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Heterogeneous Manifestations of Posttransplant Lymphoma in Renal Transplant Recipients: A Case Series

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ABSTRACT

Posttransplant lymphoproliferative disorder (PTLD) occurs in 1% to 3% of adult renal transplant recipients (RTRs). PTLD has a heterogeneous presentation and is often associated with Epstein-Barr virus (EBV) and immunosuppression. We present a descriptive case series of 16 RTRs who demonstrate a variety of PTLD manifestations.

Fifty-six percent received rabbit antithymocyte globulin induction, and 37.5% received basiliximab. Maintenance immunosuppression included glucocorticoids, tacrolimus, and mycophenolate mofetil. Median time from transplantation to PTLD diagnosis was 96.5 months. PTLD involved a single site in 44% of RTRs and multiple sites in 56%. PTLD was localized to the gastrointestinal tract in 9 RTRs, in lymph nodes in 9, central nervous system in 4, bone marrow in 3, skin in 3, lungs in 2, perinephric space in 2, mediastinum in 1, and native kidney in 1. PTLD was EBV positive in 8 RTRs, monomorphic/monoclonal in 14, and of B-cell lineage in 13. Three RTRs had T-cell PTLD. Immunosuppressive agents, except glucocorticoids, were discontinued at diagnosis. Treatment was chemotherapy either alone (in 14 RTRs) or in combination with radiation. Complete remission was achieved in 62.5% of RTRs. Renal dysfunction developed in 62.5% of RTRs, and 4 received dialysis. The overall mortality rate was 62.5%, with median time of death 6.5 months after diagnosis.

PTLD that was EBV negative and had T-cell involvement presented with aggressive disease and a higher mortality. Clinicians should be aware of the various PTLD manifestations. Early diagnosis and a multidisciplinary approach to treatment is crucial for improved patient outcomes.

POSTTRANSPLANT lymphoproliferative disorder (PTLD) is a serious complication observed after solid organ transplantation. PTLD presents in 1% to 3% of renal transplant recipients (RTRs) [1,2], contributing significantly to the morbidity and mortality (30%-60%) of these patients [1]. PTLD development is associated with the Epstein-Barr virus (EBV), although not exclusively, and immunosuppression. Generally, the pathogenesis of PTLD is related to uncontrolled proliferation of EBV-infected B lymphocytes in the setting of deficient T-cell cytotoxicity [3,4]. Other risk factors for PTLD development include younger age (<20 years), rabbit antithymocyte globulin (rATG) induction [5], and viral coinfections like hepatitis C virus [6] and cytomegalovirus (CMV) [7].

PTLD encompasses a group of diseases that range from benign, self-limiting lymphoproliferation to widely disseminated, aggressive lymphoma. The World Health Organization characterizes PTLD into 4 categories: early lesions, polymorphic lesions, monomorphic lesions, and classic Hodgkin lymphoma lesions [8]. PTLD is usually of B-cell origin; however, T-cell origin, including gamma-delta T-cell lymphoma (GDTCL) and natural killer T-cell lymphoma, has also been described [9]. PTLD localizes commonly to the digestive tract and the nervous system but can involve any site, such as lungs [1,10] and skin [11]. Treatment of PTLD always consists of maintenance immunosuppression reduction and often involves additional immunochemotherapy regimens, usually centered around rituximab [12]. However, there has yet to be a clear consensus on management.

The aim of this study is to describe PTLD based on EBV status, histologic subgroups, localization, and clinical outcomes in

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adult RTRs. We present 16 adult RTRs to demonstrate the clinicopathologic characteristics and outcomes of PTLD in a single transplant center.

