Reprint from

The Nature, Cellular, and Biochemical Basis and Management of Immunodeficiencies

Symposium Bernried, West Germany
21st – 25th September, 1986

Editors:

Robert A. Good
Elke Lindenlaub

With 107 figures
and 132 tables

F. K. SCHATTAUER VERLAG · STUTTGART – NEW YORK

Control of Post-Transplant Lymphoproliferative Disorders and Kaposi's Sarcoma by Modulation of Immunosuppression*

LEONARD MAKOWKA[1], MICHAEL NALESNIK[4], ANDREI STIEBER[1], ANDREAS TZAKIS[1], RONALD JAFFE[5], MONTO HO[3], SHUNZABURO IWATSUKI[1], ANTHONY J. DEMETRIS[2], BARTLEY P. GRIFFITH, MARY KAY BREINIG[3], THOMAS E. STARZL[1]

Summary

The concept of immune surveillance states that the principle defense mechanisms against the development of neoplasia consist of certain homeostatic processes of the immune system. There now exists considerable opinion to suggest that this concept can no longer be sustained in its original form. Nevertheless, strong support for a specialized or restricted form of immune surveillance exists in the association of both spontaneous and induced states of immune deficiency with increases in certain types of neoplasia. This relationship is nowhere being better exhibited than in the spectrum of lymphoproliferative disorders occurring in patients undergoing organ transplantation and subsequent immunosuppression.

The post-transplant lymphoproliferative disorders following the transplantation of kidneys, livers, hearts, heart-lungs and pancreas, and which developed under cyclosporine steroid therapy at the University of Pittsburgh Health Center between January 1981 and August 31, 1986 were reviewed. A total of 36 (approximate incidence of 1.7%) recipients of various organs were identified as having developed lymphoproliferative disorders from 1 to 160 months following organ transplanta-

* Supported by Research Grants from the Veterans Administration and Project Grant No. AM-29961 from the National Institutes of Health, Bethesda, Maryland. Supported in part by the American Cancer Society Institutional Grant IN-58X (MN).

[1] Department of Surgery, Presbyterian University Hospital, Pittsburgh, Pa. 15213; L. M. is the recipient of a Centennial Fellowship from the Medical Research Council of Canada.

[2] Department of Pathology, Presbyterian University Hospital, Pittsburgh, Pa. 15213.

[3] Department of Medicine, Presbyterian University Hospital, Pittsburgh, Pa. 15213.

[4] Department of Pathology, Oakland Veteran's Administration Hospital, Pittsburgh, Pa. 15240.

[5] Department of Pathology, Children's Hospital of Pittsburgh, Pittsburgh, Pa. 15213.

tion. The patients ranged in age from 1 to 62 years (mean 22 years) at the time of transplantation with a male: female ratio of 2.6:1. The mainstay of immunosuppressive therapy for almost all patients was cyclosporine (CsA) and steroids. Typically, the onset of the disease took place fairly rapidly after transplantation, with 19 of the 36 cases occurring in less than 6 months, and 31 of the 36 cases occurring within the first year. Serological evidence of active infection with Epstein-Barr virus around the time of the lymphoproliferative disorder was found in 33 of 36 patients (92%). It is of note that there were twice as many primary as reactivation EBV infections. The relationship of this virus to such lymphoproliferative disorders has been repeatedly stressed in the literature.

The clinical presentation may be extremely variable, but the head and neck area and the gastrointestinal tract were the most commonly involved regions in our series.

The instinctive approach to the treatment of these post-transplant lymphoproliferative disorders would be chemotherapy. However, based on our clinical results, a more logical initial therapy appears to be manipulation of the immune system. Our results demonstrate that a drastic reduction or even complete cessation of immunosuppressive therapy elicits a rapid response in those cases amenable to this therapy. Interestingly enough, rejection did not occur in some of our cases even if the immunosuppression was reduced to up to 75% of the initial dose. Therefore, in practice we generally assess the clinical response to the tumor after a 50% reduction in immunosuppressive therapy. The remission is usually complete and the immunosuppressive regimen may later be resumed at previous or slightly reduced levels. The temptation to treat with chemotherapy should be resisted since this would further reduce the host immune response, causing an even worse exacerbation of the lymphoproliferative disorder. In those monoclonal and monomorphous tumors which do not respond to a reasonable trial of reduced immunosuppression, aggressive antilymphoma therapy may be unavoidable. In practice, these unfortunate patients are usually moribund at the outset, have a very rapid downhill course, and often die with multiple infections. Deaths both of patients with polyclonal and monoclonal tumors have seemed more related to the lateness of diagnosis than to any other factor. Add to this the fact that there is still no absolute *a priori* pathologic indicator of which tumors will and which will not respond to host immune restoration in a given patient, and that it is not as yet clear at what point, if any, reconstitution of the immune system can no longer switch off tumor growth, the case for immunosuppressive dose modulation as an initial therapy appears complete. We have presented evidence that polyclonal as well as monoclonal tumors remain subject to host control mechanisms if immune function is allowed to recover at least partially by a reduction of immunosuppressive therapy. The favorable outcome of a large number of these cases in response to

modulation of immunosuppression has raised the challenge of defining both host and tumor variables that characterize the mechanisms and limitations of immune controls in this system.

Zusammenfassung

Das Konzept der Immunüberwachung geht davon aus, daß die Hauptabwehrmechanismen gegen die Entstehung von Krebs bestimmte homöostatische Prozesse im Immunsystem beinhalten. Es mehren sich jedoch Stimmen, daß dieses Konzept in seiner ursprünglichen Form nicht länger aufrechterhalten werden kann. Dennoch gibt es deutliche Hinweise für eine spezielle oder restringierte Form der Immunüberwachung im Zusammenhang von spontanen und induzierten Immundefekten mit einer Zunahme von bestimmten Krebsarten. Diese Beziehung zeigt sich nirgends besser als im Spektrum der lymphoproliferativen Erkrankungen, die sich bei Patienten nach einer Organtransplantation mit anschließender Immunsuppression einstellen.

Es wird eine Zusammenstellung der lymphoproliferativen Erkrankungen nach Nieren-, Leber-, Herz-, Herz-Lungen- und Pankreas-Transplantationen gegeben, die sich im Gesundheitszentrum der Universität von Pittsburgh in der Zeit von Januar 1981 bis Ende August 1986 unter einer Cyclosporin-Steroid-Therapie entwickelten. Bei 36 (ca. 1,7%) Empfängern von verschiedenen Organen wurden 1 bis 160 Monate nach der Organtransplantation lymphoproliferative Erkrankungen nachgewiesen. Das Lebensalter der Patienten betrug zum Zeitpunkt der Transplantation 1 bis 62 Jahre (Mittelwert 22 Jahre), das Verhältnis von Männern zu Frauen 2,6:1. Für fast alle Patienten bestand die immunsuppressive Therapie vorwiegend aus Cyclosporin (CsA) und Steroiden. Typischerweise stellte sich der Beginn der Erkrankung recht bald nach der Transplantation ein, bei 19 der 36 Patienten innerhalb von weniger als 6 Monaten und bei 31 der 36 Patienten innerhalb des ersten Jahres. Serologisch konnte eine akute Epstein-Barr-Virusinfektion bei 33 der 36 Patienten (92%) während der Phase der lymphoproliferativen Prozesse nachgewiesen werden. Es ist bemerkenswert, daß es doppelt so viele Erst- wie EBV-Re-Infektionen gibt. Ein Zusammenhang zwischen diesem Virus und lymphoproliferativen Erkrankungen ist in der Literatur wiederholt betont worden.

