

## A 5-year old male with “leukemic form” of disseminated post-transplant lymphoproliferative disorder

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### Introduction

Post-transplant lymphoproliferative disorder (PTLD) represents an abnormal lymphoid proliferation that occurs in recipients of solid organ or bone marrow allograft. It includes a diverse group of diseases ranging from polymorphic B-cell hyperplasia to frank malignant lymphoma. Clinical presentation is variable, ranging from asymptomatic to generalized lymphadenopathy, mononucleosis-like syndrome, nodal or extranodal tumors (usually gastrointestinal tract), systemic lymphomatous involvement, and rare (less than 1% of cases) fulminant disseminated disease. PTLD is more common in children than in adults. Younger patients usually present with mononucleosis-like symptoms. We present an unusual case of a 5-year old male who developed a widely disseminated leukemic form of PTLD, involving lymph nodes, tonsils, multiple organs, bone marrow, cerebrospinal fluid, and peripheral blood.

### Case Report

A 5-year old male, an ex-23 week premature baby with a history of necrotizing enterocolitis and multiple small bowel resections, underwent a small bowel transplant at the age of two for short bowel syndrome. Three years later, he presented with bulky cervical lymphadenopathy, enlarged tonsils, and a 5-day history of fever, chills, and stridor. Laboratory data revealed a lymphocytosis of 160,000. Imaging studies showed a near-total obstruction of the nasopharynx. A cervical lymph node excisional biopsy, tonsillectomy, and adenoidectomy were performed and revealed histological evidence of post-transplant lymphoproliferative disorder. A staging work-up demonstrated PTLD in the supraclavicular, mediastinal, abdominal, pelvic, and inguinal lymph nodes; peripheral blood; cerebrospinal fluid; thoracic and abdominal organs; and in the bone marrow.

### Results

H&E stained sections of the cervical lymph node and tonsils revealed diffuse effacement of the normal lymphoid architecture by a population of large atypical lymphoid cells showing enlarged nuclei and prominent nucleoli, with brisk mitotic activity and areas of necrosis and tingible body macrophages. (Figure 1). Flow cytometric analysis demonstrated the neoplastic cells were positive for CD19, CD20, HLA-DR, and CD138. With immunohistochemistry staining, the large atypical cells were B cells positive for CD20, CD79a, CD43, BCL-2, CD30, EBV-LMP (Figure 2), and CD138. Ki-67 proliferation index was increased at 80%.

A prominent T-lymphoid background was also present. *In situ* hybridization for EBV-encoded RNA (EBER) was positive. With the patient's history of visceral transplant and recently increasing EBV titers, these findings were indicative of a monomorphic B-cell PTLD with features of an aggressive B-cell lymphoma. Bilateral bone marrow biopsies revealed extensive marrow involvement by PTLD. (Figure 3). PCR analysis was positive for monoclonal immunoglobulin heavy chain rearrangement and EBNA, leading to a diagnosis of EBV-associated monoclonal B-PTLD. Both peripheral blood and cerebrospinal fluid showed lymphocytosis with atypical lymphoid cells. Flow cytometry demonstrated a B-cell lymphoproliferative disorder consistent with PTLD.

### Conclusion

PTLD is a relatively uncommon but devastating complication of immunosuppression used to prevent rejection in transplant patients. Patients receiving liver-bowel or heart-lung allografts develop PTLD at the highest frequency (5%).<sup>1</sup> The majority of PTLD is associated with EBV-infection, and usually occurs within five years of the transplant.<sup>2</sup> The etiology appears to be an EBV-induced monoclonal or, less often, polyclonal B-cell or monoclonal T-cell proliferations in a setting of diminished T-cell immune surveillance in an immunocompromised host.

Conventionally, initial management for all patients with PTLD is reduction of immunosuppression. If disease persists following reduction of immunosuppression, alternative therapies are considered, including local therapy with radiation or surgical resection, anti-viral medications, intravenous immunoglobulins, alpha-interferon, chemotherapy, or a combination of these.<sup>3</sup>

Early lesions including plasmacytic hyperplasia and infectious mononucleosis-like PTLD are the most common type of PTLD in children.<sup>4</sup> Usually, a reduction in immunosuppression

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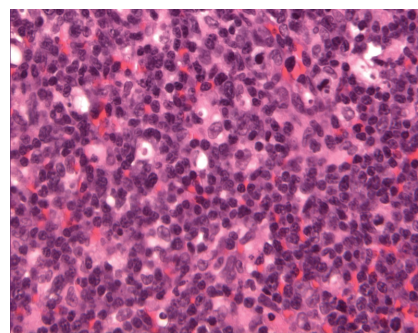


Figure 1. Lymph node with atypical lymphoid cells.

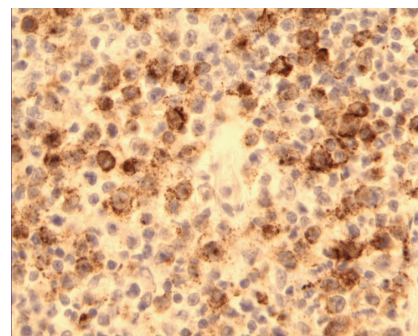


Figure 2. Atypical lymphoid cells labeled with EBV-LMP.

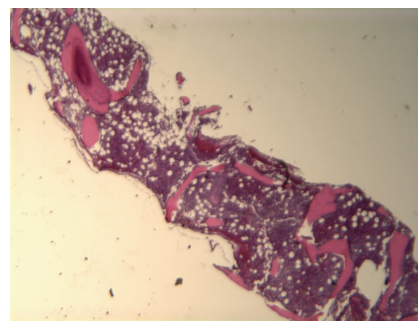


Figure 3. Extensive bone marrow involvement by PTLD.

leads to regression of disease without graft rejection, and prognosis is excellent. Polymorphic and, less often, monomorphic PTLD may also regress with reduced immunosuppression. However, acute and/or chronic rejection may ensue, resulting in graft loss and/or death. Some cases of polymorphic PTLD and the majority of monomorphic PTLD may progress to lymphoma, requiring chemotherapy.

Several adverse prognostic factors include multi-site disease, advanced stage, older age at diagnosis, and late onset disease. Overall, bone marrow allograft recipients have a higher mortality rate than solid organ allograft recipients.

In solid organ recipients, PTLD tends to involve lymph nodes, GI tract, lungs and, less

frequently, the CNS. Peripheral blood is rarely involved. Children usually present with a non-aggressive disease with early lesions including plasmacytic hyperplasia or infectious mononucleosis-like symptoms involving the oropharynx and regional lymph nodes. Our case is remarkable in that it is a "leukemic" form of disseminated PTLD with peripheral blood, bone marrow, CNS, lymph node, and extranodal involvement in a 5-year old.

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