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Kaposi sarcoma at the base of the tongue in a renal transplant patient

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SUMMARY

Oral Kaposi Sarcoma (OKS) commonly occurs in patients with AIDS. The incidence of Kaposi sarcoma (KS) is greatly increased in renal transplant recipients compared with the general population, with particular prevalence in certain ethnic groups where it can occur in up to 5% of transplant recipients. From them, only 2% can manifest first with OKS.

A man in his early 40s, 2 years after kidney transplantation, presented with a reddish-purple hypertrophic ulcerated lesion at the base of the tongue. Cervical ultrasonography revealed enlarged lymph nodes, and pathological examination of biopsies revealed KS. The patient had HIV-negative status. Following an investigation, calcineurin inhibitor treatment was stopped, and an mTOR (mammalian target of rapamycin) inhibitor treatment was started. Fiberoptic examination 3 months after beginning mTOR inhibitor treatment revealed no traces of the disease in the base of the tongue.

An isolated oral lesion should not distract clinicians from further systemic investigation for metastatic disease. OKS is a rare but serious complication in kidney transplant patients after receiving calcineurin inhibitor that could result in airway obstruction due to mass effect or bleeding and aspiration.

Early diagnosis and management of OKS in a renal transplant patient who received a calcineurin inhibitor carry a good prognosis. OKS can be managed by changing the treatment regime to an mTOR inhibitor followed by radiation therapy. This contrasts with KS treatment in non-renal transplant patients without calcineurin inhibitors who may need treatment using different modalities such as surgery and chemotherapy. We emphasise the importance of this case for nephrologists responsible for patient follow-up after renal transplantation who prescribed calcineurin inhibitors. These patients must be advised that if they feel any physical mass in the tongue, they should immediately seek an examination by an ear, nose and throat specialist. Nephrologists and patients should be aware that these symptoms should not be underestimated.

BACKGROUND

Kaposi sarcoma (KS) is an angioproliferative disease that is rare in the general population. The incidence is 0.01%–0.06% with a male-to-female ratio of 3:1, mainly affecting individuals of Mediterranean, Jewish and Arab ancestry.¹ However, the rates of KS increase up to 500-fold in solid organ transplant recipients on immunosuppressive therapy with an average time to development after transplant of 13–21 months, and up to 20 000-fold in

HIV-seropositive patients.¹ This highlights the strong correlation between immunosuppression and the development of KS. The type of immunosuppressive agent, types of organ transplanted and patient ethnicity are all associated with the probability of iatrogenic KS development.² Renal transplants are the most commonly transplanted organs in iatrogenic KS.² The development of KS in organ transplant recipients could be attributed to the transmission of human herpes virus-8 from the donor or the reactivation of the latent virus in the recipient's body.²

The clinical presentation of KS in transplant patients is often limited to the skin of the lower extremities. While oral KS (OKS) commonly occurs in patients with AIDS,³ KS at the base of the tongue in transplant patients has only been described in a few cases. Of all transplant patients, 5% develop KS, of which 2% are OKS.² Treatment with immunosuppressive medication such as calcineurin inhibitors is known to increase the rate of KS among transplant patients.¹

All forms of KS show evidence of neoangiogenesis, inflammatory cells and spindle-shaped endothelial cells, which increase around the areas of angioproliferation.⁴ The rarity of an oral lesion as an initial marker of the disease in an HIV-negative status patient is a factor that may lead to misdiagnosis.⁴

OKS usually affects the hard and soft palates, gingiva and dorsum of the tongue.² Cutaneous and mucosal lesions usually start as patches, develop into plaques and progress into nodules.²

Whatever the initial presentation, the primary approach to the management of transplant-associated KS is a marked reduction or even discontinuation of immunosuppressive therapy, which has been shown to improve the outcomes of iatrogenic KS and can be curative.²

In post-transplant patients with KS, reduction or withdrawal of immunosuppressive therapy is the first-line treatment. Naturally, this elevates the risk of acute organ rejection and failure and the possibility of recurrence if immunosuppressive therapy is restarted.⁵ The substitution of sirolimus for others, such as ciclosporin and tacrolimus, has shown KS regression without an increased risk of organ rejection.⁴

