Volume 19 Number 7
July 2013

Letter

Multiple eruptive keratoacanthomas associated with leflunomide

Laura Frances MD, Jaime Guijarro MD, Irene Marin MD, Maria del Carmen Leiva-Salinas MD, Angelica Maria Bouret MD

Dermatology Online Journal 19 (7): 16

Hospital General Universitario de Alicante, Alicante, Alicante, Spain

Correspondence:

Laura Frances MD
Hospital General Universitario de Alicante
Alicante, Alicante, Spain
laura.frances@hotmail.com

ABSTRACT

A 78-year-old woman diagnosed with rheumatoid arthritis without a history of skin tumors or immunosuppressive medication, started treatment with leflunomide. One month after the introduction of the drug, and for two consecutive years, she developed multiple crateriform nodules and papules on her lower extremities . Biopsy specimens showed keratoacanthomas and squamous-cell carcinomas. Owing to suspicion that the drug could be implicated in the appearance of these tumors, the patient decided to suspend the drug. No new skin lesions have appeared in seventeen months of clinical follow-up. There have been several published case reports of multiple keratoacanthomas associated with immunosuppressive therapy such as sorafenib and imiquimod. However, we found no mention in the literature of the eruption of multiple keratoacanthomas in patients with rheumatoid arthritis treated with leflunomide. We suggest, that the the sudden appearance of skin tumors in our patient is related to the introduction of leflunomide, but additional case reports are required to confirm this association.

INTRODUCTION

Keratoacanthoma is a relatively common epithelial tumor, considered a variant of squamous cell carcinoma. It appears as a hyperkeratotic papule that becomes a crateriform nodule in a few weeks. Spontaneous regression may occur slowly over months to leave an atrophic scar. Keratoacanthoma most often affects middle-aged adults in the fifth to seventh decade. A strain of papillomavirus has been identified in some keratoacanthomas [1], although it seems that its main trigger is ultraviolet radiation. The development of keratoacanthoma has been associated with sun exposure, chemical carcinogens, radiation therapy, and various forms of antecedent trauma, including surgery or grafting and laser resurfacing [2, 3, 4, 5, 6]. These tumors usually occur as isolated lesions, but infrequently there may be multiple eruptive lesions. Generalized eruptive kerathoacanthomas have been reported to develop in the context of a rare condition named Grzybowski eruptive keratoacanthomas [7]. In addition, other familial syndromes, familial keratoacanthomas of Ferguson-Smith and the multiple familial keratoacanthomas of Witten and Zak, have been described [8,9]. In addition multiple keratoacanthomas can be observed in Muir-Torre syndrome (a genodermatosis that is associated with keratoacanthomas, sebaceous neoplasms, and gastrointestinal tract malignant condition, most commonly of the colon). Recently, cases have been reported of eruptive multiple keratoacanthomas associated with the use of new immunosuppressive and immunomodulatory therapies [10]. The drug most often associated with eruptive keratoacanthomas development is sorafenib [11] followed by imiquimod [12], but a few cases have also been described with cyclosporine and vemurafenib [13], which was recently approved by the US Food and Drug administration for advanced melanoma.

CASE REPORT

A 78-year-old woman diagnosed with rheumatoid arthritis without a history of skin tumors or immunosuppressive medication, started treatment in August 2009 with leflunomide plus other drugs such as low-dose systemic corticosteroids, alendronate, and etoricoxib, but no other immunosuppressive or immunomodulatory therapy was added. A month after initiating this therapy the patient developed a left lateral shin skin tumor that was surgically removed in another medical center with unknown histological diagnosis. Two months later three new small lesions appeared adjacent to the initial scar (Figure 1).

Analysis of the three surgical specimens revealed an atypical endophytic and exophytic squamous cell proliferation with crateriform architecture, an epidermal collarette, and a large central keratin plug consistent with well-differentiated, keratoacanthomas. Since then, and for two consecutive years, the patient has developed multiple ulcerated nodules on both lower extremities (approximately 10 lesions) with similar clinical appearance, in addition to generalized actinic keratoses (Figure 2 and Figure 3). Subsequently, our patient underwent four surgical procedures to remove these lesions that were all histologically diagnosed as squamous-cell carcinomas and keratoacanthomas. The patient had no other pathologies (except arthritis) or other immune disorders that could justify the skin tumors, so we think that a drug could be the cause. Reviewing the chronology of the pathology, we realized that the start of the skin tumors coincided with the introduction of leflunomide two years earlier. The patient, who also suspected this association, decided to voluntarily suspend the treatment in May 2011, and no new new skin lesions on her extremities have appeared in the seventeen months of follow-up after discontinuing leflunomide, after two years of the development of multiple keratoacanthomas (Figure 4).

