Cutaneous involvement of marginal zone B-lymphoma noted after topical imiquimod; more than a coincidence?

Sir,

Topical imiquimod is a toll-like receptor (TLR) 7/8 agonist approved for the treatment of non-melanoma skin cancer (NMSC). Its side effects are usually local and less frequently systemic.[1] We report a case of secondary marginal zone B-lymphoma (MZL) that involved the areas where topical imiquimod was applied to treat actinic keratoses and superficial basal cell carcinomas.

An 84-year-old male presented with persistent superficial basal cell carcinomas (BCC) and actinic keratosis (AK) on both cheeks [Figure 1]. These were previously treated with surgery and methyl-aminolevulinate photodynamic therapy (MAL-PDT). However, since some lesions were not responding to photodynamic therapy, it was decided to try topical imiquimod in order to avoid another surgical procedure. Six weeks after initiating the treatment, the patient developed erythematous and edematous plaques on both cheeks [Figure 2]. There was associated cervical lymphadenopathy. Skin biopsy showed aggregates of small and medium sized lymphocytes with some plasma cells occupying the whole dermis; there was neither formation of germinal centers nor evidence of epidermotropism [Figure 3]. The immunohistochemical study was strongly positive for CD20 [Figure 2], CD79a, BCL2 and light chain restriction, with decreased expression of CD3, CD4, CD 123 and UCH L1, and negative for CD8, CD5 and CD10.

Immunophenotyping of peripherial blood revealed that 38% of B lymphocytes had a marginal zone immunophenotype and 14% of bone marrow lymphocytes presented with a condensed chromatin pattern and small nucleoli. Upper gastrointestinal endoscopy was normal. Thoracic, abdominal and pelvic computed tomography showed a small, 7 mm nodule lower lobe of the right lung. The patient and his family declined further invasive tests. Considering all these findings, and in accordance with the definition of the WHO-EORTC,[2] we made the diagnosis of

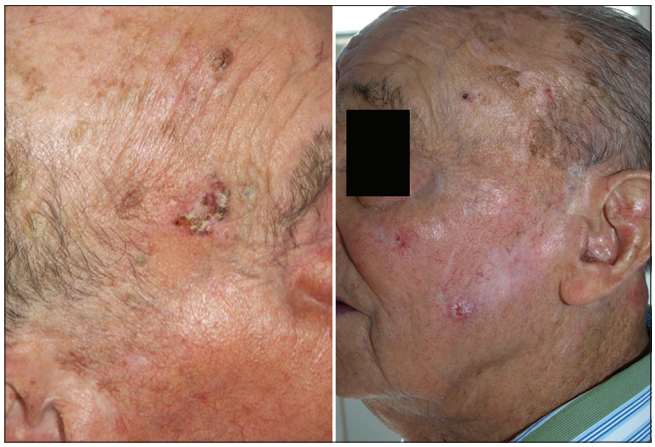

Figure 1: Basal cell carcinoma on the right temple and multiple actinic keratoses on left cheek, before imiquimod application

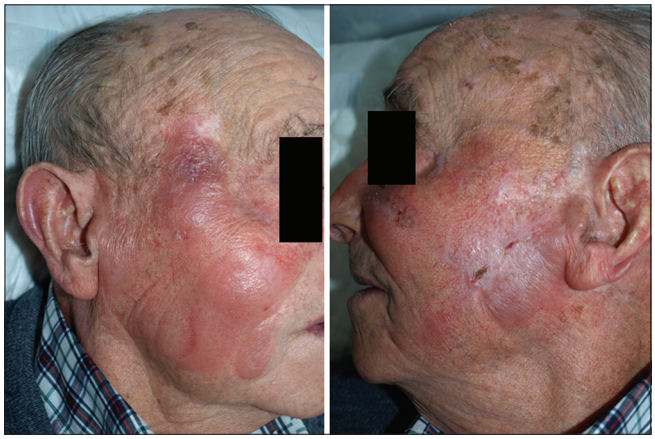

Figure 2: Erythematous and edematous plaques on both cheeks which appeared after topical application of imiquimod

