discrete desquamation and more severe clinical complaints on the feet (Figure 1). The lesions were stationary and limited to the palms and feet. The patient reported no other drug intake or allergic background. No pruritus was reported.

Patient medication included Sorafenib at 400 mg twice daily, started 6 weeks prior to present consultation.

The patient refused biopsy for histopathological evaluation.

We tried topical steroids and urea 10% cream to improve the symptoms, but achieved no results after one month of continuous topical therapy. Despite the uncomfortable dermatological problems, the patient was advised to continue with sorafenib chemotherapy.

The list of sorafenib-related adverse reactions is long and gets even longer with new reports including hand-foot syndrome.[4] It has been classified into 3 grades based on clinical features:[5]

- **Grade I:** slight erythema and swelling with minimal dysesthesia;
- **Grade II:** pain is present along with other clinical changes and interferes with daily life;
- **Grade III:** blistering, desquamation and even ulceration accompanied by extremely severe pain.

Although the exact mechanism of these adverse reactions is still unclear, some possible explanations could be the pressure exerted on palms and feet and secondary increased blood flow to these areas. Therefore, the side effect is not an allergic reaction to a culprit drug.

The present case is a typical grade 3 hand-foot syndrome related to sorafenib treatment for advanced hepatocellular carcinoma.

Skin toxicity related to sorafenib has a great impact on the patients' quality of life and represents a challenge in oncology practice. Patient reassurance is crucial to avoid chemotherapy abandonment. ❑

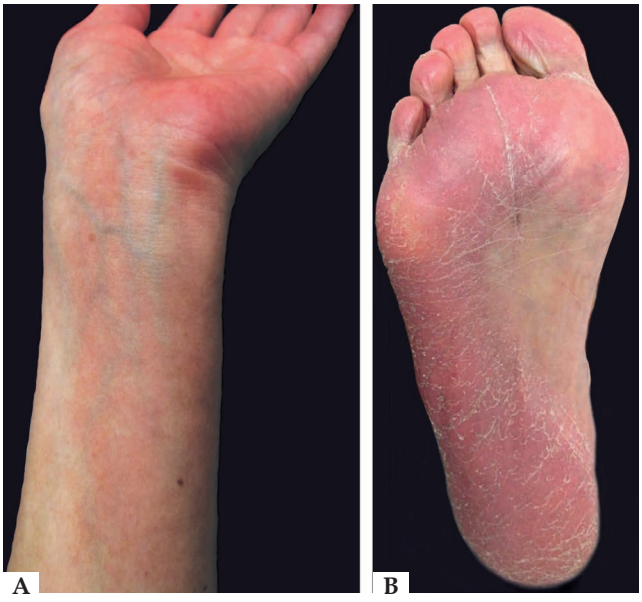


**Figure 1: I**ntense erythema on the right hand **(a)** and right foot **(b)** and desquamation on the right foot accompanied by invalidating pain

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## Biologic therapy-induced pemphigus*

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Dear editor,

Pemphigus is an autoimmune bullous disease that can affect the skin and mucous membranes, mediated by autoantibodies against desmosomal desmogleins, the main adhesion structures

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between keratinocytes.[1] Many are the factors attributed to its development, but drugs are the main cause.[1] Medications can cause or exacerbate pemphigus lesions.[1] Drug-induced pemphigus lesions are histopathologically identical to those of idiopathic pemphigus vulgaris.[2] Due to the lack of reports in the literature, we present a case of biologic-induced pemphigus, in a patient in whom the medication was being used to treat severe rheumatoid arthritis.

We present a case of a 41-year old female patient, phototype II, that presented with cutaneous redness, peeling, and pruritus on the thoracic region in the past 15 days, after sun exposure. On physical examination, erythema and telangiectasia were observed in the malar regions and dorsum of nose, along with papules and erythematous, scaly plaques on the neckline (Figure 1).

