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Post transplant Kaposi's sarcoma among Nigerians: a report of two cases

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Summary
With the establishment of kidney transplant centres in Nigeria and increase in the number of kidney transplant recipients returning home for follow up after successful transplant abroad, an increasing number of patients with post transplant complications are likely to be seen. There is the need for physicians vested with the care of these patients to be aware of the post transplant complications so that early diagnosis and effective treatment can be instituted so as to save both the patient and the allograft. Two out of seventeen renal transplant recipients followed up in our unit had post renal transplant Kaposi's sarcoma. Both were successfully treated with withdrawal of cyclosporin, reduction of other immunosuppressives and introduction of low dose Mycophenolate Mofetil (MMF). One had a course of radiotherapy followed by weekly intravenous vincristine and the other only had vincristine with complete remission of the lesions in both patients. Post transplant Kaposi's sarcoma occurs in Nigerian transplant patients and this report highlights the need for increased awareness and high index of suspicion of post transplant Kaposi's sarcoma among kidney transplant recipients.

Keywords: *Kaposi's sarcoma, Nigeria, post transplant*

Résumé
Les cntres de transplantations des reins a augmente le nombe de recipients au Nigeria. Par contre cette exercice a l'etranger presentent des complications croissante des leretour au bercaille. Il est imporant aux medecins d etre eveille sur les sions pour ces patients et les complications post-transplantations pour un diagnsotie precose et traitement efective. Deux sur si-sept reciepients etaient suivi dans notre unite renale ayant un sarcome de Kaposi post-transplantation. ces deucx patients etaient traites avec le cyclosporin, reduisant les autres medicamenst immunosuppressie et l'emploi d une faible dose de mycophenolate mofetil(mmf). L'un des deux patients suivaient une radiotherapie avec du vincrstine intraveneux hebdomadaire et l'autre recue uniquement le vincristine avec une remission complete des lesions chez ces patients. Le sarcome de Kaposi post-transplantation est documeente aux patients nigerian suivant la transplantatin renale. Cette etude illumine le besion d'augmenter la sensibilisation et l'index de suspision eleve aux patients ayant une transplantation renale.

Introduction

Kaposi's sarcoma (KS) was first described by a Hungarian dermatologist Moritz Kaposi in 1872 when he described five men with aggressive "idiopathic multiple pigmented sarcomas of the skin" [1]. Subsequently, other investigators described four clinical subtypes with identical histological features but occurring in specific populations and having different sites of involvement and rates of progression. These are classic, endemic, transplant associated and epidemic or AIDS-associated KS [2].

Chang and his colleagues identified DNA fragments of human herpes virus 8 in Kaposi's sarcoma skin lesions from a patient with AIDS [3]. Since then it has been shown that over 95% of KS lesions regardless of their source or clinical subtype, are infected with human herpes virus 8 (HHV8) [2]. Furthermore, it has been demonstrated that the virus can be transmitted sexually and by other means such as mother to infant transmission and possibly through organ transplant [2]. There has been an increase in the incidence of KS among AIDS patients and in patients given immunosuppressants after an organ transplantation [4]. KS has been shown to account for between 3 – 9 % of all tumours in kidney transplant recipients (KTR) [5].

Epidemiological data has shown that the incidence of KS in KTR is higher among individuals of Mediterranean, Arabic or Jewish ancestry. Blacks are also reported to have a higher incidence of KS than Caucasians [6].

We report on two cases of cutaneous manifestation of KS in kidney transplant recipients and discuss the literature.

Case one

A 58 year old retired civil servant with end stage renal disease secondary to hypertension who was started on maintenance haemodialysis for three months and later had a live related renal transplant in September 2002. The immunosuppressive regimen (IS) included cyclosporin (cyA), Prednisolone and Azathioprine (Azt). He enjoyed a stable

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graft function with no rejection episodes recorded. Fifteen months post transplant, he noted multiple dark coloured, smooth surfaced nodular lesions on anterior aspect of his shins bilaterally and also on the sole of his right foot. He was referred to a dermatologist and with the appearance of more lesions, a skin biopsy was performed and histological features of KS were reported (figure 1). Clinical and physical findings showed no evidence of visceral involvement. His IS were reviewed with the removal of cyA, and low dose Mycophenolate Mofetil (MMF) was introduced. He also had a course of radiotherapy and was later started on vincristine 2mg intravenously weekly. After six weeks he showed significant improvement with regression of the tumour. However a discharging wound formed on the residual lesion and a swab culture grew *Pseudomonas spp.*, which was sensitive to Ciprofloxacine. Complete healing of the wound followed the administration of this antibiotic. At 10 weeks clinic visit he had a complete remission of the lesion and for over one year now, patient has remained in remission with good allograft function.

