



Figure 2: Appearance of new erosive lesions on the face and mucositis with predominance in lips.

Treatment with oral prednisone at a dose of 1 mg/kg, mupirocin and topical ketoconazole was initiated, on suspicion of super infection. In spite of this treatment, the lesions did not improve.

A skin biopsy was performed showing lichenoid dermatitis with dyskeratotic keratinocytes, compatible with toxicoderma and paraneoplastic pemphigus, lichenoid variant. Direct immunofluorescence (DIF) on skin was negative for all antisera. Indirect immunofluorescence (IIF) in blood with anti-desmoglein antibodies was also negative. A study of dihydropyrimidine dehydrogenase deficiency (DPD) was also requested, which ruled out deficiency of this enzyme.

With these results we decide an empirical withdrawal of 5-FU treatment and irinotecan was maintained in monotherapy. After the suspension of the drug the patient evolved favourably, with great improvement of the cutaneous lesions until their complete disappearance.

Discussion

5-FU is an antimetabolite, analogous to pyrimidines, that inhibits the enzyme thymidylate synthase and, therefore, disrupts the synthesis of thymidine necessary for DNA replication. The most common side effects are myelosuppression, diarrhoea, mucositis and, somewhat less frequently, dermatitis. A large variety of cutaneous affections associated with this drug have been described, such as alterations of pigmentation, palmar-plantar erythrodysesthesia, lupus erythematosus-like lesions, seborrheic dermatitis, photosensitivity, nail abnormalities or septal granulomatous panniculitis [2-5]. Among these, the most typical cutaneous condition associated with 5-FU is palmar-plantar erythrodysesthesia, which appears rarely with bolus administrations, but is most often seen with continuous infusion (upto 34%) [6]. Capecitabine, an oral prodrug of 5FU, is most frequently associated with this toxicity (50%-60% of patients), since it simulates a prolonged infusion [7-10].

Maculopapular cutaneous reactions such as those presented by our patient have been more frequently associated with some chemotherapeutic agents such as fludarabine, cladribine, gemcitabine and pemetrexed, but rarely with 5-FU [4].

The DPD is the enzyme that limits the degradation of 5-FU and plays an important role in its toxicity. A decreased activity of this enzyme leads to a reduction in the catabolism of 5-FU with the consequent increase in toxicity. DPD activity varies widely due to genetic polymorphisms, and although a complete deficiency is rare, it is estimated that 3-5% of the population has partial DPD deficiency. When there is a deficit, the administration of 5-FU mimics an

accidental overdose, with fever, marked neutropenia, mucositis, stomatitis and diarrhea [11,12]. Due to the striking cutaneous-mucosal toxicity in our case, it was considered important to rule out a deficit of DPD.

The appearance in our patient of erythematous plaques with intense erosion and exudation together with the association of stomatitis made the differential diagnosis fundamentally with a blistering disease, especially paraneoplastic pemphigus (PPN). Other possible diagnoses were erythema multiforme, lichen planus and mycotic and herpetic infections [13].

