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Diagnostic dilemma: Multiple Autoimmune Syndrome versus incomplete Graham-Little-Piccardi-Lassueur Syndrome overlap mixed connective tissue disease

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ABSTRACT

Objectives. We present a very rare case of incomplete Graham-Little-Piccardi-Lassueur syndrome (GLPLS) overlap with Mixed Connective Tissue Disease (MCTD) versus Multiple Autoimmune Syndrome (MAS).

Case Presentation. A 53- year-old female with a long history of more than two years of patchy hair loss on scalp like "footprints in the snow", partial loss of eyebrows' hair, face erythema, scaly atrophied red/brown patches on face, grouped follicular papules 2-3 mm in diameter with a pointed or hair-like horny spine extending approximately 1-2 mm around the tip of the follicle on lumbar area. The histopathological results from biopsies of scalp and lumbar areas confirmed the clinical diagnosis of cicatricial alopecia induced by lichen plan pilaris (LPP) and also presence of lichen spinulosus (LS) on lumbar area. The description provided by pathologist is however borderline regarding so called interface dermatosis like chronic cutaneous lupus erythematous (CCLE) or Pseudopelade of Brocq (PPB) as the end stage of CCLE or LPP. Blood tests showed both Antinuclear antibodies and U1-nRNP in high titers and the absence of anti-Sm, anti SS-A, anti SS-B and anti-dsDNA antibodies, and also peculiar antibody patterns of MCTD.

Outcome. After thorough investigation, MCTD was proven by antibodies results. After one year of treatment a lot of clinical features dramatically responded under therapy.

Conclusions. Clinical manifestations in the pathology with strictly cutaneous or systemic localization in conjunction or overlap with other autoimmune diseases (grouped in the MAS) represent a rare diagnostic in daily practice.

Keywords: Graham Little-Piccardi-Lassueur Syndrome, lichen planus, systemic lupus erythematosus, Mixed Connective Tissue Disease, Multiple Autoimmune Syndrome

INTRODUCTION

LPP is also known as lichen follicularis or follicular lichen planus. LPP has been subdivided into 3 variants: classic LPP, frontal fibrosing alopecia (FFA), and GLPLS. In 17 to 28% of cases, to 50% of cases, lichen planus (LP) can be observed on other parts of the body. [1] Differentiation from discoid lupus erythematosus (DLE) is more difficult. Although LPP and DLE can be seen in the same patient, in our experience this is very rare. PPB, which can be considered as end-stage LPP and CCLE, may leave the clinical appearance of "footprints in the snow." If most of the lesions of PPB are old and the LPP is not expanding with perifollicular inflammation and hyperkeratosis, it is impossible to distinguish PPB from LPP [2].

GLPLS is an illness that mainly affects middle-aged Caucasian women with an average age of onset varying from 30 to 70 years old. Scalp alopecia often precedes the follicular eruption of horny papules (even years before). Histology of the papules is frequently lichenoid. Histology of the scalp lesions usually shows a pseudopeladic stage of cicatricial alopecia; however, it may not be recognized. The syndrome can be associated with an eruption of LP or LPP of the body hair, especially of the pubic and axillary regions [2].

