KAPOSI SARCOMA COEXISTING WITH NEW ONSET DIABETES MELLITUS IN A 42-YEAR-OLD KIDNEY TRANSPLANT RECIPIENT: A CASE REPORT

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ABSTRACT

Background: Renal allograft recipients develop several complications such as infections and neoplasms. New onset diabetes mellitus is a common transplant complication but rarely coexist with Kaposi sarcoma. **Case report**: We report the case of a 42-year-old banker who presented with polyuria, polydipsia, polyphagia, weight loss and dark spots in the lower limbs 8 months after he had received a live-related kidney transplant in India. He is not a known diabetic and had no family history of diabetes mellitus. His post-transplant immunosuppressive drugs included Myfortic® (mycophenolate), tacrolimus and prednisolone. At presentation he was wasted, dehydrated and afebrile, with multiple hyperpigmented nodules and plaques in both his lower limbs. Random blood glucose was 38mmol/l, had 2+ glucosuria and no ketones. Biopsy of skin lesions showed features of Kaposi sarcoma. A diagnosis of post-transplant diabetes mellitus and Kaposi sarcoma was made. His treatment included soluble insulin and antibiotics. Tacrolimus was changed to sirolimus and mycophenolate was reduced to 360mg twice daily. **Conclusion:** Coexistence of diabetes mellitus and karposi sarcoma occurs rarely among kidney transplant recipients. Evaluation of transplant recipient who developed diabetes for malignancies such as karposi sarcoma will improve patient and graft survival.

Keywords: Coexistence, Kaposi sarcoma, Kidney transplant, New onset diabetes

INTRODUCTION

Since the 1950's, high prevalence of diabetes mellitus had been reported among patients who developed Kaposi sarcoma.[1] Fischer *et al*[2] reported the simultaneous occurrence of Kaposi sarcoma, leukaemia and diabetes mellitus. Renal transplant recipients can develop several complications in a time dependent manner. Malignancies and opportunistic infections are the leading causes of patient and graft loss among transplant recipients.[3] Although advances in immunosuppression have curtailed the adverse effects of these complications, metabolic disorders and malignancies have remained major sources of morbidity and mortality in these patients.[4] Drugs used to suppress the immune system of recipients contribute in the development of these conditions.

New onset diabetes mellitus after Transplant (NODAT) is common among post transplant patients with a prevalence

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of 4 to 25%.[5] Prevalence of NODAT in Nigeria is not known but has been reported among kidney transplant recipients.[21] Malignancies such as Kaposi sarcoma, lymphoproliferative diseases and skin cancers are twice more common among renal transplant recipients than in the general population.[17]

Although NODAT and Kaposi sarcoma are common complications after kidney transplant, their coexistence is not common. This is the first reported case of Kaposi sarcoma coexisting with NODAT in Nigeria. It has been suggested by researchers that high blood glucose in NODAT favours the reactivation of human herpes virus 8. This in turn will lead to changes resulting in development of KS.

We report the case of NODAT and Kaposi sarcoma occurring in a 42-year-old male renal allograft recipient.

CASE PRESENTATION

A 42-year-old male banker who received live-related kidney transplant in India after maintenance haemodialysis for 8 months.

He presented 6 months post-transplant with two-week history of polyuria, polydipsia, polyphagia and weight loss. But there was no history of body swelling, dysuria, haematuria or frothiness of urine. He was not a known diabetic and had no family history of diabetes mellitus. He developed diarrhoea about 2 days before presentation passing watery, non-bloody, non-mucoid stools. There was associated post-prandial vomiting, consisting of recently ingested food non-bloody, non-bilious.

He also noticed dark spots on his legs increasing in both number and size, associated with pain and swelling of the left lower limb. No associated history of fever.

He had good allograft function on tacrolimus 2mg twice daily, mycophenolate 720mg twice daily and prednisolone 5mg daily.

On clinical examination, he was chronically ill-looking, wasted, afebrile and dehydrated. There were hyperpigmented plaques and nodules in both lower limbs and trunk. The left lower limb was swollen and tender. Pulse rate was 116 beats/minute, regular and small volume, blood pressure was 100/50 mmHg and heart sounds were 1^{st}, 2^{nd} and 4^{th}. There were no murmurs. Chest was clinically clear. He was drowsy; there were no skull or spinal abnormalities and no signs of meningeal irritation.

PCV was 34%, WBC 6.7 X 10^9/L, Platelets were adequate. Serum biochemistry results were: Creatinine – 383µmol/L, Urea –11.1mmol/L, and K+ –5.0mmol/L, Na+ –140mmol /L, Cl^- –101mmol/L and HCO_3^- –19mmol/L. Random blood glucose was 38mmol/l. The serum osmolality was 331.4 mOsm/Kg. He had glycosuria 2+ with no protein and ketones.