CASE PRESENTATION

A man in his early 40s was admitted to the hospital after reporting a lump in his throat for the previous 2 weeks. He had been transplanted with a live-donor kidney 2 years prior due to focal segmental



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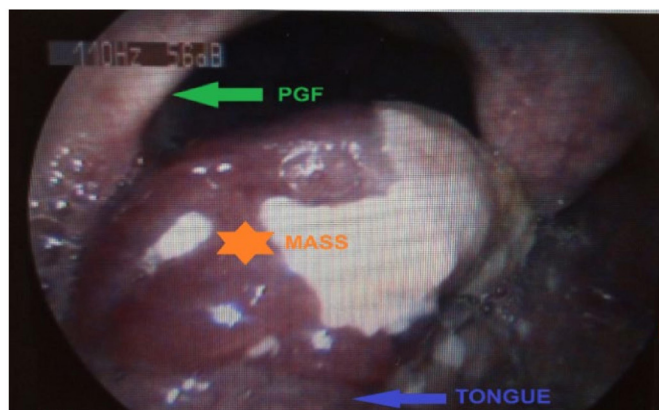


Figure 1 Fiberoptic laryngoscopy. PGF, palatoglossal fold.

glomerulosclerosis (FSGS) related to uncontrolled type 1 diabetes mellitus (T1DM), which the patient developed in his early 30s. His medical history also included hypertension. Compliance with antidiabetic drugs and insulin in the first 6 years following his T1DM diagnosis was poor. The state of his renal function due to uncontrolled T1DM and subsequent FSGS led to progressive renal damage, and the patient developed chronic renal failure in his mid-30s. The patient was started on dialysis for 18 months with no improvement in his general health status and further deterioration in renal function.

The patient was started on antirejection medication (calcineurin inhibitor and a corticosteroid) after successful transplantation—and had been on the calcineurin inhibitor for 2 years at the time of presentation. Calcineurin inhibitors are immunosuppressants that manage autoimmune conditions, including lupus nephritis, idiopathic inflammatory myositis, interstitial lung disease, atopic dermatitis and many more. Moreover, they are a mainstay of immunosuppression in solid organ transplant recipients. Known side effects of calcineurin inhibitors include hypertension, neurotoxicity, metabolic syndrome, immune system suppression, malignancy, especially squamous cell cancers, and benign and malignant lymphoproliferative disorders.

Calcineurin inhibitor levels were monitored as part of the post-transplant follow-up and adjusted accordingly. As a part of the general recommendations for patients taking calcineurin inhibitors after renal transplantation, the patient was examined annually by a plastic surgeon to detect occult skin cancer. In addition, the patient was advised to have an annual ultrasound of the abdomen to detect occult internal organ changes.

An oral examination and laryngoscopy revealed a 30×20 mm reddish-purple irregularly hypertrophic and ulcerated lesion (figure 1) occupying the base of the tongue. A physical examination of the neck revealed a lymph node enlargement.

Blood analysis was in the normal range, including complete blood count and biochemical analysis. HIV serology was negative.

A cervical ultrasound demonstrated enlarged lymph nodes up to 25 mm.

Biopsies from the oral lesion were taken. Pathological tests showed endothelial spindle cells with scattered red foci and extravasation of red blood cells. Immunohistochemical tests were strongly positive for vascular markers CD31, CD34 and vimentin (C) antigens.

A fine-needle aspiration performed on a large cervical node showed vague lymphocytic infiltration.

The diagnosis was determined as OKS based on cytological examination.

