Posttransplantation Lymphoproliferative Disorder of the Head and Neck: Imaging Features in Seven Adults

**Purpose:** To determine the cross-sectional imaging findings of posttransplantation lymphoproliferative disorder (PTLD) of the head and neck.

**Materials and Methods:** Computed tomographic (CT) scans (n = 6) and magnetic resonance (MR) images (n = 2) in seven patients with histopathologically proved PTLD of the Waldeyer (lymphoid) ring or cervical lymph nodes were retrospectively reviewed for abnormalities.

**Results:** The interval between transplantation and PTLD onset was 3.5–108 months (mean, 30 months). All patients had imaging abnormalities involving the Waldeyer ring, and focal 2.0–4.5-cm masses were present in six patients (unilateral oropharyngeal tonsil in two, bilateral oropharyngeal tonsils in one, nasopharyngeal adenoids in three, unilateral pharyngeal tonsil and ipsilateral nasopharynx in one). In three patients, the mass was centrally low attenuating at CT or isointense to fluid at MR imaging, with enhancing solid peripheral lymphoid tissue. Three patients also had nodal findings: one with a 7-cm low-attenuating nodal mass in the right neck and two with numerous bilateral lymph nodes (mostly normal sized) in the anterior and posterior cervical lymph chains. One patient also had a small mass in the upper mediastinum.

**Conclusion:** In the setting of organ transplantation, findings of masses in the Waldeyer ring or an excessive number of cervical nodes should increase the index of suspicion of PTLD.

Posttransplantation lymphoproliferative disorder (PTLD) encompasses a family of disorders and includes lymphoid hyperplasia and lymphoid neoplasia, which occur in the setting of chronic immunosuppression after solid organ transplantation. In 1968, Starzl (1) provided an early description of PTLD in renal transplant recipients. PTLD is a challenging complication of organ transplantation (1) and, if untreated, is usually fatal. Because immunosuppression carries an increased risk for the de novo development of malignancy, the occurrence of PTLD is surpassed only by that of cancers of the skin and lips (2).

The frequency of PTLD has been reported to range from 1% to 10%, with substantial variability depending on the organ transplanted (3–9). Walker et al (8) reported PTLD in 6.2% of patients after lung transplantation, 5.2% of patients after kidney and pancreas transplantation, 2.0% of patients after heart transplantation, and 1.4% of patients after liver transplantation. The difference in the frequency of PTLD among these groups may be attributed to organ-specific immunosuppressive regimens. The association of Epstein-Barr virus (EBV) infection with the development of PTLD has been well established and is hypothesized to occur through unregulated B-cell proliferation. PTLD encompasses a spectrum of clinical manifestations, in addition to a wide range of histopathologic findings, from B-cell hyperplasia to lymphoma. Lesions primarily occur in the gastrointestinal tract, central nervous system, allografted organ, and, less commonly, lymph nodes (6).

We performed this study to determine the unusual findings of PTLD of the head and neck in adult patients who have undergone solid organ transplantation, with lesions involving the Waldeyer ring (lymphoid ring) in the pharynx, as well as lesions involving...
the cervical lymph nodes. The magnetic resonance (MR) imaging and computed tomographic (CT) findings will be described.

MATERIALS AND METHODS

Clinical Data

The study group consisted of seven patients (five men, two women), aged 21–65 years (mean, 42 years), with histopathologically proved PTLD of the pharyngeal lymphoid tissue or the cervical nodes. Patients were identified by searching the pathology database for those who had been treated for PTLD at our institution during 4 years. All patients had undergone cross-sectional imaging. Our investigation in no way interfered with patient care. All patients had undergone solid organ transplantation between 1987 and 1996. One patient each underwent heart, kidney, and lung transplantation; three patients underwent liver transplantation; and one patient underwent combined kidney and pancreas transplantation. The mean age at transplantation was 35 years (range, 21–54 years). Posttransplantation immunosuppressive therapy included prednisone (n = 7), cyclosporine (n = 5), azathioprine (n = 3), tacrolimus (n = 2), and mycophenolate (n = 1). Clinical symptoms included ear pain, a mononucleosis-like syndrome, a palpable neck mass, and facial paresthesia and numbness.