MATERIALS AND METHODS

This is a descriptive study that involved retrospective data collection of 16 adult RTRs diagnosed with PTLD between 2009 and 2020. All patients received transplants and were followed up at our center, Henry Ford Hospital in Detroit, Michigan. The analysis included assessment of demographics, EBV/CMV serology, time from transplantation to PTLD diagnosis, immunosuppression (induction, maintenance, and postdiagnosis), PTLD localization and histologic diagnosis, development of renal insufficiency (estimated glomerular filtration rate [eGFR] was calculated using the Modification of Diet in Renal Disease equation, 4 (MDRD-4) equation), treatment instituted, and patient and graft survival. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

RESULTS

Demographics

Fifty percent (8) of the patients were white, 37.5% (6) were African American, and 12.5% (2) were Hispanic. Ten (62.5%) patients received a deceased donor kidney transplant and 6 (37.5%) a living donor kidney transplant (3 unrelated, 3 related). Two patients underwent a dual-organ transplant; 1 received a simultaneous liver-kidney transplant, and the other received a simultaneous pancreas-kidney transplant. Nine (56.0%) patients received rATG induction, and 6 (37.5%) received basiliximab; 1 patient received both basiliximab and rATG induction**.** Standard maintenance immunosuppression received before the PTLD diagnosis for 7 patients was tacrolimus (FK) and mycophenolate mofetil (MMF). Four other patients received glucocorticoid (GC), FK, and MMF; 1 patient was switched to GC and everolimus after diagnosis of renal cell carcinoma. The remaining patients received GC in combination with either MMF, FK, azathioprine, FK plus sirolimus, or FK plus azathioprine (Table 1).

Clinical and Pathologic Features

Patients presented with nausea, vomiting, diarrhea, abdominal pain, B symptoms, and neurologic deficits. The median time from transplantation to PTLD diagnosis was 96.5 months (<12-248 months). At diagnosis, 56% (9) of patients were aged <60 years, and 44% (7) were aged >60 years. Thirty-one percent were EBV mismatched, and 12.5% were CMV mismatched; there were 5 patients with missing EBV serology data (Table 1).

PTLD involved a single site in 44% (7) of patients and multiple sites in 56% (9). In 9 patients (56%), PTLD localized to the gastrointestinal tract: small bowel in 4 patients, liver in 3, spleen in 1, and colon in 1. PTLD also localized to the lymph nodes in 56% (9) of patients: mesenteric in 4 patients, retroperitoneal in 2, liver in 1, mediastinal in 1, cervical neck in 1, and in lymph nodes all throughout the chest, abdomen, and pelvis in 1 patient. Other PTLD localizations involved the central nervous system (CNS) (4 patients), bone marrow (3), lungs (2), mediastinum (1), skin (3), native kidney (1), and perinephric space (2). Seven

Table 1. Baseline Characteristics of Patients

Patient	Sex	Race	Age at Transplant (y)	Date of Transplant (mo/y)	Type of Transplant	Induction Immunosuppression	Maintenance Immunosuppression Before Diagnosis	EBV Serology Donor IgG +/− Recipient IgG +/−	CMV Serology Donor IgG +/− Recipient IgG +/−
1	M	W	58	6/2001	LURKT	rATG	GC + AZA	+/−	+/−
2	F	W	57	8/2010	DDKT	rATG	FK + MMF	+/−	−/−
3	M	H	56	2/2008	LRKT	Basiliximab	GC + FK	*/−	−/+
4	F	W	28	9/2001	LRKT	rATG	FK + MMF	*	−/−
5	M	A	55	7/2001	DDKT	Basiliximab rATG	GC + FK + SIR	*	+/+
6	F	W	38	9/2017	LURKT	Basiliximab	GC + FK + MMF	+/−	−/−
7	F	A	35	12/2010	SPK	rATG	GC + FK + AZA	+/+	+/+
8	M	A	35	8/1998	LRKT	rATG	GC + MMF	*/+	−/+
9	F	H	54	7/2016	SLK	rATG	GC + FK + MMF	+/+	+/+
10	F	W	64	9/2011	DDKT	rATG	FK + MMF	−/+	−/+
11	M	W	66	3/2016	LURKT	Basiliximab	GC + FK + MMF	+/+	+/−
12	F	A	55	6/2007	DDKT	rATG	FK + MMF	+/−	+/+
13	F	A	70	2/2002	DDKT	Basiliximab	FK + MMF	*/+	−/+
14	M	W	67	4/2014	DDKT	Basiliximab	FK + MMF	+/+	+/+
15	M	W	53	12/2014	DDKT	Basiliximab	FK + MMF	+/−	−/+
16	M	A	36	3/2010	DDKT	rATG	GC + FK + MMF → GC + EVL†	+/+	−/−