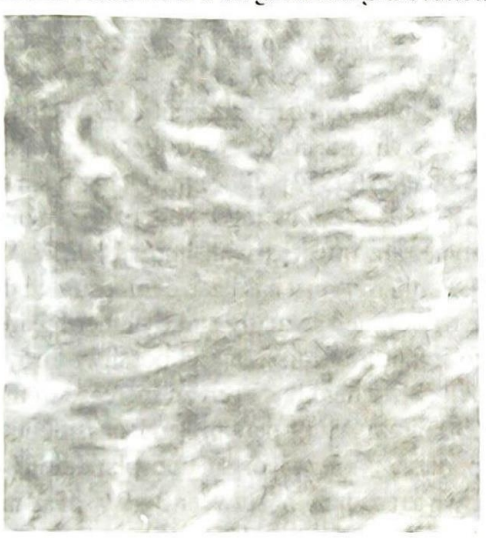

Fig. 1: *Kaposi' sarcoma showing irregular angulated vascular channels filled with red blood cells. Note the surrounding spindle shaped sarcoma cells. (H & E, X 160)*

Case two

A 48 year old businessman with end stage renal disease who had a live related kidney transplant in May 2003. Immunosuppressive regimen given included cyA, Azt and Prednisolone He had an episode of acute rejection during the first 4 weeks post transplant, which was diagnosed clinically on the basis of decreased urine output, graft tenderness, fever, progressive increase in serum creatinine concentration with associated proteinuria. It was successfully treated with a three-day course of intravenous methylprednisolone. At 13-months post transplant, a decline in his renal function was noted. His serum cyclosporin was noted to be high and allograft biopsy showed features consistent with cyclosporin toxicity. This led to review of his IS drugs with removal of cyA and introduction of MMF. He however developed severe gastrointestinal side effects and had to be admitted because of vomiting and abdominal discomfort with some dehydration. During this admission a brown smooth surfaced nodular lesion was observed on the lateral aspect of his left thigh during routine physical examination (figure 2). It was also noted to be associated with scrotal swelling and differential swelling of the left lower limb. Though the patient had noted it earlier, he did not report it. A skin biopsy was performed and histological features of KS were reported. His IS were reduced and he was started on vincristine. At 10 weeks clinic visit there was regression of the lesion (figure 3) and the patient remained stable with no recurrence of the lesion after 6 months of follow up.

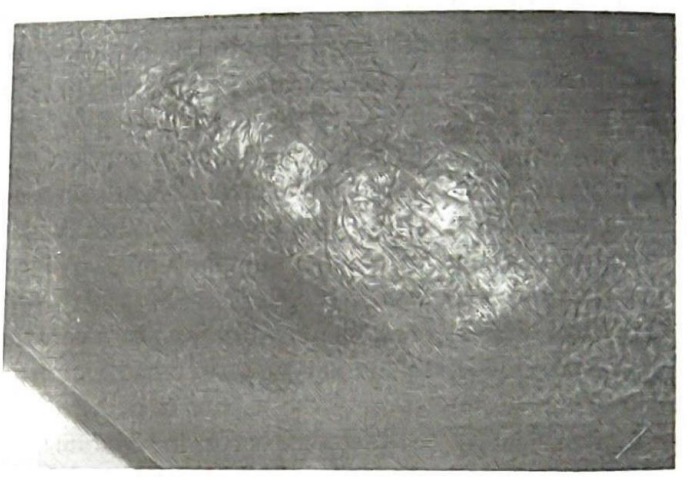

Fig. 2: *Picture of Cutaneous Kaposi' sarcoma lesion in a kidney transplant recipient before treatment*

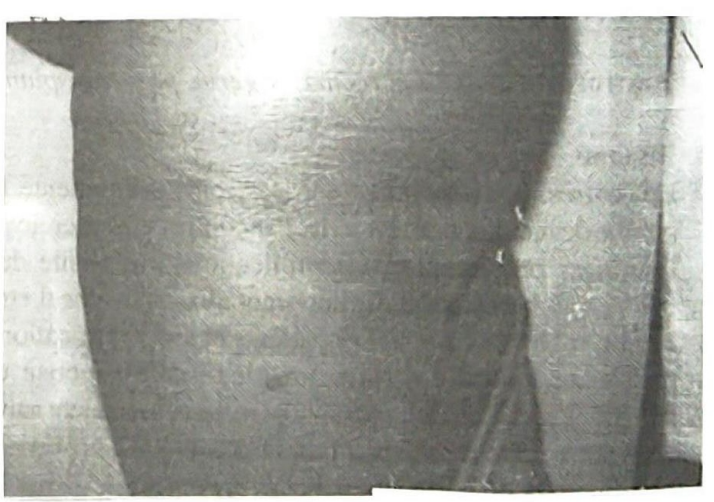

Fig. 3: *Site of Cutaneous Kaposi' sarcoma lesion in akidney transplant recipient (same patient as fig. 2) after treatment.*

