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# Epstein Barr Virus–Negative Lymphoplasmacytic Proliferation Limited to the Renal Allograft: A Unique Presentation of a Rare Disease

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## INTRODUCTION

Posttransplant lymphoma, classified as posttransplant lymphoproliferative disorder (PTLD) in the majority of cases, affects 1% to 3% of kidney transplant recipients and is associated with significant morbidity and mortality.[1,2] The clinical presentation is variable, ranging from 1 site to multiorgan disease. Renal allograft involvement is seen in as many as 13% of recipients with histologic features of predominantly monomorphic or polymorphic B-cell proliferation.[3] Posttransplant lymphoma presenting as plasmacytic infiltration confined to an allograft has been described in few cases. We present a rare case of Epstein Barr virus (EBV)–negative, lymphoplasmacytic proliferation limited to an allograft incidentally found on the protocol biopsy.

## CASE PRESENTATION

A 53-year-old man developed end-stage renal disease secondary to IgA nephropathy. The native kidney biopsy demonstrated IgA nephropathy with no evidence of monoclonal disease including immunofluorescence revealing diffuse, coarsely granular mesangial positivity with IgA (3+), C3 (2+), kappa (3+), and lambda (3+). The patient ultimately required hemodialysis, and 1 year later he underwent a living unrelated kidney transplant from a female donor with human leukocyte antigen 6/6 mismatch, no circulating preformed donor-specific antibodies, and calculated panel-reactive antibodies of 0%. Both the donor and recipient were positive for cytomegalovirus and EBV. The patient was induced with alemtuzumab and maintained on tacrolimus, mycophenolate mofetil, and prednisone. The implantation allograft biopsy was normal. The postoperative course was unremarkable, except for low-grade BK viremia managed with the reduction of mycophenolate mofetil from 750 mg to 500 mg twice daily. Allograft function remained stable (creatinine 1.2–1.4 mg/dl). The patient presented for a routine 4-month visit and surveillance allograft biopsy with no complaints and stable kidney function.

Renal pathology (Figure 1) revealed an expansile, diffuse, and dense plasma cell–rich interstitial inflammatory cell infiltrate involving the entire interstitium with ill-formed granulomata and severe tubulitis. BK *in situ* hybridization was negative. Immunoperoxidase studies performed on paraffin sections revealed the plasma cell population was IgG and lambda restricted. The plasma cells were CD19, CD45, and CD56 positive. CD20 showed associated clusters of B cells, and the assessment of light chain restriction could not be performed due to inadequate tissue. *MYD88* L265P mutation analysis was negative. EBV *in situ* hybridization was negative. Fluorescence *in situ* hybridization for chromosomes X and Y showed an XY pattern in the lymphoid infiltrate and an XX pattern in the kidney tissue confirming recipient origin (Supplementary Figure S1).

Further studies revealed cytomegalovirus viremia (peak 1130 IU/ml), which resolved with further