Das klinische Bild kann extrem variabel sein, aber der Kopf-Hals-Bereich und der Gastrointestinaltrakt waren die am häufigsten betroffenen Regionen in unserem Patientengut.

Die naheliegende Behandlungsmethode dieser nach einer Transplantation auftretenden lymphoproliferativen Erkrankungen wäre die Chemotherapie. Auf-

grund unserer klinischen Ergebnisse scheint jedoch die Manipulation des Immunsystems besser als Anfangstherapie geeignet zu sein. Unsere Ergebnisse zeigen, daß eine drastische Einschränkung oder sogar ein totaler Abbruch einer immunsuppressiven Therapie ein schnelles Ansprechen jener Patienten bewirkt, die einer solchen Therapie zugänglich sind. Interessanterweise kam es bei einigen Fällen selbst dann nicht zu einer Abstoßung, wenn die Dosis der Immunsuppressiva bis zu 75% der Anfangsdosis reduziert wurde. Deshalb bestimmen wir in der Praxis im allgemeinen das klinische Ansprechen des Tumors nach einer 50%igen Reduzierung der immunsuppressiven Therapie. Im allgemeinen kommt es zu einer vollständigen Remission, und die immunsuppressive Therapie kann später mit der ursprünglichen oder einer leicht verminderten Dosis wieder aufgenommen werden. Der Versuchung, Chemotherapie anzuwenden, sollte widerstanden werden, da diese die Immunantwort des Wirtes weiter reduzieren und damit sogar zu einer Verschlechterung der lymphoproliferativen Prozesse führen würde. Bei solchen monoklonalen und monomorphen Tumoren, die nicht auf einen vernünftigen Versuch, die Immunsuppression zu reduzieren, ansprechen, ist eine aggressive Antilymphoma-Therapie wahrscheinlich nicht zu vermeiden. In der Praxis erweisen sich diese unglücklichen Patienten gewöhnlich von Anfang an als moribund; es geht rapide mit ihnen bergab und sie sterben häufig an multiplen Infekten. Der Tod von Patienten mit polyklonalen wie auch von solchen mit monoklonalen Tumoren schien mehr auf die zu späte Diagnose als auf irgendeinen anderen Faktor zurückzuführen zu sein. Außerdem gibt es bis jetzt keinen absolut à priori pathologischen Indikator dafür, welche Tumoren auf eine Immunrestoration in einem bestimmten Patienten ansprechen und welche nicht. Es ist bisher nicht klar, an welcher Stelle, wenn es überhaupt eine gibt, eine Rekonstitution des Immunsystems das Tumorwachstum nicht länger hemmen kann und ob der Fall für eine Modulation der immunsuppressiven Dosis als Anfangstherapie geeignet erscheint. Wir haben deutlich gemacht, daß sowohl polyklonale als auch monoklonale Tumoren den Wirts-Kontroll-Mechanismen unterworfen bleiben, falls wenigstens eine teilweise Erholung der Immunfunktion mittels Reduzierung der immunsuppressiven Therapie ermöglicht wird. Der günstige Verlauf bei einem großen Teil dieser Fälle hinsichtlich des Ansprechens auf die Modulation der Immunsuppression hat dazu herausgefordert, sowohl die Wirts- als auch die Tumorvariablen zu definieren, die den Mechanismus und die Grenzen der Immunüberwachung in diesem System bestimmen.

Résumé

Le concept de surveillance immunitaire stipule que le principal mécanisme de défense contre le développement de néoplasies consiste en une certaine homéosta-

sie du système immunitaire. Ce concept ne semble plus actuellement être défendu au moins dans sa forme initiale. Cependant, l'association de déficits immunitaires spontanés ou induits à l'augmentation de certains types de néoplasies constitue un argument important en faveur d'une forme de surveillance immunitaire spécialisée ou restreinte. Cette relation est nulle part mieux démontrée que dans le spectre des désordres lymphoprolifératifs survenant chez des patients ayant subi une transplantation d'organe suivie d'un traitement immunosuppresseur.

Les désordres lymphoprolifératifs survenant après transplantation de rein, foie, cœur, cœur-poumon et pancréas, et développés au cours d'un traitement par la cyclosporine et les stéroides au Pittsburg Health Center de janvier 1981 à août 1986 ont été analysés. Au total, 36 transplantés (incidence approximative de 1.7%) ont développé des désordres lymphoprolifératifs de 1 à 160 mois suivant la transplantation. L'âge des patients au moment de la transplantation s'échelonnait de 1 à 62 ans (moyenne 22 ans) et le groupe comportait 2,6 hommes pour 1 femme.

La plupart des patients avaient comme traitement immunosuppresseur essentiel la cyclosporine associée aux stéroïdes. Dans la plupart des cas, le début de la maladie survenait assez rapidement après la transplantation, en moins de six mois dans 19 des 36 cas observés, et en moins d'un an dans 31 cas sur 36. Des preuves sérologiques d'une infection active par le virus d'Epstein Barr ont été trouvées chez 33 des 36 patients (92%) au moment de l'apparition du désordre lymphoprolifératif. Il faut noter qu'il y aurait deux fois plus d'infections primaires que de réactivations d'infections à virus EBV. La relation entre ce virus et de tels désordres lymphoprolifératifs a été souvent soulignée dans la littérature.

La forme clinique peut être extrêmement variable, mais la région de la tête et du cou ainsi que le tractus digestif étaient les régions les plus souvent atteintes dans notre série de patients.

L'approche instinctive du traitement de ces maladies lymphoprolifératives devrait être la chimiothérapie. Cependant, d'après nos résultats cliniques, la thérapeutique initiale la plus logique semble être la manipulation du système immunitaire. Nos résultats démontrent qu'une réduction drastique ou même un arrêt total de la thérapeutique immunosuppressive entraîne une réponse rapide dans les cas où une telle réduction est envisageable.

