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Case Report

The Burden of Post-Transplant Malignancies: Four Illustrative Cases of Diverse Etiologies

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Introduction

Patients with end-stage renal disease (ESRD) who undergo renal transplantation have overall higher survival and improved quality of life than patients on long-term dialysis [1]. Modern advances in immunosuppressive therapies offer a longer life expectancy. However, immunosuppression, which affects T cell activity, immunosurveillance, and the immunological management of oncogenic viral infections, is responsible for the increased risk of post-renal transplant malignancies [2]. It is the third most common cause of mortality in kidney transplant recipients, after infections and cardiovascular mortality. The overall incidence of malignancies is much higher than in the general population as well as patients on maintenance haemodialysis [3]. Post-transplant malignancies usually develop de novo, by donor-related transmission, or by recurrence of patient's pre-transplant malignancy [4].

Here we present 4 cases of post renal transplant malignancies with varied aetiologies.

Keywords: Kidney Transplant Recipients; Post-Transplant Malignancy; Post-Transplant Lymphoproliferative Disorder; Cervical Cancer; Squamous Cell Carcinoma.

Case 1

A 61year male with hypertension since 30 yrs, chronic kidney disease (CKD) with Native Kidney Disease (NKD) FSGS, on Maintenance hemodialysis (MHD) thrice weekly, underwent live related renal transplant in 1986 with uncle as donor, 3/6 HLA (Human leucocyte antigen) match and no previous history of sensitization, with NIL induction.

He had immediate graft function and was on dual immunosuppression, azathioprine and wysolone, found to have HBsAg positive in 1992, started on entecavir.

He reported to the hospital with cough and shortness of breath in October 2023 for which he underwent HRCT chest, which showed normal lung fields with left axillary lymph node enlargement of 2 x1.5cm.

After a course of antibiotic, he underwent Fine needle aspiration cytology (FNAC) which showed Polygonal non-native cells with moderate amount of vacuolated cytoplasm, with hyperchromatic nuclei and prominent nucleoli along with macrophages and necrosis in the background which was suggestive of metastatic carcinoma.

Immunohistochemistry was positive for p40 and ki was 88%, Diagnosis of metastatic squamous cell carcinoma was made. In view of unknown primary, PET CT was done, which revealed only left axillary and sub pectoral lymphadenopathy. He underwent left sided lymph node dissection for the same.

Histopathology showed moderately differentiated squamous cell carcinoma with peritumoral lymphomononuclear infiltrate. He underwent adjuvant EBRT (External Beam Radiation Therapy) to left axilla.

One month later, he presented with swelling of right upper limb, USG (Ultrasonography) with doppler revealed cephalic vein thrombosis with axillary lymph node of size 2.5x1.5cm. He underwent FNAC from the node which showed clusters of cells with atypical features like nuclear pleomorphism, hyperchromatic and increased mitotic activity suggestive of metastatic carcinoma.

IHC (immunohistochemistry) was Positive for TTF, P40, GATA-3 and negative for Napsin suggesting Poorly Differentiated Squamous Cell Carcinoma with lung as a primary (based on IHC) shown in Figure 1.

Currently he is on follow up with radiation and medical oncologist for the same. His immunosuppression wasn't modified and was continued on same dual immunosuppression.

Case 2

A 42-year male, CKD due to presumed Chronic glomerulonephritis (CGN) on MHD thrice-weekly with dialysis vintage of 10 years, underwent deceased donor renal transplantation in March 2019. He received Anti thymocyte globulin as induction agent, and was on triple immunosuppression, with stable graft function (creatinine -1.1mg/dl).

In September 2021, he was diagnosed with CMV (cytomegalovirus) disease for which he received intravenous ganciclovir, followed by oral valganciclovir. Despite recovery from CMV disease, he had persistent leucopenia, for which MMF (mycophenolate mofetil) was replaced with azathioprine 2mg/kg/day.

