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REVERSIBILITY OF LYMPHOMAS AND LYMPHOPROLIFERATIVE LESIONS DEVELOPING UNDER CYCLOSPORIN-STEROID THERAPY

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Summary

Post-transplant lymphomas or other lymphoproliferative lesions, which were usually associated with Epstein-Barr virus infections, developed in 8, 4, 3, and 2 recipients, respectively, of cadaveric kidney, liver, heart, and heart-lung homografts. Reduction or discontinuance of immunosuppression caused regression of the lesions, often without subsequent rejection of the grafts. Chemotherapy and irradiation were not valuable. The findings may influence policies about treating other kinds of post-transplantation neoplasms.

Introduction

AN increased incidence of malignancy, with a disproportionate representation of lymphoreticular tumours, has for 15 years been a well-recognised complication of immunosuppression in organ transplant recipients.^{1,2} The dimensions of the hazard have been followed by Penn³ through a registry to which transplantation surgeons throughout the world have contributed. Meanwhile, evidence has accumulated that lymphomas in patients with natural or iatrogenic immunodeficiency may be associated with infection by the Epstein-Barr virus.⁴ The ominous implications of the term lymphoma have been softened by calling such tumours “pseudolymphomas”⁵ or “lymphoproliferative disorders”.⁶

In this communication, we describe how lymphoproliferative neoplasms that developed under therapy with cyclosporin and steroids in renal, hepatic, and cardiac graft recipients, underwent resolution if immunosuppression was reduced or stopped—in contrast to a lethal course no matter what else was done in the absence of this simple step. The observations have shown that the much publicised cyclosporin lymphomas are relatively innocuous if appropriately treated.

Methods

Case Material

17 recipients of various organs had lymphoproliferative disorders two to sixty-eight months after cadaveric organ transplantation (table I). The patients were 13 to 62 years old at the time

of transplantation and had a male/female distribution of 13/4. Donor-recipient tissue matching was completely random for the non-renal transplantations and nearly so in the renal cases.

The incidence of the lymphoproliferative complications varied with the kind of transplant. Between December, 1979, and June 1, 1983, 315 patients were treated with primary or repeat renal transplantation, of whom 8 (2.5%) had lymphoproliferative complications. In addition, 129, 48, and 6 patients were treated with primary liver, heart, and heart-lung transplantations, respectively, and in these organ subgroups there were 3, 3, and 2 lymphoproliferative complications—an incidence in the respective non-renal organ graft categories of 2.3%, 6.3%, and 33.3%. Lymphoid lesions subsequently developed in a fourth liver recipient whose therapy with azathioprine was changed to cyclosporin 5 years after transplantation.

For the kidney recipients immunosuppression was with cyclosporin and prednisone, as previously described;⁷ 3 of the 4 liver recipients were treated similarly.⁸ The other liver recipient (case 9) had had a transplantation on Aug 31, 1977, under azathioprine, prednisone, and antilymphocyte globulin (ALG); she was switched to cyclosporin and low doses of prednisone in September, 1981, because of recurrence in her graft of the chronic active hepatitis that had destroyed her native liver.

In addition to cyclosporin and prednisone, 1 of the heart and 1 of the heart-lung recipients were given antithymocyte globulin (ATG) (table I); both of the heart-lung recipients were treated also with azathioprine (table I).

In several cases the lymphoproliferative lesions gave rise to gastrointestinal perforation, obstruction, or haemorrhage (table I). Generalised lymphadenopathy and fever were common in a syndrome indistinguishable from infectious mononucleosis. 3 patients (1 kidney, 1 liver, and 1 heart recipient) were not diagnosed until necropsy, but in the liver recipient (case 10, table I) a cervical lymph node biopsy specimen taken three months before death contained a typical lymphoproliferative lesion that was incorrectly diagnosed as non-specific reactive hyperplasia. The organs known to have been involved in each patient are summarised in table I.

