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Case Report

Diagnostic Challenge in Renal Transplantation: Splenosis vs. Post-Transplant Lymphoproliferative Disorder—A Case Report

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Abstract: Splenosis is a benign, acquired condition characterized by the auto-implantation of focal deposits of splenic tissue throughout the peritoneal cavity, most commonly occurring after splenic injury and/or splenectomy. Post-Transplant Lymphoproliferative Disorder (PTLD) is a well-known complication of solid organ transplantation that results from unregulated B-cell proliferation due to chronic immunosuppression. Given their clinical and radiologic similarities, these two entities may pose a diagnostic dilemma in select solid-organ transplant recipients. We present the case of a 54-year-old kidney-transplant recipient presenting with abdominal pain and found to have a retroperitoneal soft-tissue mass concerning for PTLD. He underwent a CT-guided biopsy of the mass, and histopathological studies revealed lymphoid tissue consistent with splenic tissue, thus ruling out PTLD. The patient subsequently underwent symptomatic management, with the eventual resolution of his symptoms. The early diagnosis of PTLD is paramount, as prompt intervention has a substantial impact on the high rate of morbidity and mortality associated with this condition. Additionally, the diagnosis of splenosis in the setting of a retroperitoneal mass is critical in order to avoid invasive diagnostic and therapeutic procedures that may result in significant complications. A detailed surgical history, including prior splenic trauma and/or splenectomy, should raise clinical suspicion for splenosis and guide further diagnostic and therapeutic decision making.

Keywords: post-transplant lymphoproliferative disorder; splenosis; solid organ transplantation

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1. Introduction

Post-Transplant Lymphoproliferative Disorder (PTLD) is a group of disorders that are known to occur following hematopoietic stem-cell and solid-organ transplantation. PTLD occurs due to unregulated proliferation of B-cell populations and decreased T-cell immune surveillance, and is estimated to occur in 10–15% of solid-organ transplant recipients. Prompt diagnosis and treatment is critical, as mortality rates have been reported as high as 50–70% [1,2]. The evaluation of a patient with suspected PTLD is largely guided by the history and physical examination. Historical risk factors for PTLD include previous EBV infection [3–7], a mismatch for cytomegalovirus (CMV) in a seronegative recipient [8], the duration and dose of immunosuppression [8], age <10 and greater than >60 years [2], white race [9,10], and a number of polymorphisms in cytokine-related genes [8]. Common clinical features can include malaise and fatigue, as would be seen with a mononucleosis-like disease, in addition to B-symptoms such as fever, night sweats, and weight loss associated with lymphadenopathy. Presenting signs and symptoms can be varied, and definitive diagnosis can only be made with pathological confirmation either by excisional or core needle biopsy. Once the diagnosis is confirmed, treatment strategies include reduction of immunosuppression, anti-CD20 monoclonal antibodies (i.e., rituximab), chemotherapy, radiotherapy, Epstein–Barr Virus-specific cytotoxic T-lymphocytes, and surgical excision [8].

Nonetheless, studies have shown that mortality rates can still reach up to 30% with the therapies described above [11,12], underscoring the importance of establishing the correct diagnosis in a timely fashion.

Splenosis is an acquired, benign condition that is characterized by auto-implantation of focal deposits of splenic tissue in various compartments of the body cavity. This most commonly occurs following splenic injury or splenectomy, and its prevalence has been reported as high as 67% in patients with a history of splenic trauma [13]. These implants are typically found incidentally during cross-sectional imaging for other suspected pathologies, and they often require no treatment given the lack of symptomatology. However, in rare cases they may lead to chronic testicular or abdominal pain, GI bleed, or intestinal obstruction [14,15] requiring medical, percutaneous, or surgical intervention. Given their clinical and radiologic similarities, differentiating these two entities may pose a diagnostic challenge in the transplant population, illustrating the importance of prompt diagnosis to ensure the timely treatment of PTLD and avoidance of invasive procedures in patients with splenosis.

Here, we discuss a case of splenosis in the setting of a previous renal transplant and a newly identified retroperitoneal soft tissue mass, highlighting a number of key historical, clinical, and diagnostic factors that can influence decision making when both splenosis and PTLD are in the differential.

2. Case Report

A 54-year-old male with a history of end-stage renal disease secondary to IgA nephropathy and living-unrelated kidney transplant in 1996 with adequate graft function presented to his primary care physician with persistent abdominal pain following a relatively uncomplicated COVID-19 infection. His pertinent transplant-related history included an episode of CMV colitis one month after transplant that was successfully managed with ganciclovir. Shortly thereafter, he was found to have an elevated creatinine of 3.0 mg/dL on routine labs (baseline 2.1 mg/dL). Ultrasound of the allograft was unremarkable, but a kidney biopsy revealed moderate to severe acute cellular rejection. He was treated with solumedrol and Atgam® (Pfizer Inc., New York, NY, USA), with return of creatinine to baseline. Following treatment, he had no further documented episodes of rejection and had an uneventful course over the following 25 years.