Histopathologic Findings

The diagnosis of PTLD was histopathologically established with the presence of atypical lymphocytic infiltrates and/or destruction of the normal parenchymal architecture at the biopsy sites in the neck. PTLD was classified according to a system proposed by Nalesnik et al (10) and Knowles et al (11), with subtypes that include plasmocytic hyperplasia, polymorphous B-cell hyperplasia, polymorphous B-cell lymphoma, non-Hodgkin lymphoma, and multiple myeloma.

To determine the frequency of EBV infection in the tissues affected by PTLD, in situ hybridization for the EBV genome was performed with all specimens. Testing included evaluation for EBER1, an RNA sequence that is abundantly expressed during latent EBV infection, and tandem repeats of NofI, a DNA sequence that is amplified during active EBV infection.

Imaging

CT and MR imaging of the neck were performed in six and two patients, respectively. CT was performed at our institution with a helical scanner (model 9800; GE Medical Systems, Milwaukee, Wisconsin), with acquisition of a set of 5-mm-thick transverse images that covered from the skull base to the aortic arch. Two sets of images were obtained during each CT examination, one optimized for bone detail and the other optimized for soft-tissue detail. Only one patient underwent CT after intravenous administration of 100 mL of iodinated contrast material (iohexol, Omnipaque; Nycomed, Princeton, New Jersey). In the remaining patients, CT scans were obtained without contrast material because of renal insufficiency or to prevent potential complications in transplanted kidneys.

MR images were obtained with a 1.5-T system (Signa; GE Medical Systems) by using an anteroposterior volume neck coil (Medical Advances, Madison, Wisconsin). The imaging protocol consisted of a sagittal T1-weighted conventional spin-echo sequence (repetition time msec/echo time msec = 400–600/11–17) followed by a transverse T2-weighted fast spin-echo sequence (3,500–4,000/85–90 [effective]) and a transverse T1-weighted spin-echo sequence (600/11–17). Images of the neck extended from the level of the cavernous sinus to the upper mediastinum. Then, 0.1 mmol of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) per kilogram of body weight was intravenously administered, and transverse T1-weighted spin-echo images were obtained with imaging parameters similar to those used for the nonenhanced images. Fast spin-echo and contrast-enhanced images were obtained after the application of frequency-selective fat-saturation techniques. For the sagittal T1-weighted localizing sequence, the section thickness was 5 mm with a gap of 1 mm, and the field of view was 30 cm. All other sequences were performed with interleaved images and a section thickness of 5 mm. Other imaging parameters included one or two signals acquired and a 24–26-cm field of view. A 256 × 128 matrix was used for sagittal and contrast-enhanced T1-weighted images, and a 256 × 192 matrix was used for nonenhanced transverse T1- and T2-weighted images.

Images were retrospectively reviewed in consensus by two head and neck radiologists (L.A.L., D.M.Y.), who looked for abnormalities of the Waldeyer ring and cervical lymph nodes. In the patient who underwent both CT and MR imaging, both sets of images were evaluated together. Specifically, images were assessed for the presence of (a) generalized enlargement and/or focal masses of the pharyngeal lymphoid tissue and (b) lymphadenopathy. In addition to size, masses were evaluated for changes in attenuation and signal intensity (relative to that of muscle and cerebrospinal fluid) at CT and MR imaging, respectively, which are suggestive of increased free water concentration. The degree of enhancement was assessed by comparing the attenuation or signal intensity of the masses with that of muscle, the submandibular glands, and the mucosa. Lymph nodes were considered to be abnormal if they were enlarged according to radiologic criteria (diameter > 1.5 cm in the submandibular, submental, and jugulodigastric regions; diameter > 1.0 cm in the remainder of the neck) or if there were an excessive number regardless of their size (multiple groupings of three or more nodes, each at least 5 mm). In addition, the upper mediastinum and thymic region was assessed for focal lesions. Radiologic findings were compared with results of histologic analysis of the specimens.

The medical records of all patients were retrospectively reviewed by one author (R.L.K.) to determine the predisposing disease that led to organ failure, time between transplantation and onset of PTLD, presence of PTLD in other organ systems, initial therapy, and response to therapy.