Il faut noter que dans certains cas, il n'y a pas eu de rejet, même lorsque l'immunosuppression était réduite de 75% par rapport à la dose initiale. En pratique, nous contrôlons en général la réponse clinique après une réduction de 50% de la thérapeutique immunosuppressive. La rémission est en général complète et la thérapeutique immunosuppressive peut être ensuite reprise aux doses antérieures ou légèrement plus faibles. La tentation de traiter ces patients par une chimiothérapie doit être surmontée car ce traitement réduirait encore les défenses immunitaires de l'hôte, entraînant même une aggravation du désordre

lymphoprolifératif. Au cours de ces tumeurs monoclonales et monomorphes qui ne répondent pas à un essai raisonnable de réduction de l'immunosuppression, une thérapeutique spécifique plus agressive peut être inévitable. En pratique, ces patients meurent souvent d'infections multiples. La mort des patients ayant des tumeurs monoclonales et polyclonales semble plutôt en rapport avec un diagnostic tardif. Si l'on ajoute à cela le fait qu'il n'y a pas encore de marqueur pathologique absolu permettant de distinguer des tumeurs qui répondront ou pas à une reconstitution immunitaire chez un patient donné, et qu'il n'est pas encore évident de savoir à quel point la manipulation du système immunitaire peut inhiber la croissance tumorale, la modulation de la thérapeutique immunosuppressive paraît nécessaire dès le début du traitement.

Nous avons démontré que les tumeurs monoclonales ou polyclonales peuvent être soumises à des mécanismes de contrôle à condition que la fonction immune puisse être au moins partiellement restaurée par une réduction de la thérapeutique immunosuppressive. L'issue favorable dans un grand nombre de cas, après modulation de l'immunosuppression a fait naître l'idée de définir les paramètres de l'hôte et de la tumeur qui caractérisent dans ce système les mécanismes et les limitations du contrôle immunitaire.

* * *

Key Words: *Organ transplantation – post-transplant tumors – post-transplant lymphoproliferative disorders (PTLDs) – Kaposi's sarcoma – immunosuppression – immune modulation.*

Introduction

The concept of immune surveillance, proposed almost 80 years ago (1), and more recently reiterated by THOMAS (2) and BURNET (3, 4) states that the principal defense mechanisms against the development of neoplasia consist of certain homeostatic processes of the immune system. There now exists considerable opinion that this concept can no longer be sustained in its original form (5, 6). Nevertheless, strong support for a specialized or restricted form of immune surveillance exists in the association of both spontaneous and induced states of immune deficiency with increases in certain types of neoplasia (7–16). This relationship is nowhere being better exhibited than in patients undergoing organ transplantation and subsequent immunosuppression (8, 9, 13, 15, 17, 18–21).

It is clear that transplant patients receiving any form of immunosuppressive therapy have a higher propensity for the development of certain categories of tumors (17), especially lymphoproliferative disorders and Kaposi's sarcoma. Striking evidence that modulation of the immune system can control the growth of such neoplasia is offered by reports of remission of Kaposi's sarcomas and reversibility of lymphoproliferative lesions following reduction or cessation of immunosuppressive therapy in transplant patients (9, 18, 22–27). This chapter will deal primarily with our experience with and approach to post-transplant lymphoproliferative disorders (PTLDs) under cyclosporine-steroid therapy. This group of patients represents the largest single institutional series reported to date. Similarly, Kaposi's sarcoma occurring after renal transplantation in our patient population will also be presented.

Definition of post-transplant lymphoproliferative disorders

This group of disorders represents a collection of abnormal lymphoid proliferations occurring in transplant recipients, usually in association with active infection by the Epstein-Barr virus (EBV) (18, 28, 29). Histologically, the lesions are characterized by polymorphous to monomorphous proliferations of lymphoid cells. In polymorphous forms all stages of lymphocyte transformation may be represented. Monomorphous forms are indistinguishable from non-Hodgkin's lymphoma occurring in non-immunosuppressed individuals.

Precision in correlating histologic appearance and clinical behavior is complicated by the fact that some monoclonal tumors appear amenable to conservative intervention, whereas some polyclonal tumors may pursue a fulminant course leading to the death of the patient.

In light of these nosologic difficulties we employ the term PTLD in a generic sense to apply to any atypical, invasive and diffuse lymphoproliferation occurring in immunosuppressed transplant recipients. The adjective polymorphous or monomorphous is added based on the particular histologic appearance. The proliferation is also categorized as polyclonal or monoclonal based on the results of immunophenotypic or immunogenotypic assays. The presence or absence of EBV is determined as well. Whereas EBV is almost always found, we would include as PTLD any lesion that meets the above histologic criteria and in which EBV cannot be isolated.

We have, on occasion, also used the term PTLD to apply to non-invasive, usually nodal-based, diffuse lymphoproliferations. These lesions, also associated with EBV, usually have a predominant plasmacytoid appearance and may be associated with retention of underlying architecture. We qualify such lesions as reactive

processes. They may occur alone or may be associated with more advanced and invasive lesions elsewhere. In order for this group of lesions to receive a final designation as PTLD, it is necessary that evidence of EBV be found.

Epstein-Barr virus: General considerations

Existing evidence clearly indicts the Epstein-Barr virus as a major co-factor in the pathogenesis of PTLDs (16, 18, 20, 28, 29). The demonstration of such a direct relationship has allowed a better understanding of the interaction between tumor pathophysiology and the immune system, and of more immediate importance, has given insight into a more rational and effective form of therapy for this disorder.

EBV is a double-stranded DNA organism of the Herpes virus family. In man, EBV infects B-lymphocytes and is the causative agent of infectious mononucleosis. It attaches to the cell via the C3d receptor (30) and, in vitro, penetrates the cell membrane within 12 hours (31). Its life cycle follows four stages: latent, then early, middle and late replicative. All latently infected cells contain the Epstein-Barr nuclear antigens (EBNAs), of which several types are known. Concurrently, the lymphocyte determined membrane antigen (LYDMA) is produced. Early antigens (EAs) are produced during the early replication phase and are necessary for DNA synthesis, which occurs during the middle replicative phase. Additional membrane antigens and viral capsid antigens (VCAs) are formed during the late replicative phase. The replicative activity is not only confined to the virus, but by analogy extends to the host lymphocyte as well. In vivo, 5–20% of the B-lymphocytes are EBNA-positive during the first week of infectious mononucleosis (31). These cells resemble plasma cells and produce immunoglobulins (32, 33). By the second week of this condition, <2% of the circulating B-cells are EBNA-positive and no longer show plasmacytic differentiation. The early host response to infection includes NK cell activity and interferon production (14, 34). The early T-lymphocyte response is believed to offer cytotoxic activity in a non-HLA restricted manner, but this is soon surpassed by the emergence of a strong T-cytotoxic/suppressor population. These latter cells are directed against LYDMA (31) and are also thought to play a role in suppressing the maturation of B-cells into plasma cells. The T-c/s cells account for the atypical lymphocytosis observed during the disease and by their cytotoxic actions liberate EBNA from the infected cells. Anti-EBNA antibodies are characteristically identifiable in the serum 30 to 50 days after disease onset and normally persist for life. Although the infection and B-cell proliferation are eventually brought under control by the host's immune mechanisms, the virus remains indefinitely in a latent form. Recurrence of the lytic cycle is usually prevented by specific host memory T-lymphocytes.

Patient population

The incidence of PTLDs following the transplantation of kidneys, livers, hearts, heart-lungs and pancreas, and developing under cyclosporine (CsA)-steroid therapy at the University of Pittsburgh Health Center between January 1981 and August 31, 1986 is listed in Table 1 according to year and organ type. Tumors prior to this date occurred while the transplant team was based at the University of Colorado and are included as part of this series.