Infectious Disease Studies

Serological evidence of active infection with the Epstein-Barr virus (EBV) was found near the time of the lymphoproliferative complication in 15 (88%) of the 17 patients (table II). Although Epstein-Barr virus nuclear antigen (EBNA) was demonstrated in only 6 of 12 tumour specimens in which the appropriate touch preparation tests were obtained (table II), 7 of 8 tumours examined by DNA hybridisation studies contained EBV genomes including 3 that had negative EBNA touch preparations. The diagnosis of active EBV infection in 88% of these patients was about four times more frequent than documented by Ho et al⁹ in transplant patients (Pittsburgh experience) who did not have lymphoproliferative complications. Primary and reactivation EBV infections were almost equally represented.

Other infections were catalogued that occurred just before, or at the time of, the lymphoproliferative complication (table I). 8 of the 17 patients had no other infections and another 3 had only *Herpes simplex*. 6 of the 17 patients had severe contemporaneous infections which in 4 cases were a major factor in their deaths (table I).

Histopathological Studies

Formalin-fixed paraffin-embedded tissue was available for light microscopy in all 17 cases. Lymphomas were independently classified by 3 of the authors (M. A. N., R. J., and K. A. P.) in accordance with the National Cancer Institute's working formulation of non-Hodgkin's lymphomas.¹⁰ Sections were also stained for cytoplasmic immunoglobulin light and heavy

chains by the avidin-biotin-peroxidase complex method of Hsu¹¹ with pronase digestion. Rabbit antisera specific for gamma, mu, delta, kappa, and lambda chains of immunoglobulins were obtained from Dakopatts, A/S Copenhagen, Denmark. Rabbit antisera specific for J chain and alpha chain came from Nordic Laboratories, Tilburg, the Netherlands. The specificity and optimum dilution of each antiserum were tested by double diffusion in agar and immunoelectrophoresis and by use of specimens with plasmacytic monoclonal proliferation of known light and heavy chains. Sections were also stained for α_1 -antitrypsin and albumin.

Frozen tissue was available in 12 cases and was used for the detection of EBNA by the anti-complement immunofluorescence technique.⁹ In 5 cases, specimens were taken for electron-microscopy. These were fixed in 2% glutaraldehyde, post-fixed in osmium, and embedded in epoxy resin.

Clonality of tumours was assessed by kappa:lambda light chain ratios independently determined in two separate laboratories by M. A. N. and K. A. P. A kappa:lambda ratio of 5:1 or greater was considered indicative of monoclonal kappa proliferation. Conversely, a lambda:kappa ratio of 3:1 or greater implied monoclonal lambda proliferation.

Results

Nature of the Lesions

By conventional histopathological criteria, 15 patients were diagnosed as having non-Hodgkin's diffuse malignant lymphoma. Of these, 11 were classified as large cell noncleaved, 3 as large cell immunoblastic, and 1 could not be further defined. The other 2 patients had atypical lymphoproliferation characterised by a predominance of plasma cells (table III).

11 of the 15 lymphomas and both atypical lymphoproliferations were of B cell origin as judged by immunoglobulin staining; in 4 lymphomas, immunoglobulins could not be demonstrated. Of the lymphomas, 3 were exclusively monoclonal, 4 were exclusively polyclonal, and 2 patients with several lymphoma nodules had both monoclonal and polyclonal lesions. 6 lymphomas could not be assessed because insufficient cells stained for light chains. Both patients with lymphoproliferation had polyclonal lesions (table III).

No viral particles were detected by electron microscopy in the 5 cases studied.

Response to Therapy, Patient Survival, and Graft Function

Renal recipients—1 patient (case 2) who died of pneumonitis with a functioning graft had multifocal lymphomatous lesions at necropsy. The 7 patients in whom the diagnosis was made from biopsy specimens are alive and all are thought to be tumour-free. They had in common the reduction or discontinuance of immunosuppression (table I). In 4 of the 7, no chemotherapy or irradiation was used; 2 of these patients had monoclonal tumours. Only 1 of the 7 surviving patients was treated with acyclovir.