In February 2022, He had asymptomatic graft dysfunction with serum creatinine of 2.2mg/dl (baseline creatinine-1.1mg/dl), following which he underwent allograft biopsy, which showed intranuclear viral inclusion bodies which were positive for SV40 suggestive of Polyoma virus nephropathy. Immunosuppression was modified in terms of reduction in tacrolimus dosage. Subsequently his graft function improved to 1.2mg/dl.

In August 2023, he presented again with fever, Malena and malaise for 3months, and underwent Upper GI-scopy, which showed gastric ulcer. Histopathology report from the same showed fragments of gastric mucosa lined by columnar epithelium with focal ulcerations along with sheets of atypical lymphoid cells which were medium to large sized with vesicular nuclei. Immunohistochemistry was positive for CD3, Cd20, CD8, CD 56.ki67 was 91%, and IHC was negative for CD4, CD30, Tdt and Pan CK as shown in Figure 2. Hence it was diagnosed as monomorphic T/NK cell PTLD.

He also had recurrence of CMV disease (1lac copies/ml) during the same time, and was treated with IV ganciclovir.

In addition, he developed secondary bacterial sepsis, for which his immunosuppression was stopped and was treated with higher antibiotics.

However, he had multiorgan dysfunction and succumbed within 2 weeks of admission.

Case 3

A 53-year-old female, hypertensive for 11 years, diagnosed with CKD with Native kidney disease being Presumed CGN for the last 5 years, with a dialysis vintage of 16 months, underwent a cadaveric renal transplant in June 2021, received ATG as induction agent had immediate graft function and was on triple immunosuppression. She had stable graft function with creatinine of 1mg/dl thereafter.

2 yrs post transplantation, she underwent a routine pap smear testing in June 2023, which showed predominantly parabasal cells along with few intermediate and squamous epithelial cells. Some of the parabasal cells showed enlarged nucleus with increased N:C ratio and coarse chromatin. Few of the singly scattered cells showed pyknotic hyperchromatic nuclei and intracellular keratinization, consistent with High Grade Squamous Intraepithelial Lesion (HSIL).

In view of HSIL, she underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with upper 1/3rd vaginectomy with left pelvic lymph node dissection. Histopathology confirmed the findings of Pap-smear.

Follow up pap smear done 2 months later, showed irregular nuclear membrane with powdery chromatin, hyperchromatic nucleus and moderate amount of cytoplasm in few superficial, intermediate, parabasal and basal cells. Occasional parabasal cells also showed orangeophilia. These features were suggestive of malignancy, possibly Residual disease / Recurrence in a Known Case of HSIL.

She then underwent vaginectomy, which revealed similar histopathological findings. IHC was Positive for P40, P16 and Ki67 was increased, as shown in Figure 3. Final diagnosis of Squamous Cell Carcinoma In situ was made.

She was discharged with no fresh complaints and normal graft function with no change in her immunosuppression.

Case 4

A 32-year female known case of CKD secondary to presumed CGN with dialysis vintage of 1 year, underwent a live related renal transplant with mother as donor in September 2016. She had immediate graft function, was on triple immunosuppression, and had stable graft function with creatinine of 0.8mg/dl. She visited to our hospital for the first time in July 2023 with complaints of abdomen pain, weight loss, loss of appetite for 2 months and decreased urine output for a week. She was evaluated and was found to have creatinine of 2 mg/dl with CT scan Abdomen suggesting subacute intestinal obstruction, which was managed conservatively.

Two days later, she developed fever, abdominal pain and dizziness, with hypotension. Her immunosuppression was stopped and was treated with intravenous antibiotics. She was taken up for diagnostic laparotomy which showed ulcer with proliferative growth in proximal descending colon. Histopathology was Suggestive of Non-Hodgkin Lymphoma of High Grade. Further IHC showed Diffuse Large B Cell Lymphoma, GCB (Germinal center B cell) Type, shown in Figure 4 and Figure 5. Her general condition deteriorated with septic shock requiring inotropic support and Continuous Kidney Replacement therapy (CKRT). She succumbed after 10 days of hospitalisation (Table 1).

