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Psoriasis, sarcoidosis, and bullous pemphigoid: more than a coincidence in a single patient?

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To the Editor:

Psoriasis is a chronic and systemic inflammatory disease associated with various comorbid diseases, including metabolic syndrome, arthritis, myocardial infarction, and stroke. Other autoimmune diseases such as vitiligo and bullous pemphigoid (BP) have been reported in patients with psoriasis [1-3]. Sarcoidosis is a multisystemic granulomatous disease characterized by hyperactivity of the cell-mediated immune system. Interleukins IL2, IL12, IL18, and tumor necrosis factor (TNF) are involved in the pathogenesis of sarcoidosis. Cases of anti-TNF-induced sarcoidosis have been reported in patients under treatment for inflammatory conditions such as psoriasis [2]. Sarcoidosis-like reactions induced by anti-IL12/23 and immune-checkpoint inhibitors have been also reported [4,5]. We here describe a patient diagnosed with psoriasis, sarcoidosis, and bullous pemphigoid. The coexistence of these conditions in a single patient has not been previously described.

A 69-year-old man undergoing combination therapy with ustekinumab and ultraviolet-B (UVB) phototherapy for severe psoriasis developed tense blisters affecting the palms and soles. UVB was stopped, a phototoxic reaction was excluded, and histologic examination of a blister confirmed the diagnosis of bullous pemphigoid (BP), (**Figure 1**). Oral and topical corticosteroids were needed until all blisters had disappeared. Before the appearance of the BP, our patient had been treated with an anti-TNF agent, etanercept, for 12 months followed by anti-

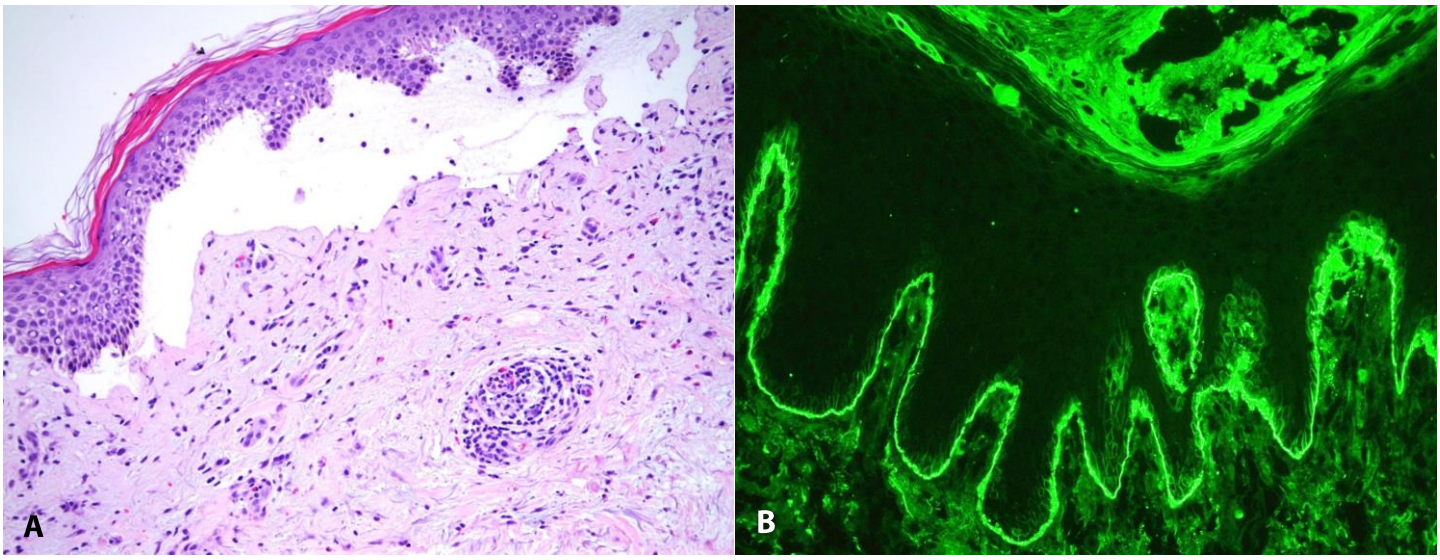

Figure 1. ***A)*** *H&E histopathology showing subepidermal blister and dermal eosinophilic infiltrate, 200×.* ***B)*** *Immunofluorescence biopsy showing linear deposition C3 along the basement membrane zone, 200×.*

IL12/23, ustekinumab, for one month. In addition, during treatment with ustekinumab, he was referred to the pneumologist because of relapsing bronchitis episodes with which he had been suffering for about four months; this had started while he was still undergoing the anti-TNF therapy. The patient also suffered cough and fatigue without other extrathoracic signs. A chest computed tomography showed bilateral hilar lymphadenopathy (**Figure 2**). Noncaseating granulomatous lymphadenitis was found by fine needle puncture of the mediastinal lymph nodes. Respiratory function tests revealed a mild restrictive pattern. The diagnosis of drug-induced type II sarcoidosis was established. Although this condition had started during etanercept therapy, ustekinumab was discontinued because there have been a few reports of association of this drug and sarcoidosis-like reactions. He was then treated with methotrexate. At present, after 10 years of follow-up, the patient has not shown new blisters or respiratory symptoms. His pulmonary sarcoidosis has remained stable both clinically and radiologically, but recurrent exacerbations of psoriasis have been successfully managed by increasing the dose of methotrexate.