RESULTS

All seven patients had abnormalities involving the Waldeyer ring, including generalized lymphoid enlargement in one patient and focal masses in six patients. In the six patients with focal masses involving the Waldeyer ring (unilateral oropharyngeal tonsil in two patients, bilateral oropharyngeal tonsils in one, nasopharyngeal adenoids in three, unilateral tonsil and nasopharynx in one), the lesions were 2.0–4.5 cm in diameter (Figs 1–3). In the three patients who underwent contrast-enhanced CT (n = 1) or MR imaging (n = 2), the masses showed a prominent central area of low attenuation at CT and a central area of signal intensity similar to that of cerebrospinal fluid at MR imaging, with thick peripheral tissue that showed enhancement similar to that of the submandibular glands (Figs 1, 3). In addi-
Figure 1. Patient 3. Contrast-enhanced transverse CT scans obtained in a 53-year-old woman after bilateral lung transplantation. PTLD was proved with CT-guided biopsy results. (a) Scan obtained at the level of the nasopharynx demonstrates a low-attenuating mass (arrows) at the level of the fossa of Rosenmüller and lateral nasopharyngeal wall on the left. An abscess was suspected. (b) Scan obtained 2 cm inferior to a demonstrates extension of the mass to the oropharynx and tonsil. The mass is characterized by a central hypoattenuating area consistent with necrosis (arrow). Circumferentially, there is a thick rind of solid lymphoid tissue (arrowheads). The mass at this level is predominantly submucosal within the parapharyngeal space. (c) Scan obtained at the level of the upper thorax demonstrates a small mass (arrow) in the superior mediastinum.

Figure 2. Patient 5. Nonenhanced transverse CT scans obtained in a 21-year-old man with acute onset of PTLD 4 months after kidney and pancreas transplantation. Nonenhanced CT was performed owing to renal failure due to acute rejection of the transplanted kidney. (a) Scan shows large masses involving the bilateral tonsils of the Waldeyer ring at the level of the oropharynx, which meet at the midline (arrowhead). These were sampled at biopsy, and PTLD was proved at histopathologic examination. (b) Scan obtained more inferiorly demonstrates bilateral lymph nodes (arrows) that were suspected of being involved with PTLD; however, the nodal diameters remained within normal size criteria.

Histopathologic examination of the specimens revealed polyclonal plasmocytic hyperplasia (n = 1), polymorphous B-cell hyperplasia (n = 1), polymorphous B-cell lymphoma (n = 3), non-Hodgkin lymphoma (n = 1), and multiple myeloma (n = 1). In the patient with multiple myeloma, findings on bone radiographs were consistent with myeloma, and myeloma was also confirmed with analysis of bone marrow aspirate. In the three patients with pharyngeal lesions with imaging findings suggestive of necrosis, necrosis was confirmed at histopathologic examination. The EBV genome was detected with immunohistochemical results in five of seven specimens, with EBV EBER1-positive results in four of five specimens and EBV NofI tandem repeats-positive results in two of three specimens (two specimens were not tested for EBV NofI tandem repeats).

The interval between transplantation and the onset of PTLD ranged from 3.5 to 108 months (mean, 30 months; median, 11 months) (Table). All patients initially had PTLD of the neck. Three patients were subsequently found to have PTLD involving other organ systems, including the rectosigmoid and lungs in one patient, the periarcial lymph nodes in another, and the allografted kidney in the third. Patients were treated with combination therapy, including reduction in their immunosuppression regimen (n = 7), surgery (n = 2), chemotherapy (n = 2), and radiation therapy (n = 2) (Table).
Outcomes in the five patients with neoplasia included complete remission (n = 1), partial remission (n = 1), and progressive disease (n = 3). At the time of manuscript preparation, two patients had died.

**DISCUSSION**

PTLD is a serious complication of solid organ transplantation, and clinical findings range from focal to disseminated disease. The frequency has been reported to range from 1% to 10% in transplant recipients, depending on the organ transplanted (3-9) and the type and length of immunosuppressive therapy (6,8). With the potency of current medications aimed at prevention of organ rejection, the frequency of PTLD has increased (6). In addition, the interval between transplantation and the onset of this complication has decreased (6). PTLD represents uncontrolled B-cell proliferation with histologic characteristics that range from polymorphic cellular expansion of large and/or small lymphocytes to monomorphic large cell non-Hodgkin lymphoma.