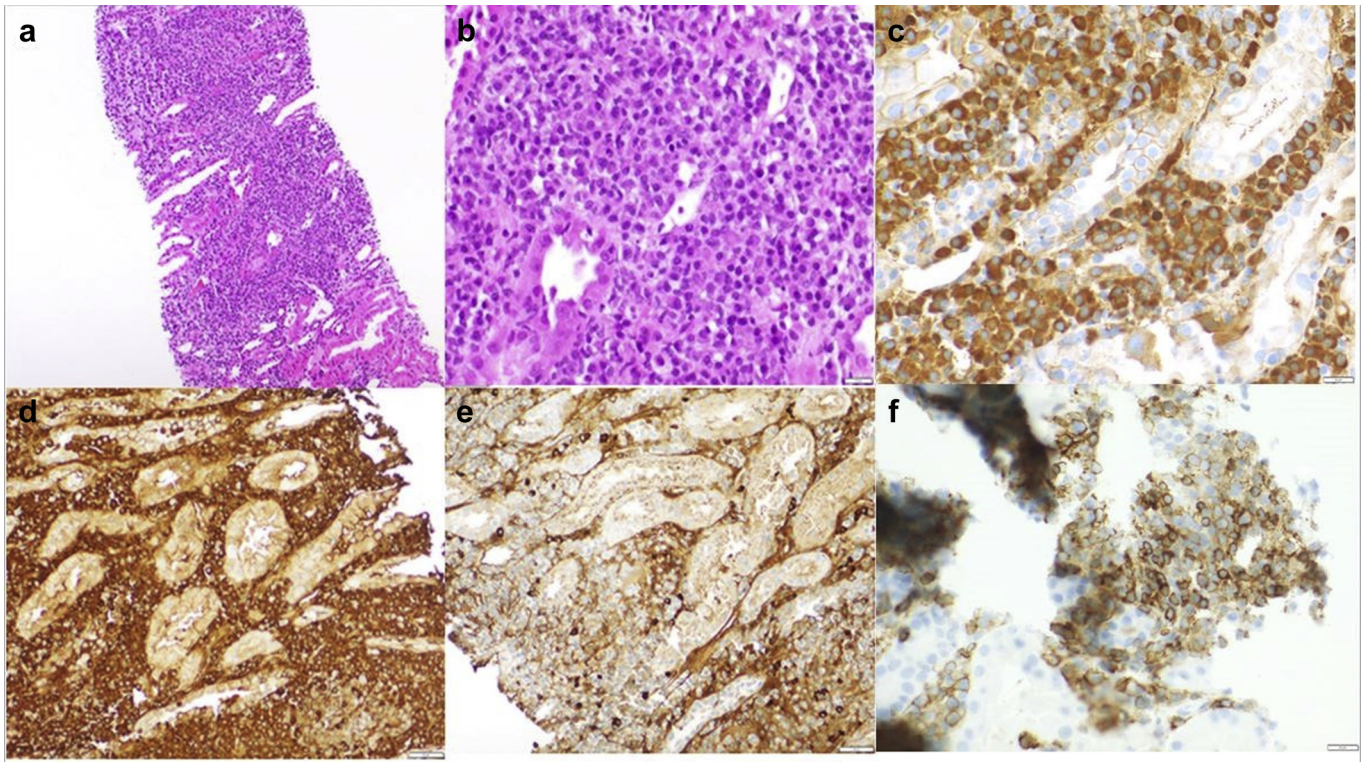


**Figure 1.** The 4-month protocol biopsy shows an (a) expansile infiltrate of atypical cells with (b) plasmacytoid features. The neoplastic cells demonstrated a restricted staining with (c) IgG and (d) lambda light chain. (e) The neoplastic cells did not stain with kappa light chain. (f) The neoplastic cells demonstrated dim staining with CD45 (100 × 56 mm [300 × 300 dpi]).

reduction of mycophenolate mofetil to 250 mg twice daily and treatment with valganciclovir; normal urinalysis; negative serum EBV DNA; lactate dehydrogenase of 158 U/l (reference 122–222 U/l); and a positive monoclonal protein screen with serum monoclonal IgG lambda with an M-spike of 0.3 g/dl with a normal kappa/lambda ratio (kappa = 2.77 mg/dl, lambda = 2.73 mg/dl, and a ratio of 1.01). The peripheral blood flow cytometry, bone marrow biopsy, and positron emission tomography–computed tomographic scan were normal. Given the dense infiltrate on biopsy, the patient was treated with rituximab 375 mg/m$^2$ weekly for 4 weeks. The patient tolerated therapy without adverse events, and serum creatinine improved to 1.1 to 1.2 mg/dl. The follow-up kidney biopsy at 1 year posttransplant demonstrated a small, focal polytypic, lambda-dominant lymphoplasmacytic infiltrate in the medulla (Figure 2). Repeat serum monoclonal protein studies were normal. Additional rituximab was held, and follow-up serum creatinine 6 months later remained stable at 1.1 mg/dl.

## DISCUSSION

Our case poses several unique features as well as diagnostic and management dilemmas. The protocol biopsy obtained early posttransplant revealed a dense, plasma cell–rich infiltrate that was confined to the allograft. The differential diagnosis of a plasma cell infiltrate in the renal allograft includes acute rejection, infection, drug hypersensitivity, BK nephropathy, myeloma, and lymphoma.[4] The monotypic staining pattern with IgG/lambda restriction and otherwise negative evaluation for other etiologies was most consistent with EBV-negative low-grade B-cell lymphoma with plasmacytic differentiation (marginal zone lymphoma) or plasmacytoma-like monomorphic lymphoma.

