

# Posttransplant Lymphoproliferative Disorder: Extranodal Marginal Zone Lymphoma Occurring After Renal Transplantation

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## Case 1

Patient 1 is a 58-year-old man who received a living-donor renal transplant from his nonidentical sibling as a consequence of lupus nephritis in June 1989. He was started on immunosuppressive therapy with cyclosporine and had an unremarkable posttransplant course. The patient then presented in December 2004 for evaluation prior to undergoing cataract surgery (173 months after transplantation). Physical examination at that time revealed an enlarged spleen.

A computed tomography (CT) scan of the chest, abdomen, and pelvis was performed to further evaluate the splenomegaly and was significant only for the enlarged spleen. A whole-body positron emission tomography (PET) scan was performed, which demonstrated splenomegaly with increased <sup>18</sup>F-fluoro-2-deoxyglucose uptake (no other areas of increased uptake were noted). A subsequent bilateral bone marrow biopsy showed involvement with marginal zone non-Hodgkin lymphoma (NHL). Bone marrow flow cytometry revealed a population of cells which were CD5- and CD10-negative and CD79a- and CD20-positive.

In February 2005, the patient's immunosuppressive regimen of cyclosporine 75 mg twice daily was decreased to 50 mg twice daily. Allopurinol therapy was begun due to elevated uric acid levels, and the patient's primary hematologist began planning induction chemotherapy with fludarabine (Fludara, Berlex) and rituximab (Rituxan, Genentech/Biogen Idec). The patient then presented to our institution for a second opinion prior to starting this regimen. During the initial evaluation, the patient was found to have no overt symptoms, and his review of systems was unremarkable. His physical examination

revealed a palpable spleen 9 cm below the costal margin. He had no appreciable lymphadenopathy.

His laboratory examination revealed a white blood cell (WBC) count of 3,500 cells/ $\mu$ L with an absolute neutrophil count of 2,490 cells/ $\mu$ L and an absolute lymphocyte count of 560 cells/ $\mu$ L (normal range, 850–3,900 cells/ $\mu$ L), hemoglobin of 12.6 g/dL, and platelet count of 112,000 cells/ $\mu$ L. His comprehensive metabolic panel was normal except for a blood urea nitrogen level of 38 mg/dL and a creatinine level of 1.5 mg/dL. Uric acid and lactate dehydrogenase (LDH) levels were within normal limits. Beta-2 microglobulin level was elevated at 5.8 mg/L (normal range, 0.0–3.0). Epstein-Barr virus (EBV) immunoglobulin (Ig) G antibody was positive, but EBV IgM antibody was not detected from the peripheral blood.

The final diagnosis in this patient, extranodal splenic marginal zone NHL with 20% bone marrow involvement, was thought to be secondary to the immunosuppressant regimen instituted after his renal transplant. We did not believe chemotherapy with fludarabine was indicated at this time due to the chronic, indolent nature of this low-grade lymphoma. Treatment options were discussed with the patient, including continued reduction of his immunosuppressive therapy as tolerated, splenectomy, rituximab therapy, and observation. Because his blood counts remained stable and he continued to be asymptomatic, a “watch and wait” approach with close clinical observation was agreed upon. If he were to become symptomatic or develop worsening cytopenias, rituximab would then be initiated. As of June 2006, the patient remained stable and had not required any therapy for the lymphoma.

## Case 2

Patient 2 is a 26-year-old woman who had a cadaveric renal transplant in May 2000 secondary to renal failure

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due to Wegener granulomatosis. Prior to her surgery, EBV cultures showed that she was IgG antibody–positive and IgM antibody–negative. Her immunosuppressive medications at this time consisted of tacrolimus (Prograf, Astellas) 15 mg twice daily and prednisone 5 mg daily. Her posttransplant course was complicated by a cytomegalovirus (CMV) infection requiring ganciclovir treatment. Both the patient and donor were CMV–negative at the time of transplantation.

