Adenotonsillar Enlargement in Pediatric Patients Following Solid Organ Transplantation

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Objective: To evaluate the management of adenotonsillar hypertrophy in pediatric patients after transplantation.

Design: A retrospective medical record review after transplantation of all pediatric patients undergoing adenotonsillectomy at the University of California, Los Angeles, Medical Center during a 14-month period.

Setting: A tertiary care center.

Patients: There were 16 patients in our review, 11 boys and 5 girls. Nine patients had undergone liver transplantation, and 7 had undergone kidney transplantation.

Intervention: Fourteen patients underwent adenotonsillectomy, and 2 underwent adenoidectomy alone. Indications for surgical intervention included progressive symptoms of upper airway obstruction, recurrent tonsillitis, and/or evidence of notable adenotonsillar enlargement on physical examination.

Results: The mean ± SD age at the time of transplantation was 3 years 1 month ± 3 years 5 months. The mean ± SD duration from allograft transplantation to adenotonsillectomy was 5 years 1 month ± 2 years 4 months. Histopathologic examination revealed that 1 kidney transplant recipient had posttransplantation lymphoproliferative disorder. Eleven patients were found to have Epstein-Barr virus–related lymphoid hyperplasia. All patients experienced clinical resolution of their symptoms after surgery.

Conclusions: Posttransplantation lymphoproliferative disorder is a condition associated with the Epstein-Barr virus infection in the setting of immunosuppression. Early presentation of posttransplantation lymphoproliferative disorder in children may be manifested by adenotonsillar enlargement. In addition to the role in relieving upper airway obstruction and decreasing upper respiratory tract infection, adenotonsillectomy may be critical in the prompt evaluation and treatment of posttransplantation lymphoproliferative disorder.

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MMUNOSUPPRESSION following solid organ transplantation is increasingly successful in preventing organ rejection. This has resulted in increasing numbers of surviving transplant recipients. However, immunosuppression also predisposes the transplant recipient to an increased risk for opportunistic infections and neoplastic disorders, particularly tumors of the lymphoreticular system.

Posttransplantation lymphoproliferative disorder (PTLD) is characterized by abnormal proliferation of lymphoid tissue.

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SUBJECTS AND METHODS

The subjects of this report are pediatric transplant recipients who presented with adenotonsillar hypertrophy at the University of California, Los Angeles, Medical Center from March 5, 1998, to April 22, 1999. All patients subsequently underwent tonsillectomy, adenoidectomy, or both. Clinical information was obtained from a retrospective review of their medical records.

TRANSPANTATION HISTORY

The medical records of these patients were reviewed for the following information: type and indication of allograft transplantation, age at the time of transplantation, type of immunosuppression, and history of rejection and retransplantation.

CLINICAL SIGNS AND SYMPTOMS

Symptoms referable to adenotonsillar enlargement were recorded. The clinical signs associated with PTLD, including fever, impaired general condition, poor appetite, weight loss, and irritability, were also recorded. Risk factors associated with the development of PTLD, such as young age and tacrolimus immunosuppression, were reviewed. The patients’ age at presentation of adenotonsillar hypertrophy and tonsillar size were recorded. The size of the patients’ tonsils was based on the classification system that 4+ tonsils represented greater than 75% obstruction of the oropharynx; 3+, tonsillar enlargement and less than 75% obstruction; 2+, normal-sized but visible tonsils; and 1+, nonvisualized tonsils.

SURGICAL INTERVENTION

Fourteen patients underwent tonsillectomy and adenoidectomy. Two patients underwent adenoidectomy alone. The perioperative hospital course of each patient was examined, with attention given to any postoperative complication.

DIAGNOSIS OF EBV AND PTLD

The pathological diagnosis of the tonsil and adenoid specimen was made using standard histological, immunohistochemical, and molecular genetic techniques. Table 1 summarizes the PTLD classification schema, which is based on the Society for Hematopathology Workshop 1997 recommendations. Tissue samples from all patients were reviewed and classified according to this schema. Epstein-Barr virus was detected by in situ hybridization for EBV-encoded RNA. Clonality of the B-cell proliferation using immunohistochemical staining of B cell–associated κ and λ chains was performed in 8 patients.