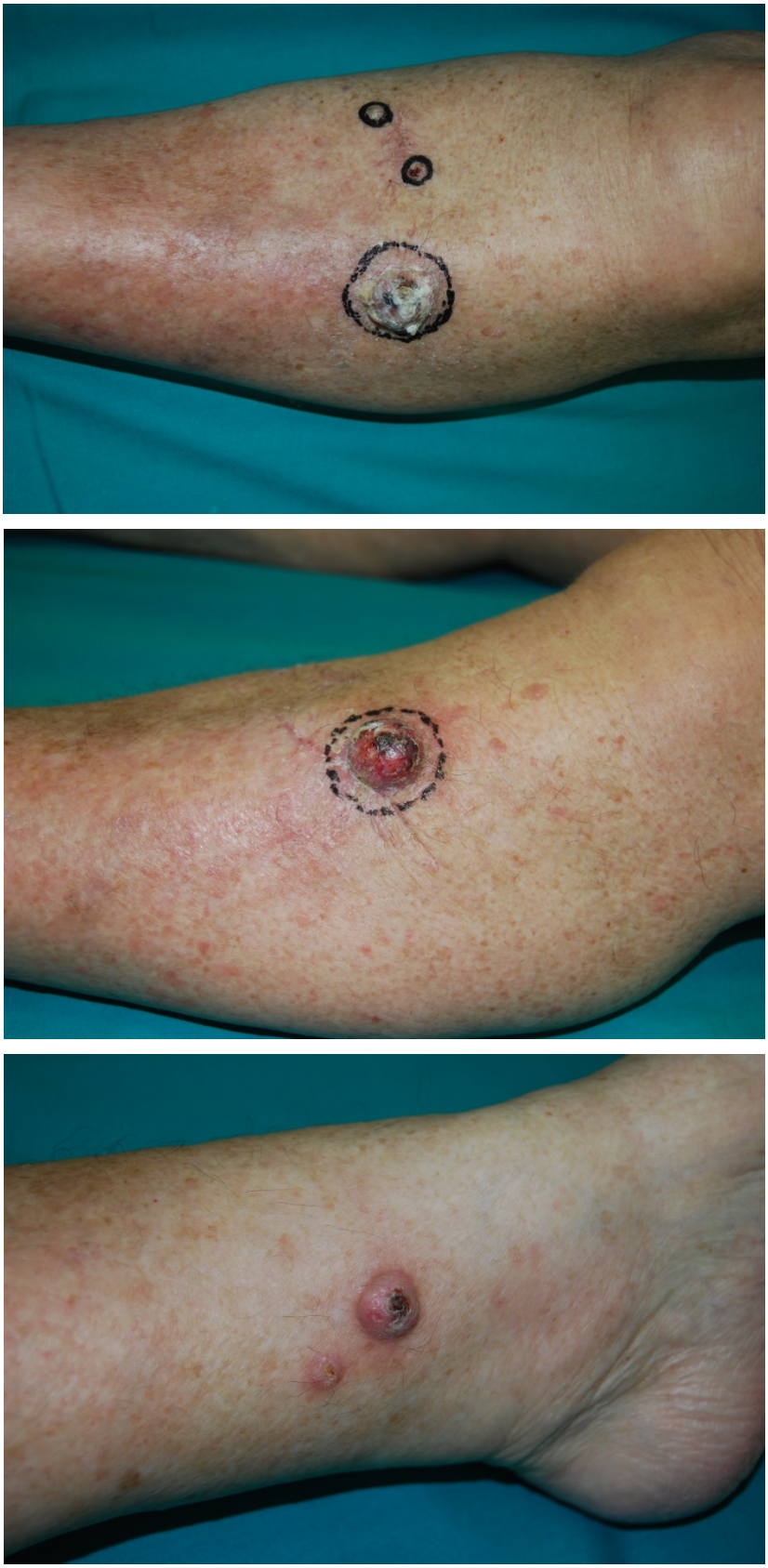

Figure 1, 2, 3. Multiple hyperkeratotic papules and crateriform nodules on lower extremities

