

Post-Transplant Lymphoproliferative Disease

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Abstract

Post-transplant lymphoproliferative disease is a major and life-threatening complication of chronic immunosuppression therapy following solid organ transplant and hematopoietic stem cell transplantation. It is commonly associated with Epstein-Barr virus infection and affects patients bimodally in the first year or 4-5 years post-transplant. US, MRI, CT, and PET-CT can be used to identify, stage, and follow the disease.

Keywords: immune suppression, liver transplantation, hematology oncology

Clinical Summary

A young child with a history of liver transplant due to biliary atresia and a failed Kasai procedure presented to the emergency department with a 5-day history of nasal congestion and 2 days of fever. Laboratory analysis showed an elevated erythrocyte sedimentation rate, C-reactive protein, hemoglobin, lactate dehydrogenase, and white blood cell count. Additional lab tests showed the patient to be positive for Epstein-Barr virus (EBV) and cytomegalovirus. CT of the chest, abdomen, and pelvis was obtained for further evaluation.

Imaging Findings

CT of the chest, abdomen, and pelvis (Figure 1) showed multiple new pulmonary nodules and masses scattered throughout both lungs.

Diagnosis

Post-transplant lymphoproliferative disease (PTLD)

The differential diagnosis for multiple enlarged lymph nodes in a patient after transplant includes infectious or inflammatory lymphadenopathy, lymphoma, and metastatic disease.

Discussion

PTLDs are among the most serious, life-threatening complications of chronic immunosuppression following solid organ or allogeneic hematopoietic stem cell transplantation (HSCT). PTLDs comprise a spectrum of lymphoproliferative disorders that include most of the hematologic cancers, including Hodgkin and non-Hodgkin lymphomas, as well as leukemias and plasma cell neoplasms. EBV is associated with most cases and has been

shown to be a key driver in pathogenesis, though the mechanism is not fully understood.

The incidence of PTLD varies depending on the type of transplant and the required levels of immunosuppression. Incidence is lower in patients who have received HSCT or liver transplant (1-2% over 5 years) and higher in patients who have received intestinal or multiorgan transplants in HSCT (11-33% over 5 years).¹⁻³ The incidence of PTLD has a bimodal distribution with a peak in the first year and a later peak 4-5 years after transplantation.³

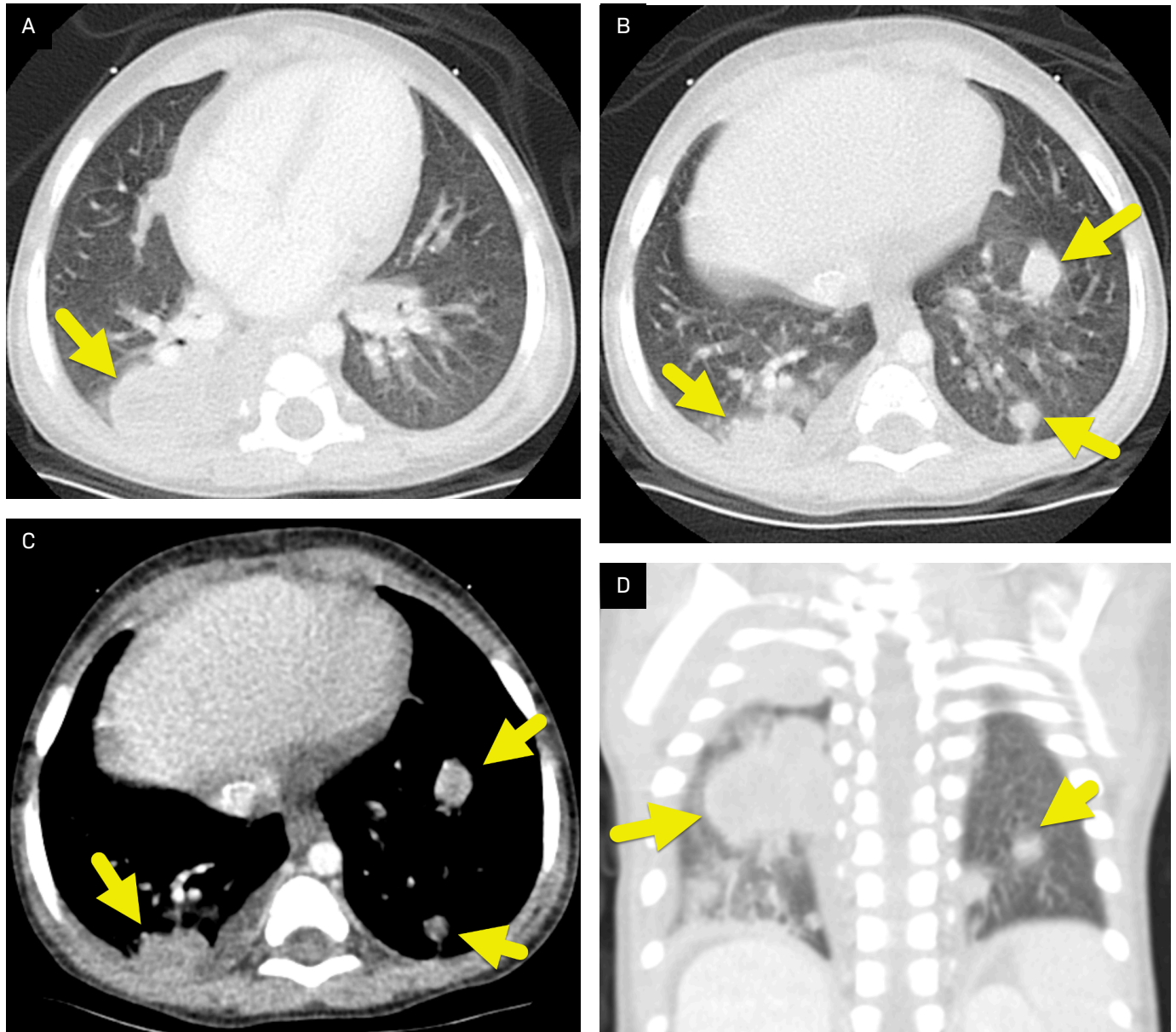
Patients may present with varied symptoms depending on the type of PTLD and the location of the disease. Thus, a high degree of clinical suspicion is critical for early diagnosis and treatment. Clinical manifestations may include symptoms of malaise, fatigue, fever, night sweats, weight loss, hepatosplenomegaly, lymphadenopathy, and mononucleosis-like symptoms. Rising EBV titers in this clinical setting should raise suspicion of PTLD.