OUTCOME

All patients were examined at their 1-month postoperative follow-up visit. Resolution of signs and symptoms secondary to adenotonsillar hypertrophy was noted. Their subsequent medical history and follow-ups with their respective transplant services were also reviewed, with particular attention given to whether any patient developed lymphoproliferative disorder. The duration of the follow-up was recorded.

RESULTS

All 16 patients were treated at the University of California, Los Angeles, Medical Center from March 5, 1998, to April 22, 1999. There were 11 boys and 5 girls. The clinical characteristics of the patients are given in Table 2. Patients are listed in Table 2 according to the type of transplantation they underwent and their age.

Nine patients had undergone liver transplantation and 7 had undergone kidney transplantation. All 9 liver allograft recipients had developed end-stage liver disease secondary to biliary atresia. Indications for kidney transplantation included glomerulonephritis, nephric dysplasia, focal segmental glomerulosclerosis, polycystic kidney disease, and Alport syndrome. The immunosuppression regimen of each transplant recipient is listed in Table 2.

Age at the time of transplantation ranged from 7 months to 10 years 8 months (mean ± SD, 3 years 1 month ± 3 years 6 months). Age at the time of adenotonsillectomy ranged from 4/2 years to 10 years 4 months (mean ± SD, 8 years 7 months ± 3 years 11 months). The time from allograft transplantation to adenotonsillectomy ranged from 14 months to 11 years 9 months (mean ± SD, 5 years 1 month ± 2 years 4 months).

The signs and symptoms of adenotonsillar hypertrophy are shown in Table 3. One patient (patient 14) presented with a 2-week history of persistent fever, nasal airway obstruction, somnolence, and poor appetite. He underwent adenotonsillectomy, and PTLD was diagnosed. Of the remaining 15 patients, 13 presented with symptoms of obstructive sleep disorder or nasal airway obstruction. Of the 2 patients who did not have airway obstruction, one had recurrent tonsillitis and a second had asymptomatic, asymmetric tonsillar enlargement. Thirteen patients had 4+ tonsils, while 1 patient had 3+ tonsils. The 2 patients without tonsillar hypertrophy were found intraoperatively to have adenoid hypertrophy. These 2 patients underwent adenoidectomy alone. There were no perioperative complications in any of the patients.

The histopathologic diagnosis and immunohistochemical staining results of each patient are shown in Table 3. Features of PTLD were demonstrated in the adenoid and tonsil specimen in patient 14. His adenoid tissue showed diffuse effacement of normal adenoidal follicles by a polymorphous proliferation of small lymphocytes, immunoblasts, plasma cells, and plasmacytoid lymphocytes (Figure 1). Focal necrosis was also demonstrated (Figure 1, right). In situ hybridization for EBV-encoded RNA in this patient showed strong nuclear staining (Figure 2). The results of κ and λ light chain marker staining were both positive, suggesting that the B-cell proliferation was polyclonal. Histopathologic evaluation results were, therefore, consistent with PTLD, polymorphous type. His immunosuppression consisted of...
cyclosporine and prednisone. Review of his serum cyclosporine level during the preceding year showed that it never exceeded 275 ng/mL (normal, 100-400 ng/mL). He subsequently underwent serologic evaluation for EBV. His anti–EBV IgM antibodies were 1.48 relative enzyme-linked immunosorbent assay units (normal, ≤0.9) and his anti–EBV IgG antibodies were greater than 5.0 relative enzyme-linked immunosorbent assay units (normal, ≤0.9). These results were consistent with an acute EBV infection. In addition, polymerase chain reaction was used to detect viral sequences in circulating lymphocytes. His EBV by polymerase chain reaction was 870 copies of viral DNA (normal, 0-5 copies), again suggesting active EBV infection. He underwent computed tomographic scanning of his neck, chest, abdomen, and pelvis. This revealed bilateral cervical lymphadenopathy. The remaining results of his computed tomographic scans were normal. Cyclosporine therapy was discontinued, and low-dose prednisone therapy was maintained. He did not undergo chemotherapy. This patient was discharged from the hospital 10 days after tonsillectomy and adenoidectomy with resolution of symptoms. Laboratory evaluation on follow-up has not demonstrated evidence of organ rejection.