The patient has had rheumatoid arthritis for 10 years, for which she was using methotrexate and prednisone (5 mg/day) for 5 years, secukinumab for 3 months and paracetamol as needed. She was allergic to dipyrone. The patient had already used chloroquine diphosphate (discontinued more than 10 years ago due to retinal maculopathy), etanercept (between 2008 and 2010) and adalimumab (between 2011 and 2012, both discontinued due to lack of clinical response). Her Family history included mother with hyperthyroidism.

Serology revealed rheumatoid factor 80 UI/ml and ANA with nuclear fine speckled pattern 1:1.280. Other autoantibodies were negative. The histopathology showed focal area with suprabasal acantholysis involving the follicular epithelium, besides acanthosis and crust with fibrin and leukocytes (Figure 2). Immunohistochemistry for IgG and C3 was positive, with intercellular distribution, corresponding to, along with the clinical history, the diagnosis of drug-induced pemphigus (Figure 2).

In cooperation with rheumatology, we decided to discontinue secukinumab, increase the dose of methotrexate and add topical steroid, with gradual improvement of the lesions within a month (Figure 1). Since it was considered a relatively mild case, with rapid improvement, and since the patient had severe rheumatoid arthritis, with deformities, a biologic drug was reintroduced. The rheumatologists opted to use tocilizumab, and 15 days after the new treatment, the patient presented with the same lesions, this time with vesicles of approximately 5 mm in the inframammary region, abdomen and upper limbs, that improved after discontinuing the medication once again. Histopathology of the new lesions confirmed the previous diagnosis, with positive direct immunofluorescence for intercellular IgG and C3, corroborating the diagnosis of drug-induced pemphigus.

The possibility of association of medications with new cases of pemphigus should always be suspected, since many cases can be caused and worsened by drugs, in special penicillamine, followed by the group of ACE inhibitors. The time gap between drug exposure and onset of skin lesions varies, making the diagnosis even more difficult when the patient uses multiple drugs concomitantly.[3]

There are 3 groups of drugs with different chemical structures involved in the development of pemphigus. The thiol group, to which penicillamine belongs, includes drugs with the ability to activate proteolytic enzymes, to interfere in the enzyme activities of the keratinocytes and to bind to desmoglein 1 and 3, inciting the immune response or preventing their role in cellular adhesion. The phenol group, that includes aspirin, rifampicin and levodopa, causes acantholysis, participating in the regulation and synthesis of complement and proteases. The third group — nonthiol and nonphenol — encompasses other drugs that take a part in the acantholysis process via many mechanisms.[1]

Biologic drugs, such as the ones used by the patient, are in the third group. Secukinumab, a monoclonal antibody anti-IL-17 and tocilizumab, a IL-6 receptor antagonist, are utilized by those patients that are unresponsive to TNF-alfa antagonists.[4] Secukinumab has a half-life of 22 to 31 days, tocilizumab's half-life is 11 to 13 days

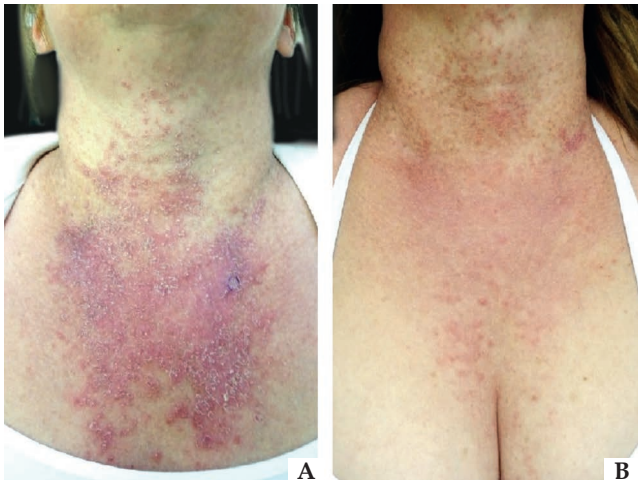


**Figure 1: A)** Erythematous scaly papules and plaques, with some superficial ulcerations on the neckline; **B)** Improvement after treatment.

