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Extrapulmonary tuberculosis developed on a chronic psoriasis vulgaris patient, treated with Adalimumab

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ABSTRACT

The use of anti TNF-α in psoriasis vulgaris has been part of a groundbreaking discovery in the treatment of patients. Unfortunately, there is an increased risk of developing infections, especially tuberculosis, during the administration of this medication, which is why attention is being drawn to the more complex investigation of these patients to identify all possible locations of tuberculosis. The case of a patient that had first been diagnosed with psoriasis vulgaris in 1990 is presented. While under biological therapy with adalimumab, the patient developed extrapulmonary tuberculosis (TB). The onset of tuberculosis raised a problem regarding the treatment options for psoriasis vulgaris. Therefore it was a challenge for physicians to choose an effective psoriasis treatment that would not interfere with the tuberculostatic treatment.

INTRODUCTION

A significant advance in the treatment of inflammatory and chronic disease such as psoriasis, is represented by tumor necrosis factor-alpha antagonist drugs (Blanco Perez et al., 2010).

Adalimumab is the first fully human recombinant immunoglobulin G1 monoclonal antibody that binds and neutralizes soluble and membrane-bound tumor necrosis factor (TNF), so that it cannot interact with p55 and p75 cell-surface TNF receptors. It also induces apoptosis in mononuclear cells with TNF receptors. Finally, adalimumab is responsible for leukocyte migration in psoriasis (Shivani et al., 2016).

It is confirmed, by daily practice, that anti TNF-α therapy is also associated with increased susceptibility to infections, especially tuberculosis and reactivate latent tuberculosis infection (Galloway et al., 2011, Keystone et al., 2011).

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CASE REPORT

We present the case of a 32-year-old patient of Romani ethnicity residing in rural Romania, with psoriasis vulgaris since 1990 and treated with standard therapy (topical steroids, phototherapy, Acitretin) until 2012. The patient's profession is factory shoemaker, and does not present other forms of diseases or medical treatments.Following failure in previous therapies, we decided to introduce anti TNF-α biological agents (adalimumab 40 mg every two weeks, after an initial dose of 80 mg).The patient was evaluated for the severity of skin disease, general health condition and screened for latent tuberculosis infection (LTBI), according to the national protocol. Quantiferon gold assay was negative, chest X-ray did not show any evidence of active TB infection, tuberculin skin test (TST) showed an increased value (15 mm). The patient was suspected to have an LTBI. Based on OMS 2016 Tuberculosis Report, Romania is in the top EU countries with regards to the incidence of TB infection, and those living in rural and poorer environments are more vulnerable to become infected. TB infection is airborne