Of the 15 patients who did not have PTLD, EBV-related lymphoid hyperplasia was demonstrated in 11. An example of EBV-related hyperplasia is shown in patient 1, whose adenoid specimen demonstrated diffuse lymphoid proliferation with preservation of lymphoid architecture (Figure 3). In situ hybridization for EBV-encoded RNA in this patient also showed strong nuclear staining (Figure 4). κ and λ light chain marker staining was performed on 8 specimens. With the exception of patient 12, the results of κ and λ staining were positive in all patients, suggesting polyclonal B-cell proliferation.

All patients, including the one who developed PTLD, had resolution of their preoperative symptoms on follow-up examinations. Those who demonstrated EBV-related hyperplasia underwent a reduction in the level of immunosuppressant medication. None have demonstrated clinical or laboratory evidence of organ rejection.

### Table 1. Classification of Posttransplantation Lymphoproliferative Disorders (PTLDs)*

<table>
<thead>
<tr>
<th>Categories of PTLD</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early lesions</td>
<td>Plasmacytoma-like and infectious mononucleosis-like</td>
</tr>
<tr>
<td>PTLD</td>
<td>Polyclonal and monoclonal</td>
</tr>
<tr>
<td>Monomorphic</td>
<td>B-cell and T-lymphocyte lymphoma</td>
</tr>
<tr>
<td>Other</td>
<td>T-lymphocyte rich or Hodgkin disease, plasmacytoma-like, and myeloma</td>
</tr>
</tbody>
</table>

*Based on the Society for Hematoopathology Workshop 1997 recommendations.12

### Table 2. Transplantation Characteristics of Pediatric Patients With Adenotonsillar Hypertrophy After Transplantation

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Type of Transplantation</th>
<th>Age at Transplantation</th>
<th>Indication for Transplantation</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/4 y 6 mo</td>
<td>Liver</td>
<td>7 mo</td>
<td>Biliary atresia</td>
<td>Tacrolimus and prednisone</td>
</tr>
<tr>
<td>2/M/5 y</td>
<td>Liver (twice)</td>
<td>8 mo (first) and 2 y 7 mo (second)</td>
<td>Biliary atresia</td>
<td>Tacrolimus and prednisone</td>
</tr>
<tr>
<td>3/F/5 y 7 mo</td>
<td>Liver</td>
<td>11 mo</td>
<td>Biliary atresia</td>
<td>Cyclosporine, azathioprine, and prednisone</td>
</tr>
<tr>
<td>4/M/5 y 7 mo</td>
<td>Liver</td>
<td>8 mo</td>
<td>Biliary atresia</td>
<td>Cyclosporine and prednisone</td>
</tr>
<tr>
<td>5/M/6 y 9 mo</td>
<td>Liver</td>
<td>9 mo</td>
<td>Biliary atresia</td>
<td>Cyclosporine µ suspension and azathioprine</td>
</tr>
<tr>
<td>6/M/6 y 4 mo</td>
<td>Liver (twice)</td>
<td>7 mo (first) and 13 mo (second)</td>
<td>Biliary atresia</td>
<td>Cyclosporine, azathioprine, and prednisone</td>
</tr>
<tr>
<td>7/M/6 y 4 mo</td>
<td>Liver</td>
<td>1 y</td>
<td>Biliary atresia</td>
<td>Cyclosporine µ suspension</td>
</tr>
<tr>
<td>8/F/7 y 1 mo</td>
<td>Liver</td>
<td>1 y 2 mo</td>
<td>Biliary atresia</td>
<td>Cyclosporine and azathioprine</td>
</tr>
<tr>
<td>9/F/5 y 7 mo</td>
<td>Liver</td>
<td>7 mo</td>
<td>Biliary atresia</td>
<td>Cyclosporine and prednisone</td>
</tr>
<tr>
<td>10/F/3 y 3 mo</td>
<td>Kidney</td>
<td>2 y 4 mo</td>
<td>Nephric dysplasia</td>
<td>Cyclosporine µ suspension, prednisone, and mycophenolate mofetil</td>
</tr>
<tr>
<td>11/M/6 y 8 mo</td>
<td>Kidney</td>
<td>2 y 3 mo</td>
<td>Polycystic kidney disease</td>
<td>Cyclosporine, prednisone, and mycophenolate</td>
</tr>
<tr>
<td>12/M/12 y</td>
<td>Kidney</td>
<td>10 y 8 mo</td>
<td>Alport syndrome</td>
<td>Cyclosporine µ suspension, prednisone, and mycophenolate</td>
</tr>
<tr>
<td>13/M/12 y 8 mo</td>
<td>Kidney</td>
<td>10 y 5 mo</td>
<td>Glomerulonephritis</td>
<td>Cyclosporine µ suspension, prednisone, and mycophenolate</td>
</tr>
<tr>
<td>14/M/14 y 1 mo</td>
<td>Kidney</td>
<td>2 y 4 mo</td>
<td>Nephric dysplasia</td>
<td>Cyclosporine and prednisone</td>
</tr>
<tr>
<td>15/M/15 y 1 mo</td>
<td>Kidney</td>
<td>7 y</td>
<td>Focal segmental glomerulosclerosis</td>
<td>Cyclosporine µ suspension, prednisone, and mycophenolate</td>
</tr>
<tr>
<td>16/M/16 y 4 mo</td>
<td>Kidney</td>
<td>7 y 2 mo</td>
<td>Unknown</td>
<td>Tacrolimus, prednisone, and mycophenolate</td>
</tr>
</tbody>
</table>
in immunosuppressed pediatric patients. It is clear, however, that adenotonsillar hypertrophy in an immunosuppressed child can represent PTLD.