Approximately one month following a COVID-19 infection in 2021, he had persistent, generalized abdominal pain, which was evaluated by his primary care physician. The pain was dull with intermixed episodes of sharp, periumbilical pain. He noted no exacerbating or alleviating factors. He had no specific concerns related to bowel or urinary function and reported no history of subjective fevers or chills. He did report decreased appetite and an ~23 pounds of weight loss during the COVID-19 infection, but he had regained 10 pounds since recovering from COVID-19. On examination, he had no abdominal tenderness or lymphadenopathy. Additional relevant surgical history included a trauma splenectomy at the age of 7. He had received his second dose of the Moderna® COVID-19 vaccine (Moderna, Inc., Cambridge, MA, USA) and was compliant with his dual-immunosuppression regimen (tacrolimus and mycophenolate). Relevant laboratory studies revealed a white blood-cell count of 8600 cells/uL, hemoglobin of 16.2 g/dL, and platelet count of 264,000/uL. His serum creatinine level was 1.95 mg/dL, slightly elevated from a baseline creatinine of 1.7 mg/dL. His tacrolimus level was 6.4 ng/mL and mycophenolate level was 2.4 ug/mL, both within target range. Cross-sectional imaging of the abdomen and pelvis revealed a new, 4.7 cm × 3.2 cm × 3.7 cm retroperitoneal soft-tissue mass, lateral to the inferior vena cava, with a small central calcification (Figure 1).

Given his renal transplant history and the radiological findings above, the patient was promptly referred for image-guided biopsy of the mass to rule out PTLD. Rapid on-site evaluation with modified Giemsa-stained-touch preparation of core samples showed polymorphous lymphocytes and bland spindle cells (Figure 2A). A histopathological examination demonstrated lymphoid aggregates and scattered lymphocytes with spaces

filled with red blood cells (Figure 2B). Immunostaining for CD3 highlighted scattered T cells (Figure 2C), and an immunostain for CD20 showed scattered aggregates of B cells (Figure 2D). Immunostains for CD138, and Kappa and lambda light chains revealed rare, scattered plasma cells without light-chain restriction. In situ hybridization for Eber was negative (Figure 2E). A special PAS stain showed a discontinuous basement membrane, as seen in splenic sinusoids (Figure 2F). Overall, these findings were consistent with that of splenic tissue (Figure 2), confirming the diagnosis of splenosis.

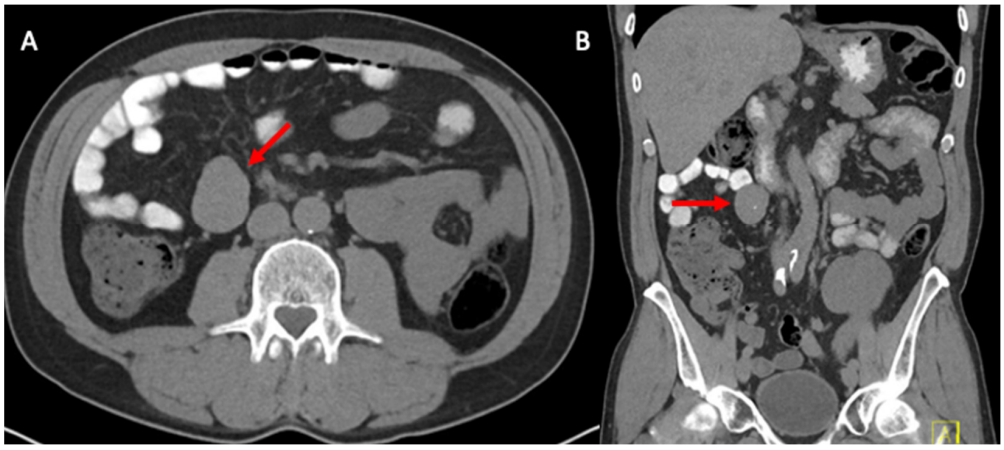

Figure 1. Contrast-enhanced computed tomography of abdomen and pelvis. (**A**) Axial and (**B**) coronal images demonstrating a soft-tissue mass located in the right retroperitoneum just lateral to the inferior vena cava (red arrow).