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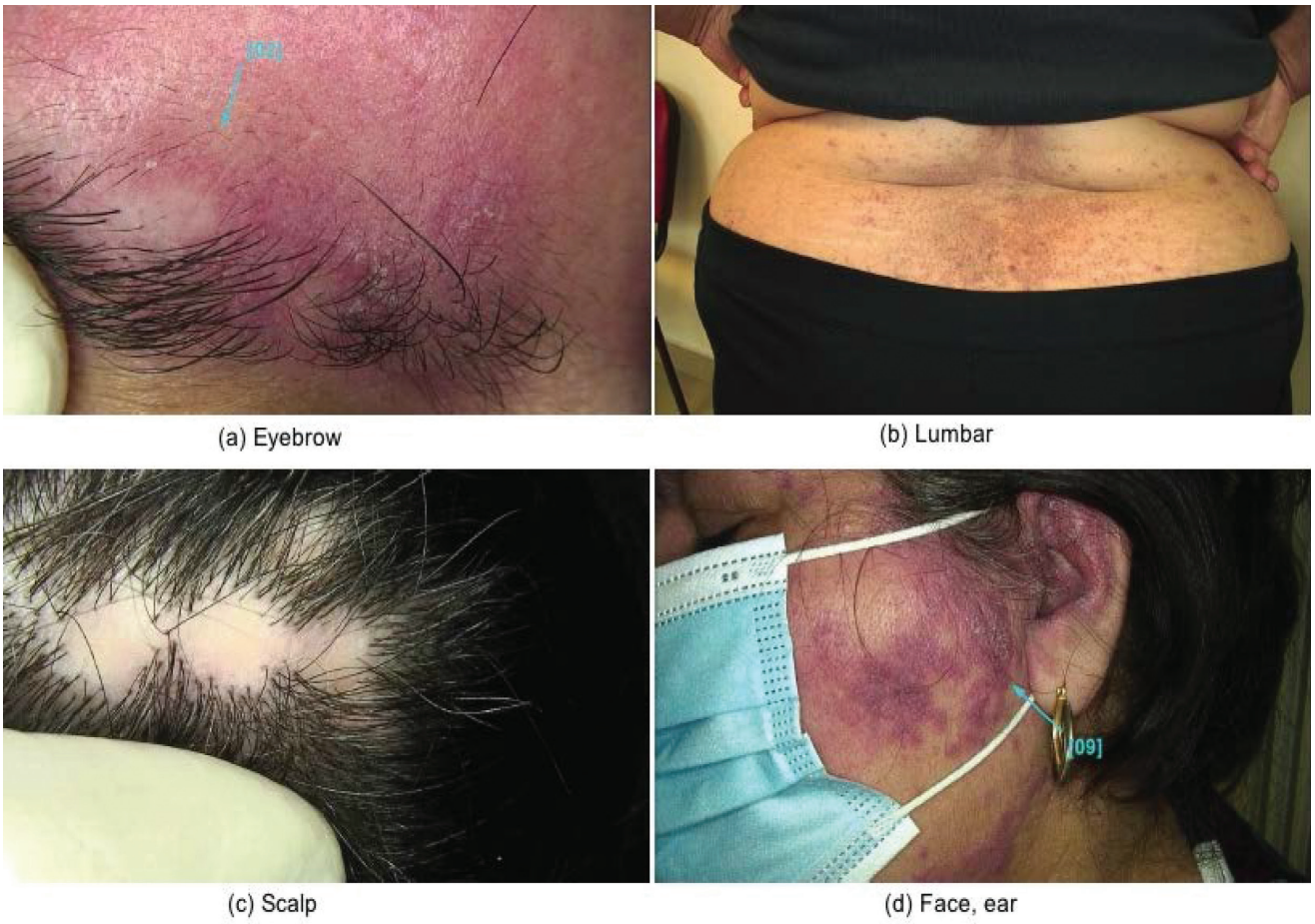

FIGURE 1. (a) Partial loss of eyebrow's hair, scaly atrophied red/ brown patches; (b) Patchy hair loss on scalp like "footprints in the snow"; (c) Grouped follicular papules 2-3 mm in diameter with a pointed or hair-like horny spine extending approximately 1-2 mm around the tip of the follicle; (d) Face erythema, scaly atrophied red/ brown patches face, ears

LP is a chronic inflammatory and immune-mediated disease that affects the skin, nails, hair, and mucous membranes. GLPLS as LP would stem from an immune response mediated by T cells against unknown antigens, determining destruction of keratinocytes [3]. Lupus erythematosus (LE) is a heterogeneous disease with a wide spectrum of presenting symptoms, from localized cutaneous LE (CLE) to severe disseminated disease in systemic LE (SLE). LE and LP may occur as an overlap syndrome (LE/LP). On biopsy of clinically ambiguous lesions, histopathological features of one or both processes can be found, obscuring the diagnosis and complicating prognosis and treatment. Thus, direct immunofluorescence has become an essential tool in helping to diagnose this condition [4].

Cicatricial (scarring) alopecia is a diagnostic intrigue. PPB likely represents the end-stage or clinical variant of various other forms of scarring alopecia. As such, it is a diagnosis of exclusion. The same pattern of hair loss can be seen in "burnt out" DLE, LPP, and other forms of scarring alopecia [5].

MCTD is a rare autoimmune disease diagnosed when a specific antibody known as anti-U1-ribonucleoprotein is present, and there are features of at least two connective tissue diseases, including systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, and rheumatoid arthritis.[6] The presence of high titers of anti–U1-RNP antibodies is associated with MCTD, a clinical entity that is characterized by overlapping clinical features of SLE, scleroderma, and polymyositis. The diagnosis of MCTD requires the presence of anti–U1-RNP antibodies and the absence of anti-Sm and anti-dsDNA antibodies [7].

CASE PRESENTATION

We present a 53- year-old female with a long history of more than two years of skin lesions located on face, scalp, trunk as shown in Figure 1.

During these two years she attended a couple of clinics and skins specialists asking treatments for her main objective, recovering scalp hair. She underwent different topical medication like: Minoxidil 2% solution, stimulating hair growth shampoos, oral vitamins, hydrating face cream. Besides a superficial clinical assessment, no other tests were ordered, nor other diagnostic procedure was done.

