Kaposi’s Sarcoma Resolves After Sirolimus Therapy in a Patient With Pemphigus Vulgaris

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Background: Iatrogenic Kaposi’s sarcoma (KS) has been reported in patients who use immunosuppressive regimens for the treatment of autoimmune disorders, malignant neoplasms, and organ transplant rejection. However, iatrogenic KS in the setting of pemphigus vulgaris (PV) has been infrequently observed. The conventional treatment strategy for iatrogenic KS has focused on reducing immunosuppression, which carries a poor prognosis owing to a substantial risk for exacerbation of the primary disease.

Observations: A 49-year-old man developed KS on his wrist after 2 years of long-term immunosuppressive therapy with prednisone, methotrexate, and dapsone for well-controlled PV. Three months after the substitution of methotrexate with sirolimus, the KS gradually resolved. With the patient on a maintenance regimen of sirolimus, in conjunction with low-dose prednisone and dapsone therapy, KS and PV have remained in remission, without further recurrence, during a 24-month follow-up period.

Conclusion: The present case introduces a novel therapy for this patient population, highlighting the efficacy of sirolimus in treating iatrogenic KS without sacrificing the immunosuppression necessary to maintain control of PV.

IATROGENIC KAPOSI’S SARCOMA (KS) has been reported in patients undergoing immunosuppressive therapies for autoimmune disorders, cancer, and organ transplant rejection.1,2 It has been infrequently described in patients with pemphigus vulgaris (PV) as a complication of long-term immunosuppression.3 The conventional treatment strategy for iatrogenic KS has focused on reducing immunosuppression, which carries a poor prognosis owing to the substantial risk for exacerbation of the primary disease.4 In the last decade, a growing literature describes the treatment of posttransplantation KS with sirolimus-based regimens, while discontinuing the use of other immunosuppressive agents.5,6 Unlike other immunosuppressives, sirolimus, which is a relatively new drug, has shown antineoplastic activity via antiangiogenic effects.5 We were unable to find any reports documenting the use of sirolimus for the treatment of iatrogenic KS in the setting of PV.

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We describe a 49-year-old man who developed localized KS on his left forearm during long-term immunosuppressive therapy for PV. The substitution of sirolimus for methotrexate resulted in complete clearance of the KS tumor. This case demonstrates the efficacy of sirolimus as a novel therapy for iatrogenic KS in a patient with PV.

REPORT OF A CASE

The patient presented with oral erosions at the age of 47 years. He was otherwise healthy, with a medical history of well-controlled psoriasis with topical therapy. His family history and a review of systems were noncontributory. The findings of routine histologic examination of a tongue biopsy specimen as well as the results of direct (intercellular pattern with IgG) and indirect (titer, 1:80) immunofluorescence confirmed the diagnosis of PV.

Therapy was initiated with oral prednisone (60 mg/d), which led to clinical improvement. After several weeks, intramuscular injections of gold sodium thiomalate (50 mg/wk) were added to the treatment regimen. During the next 3 months, as blistering activity ceased, the dosage of prednisone therapy was gradually tapered to 7.5 mg/d, and the frequency of gold injections was decreased to monthly intervals. After more than 1 year of a stable treatment regimen, new cutaneous blis-
ters developed on the patient’s extremities and genitalia. The dosage of prednisone therapy was transiently increased to 20 mg/d, and oral methotrexate (7.5 mg/wk in 3 divided doses of 2.5 mg every 12 hours) was added to the regimen. The dosage of methotrexate therapy was gradually increased to a weekly regimen of 12.5 mg in 3 divided doses (5 mg, 5 mg, and 2.5 mg) every 12 hours. An excellent clinical response was achieved for 6 months. The recurrence of new blisters prompted the addition of dapsone (50 mg/d) to the regimen. The patient continued to experience low-grade blistering of the genitalia with a regimen of prednisone (7.5 mg/d), methotrexate (12.5 mg/wk in 3 divided doses every 12 hours), dapsone (50 mg/d), and intramuscular injections of gold sodium thiomalate (50 mg/wk).