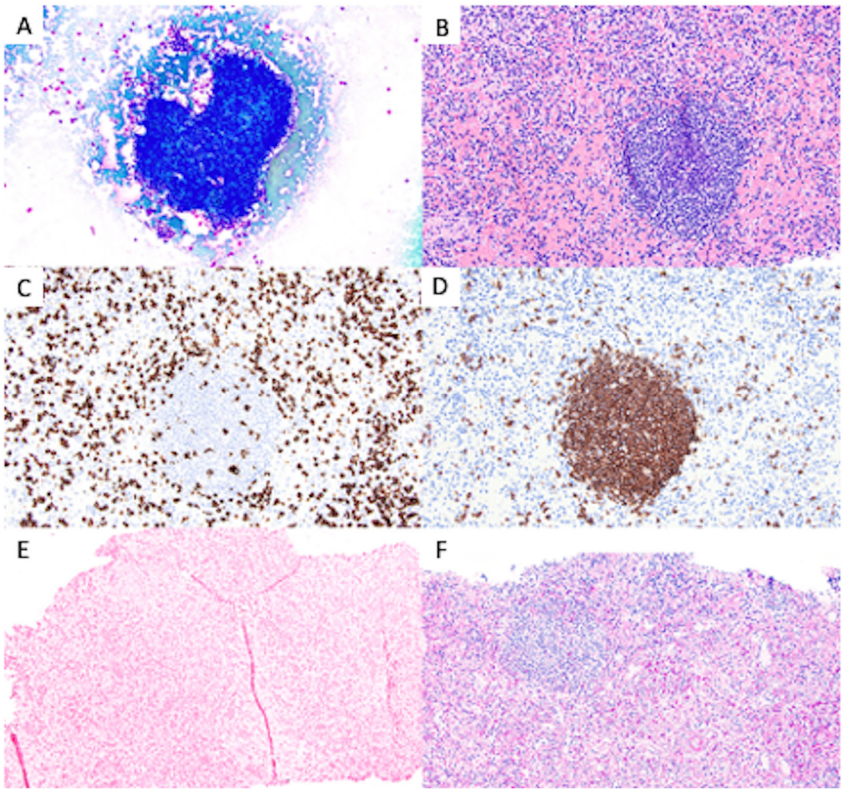

Figure 2. Pathologic examination of the mass. (**A**) Cytology of Diff-Quik-stained touch preparation of core. (**B**) Histology of hematoxylin and eosin-stained core. (**C**) Immunostain for CD3. (**D**) Immunostain for CD20. (**E**) In situ hybridization for Eber. (**F**) Special PAS stain.

Having ruled out PTLD, the patient underwent symptomatic medical treatment of splenosis, with improvement in his symptoms on follow-up. Of note, it was retrospectively found that a blood smear performed in 1997 showed Howell–Jolly bodies, suggesting an absence of ectopic splenic tissue [8], but no repeat peripheral blood smears were performed at the time of his presentation.

3. Discussion

The association between PTLD and Epstein–Barr Virus (EBV) is well known, with over 60–80% of cases known to be due to unregulated viral proliferation in the setting of chronic immunosuppression. In the other 20–40% of cases, the pathogenesis remains less understood [16]. Acute EBV infection leads to polyclonal expansion of B-cells that harbor the virus. Immunocompetent individuals generate a cytotoxic T cell response that eliminates the majority of infected B-cells; however, a small group of infected B-cells remain latently infected and can lead to PTLD when T-cell immunity wanes [17]. Specifically, in solid organ transplant patients, PTLD is seen in up to 10–15% of all patients and has been reported to be lower than in hematopoietic stem-cell transplant patients. The highest reported incidence is following transplant of small intestine (20%), lung (10%), heart (6%), liver (2.8%) and kidney (2.3%), suggesting that both the degree of immunosuppression and amount of lymphatic tissue in the allograft are contributing factors to the development of PTLD [18]. On the other hand, splenosis is a benign condition that can resemble PTLD in its clinical and radiological presentation and is not unique to the transplant population. The spleen is an organ that controls immune responses and filters senescent erythrocytes. As a secondary lymphoid organ, it is also a site for T- and B-cell storage and maturation, assisting in immunoglobulin production. Increased immunologic reactivity during acute viral infections may lead to splenic hyperplasia, with concomitant abdominal pain.

Cross-sectional imaging may reveal lymphadenopathy or a soft tissue mass, but commonly used imaging modalities, such as CT, magnetic resonance (MR), or ultrasound, are not specific, expanding the differential diagnosis and making the distinction between both entities more challenging. Although useful in cases of PTLD associated with underlying lymphoma, the utility of both PET-CT and MR is limited and may be more beneficial in assessing the response to therapy rather than providing a definitive diagnosis [19]. To date, there are no large studies that have directly compared the accuracy of various imaging techniques in the diagnosis of PTLD, and the relative importance of each modality is drawn from studies of patients with non-transplant-related lymphoma [19]. In the context of splenosis, CT and MR will typically show a mass with a density and architecture consistent with that of normal splenic tissue, but will rarely provide additional diagnostic resolution [20]. Instead, it has been suggested that SPECT-CT is superior to planar imaging alone [21,22], and a denatured red blood cell scan is still considered the gold standard for diagnosis of accessory spleens and splenosis [23].