A total of 36 (approximately 1.7%) recipients of various organs were identified as having developed lymphoproliferative disorders from 1 to 160 months following organ transplantation. The salient clinical features are described in Tables 2, 3 and 4 for kidney, liver, and heart or heart-lung recipients, respectively. The incidence of PTLD varied somewhat with the kind of transplant, being 1% for kidney, and 2.2% and 4.6% for liver and heart and heart-lung transplants, respectively.

The patients ranged in age from 1 to 62 years (mean 22 years) at the time of transplantation. Twenty of the patients were adults and 16 were pediatric patients. There was a male-female ratio of 2.6:1. The tissue matching for donors and recipients was completely random for the non-renal transplants and nearly so for the renal transplants.

Table 1. Frequency of post-transplant lymphoproliferative disorders (PTLD) at the University of Pittsburgh Health Center.

According to year	*Number of all organs transplanted*	*Number of PTLD*
Year		
1980		2
1981	148	1
1982	224	5
1983	303	10
1984	438	4
1985	526	8
1986 (8/31)	522	6
Total	2161	36
According to organ type	*Total number of transplants*	*Number of PTLD*
Organ		
Kidney	975	10
Liver	855	19
Heart	272	5
Heart-lung	43	2
Pancreas	16	0
Total	2161	36

Immunosuppressive therapy

The mainstay of immunosuppressive therapy for almost all patients was cyclosporine (CsA) and steroids. For kidney transplants who developed PTLDs, immunosuppression was with CsA and prednisone as previously described (18). Eleven of the 20 liver recipients who developed PTLDs were treated similarly. Six liver recipients also received monoclonal antibody (OKT3) and 1 patient received

Table 2. Kidney recipients with lymphoproliferative disorders.

Case	Sex	Age (yr) at Tx	Date of Tx	Time (Mo) of onset of PTLD after Tx	Organs involved	Clinical presentation	Surgery
1	F	25	Jan. 31, 1980	6	Ileum	Perforation of ileum	Small bowel resection
2	M	28	Feb. 19, 1980	3.5	Liver, spleen, heart, retroperitoneal lymph nodes (necropsy findings)	Fever	None
3	M	20	April 15, 1981	6	Ileum, small bowel, mesentery	Perforation of ileum	Small bowel resection
4	M	52	May 4, 1982	3.5	Submandibular gland	Fever, adenopathy	Local resection
5	M	56	Feb. 10, 1982	6	Prostate, ileum, mesentery	Prostatic obstruction and perforation of ileum	TURP and small bowel resection
6	M	30	July 10, 1982	4	6 sites in small bowel	Perforation of ileum	Small bowel resection
7	M	16	Dec. 12, 1982	3½	Multiple sites in small bowel	Perforation of ileum	Small bowel resection
8	F	62	March 14, 1983	4½	Stomach	GI bleeding	Biopsy
9	M	15	Jan. 6, 1985	6	Tonsils, nasopharynx	Sore throat	Tonsillectomy
10	M	11	May 3, 1985	13	Adenoid hyperplasia	Upper respiratory infection	Adenoidectomy

Tx = transplantation; CsA = cyclosporine; TDD = thoracic duct drainage; Pred = prednisone, Aza = azathioprine; ALG = antilymphocyte globulin; ATG = antithymocyte globulin.

azathioprine additionally. The remaining 2 liver recipients had their transplants in 1972 and 1977 under azathioprine and prednisone. The latter patient was converted to CsA and prednisone in 1981. In addition to CsA-prednisone therapy, 1 heart-lung patient received azathioprine, and 3 heart transplant patients were also treated with anti-thymocyte globulin (ATG). One heart-lung patient received quadruple therapy with ATG, azathioprine, CsA and prednisone (Table 4).

Contemporaneous infection	Original immunosuppression	Change in immunosuppression		Acyclovir	Other anti-tumor treatment	Fate of patient	Graft function
		CsA (mg/kg/day)	Pred (mg/day)				
None	TDD, CsA, Pred	16–6	10–10	No	None	Alive, tumor-free	Retained to date
Pneumocystis carinii	CsA, Pred	14–14	25–20	No	None	Died June 8, 1980	Functioned until death
None	CsA, Pred	18–9	20–10	No	None	Alive, tumor-free	Retained to date
Herpes simplex	CsA, Pred	11–2	20–15	No	5400 rad cervical irradiation	Alive, tumor-free	Retained to date
None	CsA, Pred	8–2	15–15	No	Doxorubicin, cyclophosphamide, vincristine: cancelled mid-course	Alive, tumor-free	Rejected 1 yr later, ReTx lost to hyperacute rejection
Herpes simplex	CsA, Pred	10–0	15–15	No	Doxorubicin, cyclophosphamide, vincristine	Alive, tumor-free	Rejected in 2 wk, ReTx retained to date
None	CsA, Pred	8–0	15–15	Yes	None	Alive, tumor-free	Rejected in 1 wk, being evaluated for ReTx
Herpes simplex	CsA, Pred	8–1	15–15	No	None	Alive, tumor-free	Retained to date
None	CsA, Pred	6–0	17.5–15	No	None	Alive, tumor-free	Retained to date
None	CsA, Pred	5.5–3.6	5–5	No	None	Alive, tumor-free	Retained to date

Clinical presentation

Typically, the onset of the disease took place fairly rapidly after transplantation, with 19 of the 36 cases occurring in less than 6 months, and 31 of the 36 cases occurring within the first year. The interval from transplant to diagnosis of PTLD was as short as 1 month or as long as 14 years. In our series, there was one instance of PTLD occurring 2 years after conversion from azathioprine to CsA therapy and 1 example of a case occurring 2 years after transplant in a patient who had received CsA-prednisone therapy from the time of transplant. The only case with onset

Table 3. Liver recipients with lymphoproliferative disorders.

Case	Sex	Age (yr) at Tx	Date of Tx	Time (mo) of onset of PTLD after Tx	Organs involved	Clinical presentation	Surgery
1.	F	1.5	Feb. 20, 1972	160	Generalized (lymph nodes, tonsils, lungs, liver, CNS, uterus, ovaries)	Fever, jaundice, mild chronic rejection, tonsillitis	Lymph node bx, tonsillectomy
2.	F	13	Aug. 31, 1977	68	Cervical nodes, right kidney	Renal mass	Resection
3.	M	17	May 9, 1982	6	Small bowel (multiple)	Fever, small bowel obstruction	Small bowel resection
4.	F	8	Nov. 1, 1982	39	Diffuse retroperitoneal (lymph nodes, kidneys, adrenal), heart, brain, bone marrow GI tract	Fever, weight loss, anorexia	Lymph node bx
5.	M	20	Dec. 1, 1982	8.5	Cervical nodes, tonsils	Fever, tonsillitis	Tonsillar bx
6.	F	21	Mar. 20, 1983	6.5	Ileum and colon (multiple)	Fever, vague intestinal symptoms	Small bowel resection
7.	F	26	Sep. 1, 1983	4	Diffuse lymph nodes, GI tract, pancreas	Multi-organ failure	Biopsy
8.	M	23	Oct. 30, 1983	2	Diffuse lymph nodes, spleen	Disseminated sepsis, severe rejection with liver mycosis	Biopsy

PCP = Pneumocystis carinii pneumonia, CMV = cytomegalovirus; CsA = cyclosporine, Pred = prednisone, AZA = azathioprine; bili = bilirubin; LFTs = liver function tests, Tx = transplant.

beyond this time period occurred 160 months after liver transplantation in a patient whose sole immunosuppression had been azathioprine and prednisone. This last patient was from an era in which lymphoproliferative complications were common, but usually identified as reticulum cell sarcomas (8, 9). HANTO et al. (20) have reported the largest series of these lesions under azathioprine-prednisone therapy with or without ALG.