The patient developed a transfusion-dependent anemia 6 months after her transplant and was referred to our institution. The anemia was normocytic, and the reticulocyte count was not adequate. A bone marrow biopsy was performed, revealing a hemorrhagic bone marrow with small amounts of hematopoietic marrow that showed large eosinophilic intranuclear inclusions within mononuclear cells, consistent with CMV. The patient's blood was also positive for parvovirus B19 by polymerase chain reaction analysis. The anemia was felt to be a result of both the parvovirus and CMV with an element of chronic disease from her renal impairments. The patient continued an extended course of ganciclovir and received intravenous Ig. Her tacrolimus dose was decreased to 5 mg twice daily, and she was started on weekly epoetin alfa (Epoen, Amgen) injections. These measures improved her anemia and her CMV titers significantly decreased over time.

In May, 2005 the patient first noticed some swelling on the right side of her neck. She lost 10 pounds over a 5-week period and experienced some intermittent epistaxis. On physical examination, she had palpable cervical and right submandibular lymphadenopathy. Her immunosuppressive medications included cyclosporine 125 mg twice daily and prednisone 2.5 mg daily.

A CT scan of her neck showed a mass on the right side, just anterior to the right submandibular gland, which measured 1.4 × 1.1 cm. A second mass was also identified within the deep cervical triangle on the right, which measured 1.45 × 1.0 cm and was the same density as the surrounding soft tissues. Lymph nodes were also noted within both deep cervical triangles of the neck, submental region, and both supraclavicular and axillary regions. An excisional biopsy of the submandibular lymph node revealed an extranodal B-cell marginal zone lymphoma (MZL) with extensive plasmacytic differentiation. A staging CT of the chest, abdomen, and pelvis showed a nonspecific interval increase in the number of mesenteric and retroperitoneal lymph nodes and no enlarged lymph nodes within the chest. A CT scan of the neck redemonstrated the findings seen 1 month earlier. PET scanning showed activity in the lymph nodes in the right submandibular and cervical areas, as well as the left side of the pelvis near the pelvic inlet. Bone marrow biopsy showed a mildly hypocellular marrow with proportional, trilineage hematopoiesis with no evidence of lymphoma.

Laboratory evaluation revealed a normal hemoglobin level of 13.1 g/dL with a normal mean corpuscular volume. Her WBC and platelet counts were both within normal limits at 5,088 (31% lymphocytes, 55% neutrophils, 8.1% eosinophils, and 5.2% monocytes) and 357,000 cells/ $\mu$ L, respectively. A comprehensive metabolic panel was also normal, with a creatinine level of 0.9 mg/dL. Serum protein electrophoresis revealed a slight elevation in the beta region at 1.4 g/dL but was otherwise normal, with no paraprotein detected. Beta-2 microglobulin level was elevated at 3.6 mg/L. LDH level was normal at 264 U/L.

The final diagnosis in this patient was posttransplant lymphoproliferative disorder (PTLD), specifically extranodal B-cell MZL with plasmacytic differentiation. This was thought to be secondary to longstanding immunosuppressive treatment for both Wegener granulomatosis and transplant rejection prevention. A decrease in her immunosuppressive regimen was recommended. Her cyclosporine dose was subsequently lowered to 100 mg twice daily. It was also recommended that the patient undergo rituximab therapy 375 mg/m<sup>2</sup> weekly for a total of 8 weeks. A repeat PET scan done after the eight rituximab treatments was negative with no evidence of residual tumor. Unfortunately, 9 months later the patient, who was doing well, collapsed and died suddenly. No autopsy was performed.