Other useful diagnostic tools include measurement of EBV viral load, which can be markedly elevated in patients with EBV-positive PTLD [24–26], but routine EBV viral load monitoring is not recommended as there are limited studies supporting its use as a diagnostic or prognostic tool in patients with suspected PTLD [19]. Rather, the measurement of viral load may have more benefit in predicting high-risk groups. For example, EBV viral load measurement may have more utility in children and seronegative adult recipients with seropositive donors, who develop a primary EBV infection with subsequent development of PTLD [19]. In some cases of splenosis, a peripheral blood smear may demonstrate the absence of asplenic blood features, including Howell–Jolly bodies, Heinz bodies, and other erythrocyte abnormalities. Alterations in basic laboratory values (complete blood count, serum chemistry) may also exist, but these are not specific for either condition. Ultimately, the definitive diagnosis of PTLD can only be made histopathologically. Most forms of PTLD will show a disruption to the underlying tissue architecture by lymphoid proliferation and the presence of EBV-infected cells [27]. In contrast, splenosis will reveal classic splenic tissue configuration, with evidence of both red and white pulp. Additional immunohisto-

chemical and phenotypic studies can be performed to further define these disease processes, including immunostains for CD2, CD3, CD8, and CD20 [28], and in situ hybridization for EBV-encoded RNA (EBER) [19]. Even still, there may be a histopathological overlap, as both splenosis and PTLD samples may stain positive for CD20, and not all cases of PTLD will be EBER-positive.

In our patient, the diagnostic complexity was further highlighted by the patient's surgical history and timing of symptom onset. The only prior cross-sectional imaging available for comparison did not demonstrate a mass in the location of the retroperitoneal soft-tissue mass, raising suspicion for PTLD, given his transplant history. However, the differential for a new, solid retroperitoneal mass in a patient with prior transplant is broad, consisting of both neoplastic and non-neoplastic processes [29]. Neoplastic conditions include lymphoid tumors, sarcomas, neurogenic tumors and immature teratomas, whereas non-neoplastic may include retroperitoneal fibrosis, extramedullary hematopoiesis, infection, or benign lymphadenopathy [29]. In this case, splenosis was not heavily considered in the initial differential, as his trauma splenectomy performed >40 years prior was weighed against his more recent kidney transplantation and potential morbidity and mortality associated with a delay in the diagnosis of PTLD. Additionally, it may be that our patient's infection with COVID-19 resulted in the enlargement of ectopic splenic tissue seeded previously in his retroperitoneum during the trauma splenectomy he had as a child, resulting in his delayed symptomatology.

Another potential limiting factor in his diagnosis was that EBV testing was not carried out, which may have affected our pre-testing probability of PTLD if the patient was found to be EBV-negative or have a significantly elevated EBV viral load. Prior to the aforementioned biopsy, no information regarding the EBV status of the patient or his living donor was available. Alternatively, other diagnostic studies could have been pursued prior to biopsy to help guide management. Given the presence of Howell–Jolly bodies on prior blood smear, it may have been reasonable to repeat the smear at the time of his presentation as an adjunctive diagnostic measure. Although definitive management would not have been based solely on the presence or absence of Howell–Jolly bodies, their absence may have delayed our decision for biopsy in favor of other diagnostic tests. For example, in such scenarios, a tagged denatured autologous red blood cell scan should be considered, as it is still the gold standard for identifying ectopic splenic tissue [23,30]. Such diagnostic testing may have allowed for the avoidance of the percutaneous biopsy and its associated risks in our patient.

4. Conclusions

The timely diagnosis of PTLD is imperative as prompt therapeutic intervention has been shown to improve mortality rates. In contrast, abdominal splenosis typically requires no specific intervention, but misdiagnosis could lead to invasive diagnostic and therapeutic procedures for a relatively benign condition. These two disease entities have a significant clinical and radiographical overlap, highlighting the need for complete clinical evaluation for the differentiation of the two. Furthermore, splenosis as an etiology of retroperitoneal soft-tissue mass in the transplant population should be increasingly considered, with the establishment of the correct diagnosis and appropriate interventions guided by careful surgical-history investigation, physical examination, and targeted diagnostic studies.

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