

Oral Kaposi's Sarcoma in a Renal Transplant Patient: Case Report and Literature Review

(Le sarcome buccal de Kaposi chez une patiente ayant subi une transplantation rénale : rapport de cas et recensement de la littérature)

- Mark Darling, BChD, MSc (Dent), MSc (Med), MChD •
- Ivor Thompson, BChD, BChD (Hons), MChD, PhD •
- Mohammed Meer, BDS, Dip Odont (Oral Surgery) •

S o m m a i r e

Des malignités, y compris le sarcome buccal de Kaposi, peuvent se former chez les patients ayant subi une transplantation, suite à une thérapie immunosuppressive. La prévalence tout comme l'incidence de ces malignités varient. Le présent article décrit le cas d'une patiente ayant subi une transplantation rénale qui suivait une thérapie immunosuppressive et qui présentait un sarcome buccal de Kaposi. Le sarcome a été enlevé et n'est jamais réapparu. Cependant, la patiente est décédée à la suite d'une pneumonite virale, consécutive à ses problèmes rénaux. L'article comprend également un recensement de la littérature, qui s'attarde particulièrement sur les symptômes buccaux des malignités liées à l'immunosuppression.

Mots clés MeSH : immunosuppressive agents/adverse effects; kidney transplantation/immunology; sarcoma, Kaposi/etiology

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The development of iatrogenic malignancies in organ transplant recipients has been well documented. Oral Kaposi's sarcoma in HIV-positive and AIDS patients has received much attention in the literature in recent years,¹ whereas iatrogenic Kaposi's sarcoma presenting in the oral cavity has not been recorded as thoroughly. The latter form may occur in organ transplant patients, months or years after the transplant.^{2,3} The frequency of malignant lesions in renal transplant patients is between 14 and 500 times higher than in the general population, and these lesions occur at a younger age in renal transplant recipients than in the general population.⁴ The prevalence of all malignancies in renal transplant patients ranges from 4% to 18% (average 6%),⁵ and the incidence rises with each year after transplantation. Malignant tumours appear a mean of 61 months after renal transplantation; for Kaposi's sarcoma the mean period is 20 months.⁶

This article describes the occurrence of oral Kaposi's sarcoma in a renal transplant patient who was receiving immunosuppressive therapy. The literature is also reviewed, with particular reference to iatrogenic oral mucosal presentation in organ transplant patients.

Case Report

A 49-year-old woman who had undergone renal transplantation 1 year previously presented with a flat purple lesion 8 mm in diameter on her hard palate. She reported that the lesion had been present for 2 months. Further examination confirmed that no similar lesions were present on her skin. Subsequent to the transplant she had started an immunosuppressive drug regimen that was administered orally: cyclosporine 150 mg twice daily along with prednisone 15 mg per day and azathioprine 50 mg per day.

The palatal lesion (an example of which, from another patient, is shown in Fig. 1) was excised and examined microscopically. The histological sections revealed a vascular proliferation composed predominantly of small slit-like blood vessels and a proliferation of endothelial cells. The endothelial cells showed a mild degree of pleomorphism, but mitotic figures could not be demonstrated (Fig. 2). Red blood cell extravasation and small periodic acid-Schiff-positive hyaline bodies were present. Immunostaining with endothelial cell markers CD31 and CD34 was strongly positive in the tumour



Figure 1: Kaposi's sarcoma of the palate and gingiva (not the patient described in the report).

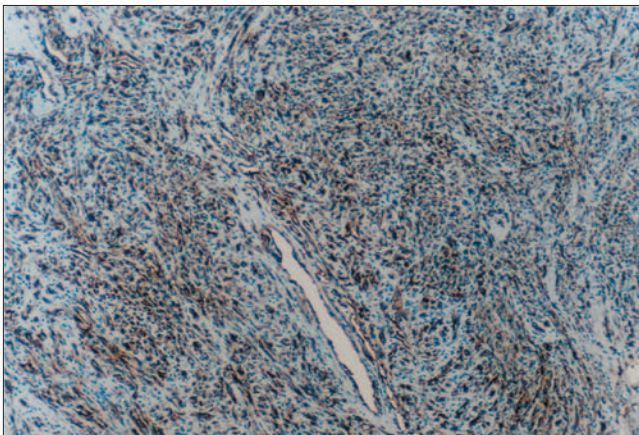


Figure 3: Photomicrograph showing positive immunostaining of tumour cells with endothelial cell marker CD31 (magnification $\times 100$).

cells (Fig. 3). Kaposi's sarcoma was diagnosed on the basis of these findings. Tests for HIV were negative.