## Discussion

### *Posttransplant Lymphoproliferative Disorder*

PTLD is a well-documented complication that arises as a result of immunosuppression in the setting of solid organ or bone marrow transplantation. Lymphoid proliferation has also been documented in congenital, acquired, or drug-induced immunodeficiency states.<sup>1</sup> PTLTs are often EBV-related and encompass a varied morphologic continuum ranging from polyclonal lesions to monoclonal proliferations indistinguishable from Hodgkin lymphoma or NHL.<sup>1</sup> The vast majority of these disorders are of B-cell origin and associated with EBV; however, T-cell- and EBV-negative disorders have been reported.<sup>2</sup> The preponderance of the monomorphic B-cell neoplasms ranges from diffuse large cell lymphoma (most common) to Burkitt lymphoma, plasma cell myeloma, or plasmacytoma-like lesions. Nevertheless, Hsi and colleagues<sup>3</sup> documented five rare cases of extranodal MZLs of the mucosa-associated lymphoid tissue (MALT)-type occurring posttransplantation.

The incidence of PTLT varies depending on the type of transplantation, the corresponding immunosuppressive treatment, and EBV status at time of transplant.<sup>1,2</sup> Bone marrow transplants (overall) have the lowest reported incidence, at less than 1%; renal transplants carry a 1–2%

risk; cardiac transplants a 3.4–5.0% risk; lung transplants a 7.9% risk; and mismatched, T-cell–depleted donor marrow carries the highest risk at 24%.<sup>1,5–8</sup> The incidence of PTLD has also been recognized to be highest in the first year after transplantation. The time between transplantation and the onset of PTLD is often used to distinguish between two sets of patients with possibly distinct presentations and pathogenesis: early-onset PTLD (within the first year after transplantation) and late-onset PTLD (more than 1 year after transplantation).<sup>8</sup> Some data suggest a better response to reduction in immunosuppression in early-onset as compared to late-onset PTLD.<sup>7</sup> There has been an increasing prevalence of PTLD in recent years. This increase is thought to be the result of rising numbers of both bone marrow and solid organ transplants, more pediatric transplants, and longer patient survival rates due to better supportive measures.

The role of EBV in the etiology and pathogenesis of the majority of PTLDs remains considerable. Patients who are seronegative for EBV at the time of transplant carry the greatest risk in seroconverting after transplantation while on immunosuppressant therapy. Transmission of EBV to seronegative solid organ transplant recipients occurs by either exposure through community contacts or receipt of an organ from an EBV-positive donor.<sup>9</sup> EBV-infected B cells are typically held in check by cytotoxic T cells that establish an equilibrium between cell division and cell death. Immunosuppressive therapy impairs this T-cell immune surveillance and allows EBV to undergo unregulated lytic replication. This may result in EBV-transformed B-lymphocyte clones that potentially favor the development of PTLD.<sup>9</sup>

The clinical presentation of PTLD is highly variable. Patients may present with prominent constitutional symptoms in addition to rapid enlargement of the tonsils and cervical lymph nodes. This presentation usually occurs as an early-onset PTLD.<sup>1,5,10</sup> Highly immunosuppressed patients may present with fulminant, widespread disease, as well as infiltrative multiorgan involvement and sepsis within weeks from transplantation.<sup>1,5,6</sup> PTLD presenting more than 1 year after transplant is more likely to be circumscribed anatomically, have a more indolent course, and have fewer systemic symptoms.<sup>1,5</sup> The transplanted organ itself may be the only evidence of disease in approximately 20% of cases. As a result, it may be difficult to distinguish PTLD from rejection. EBV-positive PTLD tends to occur earlier than EBV-negative disease. The majority of cases occurring more than 5 years after transplant are EBV-negative.<sup>2</sup>

The diagnosis of PTLD requires a high index of suspicion because the clinical symptoms are so variable and often nonspecific. Excisional biopsy is the preferred method to obtain a tissue specimen for the diagnosis. The

overall prognosis depends on the specific morphologic variant of PTLD, the stage (Ann Arbor Staging Classification with Cotswold Modifications) of disease, and the time from transplantation. The overall mortality from PTLD in organ recipients is approximately 60%, but the rate is upward of 80% in bone marrow allograft recipients.<sup>2</sup>

