The Effectiveness of Tonsillectomy in Diagnosing Lymphoproliferative Disease in Pediatric Patients After Liver Transplantation

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Objective: To determine the effectiveness of diagnosing forms of lymphoproliferative disease by performing tonsillectomy in pediatric patients who develop symptomatic or asymptomatic tonsillar hypertrophy during immunosuppressive therapy after liver transplantation.

Design: Retrospective chart and pathological review.

Setting: Urban tertiary referral children’s hospital.

Main Outcome Measures: The presence of a pathological stage of lymphoproliferative disease or Epstein-Barr virus (EBV) diagnosed using tonsillar specimens, resulting in a change in therapy.

Results: Of 275 pediatric patients who underwent liver transplantation, 13 had tonsillectomy performed with histopathological review of the tonsillar specimens. The specimens from 5 patients (39%) demonstrated pathological changes thought to be consistent with EBV-related changes or a form of lymphoproliferative disease. Histological changes ranged from tonsillar hyperplasia associated with EBV infection to large cell lymphoma. Immunosuppressive therapy was reduced or discontinued, and antiviral therapy was initiated.

Conclusion: Children who have undergone liver transplantation and develop tonsillar hypertrophy should undergo a diagnostic tonsillectomy, regardless of the clinical presentation, to rule out a form of posttransplant lymphoproliferative disease.

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Various forms of lymphoproliferation can develop in patients who require long-term immunosuppression, especially after whole organ transplantation. Posttransplant lymphoproliferative disease (PTLD) is characterized by abnormal, uncontrolled lymphoid cell proliferation. There is evidence to suggest that the disease is linked to primary infection with Epstein-Barr virus (EBV). The disorder is therefore more common in pediatric patients who have undergone transplantation and who are more likely to be EBV seronegative at the time of transplantation than their adult counterparts. Posttransplant lymphoproliferative disease often presents in the head and neck region, thereby making its early recognition by an otolaryngologist of utmost importance. The reported clinical presentation of PTLD varies from tonsillar hypertrophy with fever and lymphadenopathy, such as an acute infectious mononucleosis, to diffuse widespread lymphoproliferation that affects several organ systems. Less commonly, the disease manifests as a malignant monoclonal lymphoma.

Children who have undergone organ transplantation can display varying degrees of adenotonsillar hypertrophy ranging from minimal asymptomatic enlargement to life-threatening upper airway obstruction. We sought to determine how often tonsillar hypertrophy represents a manifestation of PTLD and investigated the sensitivity of tonsillectomy in diagnosing this disease in pediatric transplant recipients.

RESULTS

Thirteen pediatric patients underwent a tonsillectomy after liver transplantation between 1984 and 1998 at the Children’s Medical Center of Dallas and had their tonsillar specimens reviewed microscopically. The pathological findings were as follows: EBV-positive hyperplasia (n = 4), EBV-negative hyperplasia (n = 1), hyperplasia (EBV not specified) (n = 6), hypertrophy (n = 1), and large cell lymphoma (n = 1). Therefore, 5 (39%) of the 13 patients were found to have PTLD-related changes ranging from EBV-positive hyperplasia to large cell lymphoma. These histological diagnoses led to a reduction or cessation of im-
PATIENTS AND METHODS

From 1984 to 1998, 275 pediatric patients underwent liver transplantation at the Children's Medical Center of Dallas, Dallas, Tex. Of those patients, 13 were found by retrospective chart and pathological review to have undergone a tonsillectomy as well as histopathological review of their tonsils for manifestations of PTLD and the presence of EBV by pediatric pathologists. Prior to 1993, in situ hybridization for EBV messenger RNA (mRNA) was not performed. Any patient found to have changes consistent with a form of PTLD had their treatment altered, usually in the form of reduced or halted immunosuppression and the addition of an antiviral drug, such as acyclovir or ganciclovir.

Six patients had hyperplasia of the tonsil specimen, but the EBV status was not evaluated. Four of the 6 patients had their tonsils removed from 1990 to 1993, prior to routine EBV mRNA analysis. When the EBV mRNA was evaluated in the tonsillar specimens with lymphoid hyperplasia, 4 of 5 specimens had evidence of EBV infection.

The clinical characteristics of the patients in this series are summarized in Table 1 and Table 2. The majority of patients (8 of 13, or 62%) presented with obstructive sleep symptoms that were attributable to significant adenotonsillar hypertrophy. Others had recurrent tonsillitis with or without obstructive symptoms or a febrile, mononucleosislike picture. The clinical history of 1 patient was not available for review.

Of the 4 children with EBV-positive hyperplasia, 2 had obstructive symptoms and 2 did not (Tables 1 and 2). The 2 children without obstructive symptoms did have tonsillar hypertrophy and histories of rare or moderate bouts of recurrent tonsillitis. However, the number of infections did not meet the current indications for surgery. They underwent tonsillectomy for diagnostic purposes.