Personal history is abundant: morbid obesity (IMC>40), high blood pressure, impaired glucose tolerance, autoimmune thyroiditis. At the time of first assessment on February 2022, the blood tests revealed: Antinuclear antibodies >1/640, TSH=11.7 μUI/ml, ATPO=305 UI/ml, U1-nRNP intense positive (the other antibodies were within normal ranges), Glucose 109 mg/dl.

At physical examination her skin was affected by multiple lesions: patchy hair loss on scalp like "footprints in the snow", partial loss of eyebrows' hair, face erythema, scaly atrophied red/brown patches on face, ears and eyebrows, grouped follicular papules 2-3 mm in diameter with a pointed or hair-like horny spine extending approximately 1-2 mm around the tip of the follicle on lumbar area as shown in Figure 1.

The histopathological features of the scalp's biopsy revealed: follicular hyperkeratosis with acanthosis, hypergranulosis and scaling of the basal layer with intense peri-infundibular lichenoid changes. At the level of the isthmus of the follicular units, there is a lymphocytic inflammatory infiltrate in the band in opposition to the follicular wall, with vacuolar alterations of the outer layer of the follicular sheath with the presence of Civatte bodies.

Furthermore, the biopsy of the lesion from lumbar areas noted the following changes: Hyperkeratosis pilaris with dilatation of the infundibulum, acanthosis, hypergranulosis, perifollicular and focal dermal, perivascular infiltrate. Also, it identified both perivascular fibrosis and dermal mucin.

These tissues changes have confirmed clinical diagnosis of cicatricial alopecia induced by LPP and also presence of LS on lumbar area. The description provided by pathologist is however borderline regarding also an interface dermatosis like CCLE or PPB (as an end stage of CCLE or LPP).

DISSCUSION

Initial, the case was considered to be an Incomplete GPLS overlap MCTD. Differential diagnosis and dilemma diagnostic of this case is how to consider the cluster of autoimmune diseases found at the same patient. The question is if they are solitary concomitant diseases or if it is MAS (MCTD, CCLE, SLE, LPP, LS, PPB, autoimmune thyroiditis)? "The possibility of three or more autoimmune diseases occurring in the same patient cannot be fortuitous and suggests a pathogenic relationship between each of them (…) The grouping of these syndromes under a single heading should make the research and analysis of these morbid associations easier. Moreover, the classification adopted (…) allows a more precise definition of patients with at least two autoimmune diseases and so helps to recognize the onset of a third autoimmune disease at a later date" [8].

During one observation year she was referred to two different rheumatologists and, with no arguments, they did not want to be involved in the case management by no means other than prescribing hydroxiclorochine or diagnosis revision. They recommended only observation under a dermatologist supervision. "The clinical features of MCTD often develop over several years, and the complete clinical findings are rarely present at the start of the disease.There is no one widely accepted set of classification criteria; several criterion sets have been tested successfully, including Sharp's criteria, the Kasukawa diagnostic criteria, and the Alarcón-Segovia criteria. Diagnostic criteria may help define patients with MCTD, but in several cases, patients may not fulfill diagnostic criteria at their initial presentation. In some cases, the diagnosis of MCTD can be made based on expert opinion" [9].

Plaquenil twice a day was commenced as single therapy and subsequently at every three months the patient was evaluated. Blood tests after one year under Plaquenil twice a day revealed Antinuclear antibodies 1/640 at the same level compared to the previous test, U1-nRNP still intense positive, TSH=6.28 μUI/ml. Opposite to laboratory findings the clinical features revealed much improvement (Figure 2). After one year of treatment a lot of clinical features dramatically responded under therapy. Although no cases have been documented as such, we can see the resemblance with the serofast status that is found in patients with syphilis, which describes nontreponemal antibody tests that failed to completely serorevert (i.e., become nonreactive) after therapy.

So far, GLPLS remains incomplete (absence of noncicatricial alopecia of the axilla and groin). We can see the complete remission of LS lesions at the lumbar level, one year after treatment and the important remission of the initial inflammatory lesions with a tendency to stabilize the skin lesions, expressed by residual cicatricial pigmentation and partial follicular recovery at the level of the eyebrows. At the level of the scalp, the presence of cicatricial alopecia of the PPB type is still clinically noticeable but with no active lesions of LPP.