A, African American; AZA, azathioprine; CMV, cytomegalovirus; DDKT, deceased donor kidney transplant; EBV, Epstein-Barr virus; EVL, everolimus; F, female; FK, tacrolimus; GC, glucocorticoids; H, Hispanic; IgG, immunoglobulin; LRKT, living related kidney transplant; LURKT, living unrelated donor kidney transplant; M, male; MMF, mycophenolate mofetil; rATG, rabbit antithymocyte globulin; SIR, sirolimus; SLK, simultaneous liver and kidney transplant; SPK, simultaneous pancreas and kidney transplant; W, white.

* Unknown variable.

† Patient developed renal cell carcinoma in 2016 before posttransplant lymphoproliferative disorder diagnosis, and maintenance immunosuppression was adjusted to GC + EVL.

Table 2. Diagnosis and Characteristics of PTLD

Patient	Date of PTLD Diagnosis (mo/y)	Time from Tx to PTLD Diagnosis (mo)	PTLD Location	Histopathologic Diagnosis	PTLD EBV Status
1	11/2009	101	Bone marrow, SB, LN in mesentery and liver	Monomorphic enteropathy-associated T-cell	EBV−
2	11/2011	15	Perinephric space	Monomorphic DLBCL − NHL	EBV+
3	8/2016	102	CNS, perinephric space, retroperitoneal LN	Monomorphic DLBCL − NHL	EBV−
4	10/2018	205	Colon, SB, RLQ, mesentery LN	Monomorphic DLBCL − NHL	EBV−
5	3/2013	140	Native kidney, retroperitoneal LN, left calf skin	Monomorphic B-cell lymphoma − NHL	EBV+
6	7/2018	10	Lung	Monomorphic DLBCL − NHL	EBV+
7	1/2019	97	SB, mesenteric LN	Monomorphic DLBCL − NHL	EBV−
8	4/2019	248	CNS	Monomorphic DLBCL − NHL	EBV+
9	3/2018	20	Liver	Polymorphic B-cell lymphoma − NHL	EBV+
10	9/2019	96	Left neck skin, lung, mediastinum, LLQ mass, mesenteric LN*	Monomorphic DLBCL − NHL	EBV−
11	3/2017	12	LN in chest, abdomen, and pelvis; bone marrow, skin	Monomorphic primary cutaneous GDTCL − NHL	EBV−
12	11/2019	149	CNS	Polymorphic DLBCL − NHL	EBV+
13	2/2020	215	CNS	Monomorphic DLBCL − NHL	EBV+
14	6/2017	38	Liver	Monomorphic DLBCL − NHL	EBV−
15	3/2016	16	Left cervical neck LN	Monomorphic DLBCL − NHL	EBV+
16	11/2017	92	Liver, spleen, bone marrow, mediastinal LN	Monomorphic hepatosplenic GDTCL − NHL	EBV−

CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; EBV−, Epstein-Barr virus negative; EBV+, Epstein-Barr virus positive; GDTCL, gamma-delta T-cell lymphoma; LLQ, left lower quadrant; LN, lymph node; NHL, non-Hodgkin lymphoma; PTLD, posttransplant lymphoproliferative disorder; RLQ, right lower quadrant; SB, small bowel; Tx, transplant.

* Concurrent renal cell carcinoma.

patients had purely extranodal involvement (CNS, liver, lungs) (Table 2).

PTLD was of B-cell lineage in 13 patients. Histology was monomorphic in 11 out of these 13 patients with B-cell PTLD. Three patients had T-cell PTLD, out of which 2 patients had GDTCL (hepatosplenic and primary cutaneous) and 1 had cytotoxic enteropathy-associated T-cell lymphoma. Fifteen patients had non-Hodgkin lymphoma. PTLD was histologically EBV positive in 50% of patients. One patient also developed concurrent renal-cell carcinoma with PTLD (Table 2).