2 patients (cases 5 and 6) were treated with multiple chemotherapeutic agents (table I) and another (case 4) had 5400 rad cervical irradiation. Although the patients survived, we judge in retrospect that the decisions to use chemotherapy or irradiation may have been erroneous.

5 of the 7 patients who survived had operations to relieve the complications of bowel perforation (5 instances) or prostatic obstruction (one instance) caused by the lymphoproliferative disorders. In 3 of these patients whose immunosuppression was reduced or stopped, no remaining tumour could be found at reoperation 2½ to 5½ weeks later (cases 5–7). In 2 other patients (cases 4 and 8) with similar reductions of immunosuppression, no

residual tumour could be found at repeat cervical node or endoscopic gastric biopsy after 3 and 4 weeks.

The renal grafts on of the 7 survivors were rejected 1 week to 1 year after the reduction of immunosuppression. The kidneys of the other 4 recipients are functioning perfectly seven, seventeen, twenty-eight, and forty-three months later under low dose maintenance therapy with cyclosporin and prednisone.

Liver recipients—The patient (case 10) in whom the diagnosis of a lymphoproliferative tumour in a cervical node biopsy was missed eight months after transplantation, died in another hospital three and a half months later of airway obstruction, a few minutes after indirect laryngoscopy. Changes in immunosuppression had not been made. At necropsy the mesenteric and retroperitoneal nodes proved to contain the same kind of lymphoid tissue as had been present in the neck three months earlier. The diagnosis was plasma-cytoid B cell hyperplasia (table III). The patient had been intermittently febrile for several months during which liver function had been normal.

The diagnosis of a lymphoproliferative disorder was made from biopsy specimens in the other 3 liver recipients, and the only treatment change was reduction of the cyclosporin and steroid doses (table I). 1 of these 3 patients (case 9), whose diagnosis was made by incomplete removal of a mass in the right kidney plus biopsy of a cervical lesion, had slow deterioration of hepatic function necessitating retransplantation after four and a half months. There was only microscopic evidence of residual lymphoma then and at necropsy 3 weeks later after the patient had died of haemorrhagic pancreatitis and multiple other postoperative complications.

A patient (case 11) from whom five lymphoma-containing segments of bowel were removed at operation for intestinal obstruction had a rejection four months after the major reductions of immunosuppression shown in table I, but this was reversed with intensified therapy and he remains well and tumour-free more than a year after the diagnosis of the lymphoproliferative complication. Another patient (case 12) recovered promptly after ileocelectomy for multiple tumours and bileduct reconstruction for partial biliary obstruction. With much lower doses of cyclosporin and prednisone (table I) there has been no rejection and she is thought to be tumour-free.

Heart or heart-lung recipients—Multifocal lymphomas were found at necropsy in a heart recipient (case 13) who died of cytomegalovirus pneumonitis. The other 4 patients had lymphoproliferative complications diagnosed during life from biopsy of enlarged cervical or inguinal lymph nodes or from a tonsillectomy specimen. One of these patients (case 16), a heart-lung recipient, later had perforation of the ileum from the same lymphoproliferative process. The perforation was not diagnosed for several days and, despite emergency intestinal resection, he died of abdominal infection. Widespread infection also caused the death of a heart recipient (case 14) who was given chemotherapy, regional irradiation, and acyclovir in preference to reduction of immunosuppression. The chemotherapy caused profound bone marrow depression. In both the foregoing heart and heart-lung recipients who died of widespread infection, residual lymphoproliferative foci were present in lymph nodes and/or the gastrointestinal tract. Many of these lesions had areas of necrosis. The transplanted organs which functioned until death had minor signs of rejection.

