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Kaposi Sarcoma Associated With Infliximab Treatment

Sarcoma de Kaposi asociado al tratamiento con infliximab

To the Editor:

Tumor necrosis factor α antagonists alter the inflammatory response, which leads to an increased risk of infections^{1,2} and neoplasms.³ Such neoplasms include Kaposi sarcoma, a tumor of the vascular endothelium described by Moritz Kaposi in 1872.

We describe the case of a patient who developed Kaposi sarcoma following infliximab therapy for corticosteroid-dependent ileal Crohn disease.

The patient was a 61-year-old man referred from the gastrointestinal department for assessment of skin lesions on the right lower leg. He was an ex-smoker of 20 cigars/d and presented bilateral gonarthrosis with left knee replacement, spondyloarthrosis, hiatal hernia, chronic prostatitis, and moderate-to-severe ileal Crohn disease diagnosed in 2005. At the time of the first consultation the patient was receiving treatment with analgesics, mesalazine, budesonide, and azathioprine. Because corticosteroids could not be discontinued, he was classified as corticosteroid-dependent. The chest radiograph, abdominal computed tomography, Mantoux test, antinuclear antibodies, and serology tests (human immunodeficiency virus, hepatitis B and C virus, syphilis, and varicella-zoster virus) were all normal or negative. Following the tests, infliximab therapy was started at 5 mg/kg (500 mg/session) in weeks 0, 2, and 6.

Ten days after the second dose of infliximab, the patient developed lesions consisting of asymptomatic, erythematous-violaceous plaques of different sizes distributed on the dorsum of the foot and the anterior and medial aspects of the distal third of the right leg, and associated with edema of the limb (Figure 1). A biopsy showed proliferation of irregular fine-walled vessels in the superficial dermis and hypodermis and foci of spindle-shaped cells forming small bundles (Figures 2 and 3); immunohistochemistry was positive for human herpesvirus-8 latent nuclear antigen. Kaposi sarcoma was diagnosed.

The work-up showed no visceral involvement and infliximab was therefore discontinued, keeping the skin



Figure 1 Kaposi sarcoma. Asymptomatic erythematous-violaceous plaques distributed over the dorsum of the foot and the right leg. The lesions appeared 10 days after the second dose of infliximab.

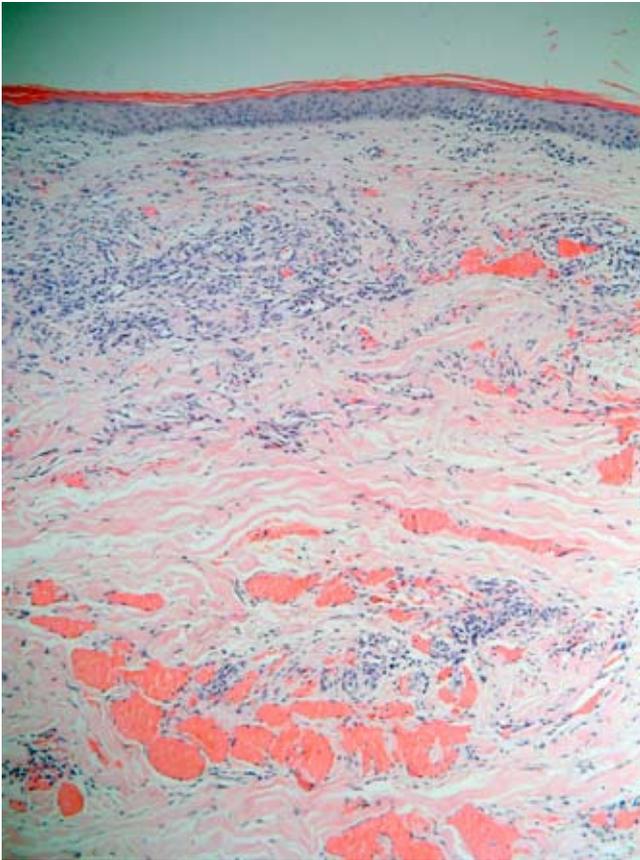


Figure 2 Biopsy of a lesion on the right leg (hematoxylin-eosin, original magnification $\times 40$). Proliferation of 2 components in the superficial hypodermis and dermis. There is a discrete proliferation of spindle-shaped cells together with irregular, very thin-walled, sinusoidal vessels that were growing around pre-existing structures, forming small bundles.