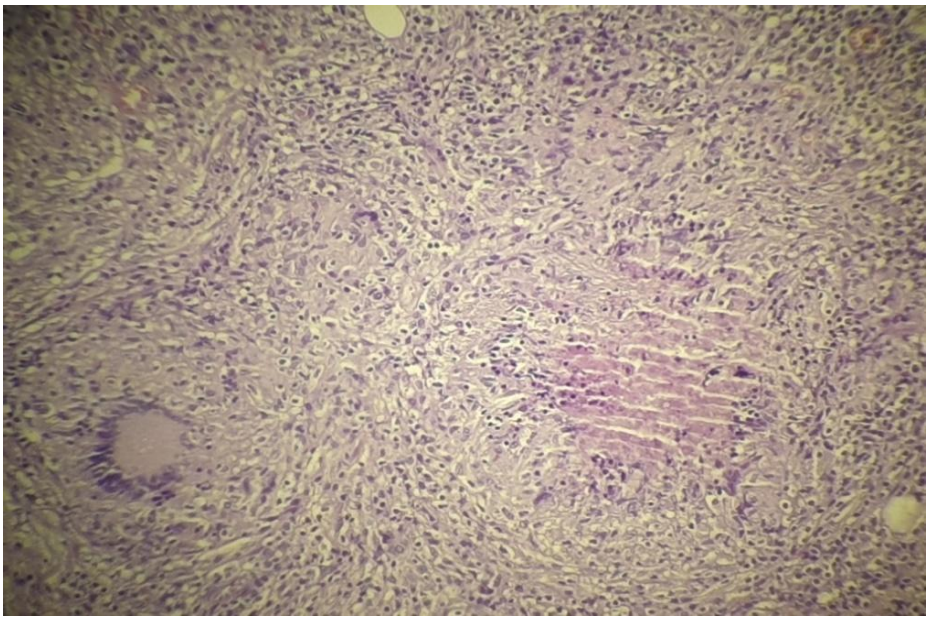

Figure 1. Histopatologic features. Epiploic tuberculosis: Epiploic adipose tissue with sub-millimetric multiple granulomas composed of the epithelioid lymphocytes and giant multinucleate cells, with nuclei displayed in the crown at the periphery of the cytoplasm, some presenting granular central necrosis. Haematoxylin and eosin stainig, original magnification ×40.

transmitted, however most infected do not present symptoms. The patient declared no TB symptoms prior to adalimumab treatment inception, therefore we suspect TB infection in childhood, with no symptoms.

We decided to initiate biological therapy (adalimumab) associated with tuberculosis chimi1oprofilaxy with HIN (Isoniazid) 300 mg/day for 9 months, and thereafter continued with only biological therapy. During the next five years of clinical follow-up, the patient was asymptomatic, with an increased level of 28 mm of TST, normal chest X-ray, while the psoriasis lesions had completely subsided, reaching PASI 100. Six weeks after the last periodical evaluation while still under biological treatment, the patient arrives in the emergency room with acute diffuse abdominal pain, with maximum intensity in the upper abdominal floor, nausea, vomiting and altered general state of health.

RESULTS

Paraclinic examinations indicate a slight hypochromic anemia, and abdominal CT reveals multiple spleen lesions, small quantities of ascites and a possible pulmonary condensation of pneumonic type; HIV test negative.

The patient underwent surgery for suspected tumor with metastasis. Intra-operative findings show: average amount of ascites from which we performed cytological examination, peritoneal and epiploid involvement, and spleen and hepatic nodules. Epiploon and duodenum biopsy is performed, together with histopatological examination. The result of ascites fluid reveals: a moderate cellular smear composed of lymphocytes, rare erythrocytes and mesothelial cells, and Rivalta reaction is positive. The sections examined histopathologically from the biopsy are: epiploic adipose tissue with sub-millimetric multiple granulomas composed of the epithelioid lymphocytes and giant multinucleate cells, with nuclei displayed in the crown at the periphery of the cytoplasm, some presenting granular central necrosis (Figures 1 and 2).

The culture from the ascitis liquid highlights the Koch bacillus, variant hominis, excluding a possible bovine infection. To our knowledge the patient did not come into contact with other TB active patients. Sputum examination is negative for pulmonary BK infection.

The patient was diagnosed with peritoneal and epiploic TB and started anti-mycobacterial therapy with significant improvement in her clinical condition. The TB diagnosis required the cessation of adalimumab and switch to a new therapy that would allow us to associate tuberculostatic treatment. We initiate Methotrexat dose of 7.5 mg/week but, without any skin improvement, at the end of tuberculostatic therapy, a new class of biological therapy is reintroduced with an inhibitor of IL17