A heart and heart-lung recipient each had tumour involution, the former (case 15) after conclusion of a course of ALG and reduction of cyclosporin and prednisone doses, and the latter (case 17) when the cyclosporin dose was drastically reduced (table I). No other treatment was given to the heart recipient. The heart-lung recipient had a course of acyclovir. Neither patient has had signs of rejection in the subsequent eight and four months.

Discussion

There is no reason to believe that the neoplasms in this report differ essentially from the post-transplantation “lymphomas” or “reticulum cell sarcomas”, arising with conventional immunosuppression, that were compiled in the Denver Registry³ (now located in Cincinnati) or in the University of Minnesota collection of “lymphoproliferative disorders”.⁶ By the National Cancer Institute classification,¹⁰ most of the lesions were B cell malignant lymphomas of diffuse large cell type; 2 were atypical B cell proliferations. 6 of the neoplasms were considered polyclonal and 3 monoclonal, and 2 further cases exhibited both types of clonality. Our criterion for kappa monoclonality was a kappa:lambda ratio of 5:1 or greater and for lambda monoclonality a lambda:kappa ratio of 3:1 or greater. However, there is no generally accepted standard for the diagnosis of monoclonality of lymphomas when the cytoplasmic immunoglobulin staining technique is used. Some investigators insist that the tumour population must stain exclusively for one light chain and/or heavy chain.¹² Others regard the tumour as monoclonal if the number of cells expressing the predominant light chain type is more than five times the number of cells expressing the other light chain type.¹³ Levy et al¹⁴ have used kappa:lambda and lambda:kappa surface immunoglobulin ratios of 3:1 and 2:1 as the dividing line. For clonality to be firmly established, other investigations such as hybridisation studies with DNA light chain probes need to be done, as have been reported by Cleary et al.¹⁵ These are being attempted on some of our specimens.

We have long recommended drastic reduction or discontinuance of immunosuppression in patients with post-transplantation lymphomas or other explosively growing neoplasms.^{5, 16–18} The concept of treatment withdrawal has not been accepted or applied widely for the reasons most clearly enumerated and defended by Simmons and Najarian.¹⁹ However, their approach, in which surgical extirpation, irradiation, chemotherapy, and most recently the antiviral drug acyclovir are the principal therapeutic tools, has had an overwhelming mortality.⁶

In contrast, the simple expedient herein reported of stopping or reducing immunosuppression in patients being treated with cyclosporin and prednisone has led to prompt and seemingly permanent resolution of lymphoproliferative tumours—provided that complications such as intestinal perforation or infection could be controlled. The only patients among 12 kidney or liver recipients whose lymphoproliferative lesions were not controlled were 2 (1 in each recipient category) who were not appropriately treated because of failure to make the diagnosis. We speculate that accidental and unknowing reversal of lymphoproliferative lesions may be a common event after transplantation since most renal transplant surgeons stop or greatly reduce immunosuppression if a patient becomes febrile and ill—an action that could not be better designed to abort an occult lymphoma.

The complete disappearance of lymphoproliferative tumours on withdrawal of immunosuppression is not a special feature of cyclosporin-steroid therapy. The same thing was described long ago after reduction or withdrawal of azathioprine, prednisone, and antilymphocyte globulin^{16,17} and documented in detail by Iwatsuki et al¹⁸ and Geis et al.⁵ Of the 5 patients reported by Geis⁵ and Iwatsuki¹⁸ and their associates whose lymphomas regressed, 1 later acquired a different neoplasm and the other 4 remained tumour free.²⁰

As with kidney and liver recipients, the only survivors among the 5 heart or heart-lung recipients in the present series were 2 who had withdrawal of immunosuppression. In 1 of the other 3, the diagnosis was not made until necropsy. A missed intestinal perforation and overwhelming infection precluded survival in another, and the third had continuation of cyclosporin and steroid plus treatment with chemotherapeutic agents which themselves can be immunosuppressive and toxic and which are probably contraindicated.