Management

Antiproliferative agents and calcineurin inhibitors (CNIs) were discontinued in all patients at diagnosis, and patients were maintained on steroid monotherapy for the duration of PTLD treatment. Fourteen patients were treated with chemotherapy regimens alone, 1 patient received chemotherapy with radiation, and 1 patient received radiation alone. For chemotherapy regimens, 7 patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), 2 patients received rituximab monotherapy, 2 patients received high-dose methotrexate, 1 patient received CHOP, 1 patient received CHOEP (CHOP plus etoposide), 1 patient received rituximab therapy with resection, 1 patient with T-cell PTLD received salvage therapy (gemcitabine, dexamethasone, carboplatin), and 1 patient with CNS PTLD received temozolomide (Table 3).

One patient with CNS, EBV negative−B-cell PTLD received 1 cycle of R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) followed by 1 cycle of R-Hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) followed by 8 cycles of high-dose methotrexate with complete remission. This patient had a relapse of PTLD 3 years after initial treatment and was given 1 cycle of R-CHOP and dexamethasone without resolution. Another patient with multifocal, EBV negative−T-cell PTLD was treated with 3 cycles of CHOEP and 2 cycles of salvage therapy with complete remission. He relapsed 4 months later and died shortly thereafter (Table 3).

Treatment was complicated by tumor lysis syndrome in 3 patients, sepsis in 3, BK viremia in 1, and pneumocystis pneumonia in 2. In patients who achieved complete remission, the immunosuppressive regimen was optimized. Although 4 patients were maintained on steroid monotherapy, other patients were treated with steroids in combination with everolimus or tacrolimus added.

Patient Outcomes

Acute renal dysfunction and graft survival. At the time of PTLD diagnosis, before treatment, the eGFR was similar to the baseline eGFR posttransplant in all patients. During treatment, the eGFR dropped in 44% (7) of patients and was preserved in 56% (9). At the end of treatment, 31% (5) of patients had a lower eGFR than their baseline, whereas 69% recovered their renal function (Table 4, Fig 1).

Table 3. Treatment and Patient Outcomes

Patient	PTLD Treatment	Posttreatment Immunosuppression	Acute Renal Dysfunction Postdiagnosis	PTLD Outcomes	Patient Outcomes	Cause of Death
1	Resection + Rituximab 1 ×	–	Yes – dialysis	No remission	Deceased	CT
2	R-CHOP: 8 cycles	GC + EVL	No	Complete remission	Surviving	
3	R-DHAP: 1 cycle; R-Hyper-CVAD: 1 cycle (1B + 1A) and partial cycle 2B; rituximab + HD-MTX: 8 cycles Relapse 3 years later; Dexamethasone + 1 cycle R-CHOP	GC + EVL (after initial treatment)	Yes	Complete remission with relapse 3 years later	Deceased	CT (family withdrew care)
4	R-CHOP: 6 cycles	GC + EVL	Yes	Complete remission	Surviving	
5	Nephrectomy; R-CHOP: 6 cycles; radiation: 20 cycles	GC	No	Complete remission	Surviving	
6	R-CHOP: 6 cycles	GC + EVL (only for 3 months)	No	Complete remission	Surviving	
7	R-CHOP: 6 cycles	GC + EVL	Yes – dialysis	Complete remission	Deceased	Infection (hospice home care)
8	Whole brain radiation + levetiracetam	GC	Yes – dialysis	Complete remission	Deceased	Infection
9	5 weeks of rituximab 4 ×	GC + FK	No	Complete remission	Surviving	
10	R-CHOP: 1 cycle	–	Yes	No remission	Deceased	CT
11	EPOCH: 6 cycles	–	Yes	No remission	Deceased	CT
12	HD-MTX: 8 cycles + rituximab on cycles 3-6	GC	Yes	Ongoing treatment	Surviving	
13	4 weeks of rituximab × 4 cycles + temozolomide × 7 every 28-day cycles	–	No	No remission	Deceased	CT (sepsis)
14	6 weeks of rituximab 4 ×	GC + EVL	No	Complete remission	Deceased	Pyoderma gangrenosum
15	CHOP: 1 cycle	–	Yes	No remission	Deceased	CT (sepsis)
16	CHOEP: 2 cycles; salvage therapy: 3 cycles	GC	Yes – dialysis	Complete remission with relapse 4 months later	Deceased	CT (sepsis)

CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisolone; CT, patient died during chemotherapy or as a result of chemotoxicity; CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; EVL, everolimus; FK, tacrolimus; GC, glucocorticoids; PTLD, posttransplant lymphoproliferative disorder; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-Hyper- HD-MTX, high-dose methotrexate.