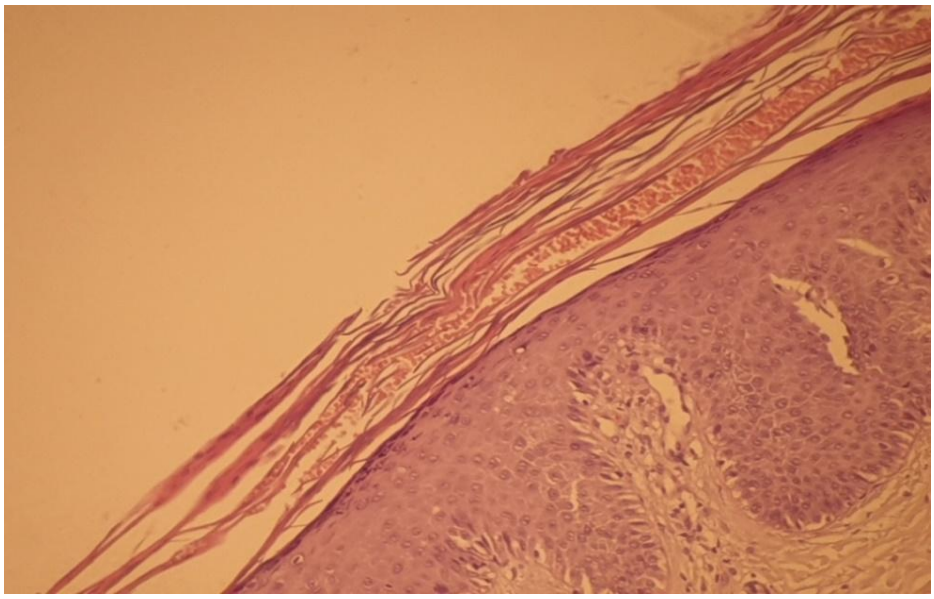

Figure 2. Histopatologic features. Psoriasis vulgaris: Epidermal acanthosis with papillomatosis and parakeratosis. Microabcesses Munro in corneous layer with rare neutrophils and erythrocytes. Haematoxylin and eosin staining, original magnification ×40.

(ixekizumab) in the doses recommended by the manufacturer, and as a result, the patient reached once again the target of PASI 100.

DISCUSSION

There is knowledge in literature of increase in tuberculosis onset after infliximab treatment, however there is less available data on the association between tuberculosis after adalimumab treatment (Blanco Perez et al., 2010).

A French prospective research (Tubach et al., 2009) reported an annual incidence of tuberculosis of 9.3 per 100000 patients receiving etanercept, 187.5 per 100,000 for infliximab and 215.0 for adalimumab, compared to 8.7 per 100,000 in the general population, while a British research (Dixon et al., 2010) published in 2010 showed that the TB incidence was highest for adalimumab (144 at 100,000 person-years), followed by infliximab (136/100000 person-year) and then etanercept (39/100000 person-years) (Galloway et al., 2011).

In a country like Romania, where the incidence of tuberculosis is the highest in the European Union, screening with Quantiferon gold-assay is not a reliable investigation to detect a disseminated TB infection.

Extra pulmonary tuberculosis induced by TNF-α inhibitors is difficult to diagnose using routine imaging examinations (Sawamura et al., 2018). The increasing TST values in our patient, despite chemoprophylaxis performed, should be an alarm signal in reactivation of a latent infection (LTBI). No chemoprophylaxis treatment reduces the risk of LTBI reactivation during biological treatment for psoriasis vulgaris.

Despite the absence of any TB infection symptoms, it is imperative to further conduct investigation for possible disseminated TB. If TB develops during anti-TNF-α treatment, it is more likely to be disseminated and extra pulmonary than are other TB cases (Tubach et al., 2009; Dobler, 2016; Wan-He-Yoo, 2012).

Any abdominal complaints in patients with anti-TNF-α treatment require the exclusion of a tuberculous intestinal infection. Appropriate strategies for reevaluation can also include repeating Quantiferon gold-assay, abdominal ultrasound, fecal mycobacterial culture and CT scan.

Despite the excellent evolution of psoriasis under adalimumab therapy, we had to change the therapeutic agent in the current situation. The activation of the tuberculosis infection represented a challenge for us in choosing an effective therapy for psoriasis that did not interfere with tuberculostatic treatment. In the absence of other conventional therapies and failure prior to them, the only therapeutic alternative for psoriasis, during the tuberculostatic treatment was methotrexate given in low dose due to the immunosuppressive and cytostatic effect, which showed insignificant results.

It is recommended that patients undergoing anti-TNF-α therapy be evaluated periodically on a more complex level, in order to identify all possible locations of TB infection, with the purpose of a timely cessation of anti-

TNF-α to stop the development of TB, and replace it with another class of biological treatment, such us inhibitor of IL17 (ixekizumab), with a lower risk for reactivation of LTBI.

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