It is noteworthy with all three of the organs that reduction or even suspension of immunosuppression for long periods was not necessarily accompanied by irreversible transplant rejection. Most of the grafts were rescued along with the patients, as would have been expected if the development of a lymphoproliferative complication was presumptive evidence of over-immunosuppression. This observation should encourage further trials of this approach in liver or cardiac recipients, despite the natural apprehension that the penalty of treatment withdrawal might be a lethal rejection of the graft.

A popular hypothesis^{4,21} has been that lymphomatous neoplasms develop when B lymphocytes that are infected with Epstein-Barr virus are liberated by efficient immunosuppression from the control of one or more kinds of T lymphocytes, allowing uninhibited proliferation. The theory continues that one of the rapidly multiplying B clones can undergo a chromosomal translocation, making it an autonomous monoclonal malignancy not easily influenced by immunological reconstitution or other therapy.^{6,21} Whether such translocations occurred in the tumours described here is under study. However, it should be noted that in our series several seemingly monoclonal lesions involuted as readily as the polyclonal neoplasms.

The association of the lymphomas in our cases with an EBV infection was the same as that reported by Hanto et al⁶ from the University of Minnesota. However, the principle of treating a malignancy by allowing recovery from immunosuppression may have application beyond EBV-induced neoplasms—as has been suggested by observations with multifocal Kaposi's sarcoma, a, cytomegalovirus associated tumour.²² 2 of our renal recipients whose cyclosporin-steroid therapy was drastically reduced have had stabilisation or complete reversal of multifocal Kaposi tumours without loss of graft function; the longest follow-up with a complete “cure” is almost 2 years.²³ The way in which tumours develop under immunosuppression and can be reversed by a reduction or cessation of therapy should provide insight into, and encouragement for trial of immunostimulation techniques in treating, natural acquired immunodeficiency syndromes (AIDS).

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REFERENCES

1. Starzl TE. Discussion of Murray JE, Wilson RE, Tilney NL, et al. Five years' experience in renal transplantation with immunosuppression: survival, function, complications and the role of lymphocyte depletion by thoracic duct fistula. *Ann Surg* 1968;168:416–35. [PubMed: 4175449]
2. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969;1:106–12. [PubMed: 4944206]
3. Penn I. The price of immunotherapy. *Curr Probl Surg* 1981;18:681–751. [PubMed: 6797793]
4. Klein G, Purtilo D. Summary: symposium on Epstein-Barr virus induced lymphoproliferative diseases in immunodeficient patients. *Cancer Res* 1981;41:4302–04. [PubMed: 6272974]
5. Geis WP, Iwatsuki S, Molnar Z, Giacchino JL, Kerman RH, Ing TS, Hano TE. Pseudolymphoma in renal allograft recipients. *Arch Surg* 1978;113:461–66. [PubMed: 205191]
6. Hanto DW, Gajl-Peczalska KJ, Frizzera G, Arthur DC, Balfour HH Jr, McClain K, Simmons RL, Najarian JS. Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative disease occurring after renal transplantation. *Ann Surg* 1983;198:356–69. [PubMed: 6311121]