However, 62.5% (10) of patients had an episode of acute renal dysfunction after PTLD diagnosis. Out of these 10 patients, 40% (4 of 10) developed dialysis-dependent renal failure (Table 3). Four patients on dialysis had an eGFR of ≤40 mL/min/1.73 m^2 before PTLD treatment and had a 100% mortality rate (Table 4, Fig 1). In the other 6 patients, acute renal dysfunction resolved; however, 4 of these 6 patients eventually died. Out of the 10 patients who died in our cohort, 6 patients died with a functioning graft (Table 3).

Patient survival. Ten of 16 (62.5%) patients diagnosed with PTLD died. The median time to death after the diagnosis of PTLD was 6.5 months. Seventy percent (7 of 10) of patients died of complications related to chemotherapy (infections) and PTLD. The other remaining patients died of other causes unrelated to their PTLD diagnosis or treatment. We observed that the average eGFR (pre, during, and posttreatment) was lower in patients who eventually died of PTLD compared with patients who survived (Table 4).

Mortality was 100% (3 of 3) in PTLD with T-cell involvement and 54% (7 of 13) in PTLD with B-cell involvement. All patients with T-cell PTLD died within 12 months of diagnosis. Mortality was 83% (5 of 6) in patients who received basiliximab induction and 55% (5 of 9) in patients who received rATG induction; 1 patient who received both basiliximab and rATG survived. Although patients with bone marrow involvement had 100% (3 of 3) mortality, 78% (7 of 9) of patients with lymph node involvement died. EBV-negative PTLD had a higher mortality rate (87.5% [7 of 8]) than EBV-positive PTLD (37.5% [3 of 8]).

PTLD Outcomes

Complete remission (CR) was achieved in 62.5% (10) of patients, of which 50% (5 of 10) eventually died. In patients with B-cell PTLD, 61.5% (8 of 13) achieved CR, and 1 patient had relapse of disease. Of the 3 patients with T-cell PTLD, only 1 patient achieved complete remission but eventually had relapse of disease. Three patients with EBV-negative PTLD achieved CR, and 2 had relapse of disease. Five patients with EBV-positive PTLD achieved CR. Of the 3 patients who presented with bone marrow involvement, only 1 had relapse of disease. Of the 9 patients with lymph node involvement, 3

Table 4. eGFR Before, During, and Posttreatment

Patient	Sex	Race	Age at Diagnosis (y)	Mean eGFR Before treatment (mL/min/1.73 m^2)	Mean eGFR During treatment `(mL/min/1.73 m^2)	Mean eGFR 6 weeks Post-treatment (mL/min/1.73 m^2)
1	M	W	66	31	31	13*
2	F	W	58	41	60	43
3	M	H	64	73	86	76
4	F	W	45	49	53	53
5	M	A	67	95	94	97
6	F	W	39	67	42	74
7	F	A	44	39	25	11
8	M	A	56	30	22	13
9	F	H	55	79	78	77
10	F	W	72	83	46	32*
11	M	W	67	23	30	27
12	F	A	67	48	49	56
13	F	A	88	51	76	110*
14	M	W	70	104	103	75
15	M	W	55	83	89	89*
16	M	A	43	36	54	67

A, African American; eGFR, estimated glomerular filtration rate; F, female; H, Hispanic; M, male; W, white.
* Patient died during treatment. This is the last eGFR that was reported.

achieved CR and 2 with T-cell PTLD had relapse of disease (Table 3).

DISCUSSION

PTLD is a complication of renal transplantation primarily related to immunosuppression. It has a myriad of manifestations. PTLD localizes commonly to the digestive tract, lymph nodes, and the nervous system but can involve any site, such as lungs [1,10] and skin [11]. In our data set, the gastrointestinal tract and lymph nodes were the most common sites. We also presented RTRs with PTLD that localized to less common sites, such as the bone marrow, perinephric space, and native kidney.