The system used to classify PTLD is constantly evolving in an attempt to accommodate the wide range and growing number of subtypes of lymphoproliferation. Histopathologic criteria for the diagnosis of PTLD include lymphocytic proliferation with or without destruction of the underlying architecture of the affected tissue (depending on the classification system used). Frizzera et al (12) in 1981, Nalesnik et al (10) in 1989, and Knowles et al (11) in 1995 have developed classifications systems that subdivide PTLD lesions into three distinct categories: hyperplastic, polymorphic, and monomorphic (3). More recently, a T-cell form of PTLD has been reported (13), and this finding represents a rare, late, and aggressive complication of organ transplantation. Unlike its B-cell counterpart, T-cell PTLD is not thought to be associated with EBV infection (13).

The role of EBV infection in the pathogenesis of PTLD has been firmly established (14). EBV infects B lymphocytes, as well as epithelial cells, because the virus attaches to specific receptors located on the membranes of these cells. This receptor specificity may help explain the association of EBV in the development of squamous cell carcinoma of the aerodigestive tract epithelium (6,15).

After the primary infection, latent EBV persists for life. Latent EBV nuclear proteins induce B-cell proliferation. In the immunocompetent patient, this process is kept in check by cytotoxic T lymphocytes, which recognize and lyse EBV-infected cells. In the immunocompromised patient, however, the suppression of this immunosurveillance process may lead to the unregulated proliferation of B cells (16). Tumors are initially polyclonal and gradually progress to monoclonal lesions that harbor malignant transformations (5,16). In the setting of solid organ transplantation, EBV infection may originate from the donor or the recipient, and the infection may represent an acute process or a reactivation process (17,18). Pretransplantation EBV seronegativity is
thought to substantially increase the risk for the development of PTLD and, at some institutions, may preclude transplantation (8).

The clinical manifestations of PTLD commonly include a mononucleosis-type syndrome (fever, fatigue, sore throat), regional lymph node enlargement, or disseminated disease (19). Lymphoid tumors may be nodal or extranodal in origin. Extranodal disease is most common and frequently involves the gastrointestinal tract, central nervous system, and/or allografted organ (6). Allograft involvement may clinically mimic organ rejection, and, therefore, biopsy is necessary to prevent therapy that will exacerbate the disease process. Disseminated disease, which is the most severe form of PTLD, manifests as sepsis, generalized adenopathy, and multiorgan failure. Therapeutic interventions are often ineffective.

Because the symptoms of PTLD frequently resemble those of other complications of transplantation, particularly infection and organ rejection, a high index of suspicion for PTLD is crucial to prevent a delay in diagnosis. PTLD should always be considered in the differential diagnosis of organ rejection in the setting of chronic abdominal pain or with the development of cutaneous lesions in a transplant recipient. Oral shedding of EBV and elevation of EBV-positive serum leukocytes may aid in the early diagnosis (7). The work-up of suspected PTLD usually includes cross-sectional imaging of the head, chest, abdomen, and pelvis (20). Routine imaging of the neck has not been part of this protocol. Definitive diagnosis of PTLD is established on the basis of histopathologic analysis of tissue. Specimens are evaluated for histologic characteristics, cellular clonality, EBV infection, and human lymphocyte antigen typing.

The imaging appearance of PTLD has been described in the lungs, gastrointestinal tract, and central nervous system. For intrathoracic PTLD, chest radiography is a simple and accurate surveillance method (21,22). Findings may include pulmonary nodules, airspace consolidation, hilar and mediastinal adenopathy, pleural and pericardial effusions, and thymic enlargement (21,23–25). Although necrosis is uncommon, it has been noted in very large solitary mediastinal nodal masses (21,23).

In intraabdominal PTLD, low-attenuating mass(es) in the liver and spleen may be present at CT. Diffuse infiltration resulting in hepatomegaly or splenomegaly without a discrete mass or masses

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<th>Clinical Data in Patients with PTLD of the Head and Neck</th>
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* Time between transplantation and development of PTLD.
may also occur (26). Other abdominal findings include thickening or dilatation of the small bowel, mesenteric adenopathy, and disease in the kidney, pancreas, or adrenal glands (27).