The presenting symptoms can be extremely variable, and sometimes the patient may be completely asymptomatic. Therefore, a high index of suspicion must be maintained for early diagnosis. The presentation may include any of the following:

Contemporaneous infection	Original immunosuppression	Change in immunosuppression		Acyclovir	Other antitumor treatment	Fate of patient	Graft function
		CsA (mg/kg/d)	Pred (mg/d)				
Aspiration pneumonia	Aza, Pred, then CsA, Pred after mid 1984	10–0	10–5	No	None	Died of resp. arrest after tonsillectomy	Functioned until death
None	Aza, Pred, ALG, then CsA, Pred from Sep. 1981	8–2	15–10	No	None	Died after ReTx; had microscopic tumor	Failed slowly; ReTx
None	CsA, Pred	20–3	25–10	No	None	Alive, tumor-free	Retained to date
Generalized aspergillosis	CsA, Pred	11–0	5–5	Yes	Vincristine daunomycin prednisone	Died of multiple organ failure	Functioned until death
None	CsA, Pred	6–6	10–10	No	None	Died of airway obstruction after ENT examination	Functioned until death
Cholangitis, fungal pneumonia	CsA, Pred	13–5	10–7.5	No	None	Alive, tumor-free	Retained to date
PCP, candidiasis	CsA, Pred	13–0	15–5	No	None	Died of pneumonia	Functioned until death
CMV, Pseudomonas aeruginosa sepsis	CsA, Pred	1.2	12.5	No	None	Died of sepsis (PTLD found at autopsy)	Functioned until death

lymphadenopathy, fever, weight loss, abdominal pain, tonsillitis, night sweats, upper respiratory infection and diarrhea. The patient may present with swollen tonsils of such magnitude that emergency tracheotomy is required. In several cases PTLDs gave rise to an acute abdomen, gastrointestinal perforation, obstruction or hemorrhage (Tables 2–4). Some patients presented with a syndrome indistinguish-

Table 3 (continued).

Case	Sex	Age (yr) at Tx	Date of Tx	Time (mo) of onset of PTLD after Tx	Organs involved	Clinical presentation	Surgery
9.	M	4	Jan. 14, 1984	24.5	Terminal ileum lymph nodes, small bowel mesentery, transverse mesocolon	Abdominal pain, lymphadenopathy, large epigastric mass, hypercalcemia	Hemicolectomy then excision of mass 3 months later
10.	M	32	Apr. 2, 1984	6	Diffuse lymph nodes	Fever, anorexia	Lymph node bx
11.	F	2.5	May 10, 1984	3	Cervical nodes, tonsils	Fever, upper airway obstruction	Tracheostomy, lymph node bx tonsillectomy
12.	M	7	Aug. 6, 1984	7.5	Diffuse lymph nodes, tonsils	Fever tonsillitis	Lymph node bx tonsillectomy
13.	M	3	Aug. 7, 1984	11	Lymph nodes (cervical, retroperitoneal), tonsils	Fever, anorexia vague abdominal pain	Lymph node bx
14.	M	1.5	May 18, 1985	10	Adenoids	Upper respiratory infection, middle ear infection	Adenoidectomy
15.	F	3.5	Aug. 22, 1985	4	Diffuse lymph nodes, spleen	PCP	Biopsy
16.	F	11.5	Sep. 19, 1985	2	Diffuse lymph nodes, liver, GI tract, kidneys	Multi-organ failure	Biopsy
17.	M	5.5	Dec. 17, 1985	1.5	Diffuse lymph nodes	Fever, diarrhea, elevated bili and LFT's	Biopsy
18.	M	43	Feb. 25, 1986	5	Lungs	PCP with non-resolving X-ray findings	Open lung bx
19.	M	2.5	Apr. 10, 1986	2	Adenoids	Hoarseness	Adenoidectomy

PCP = Pneumocystis carinii pneumonia, CMV = cytomegalovirus; CsA = cyclosporine, Pred = prednisone, AZA = azathioprine; bili = bilirubin; LFTs = liver function tests, Tx = transplant.

able from infectious mononucleosis, consisting of lymphadenopathy and fever. Some of the more unusual methods of presentation included lung lesions, a renal mass, prostatic obstruction, disseminated sepsis and multi-organ failure. The presentation at times mimicked rejection. In those cases, the presence of an atypical lymphoblastic infiltrate on biopsy was often the first indicator of a PTLD.

Contemporaneous infection	Original immunosuppression	Change in immunosuppression		Acyclovir	Other antitumor treatment	Fate of patient	Graft function
		CsA (mg/kg/d)	Pred (mg/d)				
None	CsA, Pred, OKT3	5.5–0	5–0	No	None	Alive; tumor regressed, then recurred in the small bowel and was resected	Retained to date
Esophagitis (herpes? CMV?)	CsA, Pred	7.5–3.3	17.5–10	Yes	Radiation	Alive, tumor-free	Rejected; ReTx
None	CsA, Pred	15.5–7.8	10–5	Yes	None	Alive, tumor-free	Retained to date
None	CsA, Pred	22–11	15–10	Yes	None	Alive tumor-free	Retained to date
None	CsA, Pred	19–12	7.5–5	No	None	Alive, tumor-free	Retained to date
None	CsA, Pred, OKT3	35–12	7.5–5	No	None	Alive, tumor-free	Retained to date
PCP	CsA, Pred, OKT3, Aza	13.3	10	No	None	Died of sepsis, autopsy finding	Functioned until death
CMV, Candidiasis	CsA, Pred, OKT3	23	10	No	None	Died of multi-organ failure; (autopsy finding)	Functioned until death
None	CsA, Pred, OKT3	30–5–0	10–5–0	Yes	None	Died of multi-organ failure	Failed
PCP, CMV	CsA, Pred, OKT3	5.5–0	7.5–5	No	None	Alive, free of tumor	Retained to date
None	CsA, Pred, OKT3	50–30	10–5	No	None	Alive, tumor-free	Retained to date

Table 4. Heart and heart/lung recipients with lymphoproliferative disorders.