The 1 patient with large cell lymphoma presented with a 4-week history of intermittent fever (temperatures as high as 39°C) and symptoms of acute rhinosinusitis 3 months after orthotopic liver transplantation for α1-antitrypsin deficiency. A nasopharyngeal biopsy and tonsillectomy were performed, along with a maxillary sinus drainage procedure. The pathology report showed large cell lymphoma. Further workup revealed an abdominal mass adjacent to the bladder. An exploratory laparotomy was performed, with a resection of 5 cm of distal jejunum, which was also involved with lymphoma. The dosage of cyclosporine therapy was decreased by 50%, and azathioprine was added to the regimen; intravenous acyclovir therapy was also initiated. The patient responded without any further intervention until 5 years after transplantation, when PTLD recurred in the form of EBV-positive hepatitis, splenomegaly, and abdominal adenopathy. Cyclosporine therapy was discontinued, and intravenous immunoglobulin was added to the regimen, without improvement. Treatment with interferon alfa was begun and was administered every other day for 6 months, with resolution of all signs of PTLD. The patient continued a regimen consisting only of low-dose prednisone and oral acyclovir, with no signs of recurrent PTLD or rejection of his transplanted liver.

Posttransplant lymphoproliferative disease is a known complication of immunosuppression defined as an abnormal proliferation of lymphoid cells in a transplant recipient. It is thought to arise from EBV infection of B lymphocytes, resulting in their uncontrolled proliferation. Patients who have undergone transplantation are genetically immunosuppressed and therefore lack cytotoxic T-cell activity against EBV-infected cells, thereby allowing continued B-cell proliferation.

In immunocompetent individuals, EBV infection most commonly causes an asymptomatic seroconversion after infection. Some, however, will develop acute infectious mononucleosis characterized by fever, sore throat, lymphadenopathy, and hepatosplenomegaly. These manifestations represent the degree of T-cell–mediated responses to the
uncontrolled proliferation of EBV-infected cells. In transplant recipients, EBV can cause hepatitis, a mononucleosislike syndrome similar to that seen in patients who have not undergone transplantation, or it can cause PTLD.1

The incidence of EBV-related PTLD is higher in pediatric transplant recipients than in adult transplant recipients (4% vs 1%) for several reasons.2,3 Children are more likely than adults to be seronegative for EBV at the time of transplantation and are therefore at greater risk of acquiring an acute primary EBV infection after transplantation.1,2 Also, children generally have more T cells than adults. To achieve the same level of immunosuppression in children as adults, higher doses of powerful anti–T-cell immunosuppressive drugs, such as OKT3 and FK 506 (tacrolimus), are administered, increasing the risk of PTLD. In addition, both the bioavailability and the elimination kinetics of the immunosuppressive medications are different in children, requiring higher doses to achieve effect. Morgan and Supine4 pointed out that a higher cumulative dose of OKT3, as well as a longer total duration of therapy, which is needed in children, increased the rate of PTLD in a population of pediatric patients after liver transplantation. Newell et al5 similarly found that the intensity of immunosuppression was a significant risk factor for the development of PTLD. Regardless of the pathogenesis, a longer duration of antilymphocytic therapy or multiple courses of antilymphocytic agents (eg, OKT3 and FK 506) are associated with increased risk of PTLD.

Posttransplant lymphoproliferative disease has been reported to generally present as 1 of 3 clinical entities. The first entity is a mononucleosis-type illness with tonsillar hypertrophy and airway obstructive symptoms ranging from mild snoring to life-threatening airway obstruction due to involvement of tissue in Waldeyer ring. Pathological changes at this stage have been characterized by a benign polyclonal B-cell hyperplasia (Figure 1), which can show evidence of EBV positivity (Figure 2). At this stage, the follicular architecture of the tonsil is still preserved.

The second entity begins as a mononucleosislike illness, which then progresses over weeks to months and becomes a more diffuse process. Lymphoproliferation occurs in multiple organ systems, thereafter either resolving with aggressive treatment or rapidly progressing to death. Tissue biopsy specimens will show polyclonal B-cell proliferation as well as occasional cytogenetic abnormalities. Microscopically, there may be diffuse effacement of lymphoid architecture with a polymorphic pattern of B lymphocytes. The results of in situ hybridization for EBV mRNA are floridly positive (Figure 3). Intervention at this time involves possible surgical excision of involved tissues as well as reduction or cessation of immunosuppressive therapy. This treatment will hopefully allow restoration of cytotoxic T-cell activity against EBV-driven proliferation of cells. There is an incidence of rejection of approximately one third of the time during this period of reduced immunosuppression, but, fortunately, these episodes are generally of a mild degree and easily reversible. Failure to reduce immunosuppression at this time may result in the transformation from a benign lymphoproliferation to an irreversible malignant condition.

