INTRODUCTION

Posttransplantation lymphoproliferative disorders (PTLDs) are a serious complication of immuno-suppression in patients of solid organ and bone marrow allografts. The overall incidence of PTLDs in allograft recipients is around 2% with approximately 50% survival rates.1 Although most PTLDs occur due to abnormal proliferation of EBV (Epstein-Barr virus) transformed B-Cells, EBV-negative PTLDs are also seen, particularly those developing more than one year after transplantation.2,3 PTLDs of B-cell type are more frequent comprising about 90% compared to T-cell type. PTLDs include a wide range of abnormal hyperplastic and neoplastic lymphocytic proliferation, ranging from benign lymphoproliferation to an aggressive, widely disseminated disease.4

We describe the presentation and pathological features of an EBV negative patient of PTLD, a recipient of renal transplant, presenting with skin involvement in a patient of renal transplantation, 8 years after receiving the transplant.

CASE REPORT

A 32-year-old male, a body builder by profession, developed fever, hypertension and non-functioning kidneys. His renal transplantation was carried out in the year 2000 in a tertiary care public sector hospital. Since then, he had been on immunosuppressive medication taking azathioprine (300 mg daily) and prednisolone (10 mg daily) orally. In February 2008, he noticed a lump on his right thigh. He consulted a Urology Department where he was clinically examined and investigated. There was no history of fever, chills, weight loss or malaise. Laboratory investigations showed haemoglobin of 9.0 g/dl, serum creatinine of 1.6 mg/dl, sodium at 138 mmol/l and potassium at 4.8 mmol/l. There was mild left ventricular hypertrophy on echocardiography.

The lump was excised on 10th of March 2008 and sent for histopathological evaluation. Grossly, it was a single grey brown skin covered tissue fragment 4 x 3 x 2.5 cm in size. A cut section showed a subcutaneous irregular grey white 3 x 1 cm sized nodule. Representative sections were taken, processed in an automatic tissue processor and paraffin embedded blocks were prepared; 3-5 micron thick sections were cut and stained with haematoxylin and eosin.

Microscopic examination revealed a well demarcated lesion in the dermis. It was composed of diffusely scattered neoplastic cells of the lymphoid series. The cells were polyhedral having vesicular nuclei and prominent nucleoli. Necrosis was absent and mitosis was rarely seen. There were no Reed-Sternberg like cells or any population of plasma cells/eosinophils. The monotonous looking neoplastic cells were infiltrating the surrounding fibroadipose tissue. Immunohistochemical evaluation demonstrated positivity for CD 20 (Pan B-cell marker, Figure 1). Focal positivity for CD 79 a. BASAP and CD 3 were negative. Immunostain for EBER (EBV encoded RNAs) was also negative. Bone marrow aspiration performed on 28th March, 2008 showed active erythropoiesis, thrombopoiesis and lymphopoiesis with stages of maturation. No definite infiltration by lymphoma cells was reported. His CT scan, carried out on 11th April, 2008 showed bilateral cervical, axillary and abdominal lymphadenopathy with splenomegaly (Figure 2 and 3). On the basis of CT results, the patient was staged as stage III.
Immunosuppression was discontinued and CHOP regimen was started. Patient received the first cycle of chemotherapy (CHOP = Cyclophosphamide:1200 mg I/V, Doxorubicin: 80 mg I/V, Vincristine: 2 mg I/V and Methylprednisolone: 40 mg/m² of body mass surface area) on 18th April 2008 and second cycle on 14th May, 2008. His laboratory investigations at that time showed: serum creatinine level of 1.6 mg/dl, urea at 40 mg/dl, sodium at 144 mmol/l and potassium at 4.5 mmol/l. The patient received the third cycle of CHOP in June and the fourth in July 2008. He went on receiving CHOP regimen every month until he died on 26th October 2008, due to severe leucopenia and septicaemia after having received the sixth cycle of CHOP regimen.