Case	Sex	Age (yr) at Tx	Date of Tx	Time (Mo) of onset of PTLD after Tx	Organs involved	Clinical presentation	Surgery
1	M	51	Sept. 27, 1982	6.5	Lung, adrenal	Fever	Biopsy
2	M	22	Nov. 1, 1981	6.5	Cervical nodes, pharynx, lungs	Cervical mass	Biopsy
3	M	44	Jan. 20, 1983	3	Inguinal nodes	Inguinal mass	Biopsy
*4	M	20	Jan. 21, 1983	4	Cervical nodes, ileum, other lymph nodes	Cervical mass	Biopsy
*5	M	22	May 25, 1983	2	Tonsils	Tonsillitis	Tonsil-lectomy
6	M	30	Oct. 22, 1984	3	Cervical nodes	Cervical adenopathy	Biopsy
7	M	56	Jan. 19, 1985	3	Cervical nodes	Fever, cervical adenopathy	Biopsy

* Cases 4 and 5: heart/lung recipients.
PCP = Pneumocystis carinii pneumonia, CMV = cytomegalovirus; AZA = azathioprine, ATG = antithymocyte globulin.

The organs involved with PTLD in each patient are summarized in Tables 2, 3, and 4; the head and neck areas and the gastrointestinal tract were the most commonly involved regions in our series.

A fulminant course is uncommon, tends to involve multiple organs and usually leads to death within such a short period of time that stopping immunosuppression may be too late. In 3 patients the diagnosis was not made until necropsy.

Infectious disease studies

The results of studies assessing infection with EBV in PTLD patients are listed in Table 5. Serological evidence of active infection with EBV around the time of PTLD was found in 33 of 36 patients (92%). Although Epstein-Barr virus nuclear antigen (EBNA) was demonstrated in only 15 of 24 tumor specimens in which it

Contemporaneous infection	Original immunosuppression	Change in immunosuppression CsA (mg/kg/d)	Prednisone (mg/d)	Acylovir	Other antitumor treatment	Fate of patient	Graft function
CMV pneumonia	CsA, Pred	6–6	20–20	Yes	None	Died April 13, 1983, CMV pneumonia	Functioned until death
Pneumonia	CsA, Aza, Pred	8–8	20–20	Yes	Cyclophosphamide, vincristine, procarbazine, irradiation	Died Oct. 27, 1982, pancytopenia, sepsis	Functioned until death
Gastroenteritis	CsA, Pred, ATG	21–13	30–25	No	None	Died Oct. 6, 1984 respiratory failure tumor-free	ReTx April 1984
Systemic cryptococcosis	CsA, Aza, Pred	8–2	20–15	Yes	None	Died June 24, 1983, ileal perforation	Functioned until death
CMV	CsA, Aza Pred, ATG	12–3	20–20	Yes	None	Died following re-Tx, Dec. 18, 1984, tumor-free	Retained until Dec. 1984
PCP	CsA, Pred, ATG	6.6–3.3	20–20	No	None	Alive, tumor-free	Retained to date
PCP	CsA, Pred, ATG	5.8–2	20–20	No	None	Alive, tumor-free	Retained to date

Table 5. Infection with Epstein-Barr virus.

	Kidney	Liver	Heart or heart-lung	Total cases
Serological evidence of active EBV infection*	8/10	18/19	7/7	33/36
– Primary	5	13	4	22
– Reactivation	3	5	3	11
– None**	2	1	–	3
Tissue EBNA	1/5	10/12	4/7	15/24
EBV genome	3/4	2/3	4/4	9/11

* Serum was obtained prior to or at transplantation and at least at monthly intervals after transplantation. Primary infection was defined as serologic 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.

EBNA: EBV nuclear antigen, determined by immunofluorescent staining on touch preparations and frozen tissue sections.

EBV genomes were demonstrated in 9 of 11 tumors (including 6 negative tissue EBNA) which were examined with DNA hybridisation techniques by J. PAGANO (University of North Carolina), G. MILLER (Yale), or M. A. EPSTEIN (Bristol).

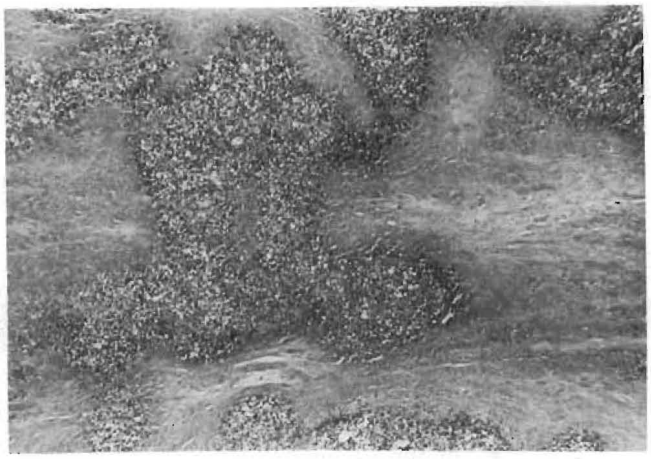

Fig. 1. Low power photomicrograph of PTLD from case report 2 shows large areas of amorphous necrotic debris interdigitating with cellular areas (Hematoxylin and eosin).

was tested for, 9 of 11 tumors examined by DNA hybridization studies contained EBV genomes. These 9 included 6 that had negative EBNA studies. It is also of note that there were twice as many primary as reactivation EBV infections.

Other infections occurring just before, or at the time of diagnosis of PTLD are catalogued in Tables 2–4. A significant number of patients had severe contemporaneous infections, which in some cases were a major factor in their deaths.

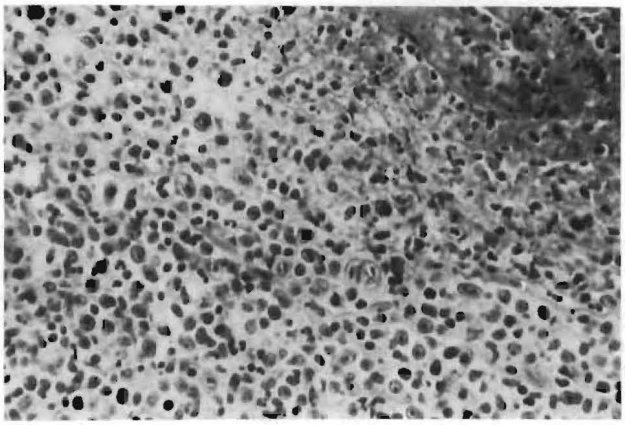

Fig. 2. A tonsillar lesion from case 1 shows the interface between viable and necrotic tissue. A large atypical cell is seen in this area. Elsewhere the lesion had a polymorphous lymphoid appearance (H and E).

Eighteen of the 36 patients had no other infections, while another 4 had only Herpes simplex infection.

Histopathology

The characteristic histologic appearance of PTLD is that of a diffuse invasive lymphoproliferation with varying degrees of cellular polymorphism, necrosis and plasmacytoid differentiation.

