Abstract

Posttransplant lymphoproliferative disease is a complication of organ transplant with a myriad clinical and anatomic manifestations, thus making diagnosis difficult without histologic confirmation. In cases of lymphadenopathy confined to the abdomen, the diagnosis can be delayed because of late presentation and difficulty obtaining a tissue for histologic analyses.

We describe the use of cross-sectional nuclear medicine imaging to locate enlarged abdominal lymph nodes; this facilitated minimally invasive laparoscopic lymph node excision biopsy to rapidly diagnose 2 cases of post-transplant lymphoproliferative disease. Prompt diagnosis has enabled early effective treatment, resulting in good patient outcomes.

Key words: 18F-fluorodeoxyglucose positron emission tomography, Histologic diagnosis, Minimally invasive laparoscopic lymph node biopsy, Posttransplant lymphoproliferative disorder

Case Report 1

A 32-year-old woman received a deceased-donor renal transplant (111 HLA mismatch) in 2007 for end-stage renal failure, secondary to familial focal segmental glomerulosclerosis. Induction of immunosuppression was performed with basiliximab. The patient developed acute graft rejection and primary herpes simplex virus infection with multiorgan failure. The patient recovered from this illness, and subsequently was managed with azathioprine- and tacrolimus-based immunosuppression. Five years after the renal transplant, the patient developed an asymptomatic erythropoietin-resistant anemia (hemoglobin 93 g/L) and a polyclonal IgG gammopathy of 20.4 g/L. Epstein-Barr virus DNA titre was 7142 copies/mL at presentation. A gallium single-photon emission computerized tomography scan showed an enlarged mesenteric lymph node measuring 1.8 × 1.3 cm with increased uptake, suggestive of malignancy (Figures 1A and 1B). Laparoscopic lymph node excision biopsy was performed using 3 laparoscopic ports with hand-assistance through a 6-cm infraumbilical incision to aid intra-operative location of the intra-abdominal lymph node. This was then successfully excised from the small bowel mesentery without complication, resulting in a 1-night hospital stay for the patient.

Histologic analyses of the lymph node showed medium to large CD20 pleomorphic cells, with the neoplastic cells negative for CD23, CD30, CD15, and Epstein–Barr virus-encoded small RNAs. This confirmed monomorphic posttransplant lymphoproliferative disorder (PTLD), diffuse large B cell lymphoma Epstein–Barr virus-encoded small RNA-negative. This was partially responsive to rituximab.

Figure 1. (A) Gallium Single-Photon Emission Computerized Tomography Scan Showing Increased Gallium Uptake in Mesenteric Lymph Nodes (B) Noncontrast Computerized Tomography Scan Shows the Enlarged Lymph Nodes Measuring 18 mm
and successfully treated with 4 cycles of cyclophosphamide, doxorubicin, Oncovin, and prednisolone therapy. 8F-fluorodeoxyglucose positron emission tomography (FDG-PET) at 1 and 2 years showed no evidence of relapse. The patient is currently healthy.

Case Report 2

A 45-year-old man underwent a live-unrelated renal transplant in Pakistan in 1997 for end-stage renal failure secondary to reflux nephropathy. As the transplant took place abroad, information regarding induction immunosuppression therapy and initial Epstein-Barr virus (EBV) status were limited. After the renal transplant, he developed cytomegalovirus disease, 2 instances of biopsy-proven rejection (both treated with steroids), and he underwent angioplasty for renal graft artery stenosis.

Seventeen years later the patient presented with weight loss, night sweats and fever, and was noted to have unexplained anemia (hemoglobin 81 g/L). Epstein-Barr viral load at this time was 1870 copies/mL, and he was receiving mycophenolate mofetil- and tacrolimus-based immunosuppression. Subsequently a computerized tomography scan was performed that showed multiple enlarged lymph nodes within the mesentery. An FDG-PET scan showed metabolically active retroperitoneal and mesenteric lymphadenopathy and a metabolically active terminal ileum with low-grade active left supravacular/upper mediastinal nodes (images 2A and 2B). The differential for this included both PTLD and tuberculosis, and thus required a lymph node biopsy to obtain histology to discern the diagnosis and direct treatment.

After discussion within the multidisciplinary team, a laparoscopic lymph node excision biopsy was performed without complication, and the patient spent 1 night in hospital postoperatively. Because of the presence of multiple enlarged nodes, the operation was a “pure” laparoscopic procedure using 3 laparoscopic ports only, as it was possible to visually identify 1 of the enlarged lymph nodes without manual tactile feedback. A mesenteric lymph node measuring 25 × 11 × 9 mm was obtained for histologic analyses. This showed an increased population of CD138 positive polytypic plasma cells. The large cells were positive for CD30 and negative for CD15. Epstein–Barr virus-encoded small RNAs (in situ hybridization) were positive in most, but immunohistochemistry for Epstein-Barr virus latent membrane protein 1 was negative - this confirmed an Epstein-Barr virus negative plasma cell variant of PTLD. The patient’s target tacrolimus level was reduced by 50% and, 6 weeks later, a repeat fluorodeoxyglucose-positron emission tomography showed an excellent response, with a significant reduction in the size and fluorodeoxyglucose-uptake of lymph nodes above and below the diaphragm. Despite an area of increased fluorodeoxyglucose uptake persisting in the jejunum, the patient reports reduced symptoms, has gained weight, and has returned to work.