Skin biopsy showed spindle cells with haemorrhagic areas consistent with a diagnosis of Kaposi sarcoma.

A diagnosis of post-transplant diabetes and Kaposi sarcoma was made.

He was commenced on soluble insulin infusion at a rate of 5 iu hourly. Intravenous normal saline was given 1litre over 1 hour then 1 litre every 4 hours. Intravenous ceftriaxone 1g 12 hourly and metronidazole 500mg 8 hourly were given. Blood glucose was monitored hourly and it dropped to 12 mmol/l after 7 hours. He was subsequently converted to subcutaneous soluble insulin at 12iu 8 hourly.

Tacrolimus was switched to sirolimus 1mg daily, Myfortic® was reduced to 360mg twice daily and he continued prednisolone at 10mg daily.

He became stable and was discharged home on Humulin 30/70 24iu in the morning and 14iu in the evening.

Figure 1: Lateral of a limb showing hyperpigmented plaques and nodules

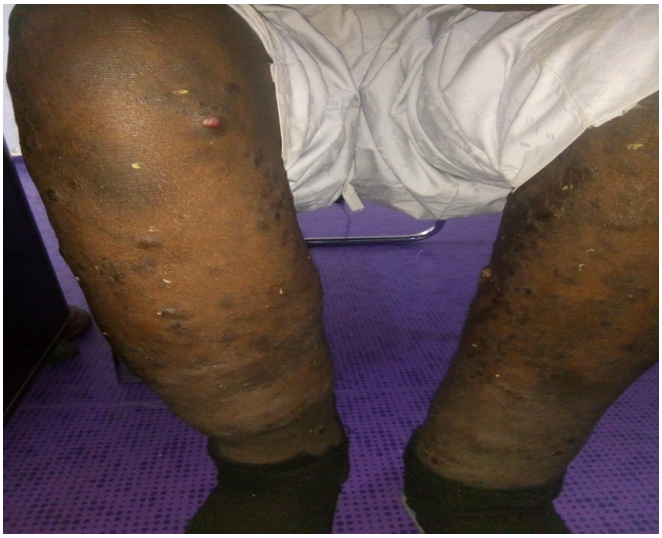

Figure 2: Hyperpigmented nodular lesions on both lower limbs

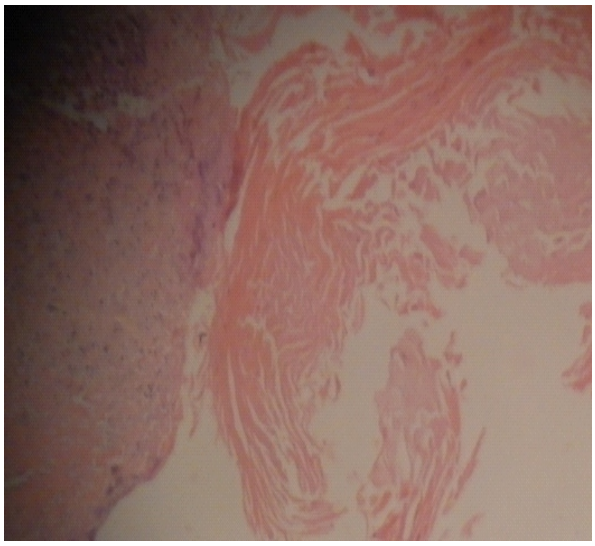

Figure 3: Skin biopsy of patient with Kaposi sarcoma showing haemorrhagic spindle shaped tumour.

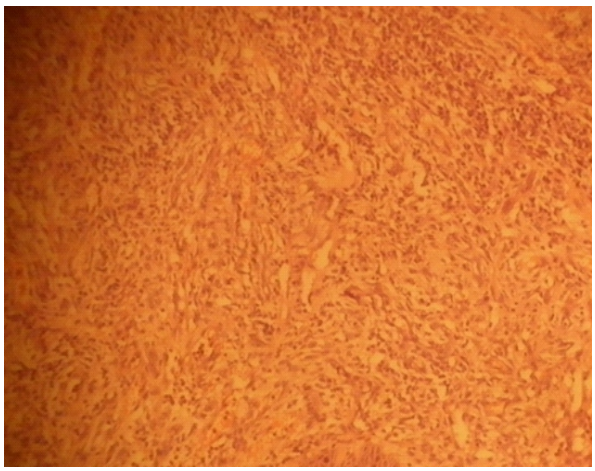

Figure 4: Showing Kaposi sarcoma at higher magnification.