Discussion

The prevalence of KS in KTR is highly influenced by the IS increasing by as much as 1000 times in cyA treated patients [7]. It has been shown that the advent of cyA witnessed an increase in the incidence of KS among KTR. This is thought to be due to more effective inhibition of the normal tumour immunosurveillence mechanisms by cyA than by other immunosuppressive drugs. According to the Cincinnati transplant tumour register (CTTR), which is a worldwide database, KS accounts for 8% of all malig-

nancies in patients on cyA compared to only 3% in other IS therapy groups [8]. Similar reports were also reported by the French collaborative study which also showed that KS lesions appear earlier in KTR on cyA with more widespread distribution of the lesions at time of diagnosis and more frequent graft loss and death [4]. Quinibi reported a 10.5 % incidence of KS in KTR on cyA as compared to 6% in those on AZT [9]. The two patients in this study were all on cyclosporin.

The diagnosis may be delayed as the skin lesion can be very small and asymptomatic hence there is the need for high index of suspicion. In one of the patients presented above, the patient never complained of the lesions, only to be detected during routine clinical examination while on admission for another reason. The gold standard test is the skin biopsy, which will show irregular, angulated vascular channels filled with red blood cells, with surrounding spindle shaped sarcoma cells. Peripheral blood film often shows increased monocytes and occasionally eosinophilia. Micro-angiopathic haemolytic anaemia has been seen on rare occasions. KS lesions may resemble other cutaneous lesions such as melanoma or lymphoma.

Alkhader proposed a detailed staging of KS in KTR into 4 subgroups which allows for an appropriately guided therapy and prognosis (table 1) [10]. The prognosis is better in stages I and II disease and worse in stage III and IV disease. According to these criteria, both of our patients had stage II disease.

Table 1. Staging of KS [10]

Stage	Characteristics
I	Limited cutaneous (involving only one extremity)
II	Disseminated cutaneous (involving more than one extremity)
III.	Generalised (involving viscera and/or lymph nodes and/ or skin)
IV	Any of the above in the presence of life threatening infection or another neoplasm.

The principle of treatment involves withdrawal/ reduction in IS, radiotherapy, and / or chemotherapy. Quinibi et al proposed a four step approach in the management of KS in KTR which involves a 50% reduction in the IS as the first step, and if no response occurs then treatment should move to the second step, which entails a further decrease in the doses of the drugs. If there is progression of the lesions in spite of this, the next step is to stop all the drugs and start radiotherapy. If there is still no change, the final step is to initiate adjunctive therapy. Studies have shown the effectiveness of reduction or withdrawal of immunosuppressive agents in the management of post transplant KS. In one study it was shown that there was resolution of KS in 4 out of 5 KTR in South Africa [6]. Data from CTTR showed that reduction or elimination of the IS was followed by complete remission in 30% of patients.

However, the decision to withdraw IS completely should take into account the severity and the extent of the cutaneous lesions, degree of visceral involvement and whether the transplanted kidney is life supporting. It was reported in some studies that complete withdrawal of IS may be associated with graft loss in up to 50% of patients [11]. Chemotherapeutic agents used include vincristine, vinblastine and bleomycin as single agents or in combination. Recently it has been shown that Sirolimus inhibits the progression of KS in KTR while exerting an anti rejection effect on the allografts [12].

Both patient and allograft survival depend on the extent of the cutaneous lesions and whether or not there is associated visceral involvement. Limited cutaneous lesion is associated with a better prognosis in which over 55% of the lesions show complete remission after treatment, while visceral involvement is associated with 55% mortality despite treatment [11].

With the current knowledge of the causative agent of KS it is now possible to screen both the donors and the recipients for HHV8 and those who are seropositive may benefit from possible antiviral therapy. Immunosuppressive therapies should be carefully monitored and agents implicated with high prevalence of complications should be restricted. Careful post transplant follow up of KTR and high index of suspicion are required so that diagnosis can be made early and appropriate treatment instituted.

With the establishment of kidney transplant programmes in Nigeria and the increase in the number of patients who had kidney transplant abroad and returning home for follow up, more patients with post transplant complications will be seen and it is therefore imperative for physicians involved in the care of these patients to have a good knowledge of such complications and also be vigilant so as to detect them early enough for prompt institution of appropriate therapies.

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