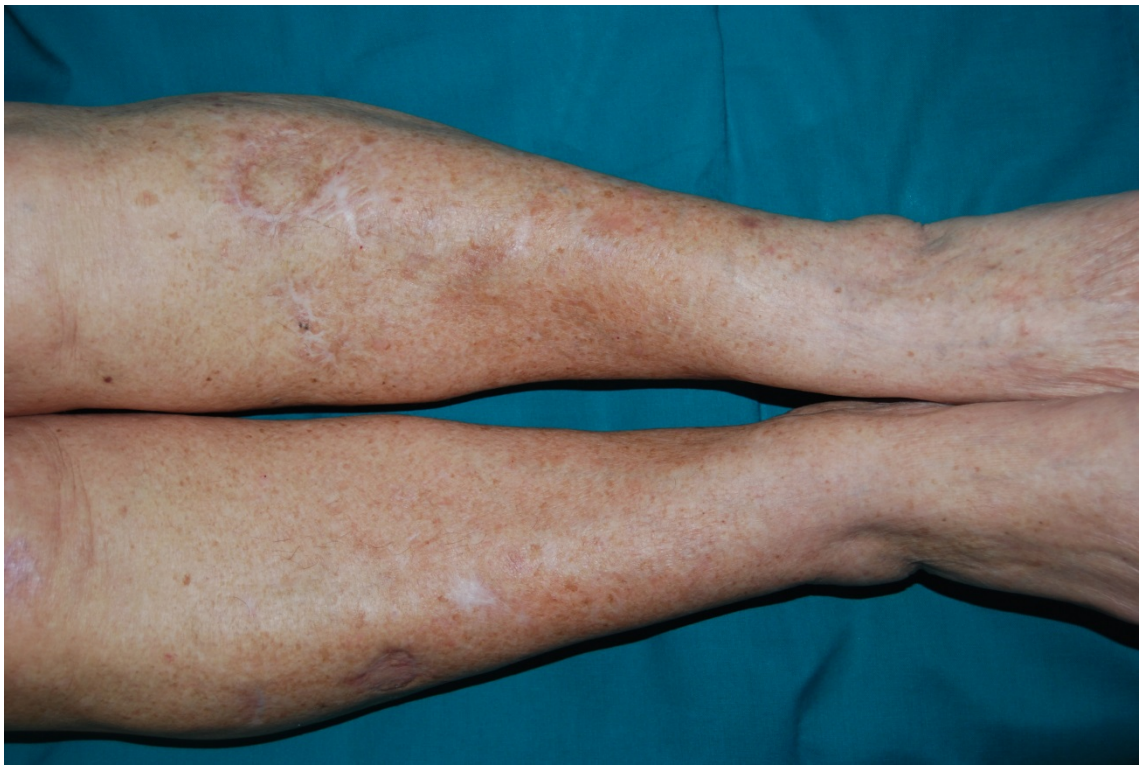

Figure 4. No new lesions after suspension of leflunomide

COMMENT

Leflunomide is a selective immunosuppressive agent used in the treatment of rheumatoid arthritis. It is an isoxazole derivative, selective and reversible inhibitor of dihydroorotate dehydrogenase (DHODH), a key enzyme in de novo synthesis of pyridines. It blocks the cell cycle of activated autoimmune T cells, arresting lymphocyte proliferation. It is a safe drug with minimal adverse effects, so it is widely used in rheumatologic therapy.

The association between leflunomide and the appearance of skin tumors has not previously been described in the literature. Chakravarty et al. [14] explored the association between the use of several immunosuppressive medications and development of non melanoma skin cancer (NMSC) in a large cohort of rheumatoid arthritis (RA) patients and concluded that the use of TNF inhibitors and prednisone were associated with an increased risk of NMSC, but no association was found between the use of methotrexate or leflunomide and development of NMSC (HR 1.12, p = 0.471, HR 0.83, p = 0.173, respectively).

We hypothesized that the sudden onset of multiple keratoacanthomas in this patient (after the introduction of leflunomide), with no history of skin tumors or other immunosuppresive treatment added, suggests a causal relationship. However, we found no mention in the literature of this association and additional case reports are required to confirm this new adverse skin effect of leflunomide.

References

1. Niebuhr M, et al. Giant keratoacanthoma in an immunocompetent patient with detection of HPV 11. Hautarzt. 2009;60:229-32
2. Kluger N,et al. Tattoos, inks, and cancer. Lancet Oncol. 2012;13:e161-8.
3. Janik JP, et al. Traumatic keratoacanthoma arising in a 15-year-old boy following a motor vehicle accident. Pediatr Dermatol. 2006;23:448-50.
4. Colomb D, et al. Multiple keratoacanthomas and coal tar disease. Rev Lyon Med. 1966 30;15:449-62
5. Gewirtzman A, et al. Eruptive keratoacanthomas following carbon dioxide laser resurfacing. Dermatol Surg. 1999;25:666-8
6. Vergara A, et al. Multiple and relapsing keratoacanthomas developing at the edge of the skin grafts site after surgery and after radiotherapy. Dermatol Surg. 2007;33:994-6.
7. Swchatz RA, et al. Generalized eruptive keratoacanthoma of Grzybowski: follow-up of the orignal description and 50-year restrospect. Dermatology 2002;205:345.
8. Agarwal M, et al. Multiple familial keratoacanthoma of Witten and Zak – a report of three siblings. Dermatology 1999;168:396.
9. Kato N, et al. Ferguson Smith type multiple keratoacanthomas and a keratoacanthoma centrifugum marginatum in a woman from Japan. J Am Acad Dermatol. 2003;49:741-6.

10. Dessoukey MW, et al. Eruptive keratoacanthomas associated with immunosuppresive therapy in a patient with systemic lupus erythematosus. J Am Acad Dermatol 1997;37:478.
11. Jantzem H, et al. Sorafenib-induced multiple eruptive keratoacanthomas. Ann Dermatol Venereol. 2009;136:894-7.
12. D'Addario S, et al. Multiple keratoacanthomas as an untoward response to imiquimod therapy for actinic keratoses. Acta Derm Venereol. 2006;86:366-7.
13. Alloo A, et al. Photodynamic therapy for multiple eruptive keratoacanthomas associated with vemurafenib treatment for metastatic melanoma. Arch Dermatol. 2012;148:363-6.
14. Chakravarty EF,et al. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005; 32: 2130-5.