Posttransplantation lymphoproliferative disorder is defined as the presence of an abnormal proliferation of lymphoid cells and is associated with EBV infection in the setting of immunosuppression. These lesions are heterogeneous and may not meet the pathological criteria for lymphoma. Posttransplantation lymphoproliferative disorder may range from polyclonal to monoclonal proliferation, representing the spectrum of lymphomatous processes. The use of immunosuppressive agents in the setting of solid organ transplantation is associated with a 20- to 50-fold increased risk of lymphoma. There is increasing evidence that the use of a more potent, multiagent approach to immunosuppression has accelerated the development of these lymphoproliferative disorders. Epstein-Barr virus has been implicated in virtually all cases of PTLD. Epstein-Barr virus is a ubiquitous herpesvirus. It infects B lymphocytes, immortalizes them, and leads to their polyclonal proliferation. The host mounts an EBV-specific T-lymphocyte response that controls the proliferation. In the immunosuppressed hosts, the cytotoxic T-lymphocyte response that controls the B-cell proliferation is limited. The subsequent uncontrolled proliferation of B lymphocytes results in PTLD.

In a review of the literature, several studies have demonstrated that lymphoproliferative disorder can present as enlargement of the adenoid and tonsil tissue. In 1985, Myer and Reilly noted a case of PTLD presenting as adenotonsillar hypertrophy in a 2-year-old recipient of a liver allograft. Fairley et al described 3 cases of oropharyngeal PTLD, 1 of which occurred in a 6-year-old heart transplant recipient who had presented with adenotonsillar hypertrophy. Lones et al noted 3 cases of PTLD.
that presented as adenotonsillar hypertrophy and concluded that adenotonsillectomy can be valuable in the early diagnosis of PTLD. In a review of 18 pediatric liver transplant recipients who developed PTLD, Sokal et al\(^2\) noted that 6 patients had tonsillar involvement. Dror et al\(^{10}\) reported that 8 of the 26 patients with PTLD in their series had tonsillar involvement.

Adenotonsillar hypertrophy in a child who has undergone solid organ transplantation may represent PTLD. Factors that increase the risk for PTLD include young age, liver as opposed to kidney allograft, EBV seronegativity, and use of tacrolimus as an immunosuppressive agent (Table 4).\(^{2,8,10}\) It is important to obtain clinical information pertinent to the transplantation, including type of transplantation, age of the transplant, type and dose of immunosuppression, and EBV serologic features, in transplant recipients with adenotonsillar hypertrophy. However, all transplant recipients are at notably increased risk of developing lymphoproliferative disorder compared with the general pediatric patient with adenotonsillar hypertrophy.