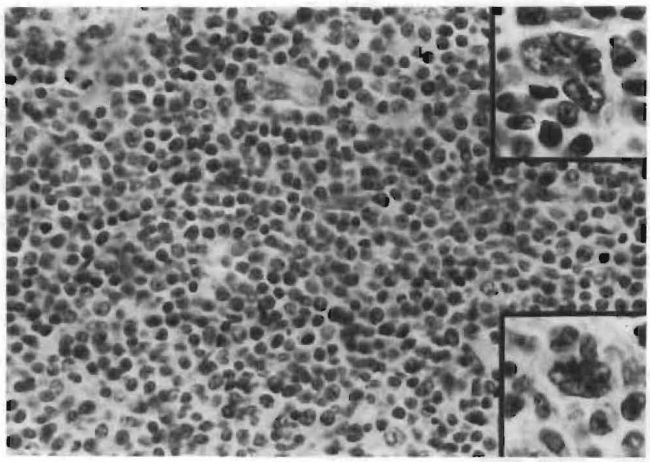

Fig. 3. Minimally polymorphous PTLD which typed as monoclonal by immunoglobulin gene rearrangement analysis. Inset: Rare atypical cells found within the tumor (H and E).

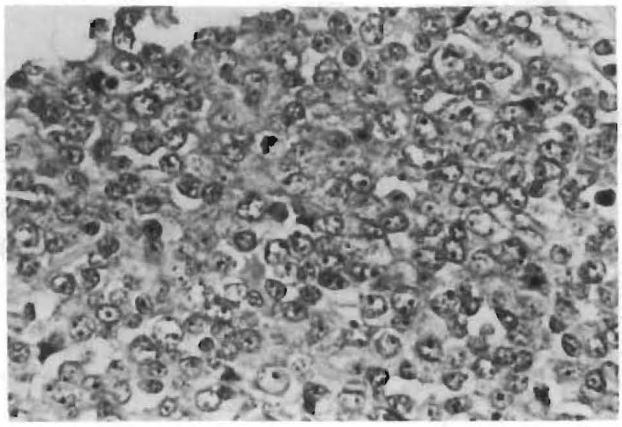

Fig. 4. Monomorphous noncleaved cell tumor found in an intrapulmonary location. Clonal analysis had not been performed on this consult biopsy from an outside institution. The patient is well without tumor 9 months after diagnosis following a reduction of immunosuppression (H and E).

On low power, the necrosis may assume the form of interweaving swaths of infarction ("geographic" necrosis) (Fig. 1) separating areas of viable cells. The interface between necrotic and non-necrotic areas may show an exaggerated cellular pleomorphism due to the superimposition of inflammatory cells, moribund cells, and scattered large atypical cells characterized by prominent nucleoli, polylobated nuclei and a moderate amount of cytoplasm ("atypical immunoblasts") (Fig. 2). These latter cells are considered by some to be harbingers of malignant transformation, but have also been described in uncomplicated infectious mononucleosis (35). The frequent propinquity of these cells to necrotic foci suggests a response to a toxic microenvironment, but similar cells can also be seen removed from such areas (Fig. 3, see also Figs. 9, 10, 15). Thus, their nature remains enigmatic. We do not consider such cells to represent evidence of a true malignant lymphoma in this patient population.

The polymorphism of the predominant population of cells in PTLDs reflects the various stages of lymphocyte transformation. In general, there is a tendency for the terminal stages of B-cell differentiation to be well represented. Thus, many of the

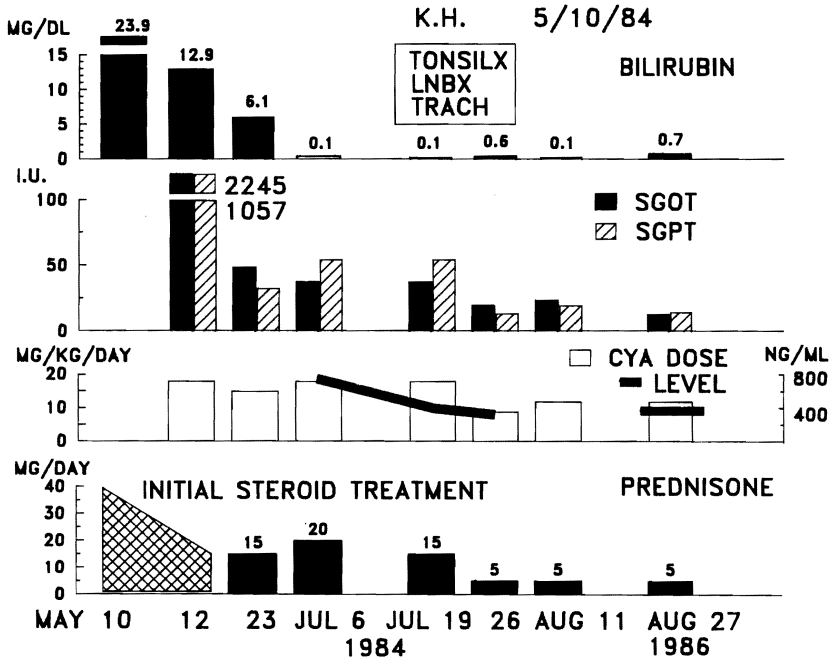

Fig. 5. Post-operative course of a 2½-year-old female liver recipient who developed PTLD resulting in acute upper airway obstruction and requiring tracheostomy, tonsillectomy and reduction in immunosuppression.

Fig. 6. Representative radiograph of upper airway obstruction in a PTLD patient. 23-year-old male 9 months after cardiac transplantation presented with upper airway obstruction. Radiograph demonstrates a large soft tissue mass in the nasopharynx.

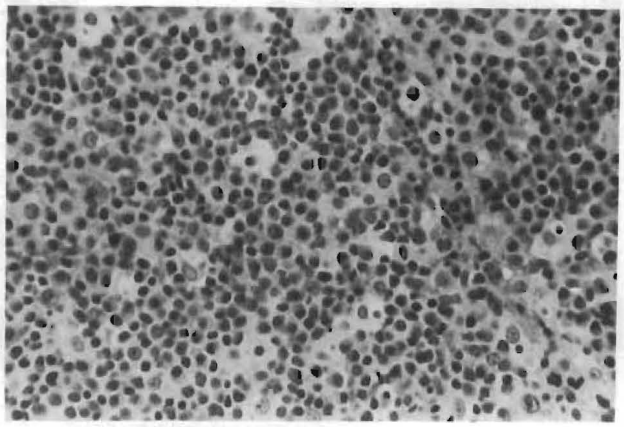

Fig. 7. Diffuse plasmacytoid proliferation from inguinal lymph node of case 1. This was associated with retention of underlying architecture and was judged a reactive process (H and E).

lesions show varying degrees of plasmacytoid or frank plasmacytic differentiation (see Figs. 7, 16). Although this may be seen in the context of diffuse proliferation and necrosis, early cases may show a nodal-based, benign appearing diffuse plasmacytic hyperplasia. We have also seen this appearance concurrently with the presentation of a more typical noncontiguous PTLD.