Pemphigus are a heterogeneous group of diseases characterized by the production of vesicles or blisters on the skin and mucous membranes caused by autoantibodies against specific proteins located at the junctions of the epithelial cells. These autoantibodies result in a rupture of the intercellular adhesion (acantolysis) leading to the formation of intraepithelial blisters [14]. Although pemphiguses are rare, they present an aggressive course. According to the clinical, histological and immunological criteria, five types of pemphigus are recognized: vulgar, vegetative, paraneoplastic, foliaceo and erythematous [15]. The variants that more frequently express oral manifestations are pemphigus vulgaris (PV) and paraneoplastic pemphigus. In the PV oral involvement precedes in the majority of cases the cutaneous involvement that consists of multiple blisters of different size, which break easily producing very painful superficial erosions. Blisters are located in any part of the body but are more frequently in the scalp, face and upper part of the trunk [15]. PPN is clinically characterized by severe oral and conjunctival involvement and more variable and polymorphic skin lesions than in PV, which preferentially affect the trunk, limbs, palms and plants and genital mucosa. Respiratory mucosa can be affected in up to 30% of cases [15-17]. PPN is most frequently associated with haematological malignancies, although cases associated with solid tumors have also been described. Its real incidence is unknown, although it is less frequent than other variants of pemphigus, it could be an underdiagnosed entity since it can be confused with other dermatoses to which it resembles [14]. The histopathological characteristics of PPN are variable, reflecting the polymorphism of its clinical manifestations. It can be observed acantholysis, which in contrast to PV, is less marked and is accompanied by lichenoid interface and/or necrotic keratinocyte dermatitis [14,16,18]. PPN is characterized by the presence of polyclonal IgG autoantibodies directed against different antigenic components of the desmosomes and hemidesmosomes [18]. DIF shows deposits of IgG and interkeratinocyte complement that can be associated to the linear or granular deposit of IgG and complement in the zone of the basal membrane, which differentiates it from PV where this pattern does not occur. In some cases, DIF is negative, which may be due to the higher frequency of lichenoid lesions in which the cellular immunity predominates over the humoral immunity, or to the presence of necrotic tissue in the biopsies [17].

IIF detects circulating IgG antibodies in the serum. Patients with PPN have antibodies that react with antigens present in all types of epithelium, including columnar and transitional, whereas PV antigens are expressed only in stratified flat epithelia. Thus, if the serum is analyzed in both stratified flat epithelium (monkey esophagus) and transitional epithelium (rat bladder), the antibodies of patients with PPN will react with the antigens present in both epithelia. However, the sensitivity and specificity of the technique is not 100% and it is more frequent to observe false negatives in PPN. In these cases, the

diagnosis can be confirmed by immunoprecipitation [15]. The PPN associated with a malignant neoplasm is usually not resolved despite the control of the neoplasm. There is no evidence of an effective treatment regimen, although improvement of the lesions with oral corticosteroid has been described at doses of 0.5-1 mg/kg [19]. Other treatments used include immunosuppression with cyclophosphamide, azathioprine, gold, dapsone, plasmapheresis and high doses intravenous immunoglobulins [15].

The histology of our patient did not show acantholysis and both DIF and II were negative. On the other hand, the corticoid treatment did not produce any clinical improvement. Therefore, toxicoderma secondary to chemotherapy was considered as the most probable diagnosis. 5-FU was discontinued empirically, because, given its cutaneous toxicity profile, it could be the drug most likely related to the patient's condition.

Improvement of the symptomatology after the suspension of the chemotherapy confirmed the diagnosis of skin toxicity secondary to 5-FU.

The clinical suspicion is essential to establish the diagnosis of toxicoderma. However, the diagnosis can be sometimes difficult due to the wide spectrum of clinical and histopathological forms that may appear and the fact that sometimes the lesions arise a time after starting the treatment, as happened in our case. Skin biopsy helps to recognize the diagnosis, since drug's etiology can be suspected when the typical pattern of a particular entity is combined with other patterns that are incongruent in this context, such as the existence of vasculitic or lichenoid damage. However, there are often no pathognomonic histological or immunological criteria to exclude other alternative causes, so the best way to confirm the diagnosis is to obtain remission of the lesions after replacing or removing the causative drug [19].

In cancer patients, a severe skin reaction associated with a drug may mean a dose-limiting toxicity or cause the complete suspension of the drug, with the prognostic implications that this entails. In these patients, the attribution of a reaction to a particular drug is, even further if possible, more complex, due to the wide range of etiologies that may underlie the appearance of cutaneous lesions, including infectious causes, paraneoplastic syndromes, tumor dissemination or nutritional deficiencies [1]. The use of combinations of chemotherapy and associations with other therapeutic agents (biological drugs, hormonal treatments, etc.) increases the difficulty to associate a particular reaction with a specific drug.

To help the clinician to familiarize himself with the different skin patterns that can be expected in relation to a particular drug, it is essential to report those cases of less described toxicities.

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