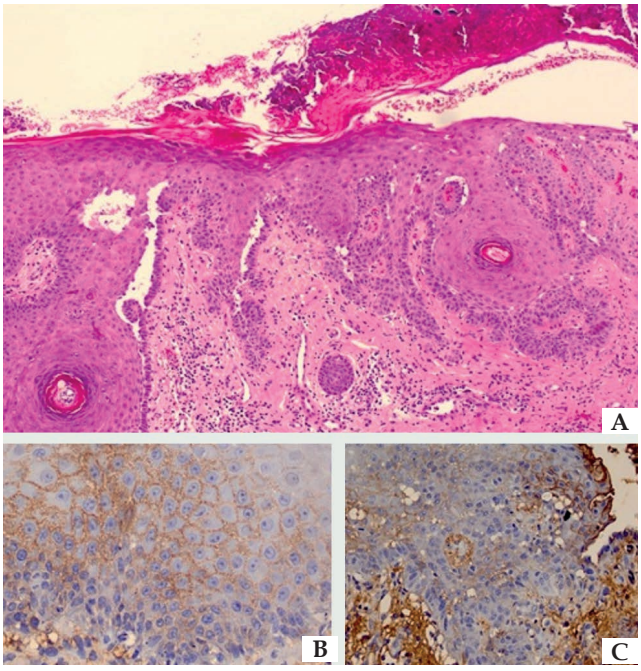


**Figure 2: A)** Focal area with suprabasal acantholysis, involving the follicular epithelium, besides acanthosis and crust with fibrin and leukocytes (HE, X100); **B)** Immunohistochemistry with expression of intercellular IgG; **C)** Immunohistochemistry with expression of intercellular C3.

in adults.[6] The metabolism of both drugs is still unknown.[5]

Biologic drugs can trigger immediate transfusion reactions and rarely induce the formation of cellular autoantibodies or even autoimmune conditions, such as lupus erythematosus, usually of late onset. The frequency of tocilizumab's infusion reactions is around 7%; in a recent study with 226 infusions in individuals with autoimmune conditions, no immediate infusion reactions were observed. Nonetheless, it is still a medication with limited use.[7]

There are no reports of biologic drug-induced pemphigus until now. We highlight the importance of the dermatologist in the pharmacovigilance phase for new drugs. ❑


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## Trigeminal trophic syndrome*


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Dear Editor,

An 80-year-old male presented with chronic non-healing ulcers involving the left side of the scalp and forehead for three months. The lesions were associated with intractable itching and vague crawling sensation. Following that, he started picking and rubbing his skin, which resulted in ulcers. His medical history was suggestive of herpes zoster involving the left ophthalmic (V1) branch of the trigeminal nerve for nine months. Physical examination revealed a 4x3-cm ulcer involving the left frontal aspect of the scalp and two other small ulcers, one involving the center of the scalp and the other above the lateral aspect of the left eyebrow, corresponding to the ophthalmic (V1) branch of the trigeminal nerve. The latter lesion showed areas of post inflammatory depigmentation (Figure 1). Routine hematological and biochemical investigations were within normal limits. Head MRI revealed age-related cortical atrophy and was otherwise normal. Systemic examination revealed no abnormality. A diagnosis of trigeminal trophic syndrome (TTS) was entertained. The patient was treated with occlusive dressings, topical antibiotics, and carbamazepine with complete resolution of the lesions within three weeks (Figure 2).

TTS is a rare clinical entity characterized by unilateral facial ulceration involving the trigeminal nerve (TN) territory following damage to its central or peripheral nerve structure. The classical clinical triad of TTS consists of trigeminal anaesthesia, facial paraesthesia, and crescent shaped ulcers.[1] The presenting features will be that of picking, rubbing, or scratching sensations on the affected areas secondary to hypoesthesia, paraesthesia, or pain resulting from damage of the sensory trigeminal fibers.[2] Adolf Wallenberg was the first to describe TTS in 1895 in a patient with lateral medullary infarction.[3]

TTS is frequently triggered by iatrogenic causes, usually following procedures for pain management in trigeminal neuralgia.[4] Other causes include stroke, acoustic neuroma, post-infectious encephalitis, trauma, amyloid deposits in the TN, and infections.[1,4,5] Herpes zoster and leprosy are also major dermatological causes for TTS.[5]


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