DISCUSSION

Diabetes mellitus in patients with kidney transplant contributes to morbidity and impacts negatively on patients and allograft survival. International consensus guidelines defined criteria for diagnosis of NODAT is the presence of diabetic symptoms and fasting blood glucose of > 7.0mmol/l or random blood glucose of >11.1mmol/l in a patient previously not known to be diabetic.[8] Patients who develop NODAT are susceptible to development of long-term diabetic complications, therefore adding to their cardiovascular risk burden.[8]

Risk factors include older age at time of transplantation, black race, higher patient weight and body mass index, cadaveric allograft recipient and type of immunosuppressive agents used. Tacrolimus and sirolimus are associated with higher risk of post transplant diabetes mellitus when compared with cyclosporine. Switching tacrolimus to cyclosporine has been found to be associated with resolution of hypreglycaemia.[11]

Two patho-mechanisms are believed to be responsible for the development of NODAT namely: insulin resistance and defect in insulin secretion. Insulin resistance caused by uraemic toxins in end stage renal disease may be aggravated in the posttransplant period by immunosuppressive drugs. Steroids cause increased hepatic gluconeogenesis and increased insulin resistance in peripheral tissues. The clinical presentation in this subset of patients is similar to type 2 diabetes mellitus.

Nam *et al*[12] demonstrated that β-cell dysfunction contributes to development of diabetes mellitus among Korean renal transplant patients. Tacrolimus causes β-cell dysfunction culminating in impaired insulin secretion rather than insulin resistance.[12]

Genetic factors are also thought to play a role in the pathogenesis of NODAT. Studies have found association between NODAT and HLA A3 and DR3.[14]

Kaposi sarcoma (KS) is the commonest malignancy in post-kidney transplant patients, especially in developing countries.[6] The aetiopathogenesis is complex and poorly understood, but it is strongly associated with human herpesvirus type 8 (HHV-8) in immunosuppressed, immunogenetically susceptible individuals. The incidence of post-transplant Kaposi sarcoma is higher in areas where HHV-8 is prevalent.[17]

Studies in mice have shown that hyperglycaemia induces the production of H_2O_2 which favours reactivation of HHV-8 through induction of mitogen-activated protein kinase (MAPK). It has also been shown that H_2O_2 mediates down regulation of histone deacetylase (HDAC) silent information regulator 1 (SIRT1) resulting in active transcription of HHV-8 lytic genes.[22] High glucose also increases susceptibility of target cells to HHV-8 infection through increased expression of cellular receptors for HHV-8 infection.[23]

Clinically KS has a varied presentation and may be seen any time post transplant from 6 weeks to 20 years. The initial lesion may be small raised dark nodule on the skin or tip of the nose. Lesions range in size from few millimetres to large plaques. Involvement of the liver, kidney, lymph nodes and lungs may occur. Rarely patients present with unexplained fever.[5,15]

Diagnosis is by biopsy of suspicious skin lesion, which show proliferation of spindle cells, and endothelial cells, extravasations of red blood cells, haemosiderin laden macrophages, and in early cases, an inflammatory cell infiltrate.[5,8]

Treatment of NODAT patients is not different from that of diabetes mellitus not associated with transplant. Haemoglobin A_{1C} level below 6.5%, fasting plasma glucose less than 6mmol/l and a 2-hour postprandial plasma glucose below 7.8mmol/l are recommended.[13] Weight reduction in overweight patients through regular exercise and diet are essential.

Modification of immunosuppression should be considered in high risk patients. Corticosteroid dose reduction significantly improves glucose tolerance during the first year after transplantation. However, any dose reduction should be weighed against the risk of acute rejection. Conversion of tacrolimus to cyclosporine in patients who fail to achieve target glycaemic control has yielded variable results.[5,9] Patients can be treated with oral hypoglycaemic agents alone or in combination with insulin.

There is no consensus on the management of immunosuppressive therapy in patients with post-transplant Kaposi sarcoma. Some experts believe in withholding or reducing the dose of immunosuppressive drugs. This is, however, at risk of losing the allograft through rejection episodes. This measure alone has caused regression of the tumour in some patients. Campistol *et al*[18] reported that switching calcineurin inhibitors to sirolimus resulted in regression of the tumour in 2 patients. The mammalian target of rapamycin (mTOR) inhibitors has been shown to have tumour suppressor properties. Sirolimus used in transplant patients was associated with significantly delayed time to first malignancy.[19] Post-transplant Kaposi that are resistant to drug modification, may benefit from doxorubicin, bleomycin and vincristine.[20] Paclitaxel has been tried in patients who have disseminated disease or whose tumour failed to regress after with-holding immunosuppression.

Coexistence of diabetes mellitus and karposi sarcoma occurs rarely among kidney transplant recipients. The preponderance of evidence for a causal link between the two diseases necessitates the need for early evaluation of transplant recipients who developed diabetes for malignancies such as karposi sarcoma.

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