The third and final stage in the progression of PTLD is the development of a frankly malignant monoclonal B-cell lymphoma. The mechanism for this conversion may be the result of a mutation in an immunoglobulin oncogene that causes deregulation in the gene, thereby leading to malignant transformation.7,8 Once this stage is reached, permanent cytogenetic changes have occurred in a B-cell clone, rendering it unresponsive to immune modulation. Systemic chemotherapy can be used at this point, often with disastrous complications related to drug toxicity and opportunistic infections.

Involvement of the head and neck is common in children with PTLD. Sculerati and Arriaga9 described 12 children with PTLD who presented with symptoms in the head and neck region. Ten of these 12 children had febrile illnesses as well as associated hypertrophy of components of Waldeyer ring. They presented with dysphagia, odynophagia, nasal airway obstruction, or noisy breathing. Cervical adenopathy was common as well, occurring in 7 of the 12 patients. Hague et al10 described a 3-year-old patient with diffuse PTLD after cardiac transplantation who experienced sudden respiratory arrest and ultimately died. Autopsy findings included hypertrophied lymphoid tissue of the head, neck, lungs, and kidneys. The massively enlarged uvula and tonsillar tissue were found to be severely narrowing the airway.

In our patients, the clinical spectrum varied from adenotonsillar hypertrophy with recurrent tonsillitis to adeno-
tonsillar hypertrophy with obstructive symptoms that might include an infectious mononucleosis–like syndrome (Tables 1 and 2). The 1 patient with lymphoma presented with an acute febrile illness and symptoms similar to those of patients with nonlymphomatous PTLD. There was not one single factor that strongly suggested a diagnosis of PTLD in our population. Therefore, a high index of suspicion is necessary to identify those patients who are at risk of developing PTLD.

A recent report by Lattyak et al9 showed that 5 of 8 cases involving pediatric liver transplant recipients with PTLD presented with head and neck involvement: 4 of the cases were diagnosed from tonsillar specimens and 1 from a cervical lymph node. A total of 10 patients, however, underwent tonsillectomy for tonsillar hypertrophy after transplantation, and the diagnosis of PTLD was found in only 4 of them. Thus, 40% of transplant recipients with tonsillar hypertrophy in that study had histopathological evidence of PTLD, a sensitivity similar to the results in our review.

In the past several years, histopathological specimens have been tested for EBV positivity, since EBV has a clear role in the disease process. In fact, tonsillar specimens can show evidence of PTLD even when the results of serological evaluations for acute EBV infection, including polymerase chain reaction for EBV DNA, are inconclusive.10 Studies to detect EBV in tissue include polymerase chain reaction analysis to detect EBV DNA, in situ hybridization for EBV mRNA (EBER), and immunoperoxidase staining for EBV-latent membrane protein.10

Treatment of PTLD varies among institutions, but most commonly involves as much of a reduction in immunosuppression as patients will tolerate. Evaluations, such as a serological determination of liver enzyme levels, indicating rejection or a patient’s potential to begin rejection, are often obtained to determine the amount that the immunosuppression can be reduced.

Adjuvant therapies, as well, are often used when a form of PTLD is diagnosed. Patients can be treated with acyclovir or ganciclovir for weeks to months after infection to prevent EBV DNA replication in actively dividing cells. Interferon alfa has also been used as an immune potentiator to inhibit the outgrowth of EBV-transformed cells after infection with the virus. It has also been shown to stimulate natural killer cell activity and EBV cytotoxic T-cell activity.11 Similarly, intravenous immunoglobulin has immunomodulatory characteristics, including the augmentation of antibody-dependent cellular cytotoxic effects and an antiviral effect as a neutralizing antibody.11

Some investigators would argue that the mere presence of EBV positivity in a tonsil specimen does not represent a form of PTLD. However, it is thought to represent a stage leading to PTLD. Thus, it is a finding that has the potential to alter a patient’s treatment and clinical course. Early intervention in the form of a tonsillectomy allows the liver transplantation team to make decisions regarding the patient’s immunosuppressive regimen and antiviral therapy on a case-by-case basis.

CONCLUSIONS

Head and neck manifestations of PTLD in pediatric patients who have undergone liver transplantation are not uncommon. Presentation varies from adenotonsillar hypertrophy with recurrent tonsillitis or obstructive symptoms to a febrile mononucleosis–type picture and, in rare cases, rapidly progressive upper airway obstruction. Tonsillectomy should be performed in any pediatric transplant recipients who have tonsillar hypertrophy, regardless of their clinical presentation, to rule out a form of PTLD. Immunohistochemical studies for EBV should be performed on the tissue samples, since these children can occasionally have inconclusive EBV serological test results. Early identification of this disorder can lead to alteration in therapy and improved outcome.

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