Lesions in the central nervous system were more commonly encountered in the era before cyclosporine (25,28). Cerebral lesions typically manifest as peripherally enhancing masses with a central area of low attenuation or with signal intensity similar to that of cerebrospinal fluid, and such lesions must be distinguished from infection (25).

PTLD affecting the neck is reportedly uncommon, and, therefore, the radiologic manifestations have not been well characterized. We have described seven adult transplant recipients in whom the primary manifestation of PTLD began with symptoms in the neck. Six patients had focal masses in the Waldeyer ring, and 50% of these patients had central necrosis and substantial submucosal extension into the parapharyngeal space. These imaging findings differed from those of lymphoma in the immunocompetent patient, which frequently appears as a solid mass that grows exophytically into the airway lumen. It is also noteworthy that in two of the three patients, the necrotic masses were initially misinterpreted as abscesses. Cervical lymphadenopathy was also present in more than 40% (three of seven) of the patients in our study, and two imaging patterns were noted: namely, a large nodal mass and clusters of normal-sized lymph nodes.

There are a few reports of PTLD of the neck described in the pediatric population (27,29,30). Donnelly et al (27) noted that eight of 27 children (all heart transplant recipients) developed PTLD of the neck. Lesions in the Waldeyer ring were present in three patients, and cervical adenopathy was present in five. Similar to our findings, these previously published results showed extreme low attenuation in one of the masses in the Waldeyer ring, as well as in a nodal mass.

It is important to note that microscopic disease may be overlooked at imaging. The presence of histopathologically proved PTLD in nodes that are normal according to imaging criteria emphasizes that the absence of abnormalities at imaging does not rule out PTLD. It further emphasizes that, as our findings suggest, clusters of nodes, although normal in size, should be viewed with suspicion given the appropriate clinical setting.

There are multiple treatment modalities for PTLD, including reduction in immunosuppressive therapy, chemotherapy, radiation therapy, surgical excision, antiviral therapy, and novel immunomodulation techniques. Treatment is determined according to the specific histopathologic finding. Reduction in immunosuppressive medication (or complete cessation in cases of lymphomatous or disseminated disease) is effective and almost always serves as the initial therapeutic option (2,6,19,31). The likelihood of a response is directly related to the clonality of the tumor. Monoclonal tumors, which more closely resemble lymphoma, are less likely to be affected. Reduction in immunosuppressive therapy may be accompanied by organ rejection and requires close clinical follow-up. Failure of tumor regression in the setting of decreased immunosuppression requires other treatment modalities, including chemotherapy and radiation therapy. Efforts in the use of antiviral drugs have shown limited clinical utility in the treatment of PTLD (2,4,20). Immunotherapeutic treatments such as anti-B-lymphocyte monoclonal antibodies, interferon alpha, and cytotoxic T-cell transfusion are currently under investigation (3).

Many factors affect the prognosis in patients with PTLD. Early-onset disease (within 1 year of transplantation) is associated with a better prognosis than is late-onset disease, with mortality rates of 36% and 70%, respectively (32). Patients with early-onset PTLD also are more likely to respond to a reduction in immunosuppressive treatment (32). Heart transplant recipients are reported (27) to have a worse prognosis than those with kidney or liver allografts, perhaps because of the more potent immunosuppressive therapy required after heart transplantation.

In conclusion, patients with PTLD affecting the neck may have focal masses in the Waldeyer ring and lymphadenopathy that manifests as large nodal masses or an excessive number of lymph nodes that are relatively normal in size. Unlike in lymphoma in the immunocompetent patient, necrosis in PTLD lesions may be more common. The presence of a mass or masses in the Waldeyer ring or cervical nodes in patients who have undergone organ transplantation should increase the index of suspicion for the diagnosis of PTLD. Masses with low attenuation on CT scans or signal intensity similar to that of cerebrospinal fluid on MR images should not be mistaken for abscesses, as was initially the case in two of our patients. Because lesions in the Waldeyer ring frequently have a large submucosal component, which makes their identification difficult at physical examination, imaging may be the most important in facilitating detection. Finally, imaging is valuable for monitoring the response to treatment (Fig 4).

References
7. Riddler SA, Breitling MC, McKnight JL. Increased levels of circulating EBV-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of post-transplant lymphoproliferative disease in solid organ transplant recipients. Blood 1994; 83:972–984.