Per the current World Health Organization 2017 classification, all lymphomas occurring posttransplant are, by definition, PTLD, except EBV-negative low-grade B-cell lymphomas (Table 1). Low-grade B-cell lymphomas may present with plasmacytic differentiation, which may be extensive with plasma cells outnumbering lymphocytes. The World Health Organization categorizes PTLD as nondestructive (plasmacytic hyperplasia, infectious mononucleosis-like PTLD, and florid follicular hyperplasia), monomorphic (monoclonal B-, T-, or natural killer–cell disorders), polymorphic, and classic Hodgkin lymphoma–like PTLD.[5] Most cases of PTLD early posttransplant are EBV related as a consequence of viral reactivation in the setting of decreased T-cell surveillance leading to malignant transformation and

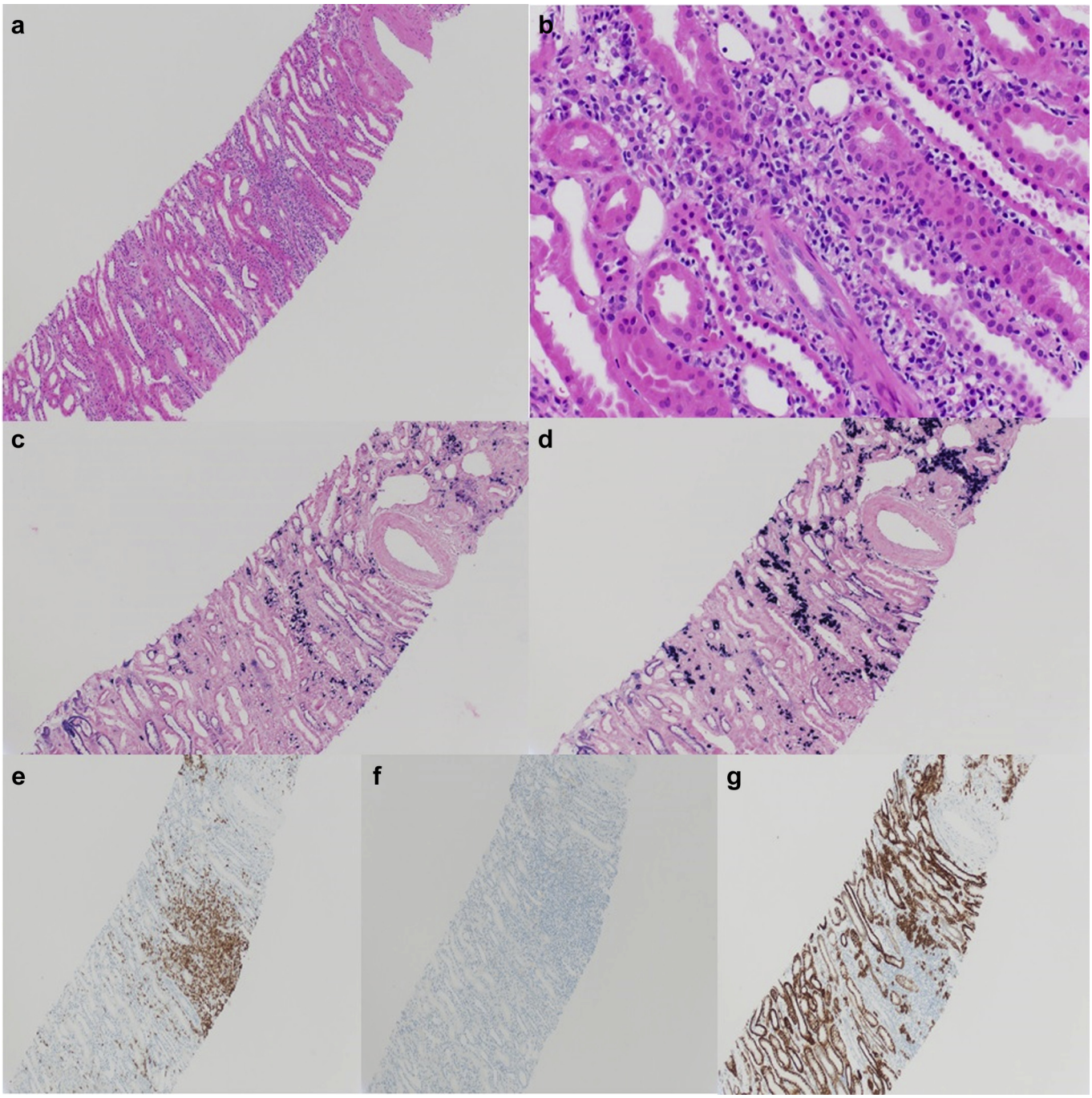


**Figure 2.** Focal, polytypic infiltrate with lambda predominance limited to the medulla. Hematoxylin and eosin at (a) 100× and (b) 400× with *in situ* hybridization stains showing polytypic cells but with lambda predominance (c, kappa and d, lambda). Immunoperoxidase stains revealed the majority of lymphocytes are (e) small, cytologically unremarkable CD3-positive T cells with essentially no (f) CD20-positive B cells. (g) CD138 highlights plasma cells singly and in small clusters. The BK *in situ* hybridization stain was negative (81 × 81 mm [300 × 300 dpi]).