The timing of PTLD development has a bimodal distribution; patients can present with early or late onset PTLD. Early PTLD (PTLD developing within 1 year posttransplant) has been argued to be clinically and pathologically different from late PTLD (PTLD developing after 1 year posttransplant) [13-15]. The relative risk of developing PTLD is the highest within the first year posttransplant and decreases during consecutive years [1]. Early PTLD is characterized as being EBV positive, CD20 positive, is induced by over-immunosuppression, and

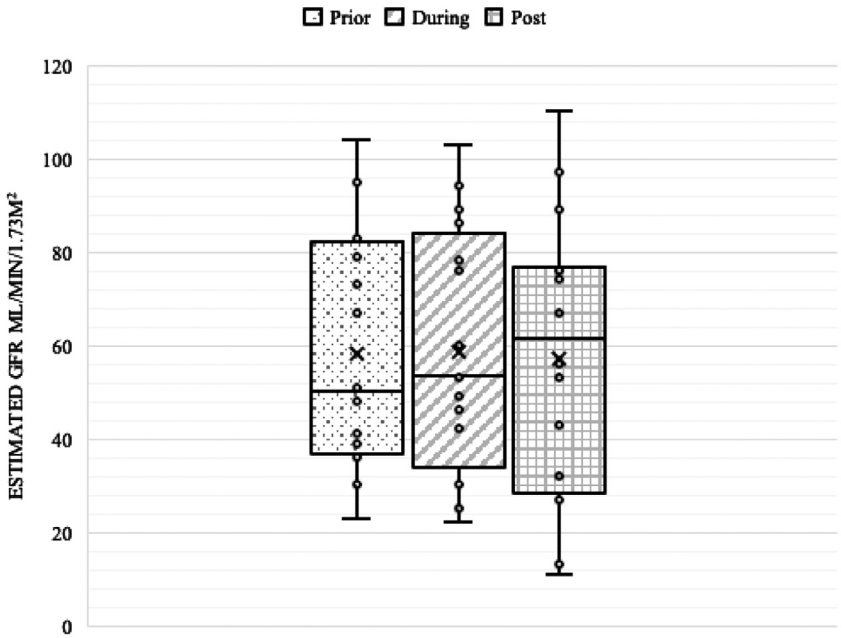

Fig 1. Estimated glomerular filtration rate (eGFR) before, during, and post-treatment. The median of the eGFRs values listed in Table 4 are charted with a standard deviation before, during, and after posttransplant lymphoproliferative disorder treatment.

commonly involves the engrafted organ [15]. Late-onset PTLD is similar to lymphomas that occur in nonimmunosuppressed patients; it is rarely EBV induced, often disseminated with lymph node enlargement, and is associated with poor prognosis [13,14]. In our data, only 2 patients developed early PTLD; 1 patient was EBV positive and achieved complete remission, and the other patient was EBV negative and died within a year of PTLD diagnosis but had a T-cell lymphoma. Our data also support previous sources in that late PTLD has a poor prognosis; 90% of deceased patients developed PTLD >1 year after transplantation. When examining patient survival based on the amount of time (in months) from transplantation to PTLD diagnosis, we observed that surviving patients developed PTLD at a median of 80 months as opposed to patients who died (median of 96.5 months). The reason for this observation is unclear. In a study conducted by Ghobrial et al and in a separate study by Khedmat and Taheri, there was no significant difference in overall survival between early and late PTLD groups [15,16]. However, the patient population in the Ghobrial et al study included a variety of solid organ transplant patients, not solely renal transplant recipients. Whether early vs late PTLD has any implications on renal transplant recipient survival remains unclear and requires further evaluation.

A modifiable risk factor for PTLD development is the induction immunosuppression that a patient receives at the time of transplantation. Our patients received either rATG, a polyclonal antibody, or basiliximab, an IL-2 receptor antagonist. Several studies have proposed that rATG induction is associated with an increased risk for developing PTLD as compared with basiliximab [17,18]. Other studies have demonstrated that polyclonal induction is not associated with a significant increased risk of PTLD development [19,20]. The effects of rATG on PTLD development are not conclusive, but there does seem to be a consensus that IL-2 receptor antagonists do not increase the risk [5,18] or are associated with a comparatively smaller risk for PTLD development [19]. Although we did not specifically look at the risk of PTLD development, in our data, patients who received rATG induction were diagnosed with PTLD at a median of 97 months compared with patients who received basiliximab (median of 27 months). The PTLD EBV status and the maintenance immunosuppression between patients who received rATG vs basiliximab were similar.