The treatment of PTLD is contentious, with no standardized approach fully accepted. However, through smaller studies and anecdotal reports, some general principles have emerged. Treatment must first be individualized to the specific parameters of each patient. Reducing the immunosuppressive therapy whenever possible should be the initial intervention. This has resulted in complete and sustainable remissions. In one retrospective study, Armitage and coauthors<sup>7</sup> reported that 89% of patients presenting with PTLD less than 1 year after transplantation responded to a reduction in immunosuppression, whereas no patients presenting after 1 year responded. The uncertainties over how much to reduce therapeutic dose and duration as well as balancing the risk of organ rejection all remain valid concerns. Other treatment modalities include surgical resection for localized disease, limited field radiation, antiviral therapy, interferon- $\alpha$ , anti-B-cell monoclonal antibodies, EBV-specific T-cell therapy, and cytotoxic chemotherapy. The anti-CD20 monoclonal antibody rituximab has become a popular treatment method in recent years. High mortality rates have traditionally caused chemotherapy to be seen as a less attractive therapeutic option in the treatment of PTLD. Mortality rates from chemotherapy upwards of 70% have been reported in patients presenting at more than 1 year after transplant.<sup>1,5,7</sup> Nevertheless, there are some optimistic results from a series of cardiac recipients treated with cyclophosphamide, doxorubicin, etoposide, bleomycin, vincristine, methotrexate, and prednisone (ProMACE-CytaBOM) after initially failing a reduction in immunosuppression. This study group showed a 75% sustained complete remission with a median follow-up of 64 months.<sup>11</sup> Low-dose chemotherapy has been used with some success in the pediatric population, but it is unclear whether these favorable results will carry over to adults.

PTLD is a potentially devastating complication resulting from prolonged immunosuppressive therapy. There have been case reports by Hsi and colleagues<sup>3</sup> and Wotherspoon and colleagues<sup>4</sup> of extranodal MZLs of the MALT-type occurring after transplant.<sup>3,4</sup> These low-grade lymphomas were reported to behave similarly to MALT-type lymphomas in immunocompetent patients and appeared not to be clinically aggressive.<sup>3,4</sup> They also tend to occur very late after transplant. The mean time to lymphoma in our two patients was 121.5 months. In the few cases reported, it seems that EBV plays no role in the pathogenesis of these lymphomas. Of note, approxi-

mately 20% of all PTLDs are EBV-negative, and upwards of 50% of renal allograft recipients who go on to develop PTLD are EBV-negative.<sup>2</sup> Both of our reported patients were indeed recipients of renal allografts. Most of the cases of PTLD extranodal MZLs reported have been gastric MALT-type lymphomas associated with *Helicobacter pylori* infection, although parotid gland involvement has also been documented.

### ***Posttransplant Lymphoproliferative Disorder in These Patients***

To our knowledge, patient 1 is the first reported case of splenic MZL occurring posttransplant. The course of patient 1 does not seem to deviate from the other reported cases in the literature. His diagnosis of extranodal splenic MZL can be characterized as late-onset, occurring 173 months after transplant. Unfortunately, his EBV status at the time of transplant remains unknown, so it is not possible to determine exactly when he turned EBV IgG antibody-positive. His asymptomatic clinical presentation also correlates with the chronic, indolent nature of this disease as reported by both Hsi and colleagues<sup>3</sup> and Wotherspoon and colleagues.<sup>4</sup> Due to this patient's lack of symptoms and only marginally low blood counts, we felt that reducing his immunosuppression (cyclosporine) was the most attractive initial approach. MALT-type lymphomas are associated with dysregulation of the host immune system given their increased incidence in other autoimmune diseases. Subjecting this patient to the morbidities of chemotherapy does not seem warranted given his presentation. Rituximab will likely be our second-line modality if his disease progresses or fails to improve with the reduction of cyclosporine.