B-cell proliferation. In our case, EBV was negative. Therefore, the infiltrate was challenging to classify by World Health Organization criteria, and the main differentials potentially had different therapeutic approaches.

PTLD limited to the allograft has been well described by others. In general, intragraft PTLD is more likely to occur early posttransplant and is more commonly associated with allograft dysfunction compared with metastatic PTLD.[6–9] Recipients with PTLD limited to the allograft have better long-term survival compared to patients with PTLD in other localizations.[S1] Plasmacytoma-like PTLD confined to the allograft is rare and has been described in 4 kidney transplant recipients. In contrast to our patient, these cases were diagnosed

**Table 1.** Teaching points

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|---|---|
| PTLD | PTLD post–kidney transplant may be present in an otherwise asymptomatic patient with normal kidney function; this case indicates the benefits of protocol biopsies in terms of an incidental diagnosis of malignancy involving a renal allograft. |
| World Health Organization 2017 Classification of Tumors of Hematopoietic and Lymphoid Tissues | Nondestructive (plasmacytic hyperplasia, infectious mononucleosis-like PTLD, and florid follicular hyperplasia)<br>Monomorphic (monoclonal B-, T-, or natural killer–cell disorders)<br>Polymorphic<br>Classic Hodgkin lymphoma-like PTLD<br>[a]Low-grade B-cell lymphomas such as follicular lymphoma or EBV-negative marginal zone lymphoma are not included |
| FISH for X and Y chromosomes | May help differentiate donor- or recipient-derived PTLD in the setting of sex-mismatch organ transplants |
| Rituximab | Improved outcomes in patients with PTLD in addition to immunosuppression reduction |

EBV, Epstein-Barr virus; FISH, fluorescence *in situ* hybridization; PTLD, posttransplant lymphoproliferative disorder.
[a]This type of lymphoma is not included in classification.

late (>1 year posttransplant) either due to the allograft dysfunction or a mass detected on the allograft. Three of the patients were treated with immunosuppression reduction and subsequently allograft nephrectomy, whereas the fourth was treated successfully with cyclophosphamide, bortezomib, and dexamethasone.[S2] Ventura-Aguilar *et al*.[S3] described plasmacytoma-like PTLD limited to the pancreas allograft in a simultaneous kidney–pancreas transplant recipient who presented with acute hyperglycemia. Before presentation, the patient had a monoclonal protein of unknown significance. The pancreas transplant biopsy showed diffuse monotypic plasma cell infiltrate, and the patient was treated with bortezomib and dexamethasone.[S3]

Kidney transplant recipients with EBV infection are at higher risk of developing monoclonal gammopathy of unclear significance that can precede the development of PTLD.[S4] Bone marrow evaluation is performed to identify clonal hematologic disorder, and imaging studies (such as positron emission tomography–computed tomography) may identify a localized plasmacytoma or lymphadenopathy in low-stage, low-grade lymphoma. This case was EBV negative, and both bone marrow biopsy and imaging were normal. The patient did have transient cytomegalovirus viremia, but it remains unclear whether cytomegalovirus viremia is associated with PTLD or monoclonal gammopathy.[S4] Regardless, the patient achieved a complete response with rituximab with resolution of the infiltrate on follow-up biopsy and improvement in allograft function.

Early presentation posttransplant leads to the possibility of donor-derived disease either due to the lymphoma already present in the transplanted kidney or the transfer of passenger leukocytes leading to microchimerism.[S5] This was excluded by the normal implantation biopsy and sex chromosome fluorescence *in situ* hybridization, which confirmed recipient origin.[S5] Our case highlights the benefits of protocol biopsies, which are useful for monitoring for rejection and recurrent glomerular disease.[S6] Although rare, malignancy may also be incidentally diagnosed on protocol biopsies.

In summary, lymphoma posttransplant can present as plasmacytic infiltrate confined to the renal allograft in an asymptomatic patient with normal kidney function. It may or may not be classified as PTLD based on the current World Health Organization criteria. The risk of allograft loss is extremely high, and very little is known regarding the appropriate therapy due to the rarity of the disease. Our case demonstrates that kidney allograft can be salvaged if appropriately treated.

## DISCLOSURE

All the authors declared no competing interests.

## PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** Fluorescence *in situ* hybridization for chromosomes X (green) and Y (red) revealed (A) an XX pattern in the kidney tissue and (B) an XY pattern in the lymphoid infiltrate confirming recipient origin.

**Supplementary References.**

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