PARAMETERS	CASE1	CASE 2	CASE 3	CASE 4
Age/Gender	61/M	42/M	53/F	32/F
Native disease	FSGS-CGN	CGN-PRESUMED	CGN – PRESUMED	CGN-PRESUMED
HD vintage	1 year	10 years	16 months	1 year
Access	L RC AVF	L RC AVF	R AV graft	L RC AVF
Donor	UNCLE -LRRT	Deceased donor	Deceased donor	Mother donor -LRRT
Co-morbidities/prior infections	HTN, HbsAg, TYPE 2 DM	BK virus nephropathy, CMV disease	-	-
Presentation	Left axillary node enlargement	Perforated Gastric ulcer	Asymptomatic	Subacute intestinal obstruction
Transplantation to current presentation duration	33 years	4 years	2 years	7 years
Diagnosis	Metastatic Squamous cell carcinoma (primary lung)	Monomorphic T/NK Cell PTLD	High grade Squamous intraepithelial lesion.	Diffuse large B cell lymphoma GCB type.
Outcome	Patient on Radiotherapy. Regular follow up. Normal graft function.	Died (CMV disease).	On follow up. Normal graft function.	Died (Septic shock).

Table 1: Patients profile and Outcomes.

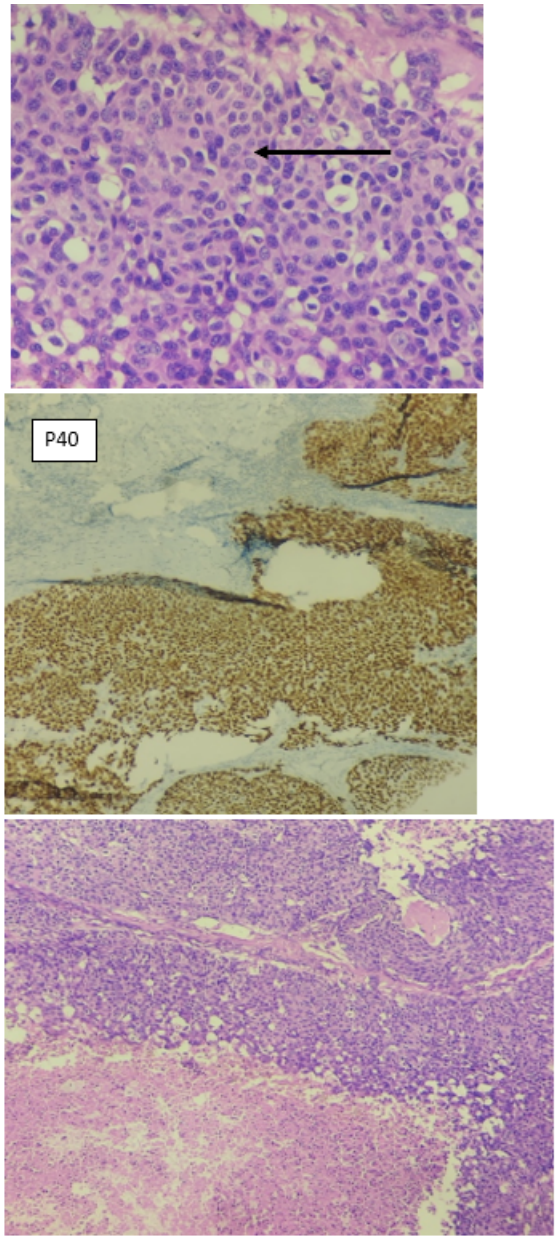

Figure 1: Clusters of cells with atypical features like nuclear pleomorphism, hyperchromatic and increased mitotic activity suggestive of metastatic carcinoma. IHC Positive for TTF, P40, GATA-3 and negative for Napsin suggesting Poorly Differentiated Squamous Cell Carcinoma.

