

# Iatrogenic Kaposi's sarcoma after immunosuppressive treatment for granulomatosis with polyangiitis (Wegener's)

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## INTRODUCTION

Kaposi's sarcoma (KS) is a lymphoangioproliferative neoplasm induced by human herpes virus 8 (HHV-8). Four clinical variants have been recognized: classical, African endemic, AIDS-related, and KS caused by iatrogenic immunosuppression. The latter is typically associated with the use of immunosuppressive therapy in organ transplant recipients; however, iatrogenic KS can also occur in patients receiving immunosuppression for other indications, such as autoimmune disorders.<sup>1</sup>

Granulomatosis with polyangiitis (GPA), formally known as *Wegener's granulomatosis*, is a multi-system necrotizing autoimmune vasculitis, which can be fatal and is classically treated with cyclophosphamide (CP) and prednisone.<sup>2</sup> To our knowledge, only 3 cases report the development of iatrogenic KS in the context of GPA.<sup>3-5</sup> We describe a case of an HIV-negative patient who had iatrogenic KS after GPA therapy, did not improve after first-line treatment reduction or withdrawal of immunosuppression, and consequently required systemic treatment with liposomal doxorubicin.

## CASE REPORT

A previously healthy 66-year-old Romanian woman had GPA diagnosed in 2012. Her treatment regimen consisted of high-dose intravenous (IV) cyclophosphamide (800 mg/mo) and systemic corticosteroids (IV methylprednisolone pulse followed by 25 mg of oral prednisone daily). After 5 months of therapy, several painless, red-to-violaceous coalescing papules appeared on her right arm, shoulder,

### Abbreviations used:

AZA:	Azathioprine
CP:	Cyclophosphamide
GPA:	Granulomatosis with polyangiitis
HHV-8:	Herpes human virus 8
IV:	Intravenous
IS:	Immunosuppressants
KS:	Kaposi's sarcoma
NS:	Not specified

and leg. After 6 months of treatment, GPA remission was achieved, and cyclophosphamide was changed to azathioprine (2 mg/kg/d) for maintenance, whereas prednisone was slowly tapered over 12 months to 10 mg/d. Despite reduced immunosuppression during the maintenance phase, the patient's lesions progressed, and the dermatology service was consulted. At the time of initial presentation to our clinic, skin lesions involved all 4 limbs and trunk (Fig 1, A). Skin biopsy confirmed plaque-stage KS (Fig 1, B) and imaging and endoscopy ruled out systemic involvement. Diagnosis of cutaneous iatrogenic KS was made, and considering the clinical remission of GPA, azathioprine was stopped and prednisone was further tapered to 8 mg/d. Two months later, despite continued reduction of immunosuppression, her KS lesions became more symptomatic with worsening pain, edema, and paresthesias. Further clinical deterioration, prompted systemic treatment with IV doxorubicin (36 mg every 3 weeks for 6 doses followed by 36 mg every 4 weeks for 2 doses and now receiving 36 mg every 8 weeks as needed). KS lesions improved after the first treatment (Fig 2), and remission was achieved on treatment completion.

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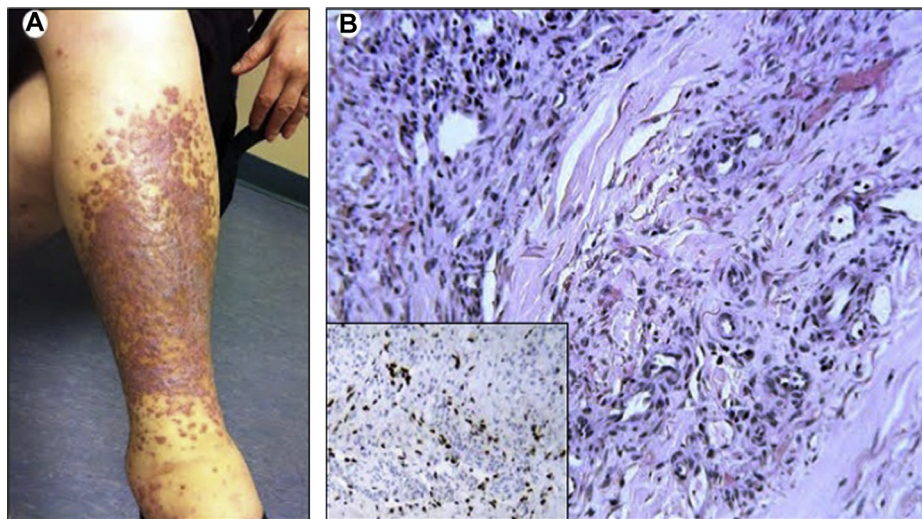
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**Fig 1.** **A**, KS lesions before treatment with doxorubicin. **B**, Left leg biopsy shows proliferation of endothelial spindle cells forming vascular spaces indicating KS plaque stage (Hematoxylin-eosin stain). Positive HHV-8 nuclear staining was detected in spindle and endothelial cells (Inset).