7. Starzl TE, Klintmalm GBG, Weil R III, Porter KA, Iwatsuki S, Schroter GP, Fernandez-Bueno C, MacHugh N. Cyclosporin-A and steroid therapy in 66 cadaver kidney recipients. *Surg Gynecol Obstet* 1981;153:486–94. [PubMed: 6269238]
8. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. *Hepatology* 1982;2:614–36. [PubMed: 6749635]
9. Ho M, Wajszczuk CP, Hardy A, Dummer JS, Starzl TE, Hakala TR, Bahnson HT. Infections in kidney, heart and liver transplant recipients on cyclosporin. *Transplant Proc.* in press.
10. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112–35. [PubMed: 6896167]
11. Hsu S-M, Raine L, Fanger H. Use: of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: A comparison between ABC and unlabeled antibody (PAP) procedures. *J Histochem Cytochem* 1981;29:577–80. [PubMed: 6166661]
12. Saraga P, Hurimann J, Ozzello L. Lymphomas and pseudolymphomas of the alimentary tract. An immunohistochemical study with clinicopathologic correlations. *Hum Pathol* 1981;12:713–23. [PubMed: 7286968]
13. Halper JP, Knowles DM, Wang CY. Ia antigen expression by human malignant lymphomas: Correlation with conventional lymphoid markers. *Blood* 1980;55:373–82. [PubMed: 6766752]
14. Levy N, Nelson J, Meyer P, Lukes RJ, Parker JW. Reactive lymphoid hyperplasia with single class (monoclonal) surface immunoglobulin. *Am J Clin Pathol* 1983;80:300–08. [PubMed: 6410903]
15. Cleary M, Warnke R, Sklar J. Monoclonality of B-lymphocyte proliferations in cardiac transplant recipients: clonal analysis based on immunoglobulin gene rearrangement. *N Engl J Med* 1984;310:477–82. [PubMed: 6363929]
16. Starzl TE, Penn I, Halgrimson CG. Immunosuppression and malignant neoplasms. *N Engl J Med* 1970;283:934. [PubMed: 4917727]
17. Starzl TE, Penn I, Putnam CW, Groth CG, Halgrimson CG. Iatrogenic alterations of immunologic surveillance in man and their influence on malignancy. *Transplant Rev* 1971;7:112–45. [PubMed: 4401720]
18. Iwatsuki S, Geis WP, Molnar Z, Giacchino JL, Ing TS, Hano JE. Systemic lymphoblastic response to antithymocyte globulin in renal allograft recipients. An initial report. *J Surg Res* 1978;24:428–34. [PubMed: 349267]
19. Simmons RL, Najarian JS. Immunosuppression and malignant neoplasms. *N Engl J Med* 1970;283:934–35. [PubMed: 4917728]
20. Kheirbeck AO, Molnar ZV, Choudhury A, Geis WP, Daugirdas JT, Hano JE, Ing TS. Malignant lymphoma in a transplant recipient treated with antithymocyte globulin. *Transplantation* 1983;35:267–68. [PubMed: 6340279]
21. Bird, AG. Cyclosporin A, lymphomata and Epstein-Barr virus. In: White, DJG., editor. *Cyclosporin A*. Elsevier Biomedical; Amsterdam: 1982. p. 307-15.
22. Harwood AR, Osoba D, Hofstader FL, Goldstein MB, Cardella CJ, Holecek MJ, Kunynetz R, Giammarco RA. Kaposi's sarcoma in recipients of renal transplants. *Am J Med* 1979;67:759–65. [PubMed: 159624]
23. Little PJ, Farthing CF, Alkhader A, Bunuan H, Haleem A. Kaposi's sarcoma in a patient after renal transplantation. *Postgrad Med J* 1983;59:325–26. [PubMed: 6348721]