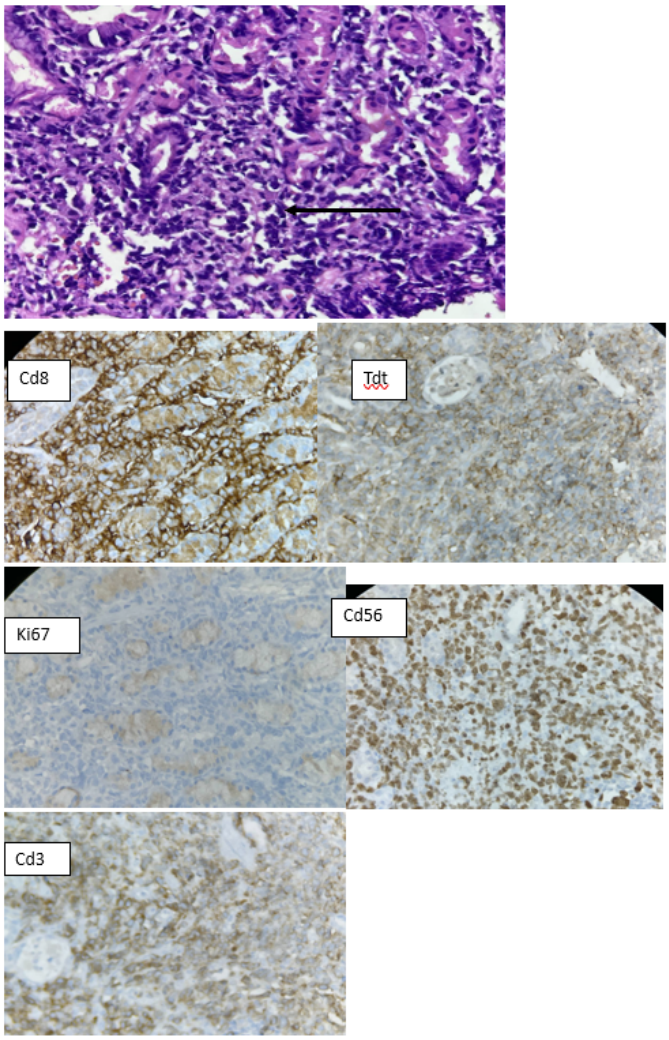

Figure 2: Sheets of atypical lymphoid cells which are medium to large sized with vesicular nuclei. Immunohistochemistry was positive for CD3, Cd20, CD8, CD 56.ki67 was 91%, and IHC was negative for CD4, CD30, Tdt and Pan CK suggesting monomorphic T/NK cell PTLD.

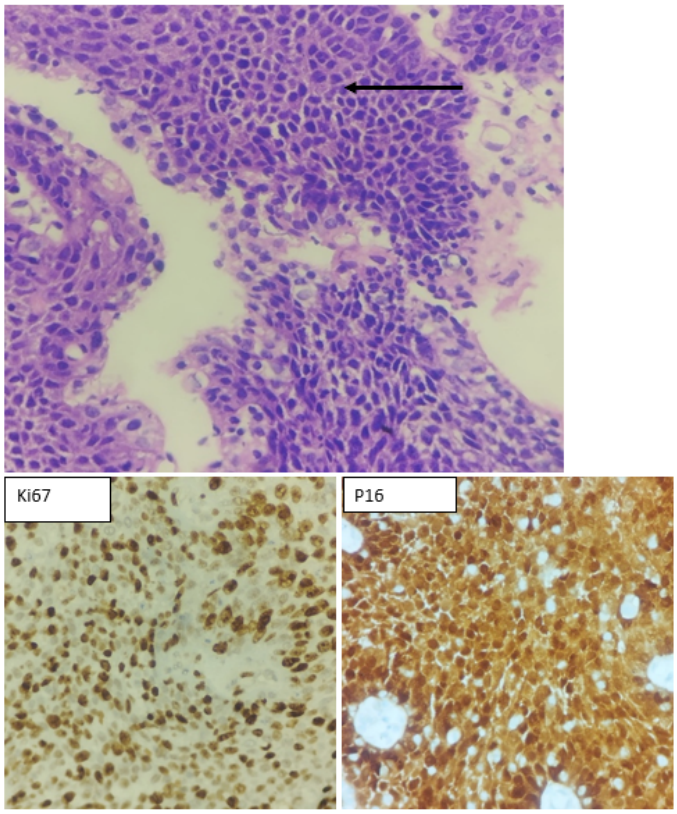

Figure 3: Parabasal cells showing enlarged nucleus with increased N:C ratio and coarse chromatin. Few of the singly scattered cells showed pyknotic hyperchromatic nuclei and intracellular keratinization, consistent with High Grade Squamous Intraepithelial Lesion (HSIL). IHC was Positive for P40, P16 and Ki67 was increased.