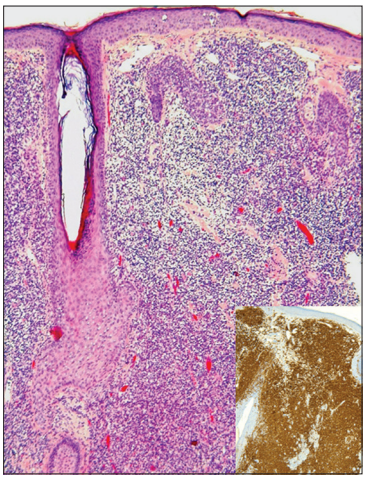

Figure 3: Small and medium size lymphocytes diffusely infiltrate the entire dermis. (H and E, CD20, ×50). Inset - immunohistochemical staining for CD 20 was positive

non-cutaneous (nodal or extranodal) marginal zone lymphoma with skin involvement, probably triggered by imiquimod. The patient was treated with rituximab (375 mg/m^2) and bendamustine (90 mg/m^2) weekly for the first four doses and then monthly with partial resolution of the skin lesions.

Cutaneous marginal zone lymphoma (CMZL) may be a primary cutaneous condition or the result of secondary involvement from non-cutaneous disease. Primary cutaneous marginal zone lymphoma is a very indolent lymphoma, which mostly affects young adults, with a distribution favoring the trunk and extremities. However, patients with secondary cutaneous marginal zone lymphoma are often older and the lesions are usually located on the head and neck. Cases of marginal zone lymphoma secondarily involving the skin can be histologically and immunophenotypically indistinguishable from primary cutaneous disease.[3]

The association between chronic antigenic stimulation and the microenvironment has been frequently reported in this type of lymphoma. The infectious agents most frequently associated with mucosa-associated lymphoid tissue (MALT) lymphoproliferations are *Helicobacter pylori, Helicobacter heilmannii,* hepatitis C virus, *Campylobacter jejuni*, *Borrelia burgdorferi*, and *Chlamydia psittaci*. These etiologic associations have led to the hypothesis that chronic or repeated immune stimulation leads to a lymphoid expansion which, in the presence of specific micro environmental factors and a genetic predisposition, can culminate in a malignant clone.[4] In primary cutaneous marginal zone lymphoma, the relationship with *B. burgdorferi* infection is the most frequently reported. Recently, Guitart *et al*.[5] also identified an association with gastrointestinal disorders, certain autoimmune conditions and some systemic malignant neoplasms indicating in some patients a possible local trigger event.

We found a single previous report of reactivation of Burkitt lymphoma after the use of imiquimod.[6] Imiquimod induces *in vitro* the production of cytokines such as TNF-α, IL-1, IL-6, IL-8, and IL-12 by monocytes, macrophages, and plasmocytoid dendritic cells through TLR 7/8 activation. The release of IL-12 itself promotes the production of IFN-γ by CD4 T lymphocytes which stimulates CD8 T lymphocytes, responsible for the death of tumoral and virus-infected cells.[1]

Toll like receptors are a part of the innate immune system that have been shown to recognize bacterial ligands

and some autoantigens which results in the activation of pro-inflammatory cytokines and chemokines. Toll like receptors also influence apoptosis and cell proliferation. Imiquimod acts via toll like receptors and the inflammatory microenvironment caused by the drug is similar to that reported by Adam *et al.*,[7] in extranodal lymphomas. They concluded that since gastric extranodal marginal zone B-cell lymphomas of MALT type exclusively express TLR 4 in contrast to other lymphomas infiltrating the stomach, the pattern of TLR expression correlates well with the putative model of lymphomagenesis and progression; this pattern of TLR expression resembles that produced by imiquimod.

Our hypothesis is that the inflammatory microenvironment induced by topical imiquimod could have triggered the involvement of marginal zone lymphoma in the treated areas. However, even though the lymphoma lesions appeared during treatment with imiquimod and there is lack of evidence of any association between methyl-aminolevulinate photodynamic therapy (MAL-PDT) and lymphoma development, a possible synergistic action between photodynamic therapy and imiquimod cannot be ruled out.

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