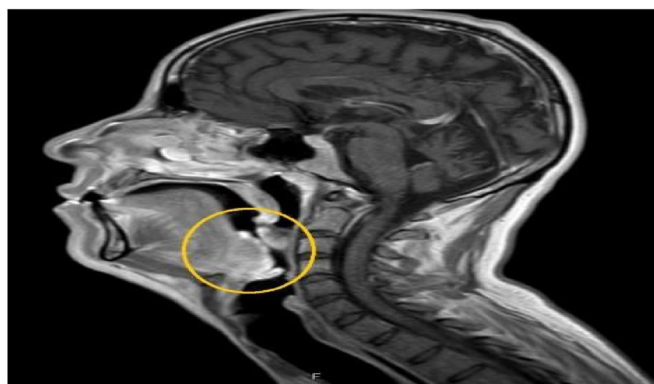


Figure 2 MRI of the mass in the base of the tongue.

Following this diagnosis, an MRI (figure 2) demonstrated a 33×11 mm mass at the base of the tongue and a 25 mm submandibular node on the right side.

The positron emission tomography (PET)-CT scan (figure 3) demonstrated a high metabolic rate in the base of the tongue (figure 3A), cervical lymph nodes bilaterally (figure 3B), epiglottis, vallecula, and anterior and posterior pillars. Disseminated foci of moderate metabolic rate were found in the axilla (figure 3C), along the oesophagus, mediastinal (figure 3D), perihepatic, retroperitoneal and pelvic lymph nodes. Tru-cut biopsies from the right axilla revealed an extensive involvement with KS.

INVESTIGATIONS

Blood analysis including complete blood count and blood chemistry was done. In addition, the following procedures were performed.

- ▶ Cervical ultrasound.
- ▶ Biopsy from the lesion at the base of the tongue.
- ▶ Biopsy of the cervical lymph node.
- ▶ Immunohistochemical test.
- ▶ MRI.
- ▶ PET-CT.

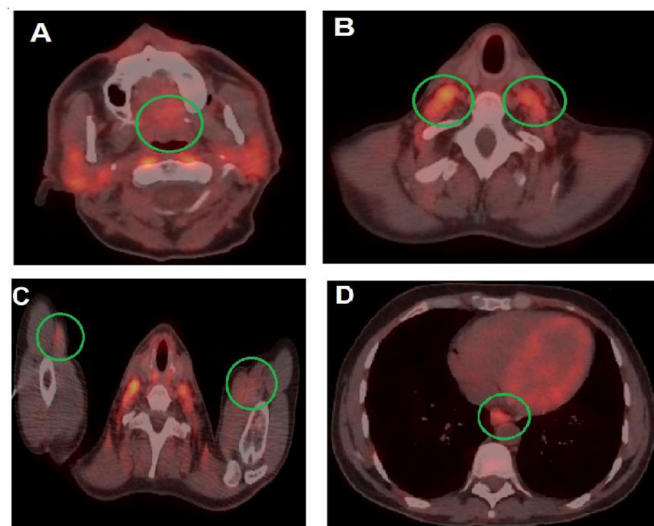


Figure 3 Positron emission tomography-CT. A disseminated disease across the lymphatic system: (A) base of the tongue, (B) cervical lymph nodes, (C) axilla and (D) mediastinum.

DIFFERENTIAL DIAGNOSIS

Clinically, KS strongly resembles certain vascular lesions, including haemangiomas, lymphangiomas, arteriovenous malformation, ecchymosis, low-grade mucoepidermoid carcinoma and bacillary angiomatosis. It may resemble pyogenic granuloma or peripheral giant cell proliferation when present on the alveolar ridge.³

From the differential diagnostic point of view, pathologies that should be included are well-differentiated angiosarcoma, fibrosarcoma, arteriovenous malformations, Kaposiform haemangioendothelioma, spindle cell haemangioendothelioma and bacillary angiomatosis.³

Because of a wide range of differential diagnoses that can be confused with OKS, to make a definitive diagnosis, an accurate clinical history and biopsy are necessary to ascertain a precise diagnosis of KS and distinguish it from other lesions.³

TREATMENT

Treatment with the calcineurin inhibitor was stopped, and the patient started with an mTOR (mammalian target of rapamycin) inhibitor and continued with a corticosteroid.