The patient did not return for a follow-up visit or for the biopsy results. She died in August 2002 (1 year after the biopsy) as a result of viral pneumonitis, secondary to renal failure and hypertension. No post-mortem examination was performed, but there was no evidence that additional Kaposi's sarcoma lesions had developed.

Discussion and Review of the Literature

The cause of Kaposi's sarcoma has been linked to a recently discovered human herpesvirus, HHV-8. HHV-8 is a DNA virus that occurs worldwide but shows major geographic variation. It has a global seroprevalence of between 2% and 10% and is presumably under immunologic control in healthy

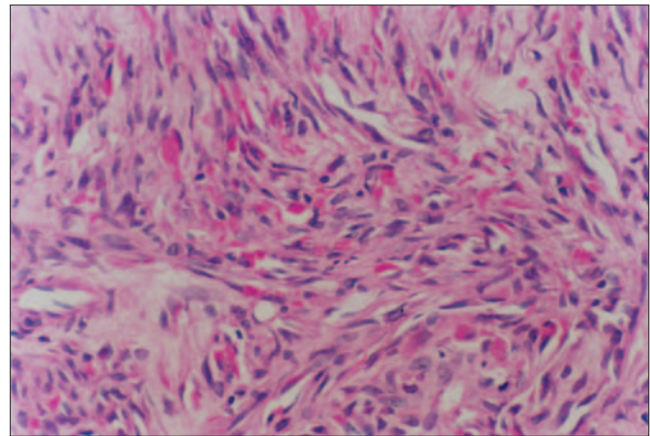


Figure 2: Photomicrograph demonstrating the proliferation of endothelial cells and numerous slit-like vascular spaces (hematoxylin and eosin, magnification $\times 200$).

individuals who become infected.⁷ This virus is transmitted mainly by sexual contact and is strongly associated with Kaposi's sarcoma, body cavity-based lymphoma, primary effusion lymphoma, multicentric Castleman's disease, anaplastic large-cell lymphoma, multiple myeloma and other non-neoplastic disorders.^{7,8} Luppi and others⁹ reported infection of an adult male kidney recipient with HHV-8 and the subsequent development of visceral Kaposi's sarcoma. The Kaposi's sarcoma developed 4 months after the transplantation. This patient later experienced progressive, severe peripheral cytopenia in the presence of normocellular or hypercellular bone marrow with hemophagocytosis. HHV-8 was the sole pathogen detected by polymerase chain reaction in the serum and in the bone marrow.⁹

Interestingly, Sarid and others¹⁰ suggested that HHV-8 may be latent in donor kidneys, with development of Kaposi's sarcoma occurring during post-transplantation immunosuppression. They described 2 patients who received kidneys that were positive for HHV-8 DNA, as well as a third patient in whom Kaposi's sarcoma developed as a result of reactivation of pre-existing infection.¹⁰ Kapelushnik and others¹¹ described the development of Kaposi's sarcoma in a 17-year-old male after he received a kidney from his HHV-8 seropositive father. Barozzi and others¹² have shown that post-transplantation Kaposi's sarcoma often derives from the seeding of donor-derived progenitors.

Four clinical types of Kaposi's sarcoma are recognized^{3,13}:

- the chronic or classic type, occurring in late adult life, usually in men of eastern European descent
- the endemic or lymphadenopathic type, seen in Africa
- the AIDS-related type
- the transplant-associated or iatrogenic type, associated with immunosuppressive therapy in patients who have received solid organ transplants.

The reported prevalence of Kaposi's sarcoma in kidney recipients has varied. Haberal and others⁵ reported a 30% prevalence of Kaposi's sarcoma and found that it

occurred more commonly in patients who had received cyclosporine as part of their immunosuppressive regimen. In contrast, Margolius and others¹⁴ reported an 8% prevalence. In their study of 989 renal transplant patients, 95 malignancies occurred in 75 patients; 5 of the 95 lesions (5%) were Kaposi's sarcoma, of which only 1 case occurred in the oral cavity. The Kaposi's sarcoma lesions presented with limited skin involvement (in 1 patient) or as disseminated forms of the disease: necrotic oral lesions (in 1 patient), disseminated skin involvement and lung metastases (in 1 patient) and widespread skin lesions with lymphadenopathy (in 2 patients). All of the patients in that study had received immunosuppressive agents: azathioprine with or without cyclosporine and steroids. Four patients experienced complete tumour regression at all sites upon withdrawal of the immunosuppressive drugs. Lessan-Pezeshki and others¹⁵ reported a 0.88% prevalence of Kaposi's sarcoma in renal transplant patients. Kaposi's sarcoma developed in 18 of 2,050 patients; all of those affected had received cyclosporine as part of their immune-suppressive regime.¹⁵ Andreoni and others¹⁶ observed a higher risk of Kaposi's sarcoma among renal transplant patients than among liver transplant patients, although more of the latter showed HHV-8 seroconversion after transplantation; 16.1% of all patients in the study were HHV-8 seropositive before transplantation.¹⁶

