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# The Surgical Implications of the Posttransplant Lymphoproliferative Disorders

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THE posttransplant lymphoproliferative disorders (PTLDs) represent a category of neoplastic-like conditions that occur in approximately 2% to 2.5% of the transplant population.[1] PTLDs have been described in transplant patients receiving all types of solid organ grafts.[1-7] Several complications result from the presence of PTLDs and their treatment. Although primarily of medical interest, lymphoproliferative disorders have important surgical implications both of a diagnostic and a therapeutic nature. Here we report our experience with the surgical implications of PTLDs in a large series of liver transplant patients.

## MATERIALS AND METHODS

Forty-six patients of a total population of 1276 (3.6%) with orthotopic liver transplants (OLT) who received transplants between January 1, 1972 and December 31, 1988 at the University of Colorado at Denver and the University of Pittsburgh developed PTLDs. This percentage represents less than one-half the cases of PTLD in patients with transplants of various solid organs at our center. However, the decision was made to analyze only those PTLD arising in OLT patients up to the end of 1988, in order to have a relatively homogenous population and a follow-up of at least 18 months. The immunosuppression consisted of azathioprine (Imuran) in combination with steroids and antilymphocyte globulin (ATG) until 1980, cyclosporine A (CyA) and steroids after 1980, with the addition of azathioprine and monoclonal ATG (OKT3; Orthoclone, Raritan, NJ) as needed for the treatment of acute rejection episodes. Thirty-six of these patients (78.3%) had some form of surgery related to PTLDs (Fig 1a). The Epstein-Barr virus (EBV) and herpes simplex virus (HSV) status were checked in almost all the patients. In well studied patients, the association of EBV and PTLD was almost universal.[1-5]

## RESULTS

The condition was diagnosed an average of 17 months after the transplant (range, 0.75-153 months, median 4 months). The organ or organ-systems involved were lymph nodes (including tonsils) in 30 patients (65.2%), gastrointestinal tract in 15 patients (32.6%), homograft liver in 9 (19.6%), other solid organs in 11 (23.9%), and other sites in 4 (8.7%) (Fig 2a).

In 18 patients (39.1%) the tumors had a nonclonal character, in 14 patients (30.4%) clonal, while in 14 patients (30.4%) the character of the PTLD was mixed or could not be determined with accuracy (Fig 2b).

The EBV status was positive for primary infection or reactivation of old disease at the time of the PTLD in 40 patients (87%), negative in 2 patients (4.3%), and unknown in 4 (8.7%) (Fig 2c).

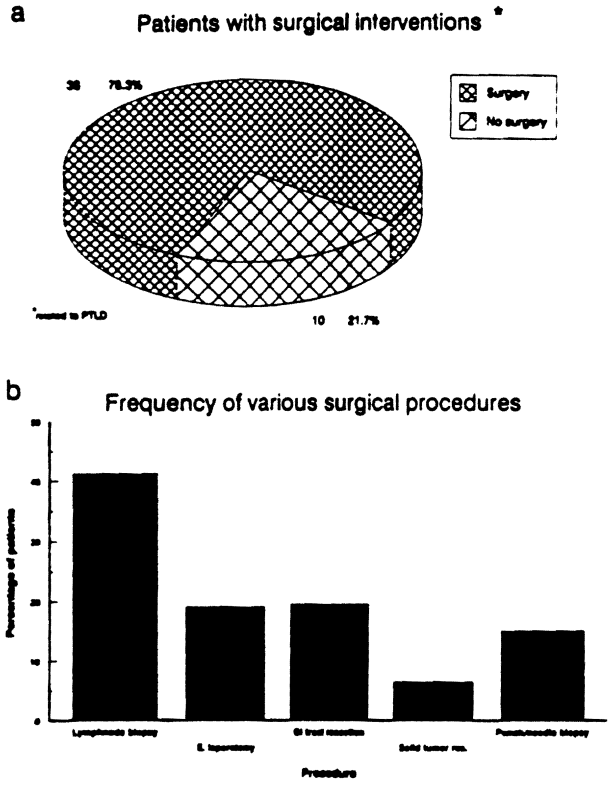


Fig 1.