Tissue diagnosis of PTLD is preferred.⁴ The World Health Organization categorizes PTLD into four subtypes: nondestructive, monomorphic, polymorphic, and classical Hodgkin

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Figure 1. (A) Axial contrast-enhanced CT of the chest shows a large mass (arrow) in the right lower lobe. (B) Axial contrast-enhanced chest CT imaged at a lower level in the lung, and (C) soft tissue windows show multiple nodules (arrows) in the lower lobes. (D) Coronal chest CT shows masses and nodules (arrows) throughout both lungs.



lymphoma. Laboratory testing is used to distinguish early PTLT from infectious mononucleosis. Findings supporting a diagnosis of early PTLT include an increased EBV genome copy number of >2000/ml of blood, expression of major histocompatibility complex class

II on cytotoxic T cells, and increased cytoplasmic gamma interferon expression in response to autologous or HLA-matched EBV-transformed B cells.⁴ When tissue diagnosis is not possible, other features such as imaging and elevated EBV DNA copy number in the peripheral blood

can be used to arrive at a presumptive diagnosis, although no definitive threshold has been established, and an increasing trend may provide more useful information than a single value.⁵

Imaging plays an important role in diagnosing PTLT, guiding biopsy, and

evaluating the response to treatment.⁶ Imaging modalities that are often used for diagnosis include US, MRI, CT, and PET CT.⁷⁻¹¹ The appearance of PTLTD can vary depending on the site of involvement.⁶ Generally, PTLTD can be classified as nodal or extra-nodal, though extra-nodal involvement is 3-4 times more common and resembles primary lymphoma of the organ in which it is found.^{12,13} Extra-nodal disease may involve solid organs, the gastrointestinal tract, or the central nervous system (CNS). For example, neuroimaging features of PTLTD are like those seen in immunocompromised patients with primary CNS lymphoma. Lesions in solid organs appear as nodules and may be solitary or multiple. The lesions are often first identified on US, where they appear as hypoechoic nodules. MRI is preferred as the next imaging modality for workup due to its superior contrast resolution. On MRI, the nodules appear hypointense on T1- and T2-weighted images, have minimal enhancement, and display restricted diffusion.¹⁴ If CT is performed, the nodules appear hypodense. On PET CT, the lesions are F-18 fluorodeoxyglucose-avid. PTLTD in the gastrointestinal tract may demonstrate wall thickening circumferentially or an eccentric mass and may include ulceration/perforation, aneurysmal dilatation, intussusception, or polypoid masses. Bowel obstruction is uncommon. When the lung and/or pleura are involved, there may be randomly distributed homogeneous nodules that rarely have central cavitation or diffuse infiltration.¹⁵ Multifocal ill-defined alveolar infiltrates may also be seen.⁶

MRI is the preferred modality used to diagnose brain lesions. Patients can have one or multiple lesions. These lesions can occur within the basal ganglia or subcortical white matter. They display homogeneous or ring enhancement with poorly defined margins.⁷ Necrosis and hemorrhage may be present. Lesions have decreased T1 signal and increased T2 intensity with surrounding vasogenic

edema and restricted diffusion. With MR spectroscopy, the choline and lactate peaks are increased, and there is a significant reduction in N-acetylaspartate.⁶

When PTLTD is nodal, it manifests similarly to lymphoma with enlargement of nodes that are nonenhancing on CT or MRI. There is a loss of normal morphological characteristics, such as the fatty hilum. Nodal PTLTD is most common in the mediastinum and retroperitoneum.⁶

Management of PTLTD involves a balance of preserving the graft while eradicating PTLTD. For early lesions, characterized by polyclonal B cell proliferation without evidence indicating malignant transformation, reduction of immunosuppression may be sufficient to treat the disease. Rituximab may be considered if immunosuppression reduction is not possible. For more advanced disease, immunosuppression reduction, in addition to rituximab (if CD20 positive), chemotherapy, and immunotherapy may be provided. Surgery may be considered for localized disease, and radiation is an option with localized disease and CNS involvement. Another option for EBV-associated PTLTD is adoptive immunotherapy using EBV-specific cytotoxic T lymphocytes or donor lymphocyte infusion that targets dividing B cells.^{5,16-18}

With these management options, prognosis for PTLTD has improved, though it can vary with type of disease, patient characteristics, and treatment. Survival has been estimated at 54.6% at 5 years, with 1-year and 5-year survival with chemotherapy at 63.8% and 52.5%, respectively, in a United States study. The 1-year and 5-year survival with surgery as the mainstay of therapy was 87.3% and 60.8%, respectively, and without therapy was 67.6% and 49.6%, respectively.

Summary

PTLTD is a major and life-threatening complication of chronic immunosuppression therapy following solid organ transplant and HSCT. It is commonly

associated with EBV infection and affects patients bimodally in the first year or 4-5 years post-transplant. US, MRI, CT, and PET-CT can be used to identify, stage, and follow the disease.

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