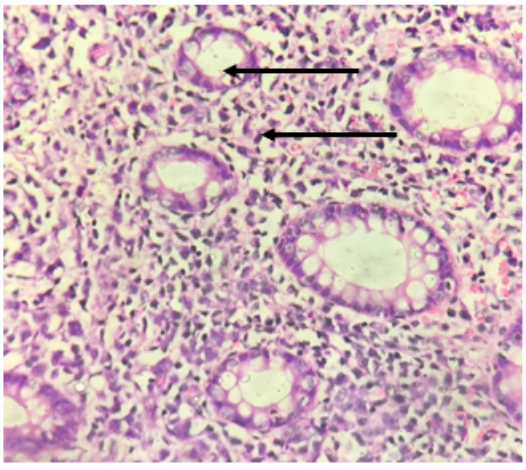

Figure 4: Submucosal lesion with sheets of small to medium sized cells with moderate nuclear pleomorphism, indistinct nucleoli and moderate eosinophilic cytoplasm along with dense neutrophilic infiltrate. Lamina propria shows inflammatory infiltrate comprised of lymphocytes, plasma cells, neutrophils and eosinophils.

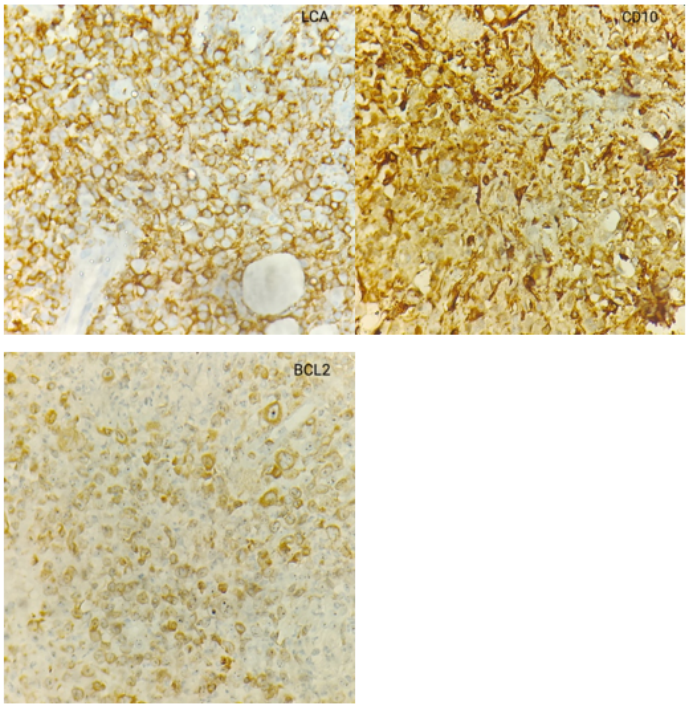

Figure 5: IHC shows Pan CK- Negative LCA – Positive Ki 67 - 68%. CD3 - Negative CD20 - Positive Bcl2 – Positive CD10 –Positive.

Discussion

The overall incidence of malignancy after renal transplantation is 3-5 times higher than in the general population. Such excess frequency is not found for all malignancies but particularly for PTLD and squamous cell carcinoma (lip, cervix, vulva, skin) [5].

The duration and intensity of immunosuppression are important risk factors for the development of malignancies. The prognosis of kidney transplant recipients (KTR) who develop recurrent or denovo cancer is relatively poor compared with the general population [6].