Patient 2 demonstrated some unique findings in her presentation of extranodal B-cell MZL with plasmacytic differentiation. She was diagnosed 70 months after her transplant, which, although it fits into the category of late-onset PTLD, was many years sooner than patient 1 was diagnosed with PTLD. One explanation for this is her use of immunosuppressive medications for Wegener granulomatosis for 4 years prior to her actual transplant. This illustrates an important concept: lymphoproliferative disease can occur from immune suppression in general, regardless of transplant.<sup>4</sup> For instance, there are also case reports in the literature of MALT-type lymphomas occurring in the setting of HIV-positive patients.<sup>4,13</sup>

This patient was EBV IgG antibody-positive at the time of transplant, so EBV did not play a role in the pathogenesis of her PTLD. Interestingly, she did become CMV IgM- and IgG-positive approximately 7 months after her transplant. CMV seroconversion after transplant has been identified as an independent risk factor for the development of PTLD.<sup>9,14-16</sup>

This patient's clinical presentation was more aggressive than that of patient 1. Consequently, we felt that it was necessary to start her on rituximab in addition to reducing her immunosuppressant therapy. Rituximab has been shown to be efficacious against B-cell PTLDs. Several anecdotes and smaller studies have been reported. Ganne and coauthors<sup>16</sup> reported 8 patients with PTLD after solid organ transplant who were administered rituximab 375 mg/m<sup>2</sup> once a week for 4 weeks in addition to decreasing their immunosuppression. Complete remission was observed in 7 of 8 cases, 87.5% (1 required two courses). One patient did not respond to rituximab and received chemotherapy, eventually losing his graft. Three patients were reported to be in remission 2.5 years later, while the remaining 4 patients remained in remission for approximately 10 months. At last follow-up, 7 patients maintained a functioning graft. No side effects were observed with therapy. This study suggests that reduction of immunosuppression with or without rituximab may be the optimal first-line approach in treating PTLD. Chemotherapy would then be reserved as a second-line therapy, potentially eliminating its associated morbidities. Milpied and colleagues<sup>17</sup> conducted a retrospective study of 32 patients with B-cell PTLD (26 solid organ recipients; 6 bone marrow transplants). The majority of patients received four weekly infusions of rituximab 375 mg/m<sup>2</sup>, with an overall response rate of 69% (20 complete response, 2 partial response). Of the 22 patients who achieved a response, 15 were alive without evidence of disease at a median follow-up of 8 months, 4 patients relapsed at a median of 7 months, and 3 died from concurrent disease.<sup>17</sup> In a study by Verschuuren and colleagues,<sup>18</sup> 3 lung transplant recipients with PTLD were treated with rituximab. Again the patients were treated with four weekly doses of 375 mg/m<sup>2</sup> of rituximab. The treatment initially resulted in complete remissions in all 3 patients. However, 1 patient relapsed after 2 months and developed partly CD20-negative PTLD; 1 patient developed hypogammaglobulinemia and died of an opportunistic infection 6 months after treatment; the third patient remained in complete remission 16 months post-treatment. This study illustrates two important concepts. First, rituximab may be an appealing first-line treatment in vital organ transplants, as decreasing immunosuppressant therapy may result in rejection and ultimately death. Second, rituximab complications exist and were evident in 2 of the 3 patients in this study. These complications were a partly CD20-negative relapse and the development of hypogammaglobulinemia.<sup>18</sup>

Patient 2 initially underwent a total of eight weekly doses of rituximab. A study by Piro and coworkers<sup>19</sup> showed that eight weekly doses as compared to four weekly doses resulted in an increased duration of response

and response rate. In a multicenter, single-arm study, patients with relapsed or refractory low-grade NHL were treated with eight weekly doses of rituximab 375 mg/m<sup>2</sup>. The overall response rate was 57% (complete response 14%, partial response 43%) with a median duration of response of 13.4 months and a median time to progression of 19.4 months.<sup>19</sup> The safety profile in this study was also similar to that of patients treated with the standard four weekly doses. Comparing this study to a multicenter, open-label, single-arm study by McLaughlin and colleagues<sup>20</sup> illustrates the significance of extended rituximab dosing. In this study, 166 patients from 31 different centers with relapsed or refractory low-grade NHL received the standard four weekly doses of rituximab 375 mg/m<sup>2</sup>. These patients had an overall response rate of only 48% (complete response 6%, partial response 42%) with a median duration of response of 11.2 months.<sup>20</sup>

