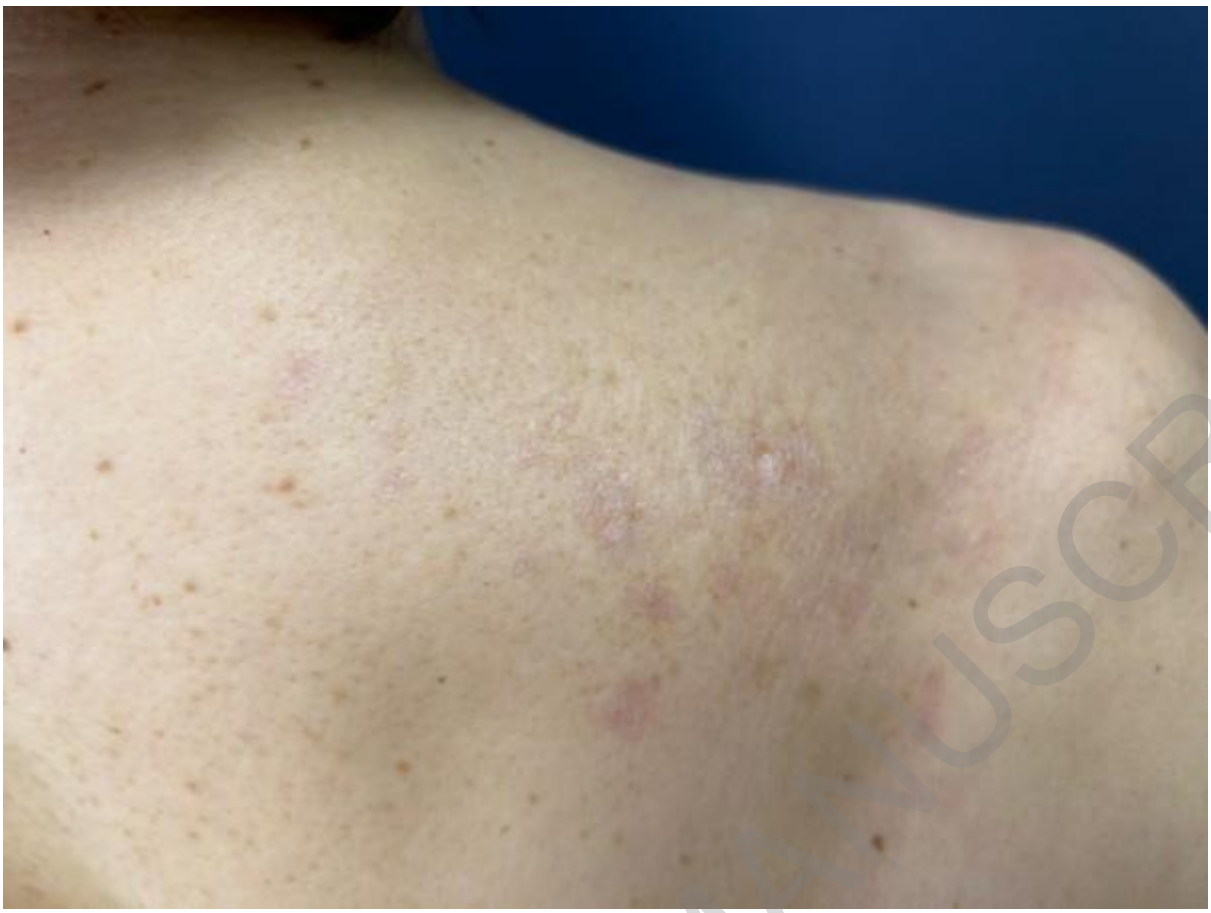

Figure 4. Sharply bordered whitish atrophic patch above the right scapula: clinical diagnosis of lichen sclerosus.