A meta-analysis conducted by Liu et al [21] suggested no significant difference between basiliximab vs rATG induction in terms of patient death; however, this study did not specifically examine transplant patients who had developed PTLD. Consequently, there is little to no literature examining the direct effects of induction on mortality in patients with renal PTLD. In our patient cohort, we observed a high mortality rate with basiliximab induction (83%) as opposed to rATG (55%) induction, with no difference in the number of deceased patients who achieved complete remission or relapsed between the groups. The direct impact of induction is likely difficult to isolate because of confounding variables such as varying posttransplant immunosuppressants and treatment regimens. However, because induction type is modifiable, studying the effects of rATG and basiliximab on PTLD patient mortality is merited to improve long-term patient outcomes.

After transplantation, patients are treated with maintenance immunosuppression often consisting of MMF, tacrolimus, and prednisone to prevent acute rejection and loss of the renal allograft. In 2 separate articles, Caillard et al suggests that MMF and Mechanistic Target of Rapamycin (mTOR) inhibitors are associated with a lower risk of PTLD development as compared with patients treated with tacrolimus [5,10], even when accounting for confounding factors (EBV status, age). Moreover, several other studies suggest that mTOR inhibitors may reduce the risk of developing PTLD via an anti-inflammatory and antiproliferative pathway [22] and are effective in treating EBV-positive PTLD, especially when combined with a PI3K/Akt inhibitor [23]. A retrospective study conducted by Sampaio et al [24] also suggests that a combination of mTOR inhibitors and tacrolimus in patients with EBV-negative PTLD is associated with an increased risk of PTLD, graft failure, and mortality. Other studies also demonstrate an increased risk of developing PTLD with tacrolimus than with cyclosporine [1,5]; further comparison of the 2 CNIs is warranted, as they are often used in standard immunosuppressive regimens. Although maintenance therapy is tailored to each patient, optimal combinations of immunosuppressive agents should be identified to decrease the risk of PTLD development. It may even possible that no single immunosuppressive agent or regimen is associated with an increased risk of PTLD but rather the cumulative immunosuppression posttransplant that leads to lymphoproliferation [25].

PTLD is often linked to EBV; however, studies have demonstrated conflicting data on the impact of histologic EBV status on PTLD prognosis and survival [10,26-29]. Studies suggest that EBV-negative PTLD is associated with a longer time to PTLD diagnosis (late PTLD) [27,29], monomorphic histology [27], and a worse prognosis [29]. Other studies argue that EBV status is not indicative of patient survival [26,28,30]. We observed that EBV-negative PTLD had a mortality of 87.5% and a longer median time (96.5 months) from transplantation to PTLD diagnosis as compared with EBV-positive PTLD, which had a mortality of 37.5% and a median time of 80 months. EBV-negative PTLD is also more commonly seen in male patients [10], a trend also seen in our data; we observed a 100% mortality in male patients with EBV-negative PTLD vs 66% mortality in female patients with EBV-negative PTLD. All EBV-negative PTLD patients also presented with a monomorphic histology, supporting findings from previous references. Interestingly, we also noted that the average eGFR (pre, during, and posttreatment) was lower in patients with EBV-negative PTLD as compared with EBV-positive PTLD.