The repeat PET scan for patient 2, performed after rituximab treatment, demonstrated marked improvement with no residual tumor and no new lesions evident. Our group has reported PTLD patients who have been able to discontinue immunosuppression and continue with preserved graft function for several years,<sup>21</sup> which may be related to immune modulation of the host environment by the monoclonal antibody. The role of rituximab in the management of PTLD required further investigation.

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## Review

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Goldfarb and colleagues<sup>1</sup> document the occurrence and successful management of late-onset posttransplant extranodal MZLs in two renal allograft recipients. These uncommon tumors are recognized as part of the spectrum of HIV-associated lymphomas but have not yet been incorporated into the current classification of PTLDs,<sup>2</sup> an umbrella term, which has been categorized into four classes of lesions, namely early lesions (usually reactive), polymorphic PTLD, monomorphic or lymphomatous PTLD, and Hodgkin lymphoma/Hodgkin lymphoma-like PTLD.<sup>2</sup> Monomorphic PTLD is further divided into B- and T-cell neoplasms in line with the World Health Organization classification, although the current PTLD system recognizes only a limited number of lymphoma types in the transplant setting. Specifically, marginal zone B-cell lymphoma is not included in the current scheme.

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The diagnosis of extranodal marginal zone B-cell lymphoma is dependent upon demonstration of a combination of histologic and immunophenotypic features.<sup>3,4</sup> Some pathologic information is provided regarding the features of each case in the current case study. Patient 1 had clinical involvement of spleen and bone marrow. The immunophenotype of the bone marrow cells in this patient is consistent with MZL, but may also be seen in many B-cell PTLDs (CD20+, CD79a+, CD5-, CD10-). However, in my experience, isolated splenic involvement (with or without marrow involvement) would be an unusual presentation for typical B-cell PTLT. Such cases seen at the University of Pittsburgh Medical Center have represented Hodgkin-like PTLT or posttransplant smooth muscle tumor, neither of which appears histologically similar to MZL. The description of the process in patient 2, diagnosed as extranodal B-cell MZL with plasmacytic differentiation, is more problematic, as extensive plasma cell differentiation may also be seen in many cases of B-cell PTLT.<sup>5,6</sup> In this case the lesion involved a submandibular salivary gland, and biopsy of that organ led to the diagnosis. Regional lymph nodes were enlarged but were not biopsied. If one assumes that they were involved by the same process, the designation of extranodal MZL would still be appropriate, as such involvement is considered to represent secondary spread from the primary extranodal site.<sup>7</sup>

By highlighting the existence of posttransplant extranodal MZL, this clinical case study also raises the question of the relationship, if any, of these tumors to the more common B-cell PTLT. Both of these tumor types can arise from post-germinal center lymphocytes, albeit by different mechanisms.<sup>3,8</sup> It would be of interest to apply recently described markers associated with MZLs, such as fluorescence in situ hybridization for t(11;18)(q21;q21), t(1;14)(p22;q32) and t(14;18)(q32;q21),<sup>9</sup> to these or similar cases to further define their genetic makeup, even accepting that such alterations occur in only a subset of MZL and do not appear to be characteristic for the splenic variety of these tumors. There are currently no reports evaluating what proportion of cases previously diagnosed as PTLT, particularly those with extensive plasmacytic change and with extranodal localization, carry any of the translocations associated with MZL. Such a study could aid in uncovering a potentially larger subset of MZL among lymphoproliferations in transplant patients.