Thirty-six patients (78.3%) had some surgical procedure related to PTLDs: 19 patients (41.3%) had a superficial lymph node biopsy, 5 patients (19.2%) had exploratory laparotomy, 9 patients (19.6%) had some gastrointestinal tract resection, 3 patients (6.5%) had resection of a solid tumor (including one patient who had a native nephrectomy), and 7 patients (15.2%) had punch or needle biopsy

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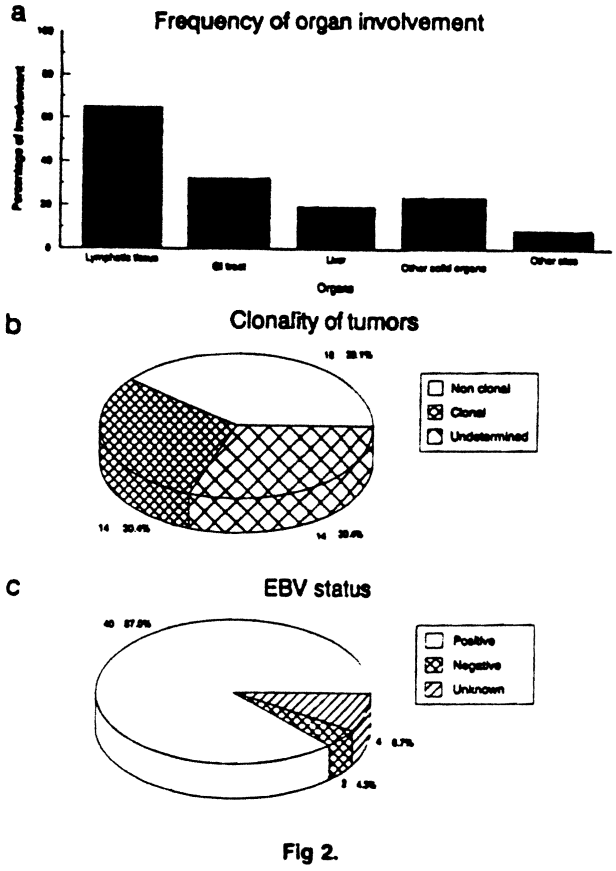


Fig 2.

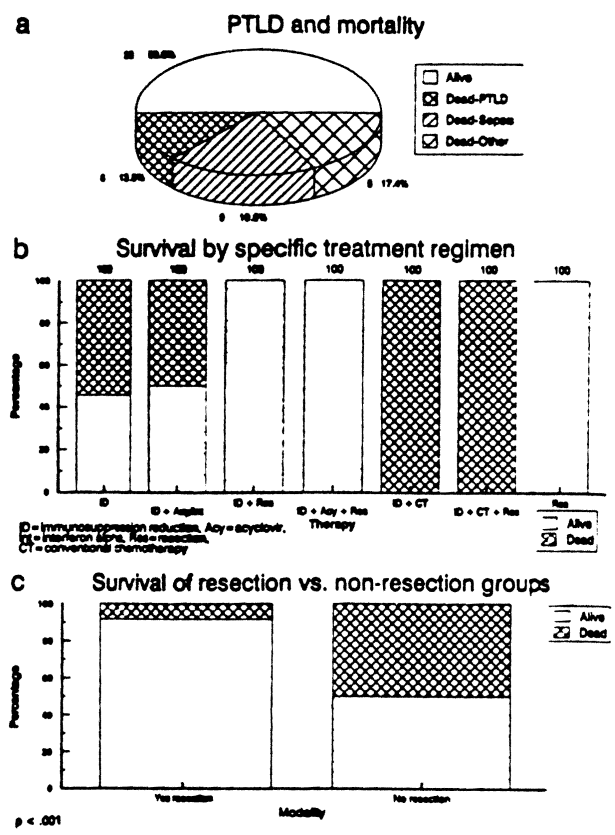


Fig 3.

(Fig 1b). Some of these patients had more than one procedure.

Although there was a total of 23 deaths (50%) in this group, only 6 patients (13%) died as a direct result of the PTLD, and none of the deaths could be attributed to the surgical intervention itself. Nine patients (19.6%) died of sepsis, and 8 patients (17.4%) died of various other causes (for eg, cardiorespiratory arrest, multiple organ failure, hemorrhage, and drowning in one patient) (Fig 3a). None of these 17 patients had evidence of PTLD at the time of their death. All survivors are apparently free of disease at the present time.