Mild blistering of the genitalia persisted for more than 12 months, when a new, isolated erythematous patch surrounded by hemorrhagic papules was observed on the distal portion of the left forearm (Figure 1A). Assumed to be a new, possibly vegetative lesion of PV, it was treated for 2 months with an increased dose of prednisone (15 mg/d) and intralesional triamcinolone (10 mg/mL). The unusual morphological appearance of the new lesion and the recalcitrant genital blistering led to the initiation of rituximab therapy (1000 mg), which was administered intravenously on days 1 and 15. When the patch on the patient’s wrist unexpectedly continued to thicken into a firm hemorrhagic annular plaque after the rituximab infusions, a trephine biopsy specimen was obtained for routine histologic analysis and direct immunofluorescence.

Microscopic examination revealed a proliferation of small vessels around preexisting capillaries throughout the dermis. The vessels had a jagged and irregular outline with a slitlike appearance that dissected diffusely through the collagen bundles. The endothelial cells lining the vessels were thin and attenuated, without significant atypia. Both the vessels and the preexisting capillaries were frequently associated with a scattered lymphoplasmacytic infiltrate. The findings were considered diagnostic of patch-stage KS (Figure 2). No immunopathologic features were detected on direct immunofluorescence, with negative staining for IgG, IgM, IgA, complement, and fibrinogen. Serologic tests were negative for human immunodeficiency virus.

Once the diagnosis of KS was established, cryosurgery was initiated with liquid nitrogen spray for a duration of 60 seconds. Methotrexate therapy was discontinued in an effort to reduce immunosuppression. Treatment with prednisone (15 mg/d), dapsone (50 mg/d), and intramuscular gold sodium thiomalate (50 mg/mo) was continued. After 1 month of observation, palpation of the KS lesion revealed increasing induration, and new pemphigus blisters were evident on the genitalia. In the absence of a response to both cryosurgery and rituximab therapy, a decision was made to initiate a trial of oral sirolimus (Rapamune) (2 mg/d).

During the first month of sirolimus therapy, dramatic involution of the KS plaque was observed (Figure 1B). The
lesion decreased in size and thickness until it was virtually imperceptible by month 3 (Figure 1C). The cutaneous blistering also diminished shortly after the sirolimus therapy was initiated. Maintenance therapy with oral sirolimus (2 mg/d) was not associated with recurrent or new KS lesions during the next 2 years. As the underlying PV remained in complete remission, gold therapy was discontinued approximately 1 year after the sirolimus therapy was initiated. No adverse events have been noted on a regimen of prednisone (5 mg/d), dapsone (50 mg/d), and sirolimus (2 mg/d).

### COMMENT

Moriz Kaposi first described KS in 1872 under the name idiopathic multiple pigmented sarcoma. Four clinical variants of KS are now recognized: classic, endemic, AIDS-associated, and iatrogenic. The cutaneous morphologic appearance ranges from bluish red macules or papules to patches or plaques; lesions can become nodular or infiltrative and disseminate to visceral organs.

The relationship between immunosuppression and KS was first reported in the organ transplant population in the 1960s. The advent of new immunosuppressive agents, and their long-term use at high doses, has increased the risk for the development of transplant-associated KS (128 to 500-fold as compared with the general population). Also, iatrogenic KS has been observed in patients receiving immunosuppressive drugs for lymphomas, multiple myeloma, and autoimmune diseases. As all variants of KS have been linked to infection with human herpesvirus 8, the pathogenesis of iatrogenic KS has been related to the permissive effect of immunosuppressive therapy on human herpesvirus 8 infection or reactivation.

The prognosis associated with iatrogenic KS correlates with the extent of disease. One-year survival rates vary substantially among patients with cutaneous (90%) or visceral (70%) involvement. The standard therapy for iatrogenic KS—withdrawal of immunosuppressive modalities—often produces a partial to complete regression through immune reconstitution and natural human herpesvirus 8 suppression. However, even after reduced immunosuppression, there is still substantial mortality from KS, as well as the risk for exacerbation of the primary disease.