The patient's clinical manifestations may also suggest the diagnosis of PTLD. The clinical signs of PTLD in children may include fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, impaired general condition, poor appetite, weight loss, and irritability.\(^1,2\) Patients with PTLD may also present with focal organ involvement within the gastrointestinal tract and central nervous system.\(^1\) In our review, PTLD was diagnosed in the 1 patient who presented with fever and impaired general condition. However, the absence of such symptoms does not preclude the presence of PTLD. Many patients with PTLD can present without any constitutional symptoms.\(^1\) Interestingly, adult cases of PTLD do not appear to involve the tonsil and adenoid region.\(^5,13\) The early involvement of the Waldeyer ring by PTLD in the pediatric patient suggests the possibility of primary exposure to EBV along with initiation of the lymphoproliferation.\(^9\)

The timing of the onset of adenotonsillar hypertrophy may also provide clues for PTLD. Posttransplantation lymphoproliferative disorder is most common during the first year after transplantation.\(^9\) However, in our series, the only patient found to have PTLD developed the disease 12 years after his kidney transplantation. Overall, the mean age of the patient at the time of organ transplantation was 3 years 1 month in our series. The mean duration from organ transplantation to adenotonsillectomy was 5 years 1 month. This suggested that either symptomatic adenotonsillar hypertrophy may not be an immediate finding after organ transplantation or this symptom is not promptly appreciated by physicians and family members.

The management of adenotonsillar hypertrophy in the immunocompetent pediatric population has been controversial. No single algorithm for decision making can encompass all clinical scenarios.\(^{11,14-16}\) On the other hand, there should be no controversy in the management of adenotonsillar hypertrophy in the posttransplantation population. Prompt surgical intervention is necessary. Adenotonsillectomy not only evaluates for PTLD but also allows for early intervention. Early intervention has been shown to affect outcome in this patient population.\(^6\) Moreover, early tonsillectomy and adenoidectomy also relieve upper airway obstruction and may help diminish the frequency of upper respiratory tract infections in these immunocompromised patients.

Our series revealed 1 case of PTLD and 11 cases of EBV-related hyperplasia. Although not classified as a
lymphoproliferative disorder, EBV-related hyperplasia predisposes the pediatric transplant recipients to complications of adenotonsillar hypertrophy. This in turn can lead to upper airway obstruction and obstructive sleep apnea.

The incidence of adenotonsillar hypertrophy in the transplant recipient is not known. A prospective study is needed to define the incidence of adenotonsillar hypertrophy and EBV-related hyperplasia in this patient population. Subsequently, the potential benefit of removing tonsils and adenoids harboring EBV in preventing PTLD can be addressed.

CONCLUSIONS

Posttransplantation lymphoproliferative disorder in the pediatric population may present with signs and symptoms of adenotonsillar hypertrophy. It is important for the otolaryngologist to consider the diagnosis of PTLD in immunosuppressed pediatric patients who present with adenotonsillar hypertrophy.

In the immunocompetent pediatric population, the indications for tonsillectomy and adenoidectomy have been widely debated. In the posttransplantation pediatric population, however, prompt excision of the tonsil and adenoid tissue is necessary. Prompt surgical treatment can yield an early pathological diagnosis, enable timely treatment, and relieve upper airway obstruction. There are still many unanswered questions regarding adenotonsillar hypertrophy in transplant recipients. The incidence of adenotonsillar hypertrophy is still not known. It is not clear whether pediatric transplant recipients are more prone to adenotonsillar hypertrophy because of the increased incidence of EBV-related hyperplasia. Epithelial cells of the Waldeyer ring may represent the principal reservoir for replicating virus. Moreover, strong evidence suggests that the donor organ is often the source of primary EBV infection. A prospective study may examine whether tonsillectomy and adenoidectomy may be a component of the preventive strategy for PTLD.

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REFERENCES