TABLE I

ORGAN RECIPIENTS WITH LYMPHOPROLIFERATIVE COMPLICATIONS

Case	Sex	Age (yr) at Tx	Date of Tx	Time (mo) "lymphoma" after Tx	Organs involved	Clinical presentation	Contemporaneous infection	Original immunosuppression	Change in immunosuppression		Acyclovir	Other anti-tumour treatment	Fate of patient	Graft function
									CyA (mg/kg/day)	Pred (mg/day)				
Kidney recipients														
1	F	25	Jan 31, 1980	5	Ileum	Perforation of ileum (resected)	None	TDD, CyA, Pred	16→6	10→10	No	None	Alive, tumour-free	Retained to date
2	M	28	Feb 19, 1980	4½	Liver, spleen, heart, retroperitoneal lymph nodes (autopsy findings)	Fever	<i>Pneumocystis carinii</i> pneumonia	CyA, Pred	14→14	25→20	No	None	Died June 8, 1980	Functioned until death
3	M	20	April 15, 1981	6	Ileum, small bowel mesentery	Perforation of ileum (resected)	None	CyA, Pred	18→9	20→10	No	None	Alive, tumour-free	Retained to date
4	M	52	May 4, 1982	3	Submandibular gland	Fever, adenopathy	<i>Herpes simplex</i>	CyA, Pred	11→2	20→15	No	5400 rad cervical irradiation	Alive, tumour-free	Retained to date
5	M	56	Feb 10, 1982	6	Prostate, ileum	Prostatic obstruction (TUR) & perforation of ileum (resected)	None	CyA, Pred	8→2	15→15	No	Doxorubicin, cyclophosphamide, vincristine; chemotherapy cancelled halfway through	Alive, tumour-free	Rejected 1 yr later
6	M	30	July 10, 1982	4	6 sites in small bowel	Perforation of ileum (resected)	<i>Herpes simplex</i>	CyA, Pred	10→0	15→15	No	Doxorubicin, cyclophosphamide, vincristine	Alive, tumour-free	Rejected in 2 wk
7	M	16	Dec 12, 1982	3½	Multiple sites in small bowel	Perforation of ileum (resected)	None	CyA, Pred	8→0	15→15	2 wk	None	Alive, tumour-free	Rejected in 1 wk
8	F	62	March 14, 1983	4½	Stomach	GI bleeding (biopsied)	<i>Herpes simplex</i>	CyA, Pred	8→1	15→15	No	None	Alive, tumour-free	Retained to date
Liver recipients														
9	F	13	Aug 31, 1977	68	Cervical nodes, right kidney	Renal mass (resected)	None	Az, pred, ALG, CyA from Sept 29, 1981	8→2	15→10	No	None	Died Sept 1, 1983, after retransplantation, microscopic tumour	Slowly failed, retransplantation
10	M	20	Dec 1, 1982	8	Cervical, mesenteric, retroperitoneal nodes	Fever, tonsillitis	None	CyA, Pred	6→6	10→10	No	None	Died Dec 13, 1982, airway obstruction after ENT exam	Functioned until death
11	M	17	May 9, 1982	5	Small bowel (multiple)	Fever, small intestinal obstruction (resected)	None	CyA, Pred	20→3	25→10	No	None	Alive, tumour-free	Retained to date after rejection
12	F	21	March 20, 1983	6	Ileum and colon (multiple)	Fever, vague intestinal symptoms (resected)	*Cholangitis, fungal pneumonia	CyA, Pred	13→5	10→7.5	No	None	Alive, tumour-free	Retained isolate
Heart (cases 3-15) and heart-lung (cases 16, 17) recipients														
13	M	51	Sept 27, 1982	7	Lung, adrenal	Fever, lung lesions	CMV pneumonia	CyA, Pred	6→6	20→20	Yes	None	Died April 13, 1983, CMV pneumonia	Functioned until death
14	M	22	Nov 1, 1981	6	Cervical nodes, pharynx, lungs	Cervical mass	Pneumonia	CyA, Az, Pred	8→8	20→20	Yes	Cyclophosphamide, vincristine, procarbazine, irradiation	Died Oct 27, 1982, pancreatitis, sepsis	Functioned until death
15	M	20	Jan 20, 1983	3	Inguinal nodes	Inguinal mass	Gastroenteritis	CyA, Pred, ATG	21→13	30→25	No	None	Alive, tumour-free	Retained to date
16	M	20	Jan 21, 1983	4	Cervical nodes, ileum	Cervical mass	Systemic crypt abscesses	CyA, Az, Pred	8→2	20→15	Yes	None	Died June 24, 1983, ileal perforation	Functioned until death
17	M	22	May 25, 1983	2	Tonsils	Tonsillitis	CMV	CyA, Az, Pred, ATG	12→3	20→20	Yes	None	Alive, tumour-free	Retained to date

Tx = transplantation; CyA = cyclosporin; TDD = thoracic duct drainage; Pred = prednisone; Aza = azathioprine; ALG = antilymphocyte globulin; ATG = antithymocyte globulin; CMV = cytomegalovirus; TUR = transurethral resection.