Pemphigus vulgaris is a chronic autoimmune disorder of the skin and mucous membranes. Systemic corticosteroids with adjuvant immunosuppressive or anti-inflammation agents are the mainstay of treatment. Untreated PV is often fatal because of susceptibility to infections as well as fluid and electrolyte disturbances. However, long-term immunosuppression may lead to complications such as infection and secondary neoplasms as a result of impaired immune surveillance. We describe a case of iatrogenic KS that developed in the setting of immunosuppressive therapy for PV.

To date, 10 cases of KS have been reported in association with immunosuppressive therapy for PV; 5 of these cases were fatal within 1 year of KS diagnosis, despite the reduction of immunosuppressive regimens. Typically, immunosuppressive medication doses are lower in patients with PV than in transplant recipients, which may account for the lower frequency of KS in this group. Also, in PV, the lower doses of immunosuppressive drugs at the onset of KS is a likely explanation for the milder clinical course; however, higher doses often lead to a more fulminating picture.

Recent case studies have revealed that sirolimus is an effective therapy for iatrogenic KS among transplant recipients, while maintaining adequate immunosuppression. Sirolimus is a macrolide antibiotic, with immunosuppressive, antiproliferative, and antiangiogenic properties, indicated for the prevention of organ rejection, specifically renal transplantation. It has been found to have antitumor effects by inhibiting mTOR and cyclosporine, function as immunosuppressives predominantly by inhibiting the production of interleukin 2.

The antitumor effects of sirolimus have been demonstrated in both in vitro and in vivo studies, using animal models. One study showed that while cyclosporine promoted tumor growth, normal immunosuppressive doses of sirolimus controlled the growth of established tumors and inhibited metastatic growth and angiogenesis in mouse models. As the production of vascular endothelial growth factor (VEGF) and activation of VEGF receptors have been implicated in the development of KS, it is noteworthy that the mechanism of sirolimus causes a decrease in the production of VEGF and inhibits the extent of stimulation of endothelial cells in response to VEGF.

Case series have extended this research to human subjects via reports of the clinical efficacy of sirolimus therapy in human transplant recipients. Two reports found that transplant recipients with biopsy-proved KS experienced regression of the tumors several months after calcineurin inhibitor therapy was replaced with a sirolimus-based regimen. Both studies demonstrated that effective levels of immunosuppression were maintained to prevent organ rejection. Moreover, over a 5-year follow-up period, sirolimus therapy was shown to prevent the onset of iatrogenic KS in kidney transplant recipients when compared with patients receiving cyclosporine. Minor adverse cutaneous events associated with sirolimus therapy include acenlile eruptions, edema, and nail disorders.

A thorough review of the current literature revealed no previous description of sirolimus therapy for iatrogenic KS in the setting of PV. Our patient developed localized, cutaneous KS after 2 years of immunosuppressive therapy for PV. His tumor did not improve after the dosage of immunosuppressive therapy was reduced. Complete cessation of immunosuppression was not an option based on the clinical activity of his PV. Therefore, sirolimus was chosen as an adjunct medication based on published data regarding its efficacy in treating iatrogenic KS. After sirolimus was
added to the patient’s regimen, his KS lesion resolved completely, without exacerbation of the PV. It seems important to emphasize that intractable blistering during concomitant prednisone, dapsone, methotrexate, and intramuscular gold therapy resolved promptly after sirolimus was introduced to the regimen. No further blistering has occurred during an observation period of more than 2 years, while all other treatment with immunomodulatory drugs was discontinued with the exception of low doses of prednisone.

Iatrogenic KS in the setting of PV has been associated with a poor prognosis when treated by conventional reduction of immunosuppression.3 This case highlights the successful use of sirolimus in treating iatrogenic KS without sacrificing the immunosuppression necessary to control the PV. Further studies are warranted to extend these observations, not only from the perspective of sirolimus treatment for KS in the setting of chronic immunosuppression but also as a new core modality for PV and related autoimmune diseases.

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