The coexistence of Kaposi's sarcoma and tuberculosis in a renal transplant recipient receiving immunosuppressive therapy has been reported.¹⁷ The lesions were aggressive and involved the oral mucosa, the cervical and mediastinal lymph nodes, the gastrointestinal tract and the lung. The tuberculosis was detected incidentally during the histological examination of an excised lymph node. The patient was given 12 months of antituberculous chemotherapy. Immunosuppression was gradually tapered over a 2- to 3-week period, and the Kaposi's sarcoma subsequently regressed completely, despite its apparent aggressive nature. The patient remained disease free after a follow-up period of 30 months. However, the kidney allograft was rejected, and the patient required reinstitution of dialysis.

The oral presentation of Kaposi's sarcoma may mimic gingival hyperplasia.^{18,19} Cyclosporine is often implicated, and 2 such cases have been reported in which Kaposi's sarcoma was present in hyperplastic gingiva of patients who were receiving cyclosporine.¹⁹ Cyclosporine on its own tends to produce a generalized, erythematous, fibrotic gingival hyperplasia, whereas Kaposi's sarcoma produces a more localized, red-purple enlargement. If the oral cavity is affected by Kaposi's sarcoma in transplant patients, the lesions are usually located on the palate or the oropharynx.¹⁸

Histopathologically, the progression of Kaposi's sarcoma can be divided into 3 phases: the patch or macular stage, the plaque stage and the nodular stage.³ The patch stage is usually characterized by a proliferation of small vessels, which results in an irregular vascular network surrounding existing vessels. The lesional endothelial cells are bland-appearing and may be associated with the presence of chronic inflammation. In this

phase the lesion may resemble granulation tissue. The plaque stage is characterized by the further proliferation of vascular channels and the development of a prominent spindle cell component. In the nodular stage, there is increased proliferation of the spindle cell component to form a nodular tumour-like mass that resembles other spindle cell sarcomas such as fibrosarcoma. However, many slit-like vascular spaces are present. All phases may show extravasated red blood cells, hemosiderin pigment and hyaline globules.^{3,20} CD34- and CD31-positive marking of the endothelial cells is valuable in confirming the diagnosis of Kaposi's sarcoma. Immunohistochemical staining of Kaposi's sarcoma suggests that it shows lymphatic differentiation rather than capillary endothelial differentiation.¹³ Immunoreactivity to capillary or lymphatic markers may vary with the type or stage of the disease, but recently vascular endothelial growth factor receptor 3 (VEGFR-3), a sensitive marker of lymphatic differentiation, has been identified in most cases of Kaposi's sarcoma.¹³

Treatment of post-transplantation Kaposi's sarcoma is directed toward reducing the immunosuppressive drug regimen. Duman and others²¹ described 12 patients who experienced Kaposi's sarcoma after renal transplantation, each of whom was receiving prednisone, azathioprine and cyclosporine. Reduction or discontinuation of these drugs resulted in complete remission in all patients.²¹

Conclusions

Kaposi's sarcoma occurring in transplant recipients may regress spontaneously if immunosuppressive therapy is reduced or discontinued. This phenomenon raises the possibility that the lesion may be a reversible hyperplasia rather than a true malignancy.²² Therefore, treatment of Kaposi's sarcoma in transplant patients usually consists of withdrawal of immunosuppression. If there is no response, chemotherapy may be started. Successful treatment has also been reported with paclitaxel.²³

The case presented here illustrates the importance of dental providers closely assessing the treatment needs of long-term transplant survivors because of the potential occurrence of secondary malignancies (including Kaposi's sarcoma, squamous cell carcinoma and lymphoma) in the oral cavity. ♦



Le Dr Darling est professeur adjoint, Division de pathologie buccale, Département de pathologie buccale, Faculté de médecine et de médecine dentaire, Université Western Ontario, London (Ontario).



Le Dr Thompson est professeur agrégé/spécialiste principal, Département des sciences diagnostiques, Division de la pathologie buccale, École des sciences de la santé buccodentaire, Faculté des sciences de la santé, Université de Stellenbosch, Tygerberg (Afrique du Sud).



Le Dr Meer est assistant clinique/registraire, Division de chirurgie buccale et maxillofaciale, École des sciences de la santé buccodentaire, Faculté des sciences de la santé, Université de Stellenbosch, Tygerberg (Afrique du Sud).

Écrire au : Dr Mark Darling, Département de pathologie, Faculté de médecine et de médecine dentaire, Université Western Ontario, London ON N6A 5C1. Courriel : mark.darling@fmd.uwo.ca.

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