Upper Airway Manifestations of Post-Transplantation Lymphoproliferative Disease Simulating Common Pediatric Conditions

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Post-transplantation lymphoproliferative disease is a heterogeneous group of lymphoproliferative disorders strongly linked with primary Epstein-Barr virus infection during immune suppression. Children are especially susceptible to the disease. Low grade PTLD is a relatively benign, infectious mononucleosis-like disease, while high grade PTLD may present as non-Hodgkin's lymphoma. If left untreated, benign disease may become malignant [1].

Management of low grade PTLD consists primarily of reduction of immunosuppressive therapy coupled with antiviral drugs such as acyclovir and ganciclovir. Other treatment options include intravenous immunoglobulins, interferon-alpha or gamma and – for tumor cells expressing the B cell marker CD20 – anti-CD20 monoclonal antibodies (rituximab). Treatment with donor-derived EBV-specific cytotoxic T cells has been used successfully, mostly in patients who developed PTLD after bone marrow transplantation. Malignant PTLD may require chemotherapy.

We describe two children, after liver transplantation, with PTLD presenting in the upper respiratory tract; a relatively common but often unrecognized presentation in children that may mimic benign childhood diseases.

PTLD = post-transplantation lymphoproliferative disease
EBV = Epstein-Barr virus

Patient Descriptions

Patient 1

An 18 month old girl was admitted for worsening dyspnea. Three months prior to admission she underwent liver transplantation due to biliary atresia after which she received immunosuppressive treatment with tacrolimus. Two weeks before admission tonsillitis was diagnosed and she was treated with amoxicillin, but there was no clinical improvement. Throat culture was negative for bacterial infection.

On admission she was dyspneic and tachypneic, and physical examination revealed enlarged, "kissing" tonsils with exudates, cervical lymphadenopathy and hepatosplenomegaly. She was afebrile. Laboratory findings included a normal complete blood count, erythrocyte sedimentation rate of 101 mm/hour and elevated liver enzymes (alanine aminotransferase 174 U/L, aspartate aminotransferase 72 U/L). EBV serology was borderline positive for immunoglobulins M (25.2 AU/ml) and G (30.4 AU/ml). EBV polymerase chain reaction in peripheral blood was positive.

The patient was treated with intravenous acyclovir and tonsillectomy was performed. Histopathologic findings from the tonsils revealed partial destruction of node architecture by a polymorphic lymphoid infiltrate consisting of plasma cells and immunoblasts. Abundant mitotic activity was noted and immunohistochemical staining was positive for CD-20, a specific B cell marker. The findings are consistent with polymorphic PTLD. Treatment consisted of reduction in the tacrolimus dose and continuation of intravenous acyclovir. The patient's breathing improved immediately after the operation and the lymphadenopathy resolved gradually over the next few weeks. Several months later EBV IgG levels rose (379.4 AU/ml) and IgM levels dropped (16.6 AU/ml). Two years later there is no clinical evidence of disease, despite a persistently positive EBV PCR in peripheral blood.

Patient 2

A 14 month old boy was admitted due to respiratory distress. Seven months previously he underwent liver transplantation due to biliary atresia after which he received immunusuppressive therapy with tacrolimus. Two weeks prior to admission he developed stridor. History was suggestive of foreign body aspiration and bronchoscopy was performed, revealing a thickened epiglottis, regional edema and irregular protrusions in the posterior pharynx. Dexamethasone treatment was initiated for the edema alongside amoxicillin-clavulanic acid for possible bacterial infection in an immunocompromised host. This treatment had little effect. A blood count obtained at the time showed marked eosinophilia (white blood cells 14.47 x 10^3/mm^3, 24.4% eosinophils) and antihistamine treatment was added, again with no clinical improvement.

On admission he was in severe respiratory distress that required intubation.

Ig = immunoglobulin
PCR = polymerase chain reaction

There were no other notable findings on physical examination. Arterial blood gas analysis performed shortly after initiation of assisted ventilation revealed a respiratory acidosis (pH 7.22 PCO_2 57 mmHg). Bronchoscopy was performed and biopsies were taken from the epiglottis, vallecula and posterior pharynx. Histopathologic examination of the collected tissue samples revealed an inflammatory infiltrate consisting of small lymphocytes, some with an irregular nucleus, and many plasma cells and eosinophils. Immunohistochemical staining was positive for CD-20 and the plasma cells were positive for both κ and λ light chains (polyclonal staining). The findings are consistent with early polyclonal PTLD. EBV serology was positive for both IgM (25.4 AU/ml) and IgG (356.5 AU/ml) and EBV PCR in peripheral blood was positive.

Treatment consisted of tacrolimus dose reduction, intravenous acyclovir and intravenous immunoglobulins. The patient's condition improved gradually. He was extubated after 4 days and discharged after 2 weeks with no respiratory distress. One month later EBV IgG levels rose further (989.6 AU/ml) and IgM levels dropped (16.3 AU/ml). One year later the patient is clinically disease-free and EBV PCR in peripheral blood is negative.

Comment

Upper airway compromise has only recently been recognized as a relatively common presentation of PTLD in children. Pickhart et al. [1], in a retrospective study of PTLD in pediatric solid organ recipients, reported that 25% had disease involving the head and neck at presentation. Koh and associates [2] reported that 50% of their patients presented with disease in the head and neck region, and Lattyak et al. [3] found that 62.5% had such a presentation. Recently, in a unique prospective study in which pediatric liver transplant patients were actively screened for development of PTLD, Nouwen and collaborators [4] reported that all new cases presented with disease localized to either the tonsils or the pharyngolaryngeal wall.

All studies report a better prognosis for children with disease presentation in the head and neck compared with children whose disease presented elsewhere [2,3]. This may indicate that PTLD localized to the head and neck region is an early manifestation of the disease. Tonsillectomy may be warranted in all cases of non-bacterial tonsillitis in children after organ transplantation [4]. If PTLD exists in the tonsils, their removal may have a therapeutic role in displacing the disease focus and reducing EBV viral load.

Clinicians treating children on immunosuppressive drugs must remain alert to the possibility of a seemingly commonplace upper airway disease being the first manifestation of PTLD. An increased incidence of allergic reactions and eosinophilia has recently been noted in children treated with tacrolimus [5]. As demonstrated in our patient # 2, this may further mislead the clinician and delay diagnosis.

Increased awareness that common upper airway symptoms in immunosuppressed children may represent early PTLD is warranted as early recognition may prevent life-threatening complications and improve long-term prognosis.

References

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