Can biologic treatment induce cutaneous focal mucinosis?

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Abstract
Skin mucinosis is a rare skin disease which clinically manifests as firm papules and waxy nodules. We report a case of a 66-year-old female psoriatic patient who developed skin mucinosis during biological therapy. Because of a previous lack of response to the local and conventional systemic treatment of psoriasis, the patient received biological therapy (infliximab from June 2008 to May 2009 – initial clinical improvement and loss of treatment effectiveness in the 36th week of the therapy; adalimumab from June 2009 to January 2010 – lack effectiveness; ustekinumab from March 2012 to the present). Throughout 2 months we observed a manifestation of the skin mucinosis as well-demarcated, yellow and brown, papulo-nodular lesions of 5–10 mm in diameter, localized on the back. Histopathological examination with alcian blue staining demonstrated mucin deposits in the dermis. On the basis of clinical and histopathological findings, the diagnosis of cutaneous focal mucinosis was established. We present the case because of the extremely rare occurrence of the disease. Scarce literature and data suggest that there is an association between focal mucinosis and thyroid dysfunction, as well as possible adverse effects of biological therapy with TNF-α antagonists.

Key words: skin mucinosis, TNF-α antagonists, adverse effects, biological therapy, psoriasis.

Introduction
Skin mucinoses are a large group of rare skin diseases in dermatology with undefined pathogenesis and etiology. There are two subgroups of skin mucinosis: those associated with thyroid diseases and those not associated with thyroid disorders. The first group includes skin changes such as generalized and limited myxedema in the course of hypothyroidism, and myxedema accompanying Graves-Basedow disease. A group of mucinoses not associated with thyroid disorders includes scleromyxedema, lichen myxedematosus, sclerosis edema and focal mucinosis [1].

Skin mucinosis is characterized by the distribution of mucin deposits in skin layers. Mucin is a glycosylated protein of high molecular weight. The accumulation of mucin in skin forms glairy material deposits. The histological study with alcian blue and Periodic Acid Schiff (PAS) staining presented mucin deposits mostly in the upper and middle dermis layers, causing the separation of the collagen fibers [1]. The biochemical study shows that the main component of mucin is hyaluronic acid [2–5]. Recent introducing of biological agents into dermatological therapy might be associated with different side effects including skin disorders.

Case report
A 66-year-old female patient with a 35-year history of psoriasis was admitted to the Department of Dermatology and Venereology, Medical University of Lodz, to be diagnosed and treated for well-demarcated, yellow-brown lesions located on the back (Figure 1). The patient was diagnosed with hypothyroidism in 2006, now in euthyresis with L-thyroxine at a dose of 100 μg. For 1 year, the patient was on antibiotic therapy due to inflammation of the urinary tract. The psoriatic skin lesions were mainly located on the patient’s lumbar region. The standard systemic therapy which consisted of photochemotherapy, methotrexate and cyclosporine did not give a satisfactory clinical response. The patient was qualified for biological treatment and, thus, underwent therapy with infliximab in standard doses in the period from June 2008 to May 2009. After an initial positive clinical improvement, efficacy of the drug was lost at the 36th week of treatment. The following step was adalimumab therapy (June 2009 – January 2010). Treatment failure forced a change of the biological agent to ustekinumab, which the patient is still receiving. The therapeutic initial response was very good, but there was a subsequent increase in PASI and methotrexate was additionally administered with a satisfac-
tory effect. After 2 months, well-demarcated, yellow and brown, papulo-nodular lesions of 5–10 mm in diameter were observed on the back. Histopathological examination showed no epidermal changes and staining with alcian blue revealed mucin deposits in the dermis (Figures 2 A, B). The laboratory results showed no abnormalities in standard blood morphology. On the basis of clinical and histopathological findings, the diagnosis of cutaneous focal mucinosis was established. The treatment of skin lesions consisted of corticosteroid ointments, which gave little clinical improvement within 2 months. No other adverse effects resulting from the biological therapy were found.

Discussion
Skin mucinoses are a heterogeneous group of diseases characterized by an accumulation of glycosylated protein in the skin layers. The presented case describes extremely rare coexistence of generalized psoriasis, hy-
Mucin synthesis is under control by various cytokines, including transforming growth factor-β (TGF-β), interleukins, tumor necrosis factors and interferon γ. In lung cancer, colon cancer and Hashimoto’s thyroiditis, the activated macrophages secrete cytokines in significantly higher amounts than in healthy subjects, which may result in skin fibroblasts stimulation and development of skin lesions characteristic to skin mucinosis [14–16]. The presented case describes cutaneous focal mucinosis development in the course of the psoriatic skin lesions. The exact mechanism leading to mucin deposits formation in psoriatic patients is unclear. Probably production of proinflammatory factors such as IL-1, TNF-α, IL-6, IL-8 can activate fibroblasts producing IL-12 and IL-18, and can cause an excessive activation of the synthesis of hyaluronic acid and the creation of mucin deposits in dermis. This phenomenon may occur due to one of the following mechanisms: an abnormal activation of dendritic skin cells XIIIa+ HAS2+ or inadequate response of fibroblasts to stimulation by IL-1β [16, 17].

In our case, the possibility of mucinosis induction by anti-TNF-α treatment should be considered. Treatment with TNF-α antagonists is conducted in a relatively short period of time, and the role of anti-TNF-α is not completely defined. One of the hypotheses considers a relation between anti-TNF-α, IFN-γ and skin dendritic cells. Skin dendritic cells in the absence of active TNF-α produce elevated amounts of IFN-α [18]. The higher level of IFN-α presumably by activation of lymphocytes leads to excessive activation of mucin synthesis by fibroblasts in the skin [17]. Another pathological mechanism which may provoke excessive mucin synthesis is the lack of the inhibitory effect of TNF-α on the population of skin dendritic cells [18].

Conclusions

Despite ustekinumab treatment in our patient we assume that mucin deposits in this case were provoked by almost 2 years’ treatment with TNF-α antagonists. This hypothesis is based on literature data and an extremely short course of ustekinumab treatment. To our knowledge, it is the first case of cutaneous focal mucinosis development in the course of anti-TNF-α therapy. Biologicals are more commonly used in dermatological practice, thus new possible adverse effects of biological therapy may be noted.

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