The role of the EBV in typical B-cell PTLT is discussed, and its absence in reported cases of extranodal MZL of the MALT-type occurring after transplant is noted. However, the status of EBV involvement in the current cases must be considered unresolved. The authors conclude that patient 2 was seropositive for EBV at the time of transplantation, and therefore the virus did not

play a role in the pathogenesis of this lesion. Although PTLTs are more common in patients who are EBV-seronegative at time of transplantation, preexistent infection does not confer absolute protection against subsequent EBV-positive posttransplant tumors.<sup>10</sup> Furthermore, EBV-positive PTLT was reported in the absence of any detectable quantitative rise in circulating EBV genomic titers in one transplant recipient with primary EBV infection.<sup>11</sup> A recent EBV-seropositive transplant recipient at the University of Pittsburgh Medical Center also developed an EBV-positive PTLT in the absence of any increase in circulating viral genomic titer (unpublished observation). Although most reported posttransplant MZLs are EBV-negative, Oertel and colleagues<sup>12</sup> recently included in a series report of PTLT a patient with EBV-positive MZL that arose 157 months after kidney transplant. Direct demonstration of viral markers within tumor tissue sample remains the best means of segregating EBV-positive and -negative cases.

Both patients in this case study received transplantation secondary to underlying diseases characterized by immune dysfunction. MZL is classically associated with the autoimmune diseases Sjögren syndrome or Hashimoto thyroiditis.<sup>3</sup> Systemic lupus erythematosus, the disease of patient 1, was associated with a 6.2-fold increase in relative risk (95% confidence interval [CI], 1.0–37) for development of diffuse large B-cell lymphoma outside of the transplantation setting in one study, but no association with MZL could be found.<sup>13</sup> Wegener granulomatosis, the disease of patient 2, was associated in one study with a standardized incidence ratio of 4.2 (95% CI, 4.2–8.3) for development of malignant lymphoma.<sup>14</sup> However, no studies specifically relate Wegener granulomatosis to MZL. The presence of underlying autoimmune disease in the two patients of the current report may be coincidental, but the possibility of a relationship between these disorders and this tumor type remains tantalizing. A study by Shpilberg and associates<sup>15</sup> suggested that underlying autoimmune disease might serve as a risk factor for subsequent PTLT. No studies have focused upon the specific clinicopathologic features of posttransplant lymphoid tumors that arise in this patient group; the current case study suggests that this may be an issue worth revisiting.

A main message of the case study by Goldfarb and colleagues<sup>1</sup> is that there exists a subset of late onset posttransplant MZL, recognition of which allows successful management using an individualized, relatively conservative stepwise approach to therapy. The authors correctly observe that consensus on treatment of posttransplant lymphoproliferations is difficult to obtain, due at least in part to the heterogeneity of lesions, relatively small numbers of patients, and differing clinical circumstances related to degree of immunosuppression and allograft

type. Several multicenter trials have been established to begin to address these issues. In the interim, I agree with the authors that an individualized approach to therapy based on a specific diagnosis may be best, balancing the immune-compromised status of the patient and survival of the graft against the clinical threat posed by the tumor. In many cases, this may allow a trial of reduced immunosuppression with or without rituximab therapy and supportive therapy as required.<sup>12,16,17</sup> In other cases, such as in patients with central nervous system tumors, Burkitt-like lymphoma, or posttransplant Hodgkin disease, and in certain patient subsets, such as heart-transplant recipients, early or primary consideration of chemotherapy and/or radiotherapy may be preferred.<sup>18-23</sup>

Goldfarb and colleagues<sup>1</sup> also emphasize extraintestinal localization of posttransplant MZL, thereby bringing this entity more directly into differential diagnostic considerations in cases of posttransplant lymphoproliferations arising outside the gut. Appreciation of the range of posttransplant lymphoproliferations has grown considerably since these lesions were first described in the 1960s.<sup>24</sup> Progress has largely been driven by close clinical observation and careful management of individual patients with these disorders. Reports of cases such as those presented by Goldfarb and colleagues<sup>1</sup> are further steps in this journey and raise new questions to be answered before we can claim that we fully understand the biology of this disease.

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