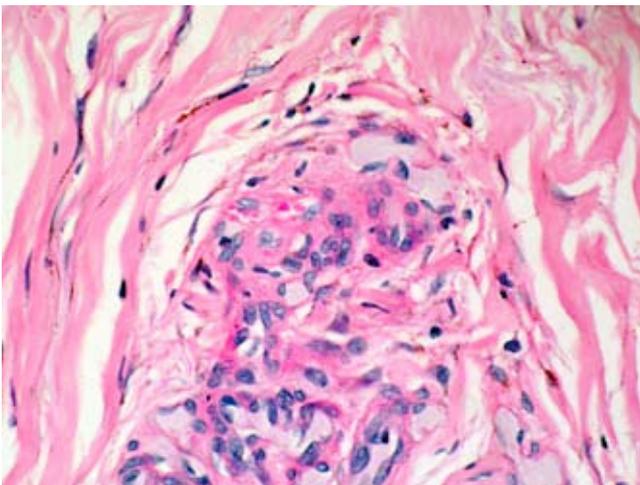


Figure 3 Biopsy of a lesion on the right leg (hematoxylin-eosin, original magnification $\times 400$). Erythrocytes are observed between the spindle-shaped cells, which contain occasional, periodic acid-Schiff-positive hyaline globules.

lesions under observation, without treatment. At the time of writing, after 11 months of follow-up, the patient had presented no new flare-ups of Crohn disease and there had been an improvement in the Kaposi sarcoma lesions, which persisted as discrete asymptomatic macules with no associated edema.

Kaposi sarcoma is classified into 4 variants: classic, endemic, AIDS-related, and iatrogenic. There is a close relationship between immunity and viral infection in the pathogenesis of the disease, and human herpesvirus 8 must be present for the condition to develop, although other factors are also necessary.⁴ Iatrogenic Kaposi sarcoma has been observed in patients receiving corticosteroids^{5,6} or other immunosuppressant drugs,⁷ such as azathioprine or ciclosporin. The clinical course of treatment-related Kaposi sarcoma tends to be linked to immune status. There is a latency period, and spontaneous resolution is likely to occur when the drug is discontinued, though the disease can be more aggressive if the immunosuppressive effect is more intense.

Our patient presented iatrogenic Kaposi sarcoma that appeared simultaneously with the initiation of immunosuppressive therapy with infliximab. Even though he had been on long-term therapy with corticosteroids and azathioprine, the lesions appeared only when infliximab therapy was started, and they showed slow involution once infliximab was discontinued, despite not interrupting the other treatments at any time.

The increasing use of tumor necrosis factor α antagonists to treat an ever larger number of diseases means that further cases of Kaposi sarcoma may be expected in patients on this type of immunosuppressive therapy.

In a literature review, we found 2 additional reports of Kaposi sarcoma in patients treated with infliximab.^{8,9} As in our patient, the lesions appeared a few weeks after the patients had started infliximab therapy, while also on corticosteroid therapy (plus azathioprine in the second case). We contribute a new case to the few published reports on this important subject.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Angioendotheliomatosis Associated With Chronic Venous Insufficiency

Angioendoteliomatosis reactiva asociada a insuficiencia venosa crónica

To the Editor:

Reactive angioendotheliomatosis (RAE) is the name introduced by Tappeiner and Pflieger in 1963 to refer to a rare condition characterized by a benign proliferation of endothelial cells. It has been observed in patients with concurrent systemic diseases, in whom vascular occlusion or underlying vascular disease favors a reactive proliferation of endothelial cells. Presentation varies from multiple foci of erythematous macules, ecchymoses, or purpuric plaques to ulcerated plaques affecting the trunk, limbs, or face.¹ Histology shows vascular proliferation with obliteration of the lumina secondary to endothelial cell hyperplasia and noninflammatory microthrombosis. The differential diagnosis must include benign and malignant vascular tumors, particularly Kaposi sarcoma and angiosarcoma. RAE has no specific treatment; it tends to be self-limiting and resolves spontaneously or after treatment of the underlying disorder.

We present the case of a 68-year-old woman who consulted for the progressive appearance of violaceous plaques on the skin of the left leg. The plaques were completely asymptomatic and had gradually enlarged over several months. Examination revealed multiple erythematous-purpuric macules and plaques on the left leg. The lesions had an irregular outline with an atrophic center that was more yellow in color and on palpation they had an infiltrated, fibrous texture. The clinical findings were suggestive of Kaposi sarcoma (Figure 1). The patient's history included chronic venous insufficiency treated surgically 30 years earlier by varicose vein stripping in the left leg and sclerotherapy in the same leg 20 years later. Based on this history, we also considered a diagnosis of stasis dermatitis. Hematoxylin-eosin staining of a histology specimen showed a vascular proliferation of capillaries lined by prominent

endothelial cells, with microthrombi that occluded the vascular lumen; there was no pleomorphism or nuclear atypia and there were few mitoses. The findings were suggestive of reactive angioendotheliomatosis (Figure 2A). Immunohistochemistry was positive for CD31, confirming the vascular origin of the proliferative cells (Figure 2B), and was negative for CD68. Additional studies, including complete blood count, biochemistry, coagulation, antiphospholipid antibodies, hepatitis serology, rheumatoid factor, protein electrophoresis, and immunoelectrophoresis, were normal or negative. The patient was diagnosed with RAE associated with chronic venous insufficiency; the injection of varicose vein sclerosant could have played an additional pathogenic role. The clinical course during follow-up was favorable, with stability, spontaneous regression, and persistence of discrete brownish macules at revision after 1 year.

RAE is a rare disorder characterized by the presence of



Figure 1 Clinical appearance of reactive angioendoteliomatosis: poorly delimited, infiltrated plaques and macules on the leg, with atrophic central areas, clinically consistent with a malignant vascular tumor.