DISCUSSION

PTLD is one of the most serious complications of immunosuppression in patients undergoing solid organ transplantation. It is a heterogenous disorder which has been classified by WHO into four categories, early lesions which include reactive plasmacytic hyperplasia and infectious mononucleosis-like lesions. Polymorphous PTLD is the second category. Monomorphic PTLD, is further classified into B-cell neoplasms and T-cell neoplasms. B-cell neoplasms comprise of diffuse, large B-cell lymphomas (immunoblastic, centroblastic, anaplastic); Burkitt/Burkitt-like lymphoma, plasma cell myeloma and plasmacytoma-like lesions. T-cell neoplasms include peripheral T-cell lymphoma not otherwise specified and other types. Hodgkin’s lymphoma and Hodgkin lymphoma-like PTLD is a fourth category.

The frequency of PTLD is estimated to be 1-4% in renal, 2% in liver, 2-10% in heart, 5% in heart and lung and 19% in intestine allograft recipients. The risk in these recipients is estimated to be 20 times that of the normal population. The incidence varies owing to several factors, including the EBV status of the recipient, the type of organ transplanted, the type and intensity of immunosuppressive therapy and the age of the patient. The time of appearance of PTLD is quite variable. It can present as early as less than a month to as late as 25 years after transplantation. Most PTLDs however, occur within the first year after transplantation. The type of immunotherapy also determines the interval to some extent. In azathioprine treated cases, interval to PTLD is reported to be 48 months, whereas with cyclo-A it is comparatively much earlier i.e. 15 months. Most of the patients with PTLD present with a tumour, two-thirds of these being extra-nodal and one-third nodal. In solid organ transplant, recipients undergoing immunosuppression with azathioprine-based regimens, PTLD tends to involve extra-nodal sites but in patients being treated with tacrolimus-based and cyclo regimens both lymph nodes and extra nodal sites may be involved. Extra-nodal sites of PTLD involvement include GIT, lungs, CNS, and the transplanted organ. All solid organ transplant recipients undergoing immunosuppression have an increased risk for development of cutaneous malignancies such as squamous cell carcinoma of the skin and Kaposi sarcoma but PTLD involvement of the skin is rare. The skin lesion may present as nodules, ulcers or erythematos plaques on the face, trunk and extremities. The time interval for appearance of PTLD is variable. Beynet et al. followed-up with recipients of renal transplant and observed development of PTLD after 6 years. In this patient, the posttransplant period was longer, with the lesion appearing after 8 years.

Most PTLDs of B-cell origin are positive for EBV infection, although T-cell lesion and EBV negative cases have also been reported. Upto 20% of PTLDs are EBV negative; among renal allograft recipients, upto 50% may be EBV negative. The present reported case also revealed a negative result for EBER. EBV negative cases tend to occur later than EBV positive cases and the majority of cases occurring more than 5 years after transplant are EBV negative, which tallies with the 8 years posttransplant period in this case as well. Risk factors for PTLD development include young age, male gender, EBV seroconversion following transplantation, cytomegalo virus disease and T-cell specific immunosuppressive therapy. Some of these risk factors were found in this case as well.

Diagnosis of PTLDs is made by a biopsy of the lymph nodes and the sites of extranodal involvement.
Serological testing for EBV may be of use to evaluate the presence of recent or remote infection and thus may provide indirect information for diagnostic work-up of a PTLD case. However, the presence of EBV infection, active or remote, is not synonymous with a diagnosis of PTLD.

Early diagnosis and appropriate therapies are essential for the successful treatment of PTLD. The most immediate treatment measure is reduction in immunosuppressive therapy with a cure rate of 25-50%, especially in WHO class 1 and 2 PTLDs. In this patient, immunosuppression was discontinued after diagnosis. Other treatment modalities include cytotoxic chemotherapy, radiation therapy, monoclonal antibodies against B-cells (Rituximab), donor lymphocyte transfusion, interferon therapy, antiviral medicines and I/V immunoglobulin therapy. This patient expired after receiving six courses of CHOP.

REFERENCES