TABLE II

EPSTEIN-BARR VIRUS

–	Kidney	Liver	Heart or heart-lung	Total cases
Serological evidence of active				
EBV infection *	6/8	4/4	5/5	15/17
Primary	3	2	2	7
Reactivation	3	2	3	8
None	2 [†]			2
Tissue EBNA	1/5	2/2	3/5	6/12

EBNA: Epstein-Barr virus nuclear antigen, looked for by immunofluorescent staining on touch preparations and frozen tissue sections. The 50% incidence of positive touch preparations was falsely low. EBV genomes were demonstrated in 7 of 8 tumours (including 3 touch preparation negative) that were examined with DNA hybridisation techniques by J. Pagano (University of North Carolina), G. Miller (Yale), or M. A. Epstein (Bristol).

* In all 17 cases, sera were obtained before or at transplantation and at least at monthly intervals after transplantation. Primary infection was defined as serological conversion from a seronegative state for IgG against EBV virus capsid antigen (VCA) after transplantation to a seropositive state. Reactivation infection represented a four-fold or greater serological rise of IgG anti-VCA. Primary and reactivation infections occurred before or around the time of tissue diagnosis of a lymphoproliferative lesion.

[†] Evidence of old infection, but reactivation not clearly demonstrated.

TABLE III
PATHOLOGICAL FEATURES OF LYMPHOMAS AND LYMPHOPROLIFERATIONS

Case	Histological diagnosis	Light chain ratio			Clonality	Predominant heavy chain	EBNA
		Kappa/lambda	Lambda/kappa	Lambda/kappa			
1	ML large cell, immunoblastic	6:0	0:2	Monoclonal kappa	Alpha	ND	
2	ML large cell, immunoblastic	100	<0:1	Monoclonal kappa	Mu	ND	
3	ML diffuse large cell noncleaved	1:9	0:5	Polyclonal		+	
4	ML diffuse large cell noncleaved	(-)		Indeterminate		-	
5	ML diffuse unclassified	(-)		Indeterminate		-	
	ML diffuse mixed small & large cell	(-)					
6	ML diffuse large cell noncleaved	0:3	3:6	Nodule 1: monoclonal lambda	Alpha	-	
		1:9	0:5	nodule 2: polyclonal			
7	ML large cell, immunoblastic	<0:1	11:6	Nodule 1: Monoclonal lambda	Gamma	-	
		1:5	0:7	nodule 2: polyclonal			
	Healing and chronic active ulcers	<0:1	6:0	Nodule 1: Monoclonal lambda	Gamma		
		1:2	0:8	nodule 2: polyclonal			
8	ML diffuse large cell noncleaved	(-)		Indeterminate		ND	
9	ML diffuse large cell noncleaved	1:5	0:7	Polyclonal		+	
10	Plasmacytoid B-cell hyperplasia	0:9	1:1	Polyclonal		ND	
	Plasmacytoid B-cell hyperplasia	(-)		Indeterminate			
11	ML diffuse large cell noncleaved	0:8	1:2	Polyclonal		ND	
12	ML diffuse large cell noncleaved	(-)		Indeterminate		+	
13	ML diffuse large cell noncleaved	(-)		Indeterminate		+	
14	ML diffuse large cell noncleaved	(-)		Indeterminate		+	
	ML large cell, immunoblastic	(-)					
15	Plasmacytoid B-cell hyperplasia	0:9	1:1	Polyclonal		-	
16	ML diffuse large cell noncleaved	8:8	0:1	Monoclonal kappa	Gamma	-	
	ML diffuse large cell unclassified	5:5	0:2	Monoclonal kappa	Gamma		
	ML diffuse unclassified	(-)		Indeterminate			
17	ML diffuse large cell noncleaved	1:3	0:7	Polyclonal		+	

ML = malignant lymphoma; (-)=insufficient data; ND=not done.