During the first 2 weeks after beginning with mTOR inhibitors, the patient received 10 courses of radiotherapy to the base of the tongue. As a complication, the patient began to have dyspnoea, and haemoptysis was found as a result of active bleeding from the KS at the base of the tongue. A preventive tracheostomy was performed to protect the patient airway during treatment.

OUTCOME AND FOLLOW-UP

Two months following radiotherapy, the tracheostomy was removed. A fiberoptic examination revealed no traces of the disease in the base of the tongue or nasopharynx. Moreover, a second PET-CT was performed, and a complete remission of the disease was documented. The patient still had one solitary lymph node in the left mammary chain and another paracanal node at the level of the left kidney vein that was still moderately metabolic. Six months after starting treatment, these two nodes appeared more metabolically active on PET-CT. As a result, the patient received a new course of radiotherapy for the chest and abdomen. Nine months after radiotherapy, the patient has no traces of OKS and is being followed up at the transplantation centre.

DISCUSSION

There was one Canadian case report on a man in his late 40s who developed OKS after renal transplant and receiving immunosuppression. It has shown that KS 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.⁶ Therefore, treatment of KS in transplant patients usually consists of immunosuppression withdrawal. If there is no response, chemotherapy may be started. Moreover, they have illustrated the importance of dental providers closely assessing the treatment needs of long-term transplant survivors because of the potential occurrence of secondary malignancies (including KS, squamous cell carcinoma and lymphoma) in the oral cavity.⁶

According to one Spanish study on the long-term complication after renal transplant and immunosuppressant, it has shown that KS is a common long-term complication in renal transplant recipients, with an increased incidence compared with the general population, and is especially prevalent in people of Mediterranean and African origin.¹ There are increasing clinical

data suggesting that withdrawal of calcineurin inhibitors and conversion to proliferation signal inhibitors in patients with KS cause regression of lesions through effects on vascular endothelial growth factor signalling. This immunosuppressive regimen may reduce KS's impact on kidney transplantation's long-term outcomes.¹

A third study on two patients with KS after a renal transplant from a university in New York mentioned that KS is a complication of immunosuppressive therapy for renal transplant recipients. Treatment is usually withdrawal of immunosuppression; non-responders often receive chemotherapy. Successful treatment with single-agent paclitaxel (PTX) has been documented in only one patient. In the mentioned two cases, KS progressed despite withdrawal of immunosuppressive therapy and patients were treated with weekly PTX. Both patients' KS regressed completely after four courses of PTX and remained in remission after 1 year of follow-up. PTX may be important in treating post-transplant KS resistant to immunosuppressive therapy withdrawal.⁷

All of the aforementioned cases are compatible with the patient we described in this case, who developed OKS after renal transplantation and received calcineurin inhibitors. In our case, the patient had remission after changing the calcineurin inhibitor to mTOR and steroids.^{1 6 7}

Main points in the discussion

1. KS is a rare but severe complication in patients after solid organ transplantation, especially kidney transplant patients receiving calcineurin inhibitors. While the skin and oral mucosa are the typical sites for KS, lesions at the base of the tongue are quite rare, with only a few reported cases.
2. Treatment for renal transplant patients who develop immunosuppression-related OKS must be reduced to the lowest levels of immunosuppression therapy, which preserves allograft function. Treatment with calcineurin inhibitors should be converted to mTOR inhibitors.
3. In post-transplant patients with KS, the first-line treatment is the withdrawal of the calcineurin inhibitors as immunosuppressive therapy. The substitution of sirolimus for others, such as ciclosporin and tacrolimus, has shown KS regression without an increased risk of organ rejection.

Learning points

- An oral lesion in post-transplant patients should not be dismissed as non-significant.
- Kaposi sarcoma should always be in mind regarding complications for a kidney transplant patient after receiving a calcineurin inhibitor.
- An early diagnosis of oral Kaposi sarcoma in a renal transplant patient who received a calcineurin inhibitor has a good prognosis.
- Renal transplantation patients who receive calcineurin inhibitors should be advised to seek an ear, nose and throat examination immediately if they feel any physical mass in the tongue.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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