T-cell PTLD is a rare outcome of renal transplantation and often presents with a higher mortality than B-cell PTLD [31]. GDTCL, specifically, is characterized by the World Health Organization into 2 distinct groups: primary cutaneous and hepatosplenic. Both GDTCLs present aggressively and are associated with a significantly worse prognosis [32,33]. We presented 3 patients with aggressive T-cell PTLDs (1 primary cutaneous GDTCL, 1 hepatosplenic GDTCL, and 1 cytotoxic enteropathy-associated T-cell lymphoma) that were resistant to

conventional chemotherapy regimens (rituximab, CHOEP) and had a 100% mortality rate within 12 months of diagnosis. Most data on T-cell PTLD consist of case reports/series, and there has yet to be an effective treatment regimen developed for this disease. Resistance and a poor long-term survival outcome with standard chemotherapy regimens have been cited throughout the literature; 2 larger case series demonstrated a poor long-term survival outcome for hepatosplenic GDTCL when treated with the standard CHOP regimen [34,35]. Treatment options that suggest improved survival for hepatosplenic GDTCL consist of non-CHOP regimens (HyperCVAD [cyclophosphamide, vincristine, doxorubicin, dexamethasone]) with alternating methotrexate and cytarabine [35]), pentostatin [36], and autologous or allogenic stem cell transplant [37]. Case reports have also demonstrated stem cell transplant as an effective potential treatment option for primary cutaneous GDTCL [38,39]. Further exploration of early treatment options is required to address this aggressive subtype of PTLD.

The goal of PTLD treatment is to achieve complete remission while preserving graft function.

Serre et al [40] noted that an eGFR of ≤30 mL/min/1.73 m^2 at the time of PTLD diagnosis and the absence of calcineurin inhibition in maintenance immunosuppression were independent risk factors for allograft loss. Among our patients who had an eGFR of ≤40 mL/min/1.73 m^2 (2 of which had an eGFR ≤30 mL/min/1.73 m^2) before treatment, 3 experienced allograft loss and there was 100% mortality.

Treatment of PTLD is not standardized but often follows international recommendations, which generally consist of reducing or stopping all maintenance immunosuppressive agents, except for prednisone, and initiating specific rituximab and/or chemotherapy regimens for more severe presentations [41]. Complete CNI withdrawal has been associated with worse long-term renal graft function [42], whereas reduction in maintenance CNI agents has been suggested to improve renal graft outcomes [40,43]. In our patients, antiproliferative agents and CNIs were completely stopped after PTLD diagnosis; 37.5% (6) of patients died with a functioning graft and 25% (4) of patients required dialysis and died with a nonfunctioning graft. Another case series also suggested potential benefit in replacing CNI agents with mTOR inhibitors instead of withdrawing all immunosuppression [44].

Treatment options involve reducing immunosuppression in conjunction with rituximab alone or in combination with other chemotherapeutic agents. Rituximab monotherapy has been demonstrated to be an effective and well-tolerated treatment for PTLD, especially PTLD that is EBV positive and CD20 positive [12]. In our data, only 2 patients were treated with rituximab monotherapy. Both patients had PTLD presenting in the liver; 1 patient had EBV-negative PTLD and died, whereas the other patient was EBV positive and achieved complete remission, similar to previous reports. Moreover, Choquet et al [45] used a PTLD prognostic-specific index (>60 years old, Eastern Cooperative Oncology Group Performance Status 2-4, and elevated lactate dehydrogenase) to predict overall survival in low, intermediate, and high-risk PTLD patients treated with solely rituximab; 2-year survival rates were 88%, 55%, and 0%, respectively. Although rituximab monotherapy is effective in low-risk patients, it may not be the optimal treatment option for intermediate- and high-risk patients.

For patients in which rituximab fails, adjunct chemotherapy can be initiated [46,47]. However, chemotherapy involves a high toxicity [47,48] and is associated with an increased mortality when given alone as opposed to in combination with rituximab [49]. Elstrom et al [48] recommend reserving chemotherapy-based treatment plans for patients in which rituximab fails, or those who have EBV-negative disease. In our data set, 60% (6) of patients died of treatment-related complications.

Limitations

This was a descriptive analysis; we did not have adequate number of patients to conduct a statistical analysis.

CONCLUSIONS

Our data demonstrate the varying manifestations of PTLD. PTLD can arise in single or multiple sites and can occur at any time after transplantation. PTLD has a myriad of presentations, and clinicians should have a low index of suspicion for this entity in immunocompromised posttransplant patients. Renal transplant recipients with T-cell PTLD, PTLD involving the bone marrow and lymph nodes, and EBV-negative PTLD have a poor prognosis despite therapy.

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