Our study cohort consisted of 4 patients, with a mean age of 47 years, ranging from 32 to 61 years. There were 2 males and 2 females. The interval between transplantation and cancer diagnosis ranged, from 2 years to 33 years.

Various Studies revealed that the mean age of KTRs with lung cancer ranged from 50 to 64 years, with male predominance and squamous cell carcinoma being the commonest type [7-10].

Smoking and prolonged duration of immunosuppression (5.4-10.8 years) were the common risk factors cited in those studies, observations in our case were consistent with above mentioned studies, except that our patient was a non- smoker.

Currently, there is no consensus on lung cancer screening protocols for solid organ transplant recipients [11]. Additionally, transplant patients are often diagnosed with advanced-stage lung cancer, with squamous cell carcinoma being more common, and overall survival after diagnosis is poor [12]. Our case emphasizes that KTRs should be under long term follow up.

Kidney transplant recipients (KTRs) face a significantly increased risk of post-transplant lymphoproliferative disorder (PTLD), with a lifetime risk 8 times higher in adult KTRs compared to the general population [13], and the highest incidence occurring within the first post-transplant year (1-3%) [14] but recent data suggest this interval to be 48-81 months [15]. The mean age of patients at the time of diagnosis as per various studies [16-22] ranged from 40 to 50 years, the observations in our cases were similar to this. The gastrointestinal tract (GIT) was involved in both our cases, mirroring findings in various studies [14-15,18,23-27].

In contrast, other studies reported involvement of lymph nodes [16], pleural cavity [17] and skin [20]. While most recipients in previous studies were EBV-positive, EBV viral load was not performed in our cases in view of financial constraints. Additionally, most studies [16-18], [23] documented polymorphic PTLD as the commonest histopathological variant, while Gianaraki et al [15] reported a rare case of monomorphic PTLD, similar to one of our case.

In a systematic review by Marks et al [28], a dose effect of rATG on PTLD risk was noted, as KTRs receiving less than 7.5 mg/kg had a lower rate of PTLD than those receiving more than 7.5 mg/kg (0.80% vs 1.27%). However, this effect was not statistically significant [28]. Our patients received 3mg/kg ATG, below the threshold associated with increased risk. High-dose azathioprine increases PTLD risk, whereas mycophenolate mofetil does not [19-32]. One of our patients received azathioprine as maintenance therapy while the other received MMF. Secondary infections, such as cytomegalovirus (CMV), significantly impact mortality in KTRs [33]. Unfortunately, our patient succumbed to clinical deterioration due to CMV infection and malignancy. Conversely, successful treatment and patient survival were documented in studies by [32,33].

The increased risk of cervical cancer in KTRs is attributed to the rapid progression of pre-cancerous lesions under immunosuppression [2]. The mean age of diagnosis as observed in various studies ranged from 38 to 49 years [34]. The duration between kidney transplant and diagnosis of cervical carcinoma varied across studies [35,36], compared to 2 years in our case. While some studies have reported vaginal discharge and post-menopausal bleeding as the common presenting symptom, others studies revealed, many were asymptomatic [35,36], and are diagnosed during routine evaluation, as seen in our case. This highlights the importance of routine Pap smear testing in early diagnosis.

Notably, high-risk HPV types (16/18) were associated with high-grade squamous cell carcinoma in previous studies [35,36]. Vaccination against HPV is a strong addition in armamentarium. It is advisable to vaccinate the high-risk patients, such as KTRs.

Conclusion

Malignancies are common cause of morbidity and mortality in kidney transplant recipients after infections and cardiovascular disorders. Our first case highlights the importance of long term follow up of KTRs and prompt evaluation of symptoms. Our third case asserts the necessity of regular screening of asymptomatic patients (especially females) and need for vaccination in few groups of patients. Our second and fourth case reiterates the fact that PTLD are common in KTRs and must be looked for during evaluation of symptoms. To achieve improvement in clinical outcomes, long term follows up, early detection, avoidance of modifiable risk factors, vaccination and prompt treatment remain the pillar stones for management.

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