CONCLUSIONS

Clinical manifestations in autoimmune pathology with strictly cutaneous or systemic localization in conjunction or overlap with other autoimmune diseases represent a small percentage in dermatological practice. Often these manifestations remain undiagnosed or incorrectly classified. It results in an incomplete diagnosis and naturally the erroneous or incomplete diagnosis attracts an inadequate ther-

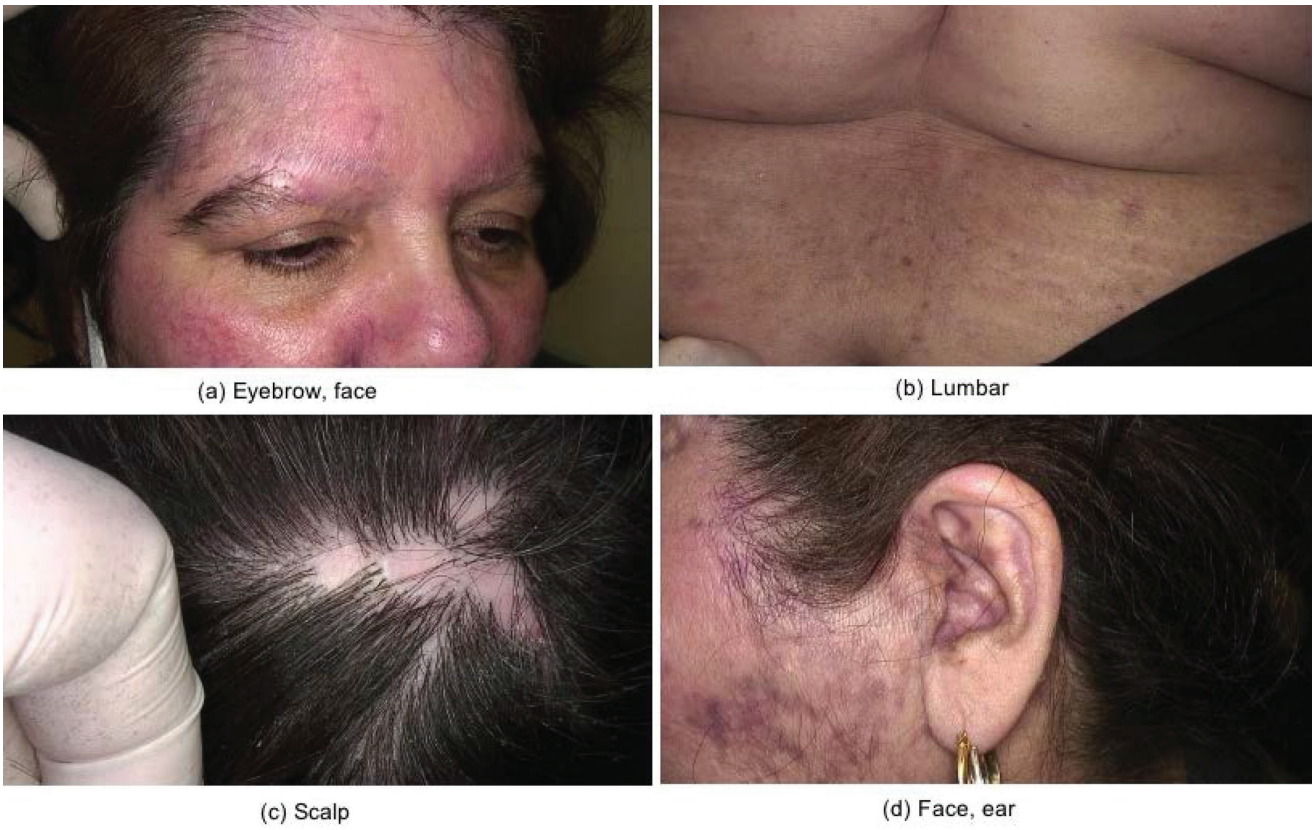

FIGURE 2. (a) Partial recovery of eyebrow's hair, residual fine scar patch; (b) Complete healing of lichenoid follicular papules; (c) Still remaining hair loss patches; (d) Residual face skin lesions with cicatricial pigmentation, face, ears

apeutic response, useless from the point of view of the pathological response and economically costly for the patient. The patient's expectations are often related to a cosmetic need (e.g. hair loss, nail deformity, social visibility) and often the associated signs or symptoms are not valued by him in requesting an immediate medical consultation, but only when the socially visible aesthetic damage is detected. Equally important can be added the superficiality of the medical consultation (it is a fact over the medical world, and should be recognized in a sincerely manner) that "focuses" on the patient's cosmetic needs without going to the next level, namely the identification of the underlying problem. This can be the result of multiple factors, among which we recall: the slow insidious natural history of autoimmune diseases, the presence of incomplete criteria, the lack of diagnostic experience of clinicians. Final diagnosis can be challenging due to variable and diverse symptoms upon presentation and the changes in symptoms over time.

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