Eleven patients (23.9%) were treated by decreasing their immunosuppressive drug dosages (one also received alpha-interferon [$\alpha$-IFN]) and 5 (45.5%) are still alive. Twelve patients (26.1%) had their immunosuppressive drugs decreased, as well as high dose acyclovir or $\alpha$-IFN therapy: 6 (50%) are still alive. Five patients (10.7%) were treated with a decrease of their immunosuppression combined with resection of at least one tumoral mass and all (100%) survived. Five patients (10.7%) were treated with immunosuppression reduction, high dose acyclovir, and resection: they are all alive (100%). One patient (2.2%) had immunosuppression reduced and conventional chemotherapy without survival. One patient (2.2%) was treated with immunosuppression reduction, conventional chemotherapy, and resection: she survived tumor-free for 5 years, but died of sepsis 6 years after OLT. Finally one patient (2.2%) was only treated with resectional therapy and survived (Fig 3b). Ten patients (21.7%) were diagnosed as having PTLD only at the postmortem examination.

## DISCUSSION

It is now quite clear that PTLDs are the end result of the modifications caused by the antirejection therapy on the host immune system. All major immunosuppressive drugs (CyA, azathioprine, antilymphocytic globulin preparations, and monoclonal antibodies) have been implicated.[2-4,8] The mechanisms known or presumed to be implicated in the development of PTLDs have been extensively studied.[1,2,9]

Two factors complicate the management: (1) since PTLDs are a result of overimmunosuppression, treatment with conventional antineoplastic chemotherapy could accelerate the process; and (2) the reduction or discontinuation of the immunosuppression, with the purpose of reestablishing the host defenses may result in graft rejection. The essence of management is to allow enough immune reconstitution to permit oncologic surveillance to be established, while maintaining graft function. The balance may be favorably altered by treatment with acyclovir, since the tumors have a viral etiology.[10,11]

Surgical intervention in transplant patients who develop

PTLDs is done either for diagnostic or therapeutic purposes.

Diagnostic biopsies were performed in 21 patients. In addition, clinical criteria (high index of suspicion, lymphadenopathy by CT scan, elevated uric acid levels[1]) were also taken into consideration. Biopsies allow both accurate diagnosis and classification[1,7] of the lesions, with the polyclonal disorders having a better prognosis.[1,2,7]

In nine patients, the surgical intervention had a therapeutic purpose. This was either intended as a primary resection of involved tissue with the goal of eradicating residual tumor or as a means of dealing with PTLD complications. Small bowel perforation was characteristic in patients with gastrointestinal involvement. The perforations commonly occurred during the early remission phase, presumably when transmural lesions were undergoing necrosis.

The accepted treatment of PTLDs is a reduction or temporary suspension of the immunosuppressive regimen, coupled with adjunctive chemotherapy with acyclovir. The early attempts at treatment with conventional antineoplastic chemotherapy lead to worsening of the patients' condition and death.[5] This is easily explainable on basis of the theory that the posttransplant lymphoproliferative disorders are the result of immunosuppression. Conventional chemotherapy adds its immunosuppressive effect to that of the antirejection therapy, thus preventing the body's defenses from successfully fighting the EBV-triggered neoplastic process. The underlying theme in patients with PTLD is thus an overimmunosuppressed status. This not only results in the lymphoproliferative disorder itself, but also leads to frequently lethal septic complications. In fact, sepsis was the most frequent cause of immediate or delayed death in our group.

Isolated visceral tumors can behave like ordinary gastrointestinal lymphomas, in the sense that an adequate local resection can be curative in many patients, even if the tumor has not regressed with reduction of the immunosuppression and acyclovir. Patients with these tumors have benefited from aggressive surgical resection: 12 of 24 patients treated only medically (50%) survived as compared with 11 of 12 (91.7%) treated with a combination of medical manipulation and surgical resection ($P < .001$) (Fig 3c). Thus surgery emerges as a very powerful tool in the treatment of PTLDs.

If operation is not performed in such cases, high index of suspicion and careful monitoring are necessary in order to diagnose early the occurrence of perforation. The patient is probably not "safe" until the complete disappearance of the mass has been documented by CT scan or endoscopy.

Tonsillar involvement has been frequent in the pediatric age group: consequently, tonsillectomy often has been the means for diagnosing PTLD in children. However, the danger of postoperative edema with acute respiratory distress dictates that only a unilateral tonsillectomy should be performed if the procedure is primarily for diagnostic purposes. Now that the disease can be treated so well by medical means, tonsillectomy is not often indicated any longer.

The mortality of liver transplant recipients with PTLDs has been higher than that for kidney transplant recipients[1,5,7]: higher immunosuppressive drug doses, more generalized organ involvement, and above all, deterioration of a vital graft without artificial organ support account for this difference.

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