**Fig 2.** Clinical appearance of KS lesions after 1 year of treatment with doxorubicin.

No clinical recurrence occurred at 12 months of follow-up.

## DISCUSSION

Patients originating from Eastern Europe and the Mediterranean belt, where exposure to HHV-8 is endemic in some regions, are at an increased risk of KS in the context of immune suppression.<sup>1</sup> Decreased immunity leads to the reactivation of HHV-8, a virus that exerts its oncogenic effects by inhibiting 2 major tumor suppressor proteins in endothelial cells; the retinoblastoma protein and p53.<sup>1</sup> Maintaining immunosuppression leads to further progression of iatrogenic KS. However, restoring immune defenses by reducing or withdrawing immunosuppression may induce spontaneous KS remission and represents the first-line therapy for iatrogenic KS.<sup>1</sup> Iatrogenic KS can present a therapeutic dilemma, as decreasing the level of

immunosuppression may not be possible or may come at the high cost of organ rejection, such as in the case of organ transplant recipients or organ damage in the case of patients with autoimmune disorders.

Most patients with untreated generalized GPA experience a rapidly progressive fatal illness. Before the advent of immunosuppressive therapy, the 5-month survival rate for GPA was only 18%.<sup>2</sup> Currently, with the use of systemic steroids and cyclophosphamide in conjunction with 18 months of maintenance therapy with less-toxic agents, GPA remission can be achieved in more than 75% of cases.<sup>2</sup> Only 3 cases of iatrogenic KS have been reported in patients with GPA (Table I). Two patients improved after reduction or withdrawal of immunosuppressant drugs. Immunosuppression could not be reversed for the third patient because of underlying disease, which eventually led to patient death. Of note, the first 2 patients improved with prednisone taper despite continuation of cyclophosphamide.

KS was also reported in patients receiving corticosteroids for other indications, including pain from ulnar nerve entrapment and autoimmune thrombocytopenia.<sup>6,7</sup> In these cases, regression of KS lesions were noted within 3 to 4 months after reduction or discontinuation of immunosuppression.<sup>6,7</sup> In-vitro studies suggest corticosteroids induce KS by indirectly inhibiting transforming growth factor beta, a protein that inhibits growth of endothelial cells.<sup>8</sup> In our patient, despite prednisone taper over 14 months and discontinuation of

**Table I.** Outcome of iatrogenic KS in patients receiving immunosuppressive therapy for GPA

	Year	Age	Sex	Ethnicity	IS before KS development	IS at time of KS improvement	Time to regression of KS after reducing IS
Deschenes et al <sup>3</sup>	2003	54	M	Caucasian	CP 150 mg/d Pred 80 mg/d	CP 50 mg/d Pred 10 mg/d	4 mo
Erban and Sokas <sup>4</sup>	1988	78	M	Polish	CP 100 mg/d Pred 60 mg/d	CP 75 mg/d	1 wk
Hoff and Rodevand <sup>5</sup>	2005	74	M	NS	CP cumulative dose 200,000 mg AZA, NS Pred, NS MTX 15 mg/wk	Not applicable	NS

AZA, Azathioprine; CP, Cyclophosphamide; GPA, Granulomatosis with polyangiitis; IS, Immunosuppressants; KS, Kaposi's sarcoma; M, male; MTX, Methotrexate; NS, Not specified; Pred, Prednisone.

azathioprine, KS lesions progressed, prompting alternative treatment.

Previous case reports and small case series reported promising results using liposomal doxorubicin, etoposide, and taxanes in the treatment of iatrogenic KS.<sup>9</sup> Liposomal doxorubicin is more effective and less neurotoxic than other chemotherapeutic agents because of its ability to extravasate through leaky vessels of angiogenic tumors, making it an ideal drug in the treatment of KS.<sup>9</sup> Moreover, the addition of polyethylene glycol to the liposomal component of doxorubicin alters the drug's kinetics resulting in a prolonged half-life, greater accumulation in KS tissues, and, consequently, enhanced tumoral toxicity.<sup>10</sup> It was proposed that doxorubicin may decrease HHV-8 viremia and lead to regression of KS by suppressing cytokine production from infected cells and by inhibiting HHV-8 replication in peripheral blood monocytes.<sup>10</sup>

This case highlights the therapeutic challenge of iatrogenic KS, as reduction or removal of immunosuppression may not always lead to resolution of KS. In these cases or in cases in which reduction of immunosuppression may not be possible, systemic therapy with agents such as liposomal doxorubicin should be considered.

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