Drug-induced sarcoidosis is a well-known paradoxical reaction. Discontinuation of the drug, which is mandatory, is usually followed by complete remission of symptoms, although treatment with oral corticosteroids and methotrexate has also been used in some cases [4]. A case of etanercept-induced sarcoidosis resolving with adalimumab has also been reported [6]. In addition, in a Danish cohort of patients with sarcoidosis there was a significantly increased prevalence of sarcoidosis in patients with psoriasis as compared to the general population [7]. The increased risk was dependent on the severity of disease [7]. Nevertheless, as it is described in two cases in the literature [8], only an asymptomatic stable pulmonary sarcoidosis was observed in our patient after withdrawal of the TNF inhibitor, so etanercept could have been an important trigger in the development of sarcoidosis since it is the TNF inhibitor more often implicated in drug-induced sarcoidosis and the pulmonary disease appeared eight months after etanercept introduction. In addition, the demonstrated association between psoriasis and sarcoidosis [7] due to its shared causal pathways driven by activated T helper (Th) 1 and Th17 lymphocytes, could influence the persistence of sarcoidosis. However, one cannot exclude the possibility that sarcoidosis was induced from other currently unknown etiologic factors.

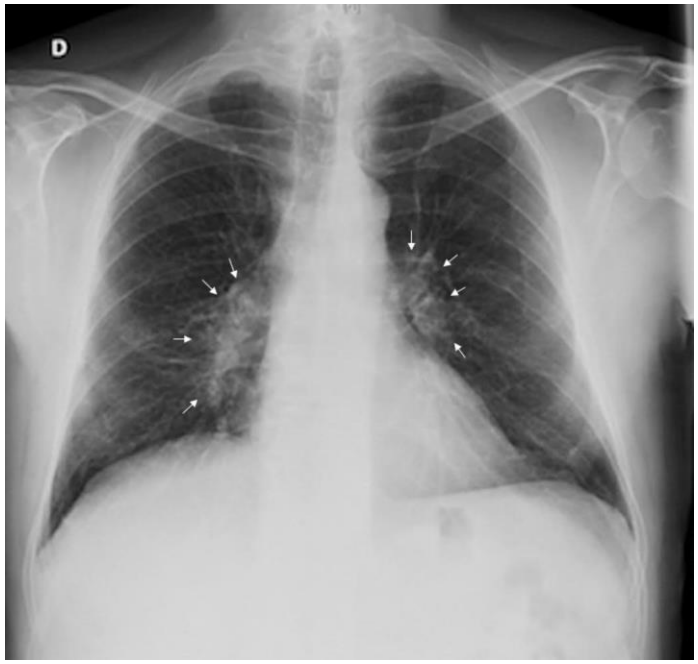

Figure 2. *Chest X-rays revealed bihilar lymphadenopathy and reticulonodular infiltrates (stage two sarcoidosis).*

On the other hand, bullous pemphigoid can be associated with other dermatoses including psoriasis. It has been suggested that a chronic inflammatory process at the dermal-epidermal junction may result in the exposure of antigens to autoreactive T-lymphocytes leading to a secondary immune response [3,9,10]. It has also been described that phototherapy may modify proteins of the basement membrane, which could induce an immune response mediated by autoantibodies [3]. There is inconsistent evidence of whether history of BP should be considered a contraindication for phototherapy.

The association of sarcoidosis and BP has been reported in only two previous patients to our knowledge, one who developed bullous pemphigoid after treatment with chloroquine for sarcoidosis [11] and another with history of pulmonary sarcoidosis who developed BP and

Kaposi sarcoma later as a Köbner phenomenon in the site of blisters [12].

We report a patient with a 20-year history of severe psoriasis who developed possible anti-TNF-induced sarcoidosis and he subsequently developed BP. We consider different possible etiologies of the BP: a UVB-induced BP, a drug-induced BP secondary to ustekinumab, or idiopathic BP, as the patient is 69-years-old with some comorbidities. Treatment with methotrexate has been successful. This coexistence has not been reported in the literature. Herein, we discuss a possible association and the therapeutic challenge.

Potential conflicts of interest

The authors declare no conflicts of interest.

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