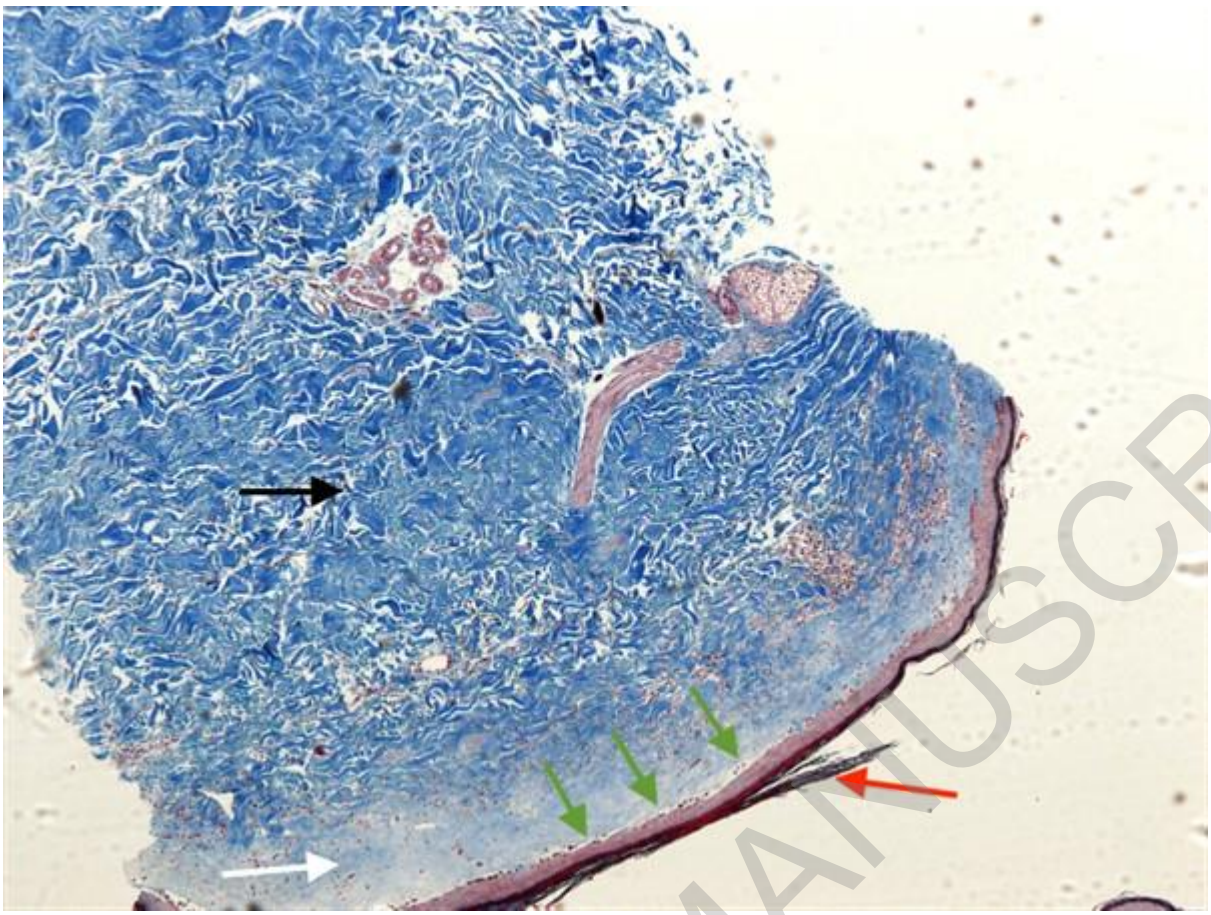

Figure 5. Histopathology of the skin lesion above the right scapula shows co-occurrence of lichen sclerosus and morphea in the same lesion. Using trichrome blue staining, lichen sclerosus appears in a lighter blue shade (white arrow) and morphea appears in a darker blue shade (black arrow). Morphea histopathologically shows a perivascular infiltrate composed of lymphocytes and plasma cells. Thickened and homogenized collagen bundles at the papillary and reticular dermis are seen, similar to the histopathological characteristics of lichen sclerosus. Lichen sclerosus also shows hyperkeratosis (red arrow), epidermal atrophy, and basal cell hydropic degeneration (green arrows).