Discussion

Posttransplant lymphoproliferative disorder was first seen as a complication of renal transplantation in 1968, and is now a well-recognized cause of morbidity and mortality after all solid-organ transplant and hematopoietic stem-cell transplant in both pediatric and adult populations. Although PTLD can occur at any point after transplant, it occurs most commonly in the first year and has an incidence of approximately 3% following renal transplantation and up to 10% following multi-visceral/intestinal transplantation. In pediatric patients, PTLD is a significant cause of morbidity as it is the most common malignancy posttransplant. Initially 3-year survival was reported to be as low as 35% to 40% with a reduction in immunosuppression being the mainstay of management. The introduction of newer therapies (eg, rituximab combined with cyclophosphamide, doxorubicin, Oncovin, and prednisolone chemotherapy) has increased 3-year survival to over 70%.

More than 85% of PTLD cases are of B-cell lineage with T-cell, natural-killer cell, and Hodgkin neoplasms occurring. The strongest risk factor for
PTLD is Epstein-Barr virus infection, as more than two-thirds of cases are Epstein-Barr virus-related. Epstein-Barr virus-transformed B cells can proliferate without T-cell control in the face of immunosuppressive treatment after transplant. Other infections, such as cytomegalovirus and hepatitis, have also been shown to increase the risk of PTLD. Further risk factors include treatment for acute rejection and heavy immunosuppressive burden, age, race, and genetic factors. The disease can affect the allograft and often can be extranodal involving the central nervous system, the gastrointestinal tract, and bone marrow; therefore, the clinical presentation of PTLD can vary depending on the organ affected. Lymphadenopathy is not always present but development of classic “B” symptoms should carry a high index of suspicion.

Once PTLD is suspected, imaging with ultrasound scan and computerized tomography scan can be used to assess organ involvement, disease extent, and ultimately response to treatment. Recently, fluorodeoxyglucose-positron emission tomography scan has been shown to be a superior imaging modality in PTLD as lymph nodes and extranodal sites have increased uptake of the isotope allowing them to be visualized more easily. Using computerized tomography alone smaller lymph nodes and extranodal sites, in particular bone marrow, can be missed. Fluorodeoxyglucose-positron emission tomography/computerized tomography compared with computerized tomography alone has a greater sensitivity (88.2% vs 87.5%) and specificity (91.5% vs 88.8%) and in 5 cases revealed further extranodal disease which resulted in upstaging of the disease and altered management.

Both cases underscore the vague presentation of PTLD; differential diagnosis included tuberculosis, lymphoma, transplant rejection, and other viral infections. As managing these differs widely, histologic confirmation was essential. In light of novel therapies targeted at specific cell markers (e.g., CD30), it is also now increasingly important to obtain a tissue sample for cell characterization to direct treatment accordingly. After diagnosis repeated fluorodeoxyglucose-positron emission tomography can be used effectively to assess response to treatment, which was demonstrated in our cases.

Surgical excision biopsy of peripheral lymph nodes is often successful in achieving a diagnosis of PTLD. If lymphadenopathy is confined to the abdomen, however, as in these cases, it can be challenging to obtain tissue. In these circumstances, ultrasound scan- or computerized tomography-guided percutaneous needle biopsy is described, but carries a lower success rate of obtaining an adequate tissue sample compared with surgery. Alternatively, laparotomy is highly invasive and undesirable in this setting; hence, our use of laparoscopic lymph node excision biopsy in these cases.

There is currently no literature reporting laparoscopic lymph node excision biopsy in cases of PTLD, but it has been shown to be accurate and safe in diagnosing abdominal lymphoma. A study by Casaccia and associates of 35 patients undergoing a laparoscopic lymph node excision biopsy to diagnose abdominal lymphoma demonstrated that it provides a sufficient sample for accurate diagnosis in 97% of cases. The median hospital stay in this series was 5.1 days, and the conversion rate to laparotomy was 5.8%, which is in line with other reports. These studies conclude that while laparoscopic lymph node excision biopsy should be performed only by a skilled laparoscopic surgeon, and in the absence of peripheral lymphadenopathy, it is a safe and effective technique with diagnostic accuracy superior to percutaneous sampling.

In our cases of patients with PTLD, in the absence of peripheral lymphadenopathy, we demonstrated that laparoscopic lymph node excision biopsy can be safely used to achieve a histologic diagnosis, which resulted in prompt and effective treatment of both patients.

References