Other cells constituting the polymorphous infiltrate range from small lymphocytes through immunoblasts. Occasionally a dimorphic appearance is seen, which suggests an infiltrate of reactive lymphocytes, possibly T-cells, into a proliferating population. Given the importance of these lesions to the immune surveillance theory and/or immune control mechanism, the paucity of information regarding infiltrating cell types is perhaps surprising. Such analysis is planned at our institution and may alter our classification of these lesions in the future.

Many PTLDs are composed of a clearly monomorphous cell population (Fig. 4). The cells in these instances are either small or large noncleaved lymphocytes with essentially no evidence of plasmacytoid differentiation. Necrosis

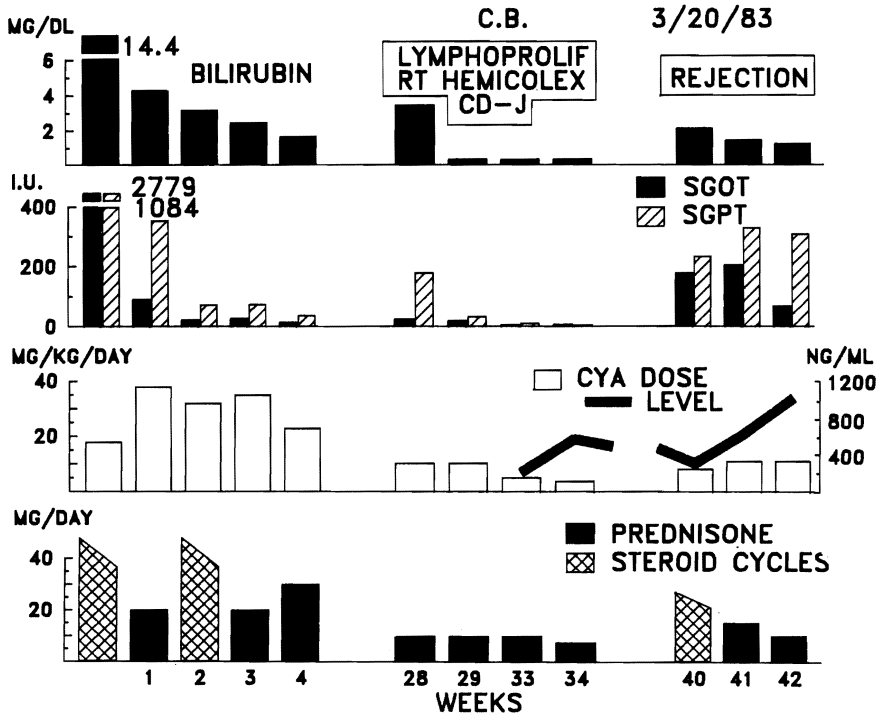

Fig. 8. Post-operative course of a 21-year-old female liver recipient who developed diffuse small bowel and colonic PTLD with GI bleeding requiring resection and reduction in immunosuppression for resolution.

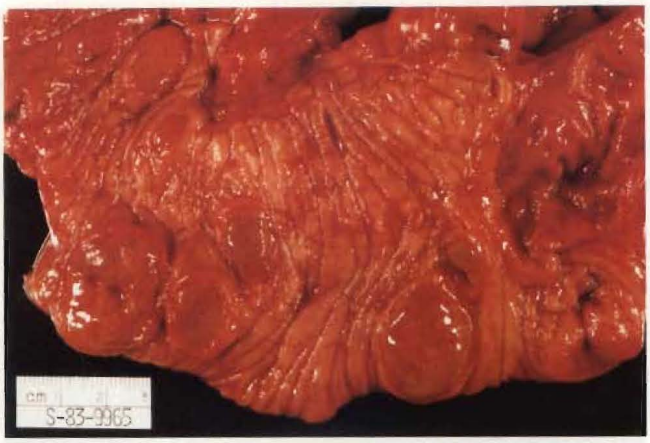

Fig. 9. Region of ileocecal valve and ascending colon from case 2 shows multiple ulceronodular tumor masses as viewed from the mucosal aspect of the bowel.

may be present or absent; single-cell necrosis may be the predominant type seen. A monomorphic pattern represents a significant departure from the usual PTLD and may be the manifestation of a lesion further advanced along the pathway of tumor progression.

Clonal designation of the tumors is an integral component of pathologic analysis (36–39). In lesions showing strong plasmacytoid features, immunocytochemical

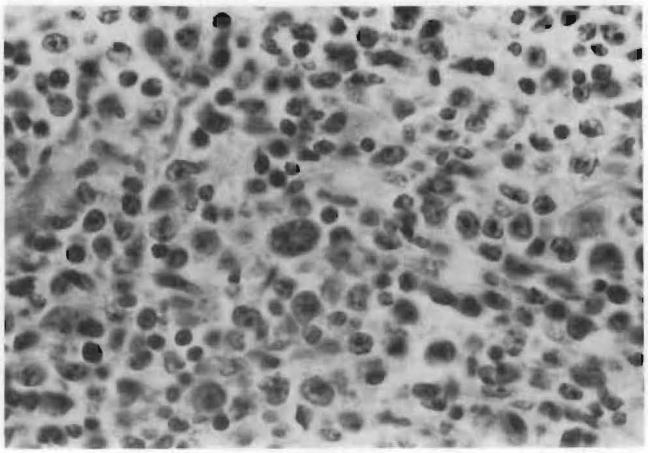

Fig. 10. Representative histologic section from one of the tumors in case 2 demonstrates a polymorphous infiltrate with a large atypical cell near the center of the photograph (H and E).

staining for immunoglobulin light chains in paraffin-embedded material may provide enough information for presumptive clonal analysis (see Figs. 16, 17, 20, 21). In many cases this approach is unsatisfactory and immunophenotypic analysis requires the use of frozen section immunohistochemistry (see Figs. 11, 12), flow cytometry (see Fig. 27) or a combination of the two. We currently favor the use of immunoglobulin gene rearrangement analysis by DNA restriction fragment length

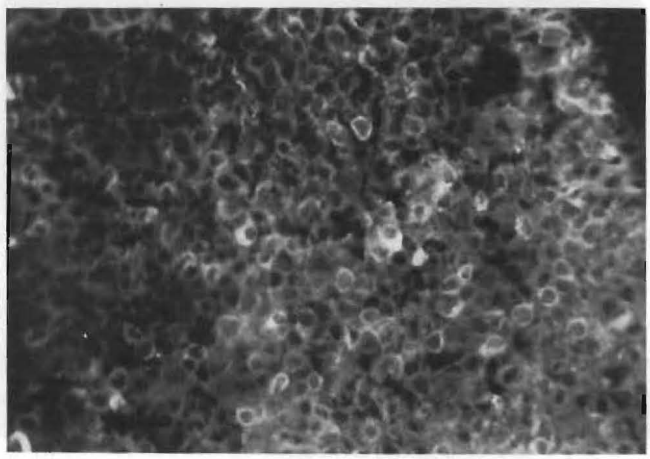

Fig. 11. Immunofluorescence preparation of frozen tumor section from case 2 shows positivity directed against kappa light chains.

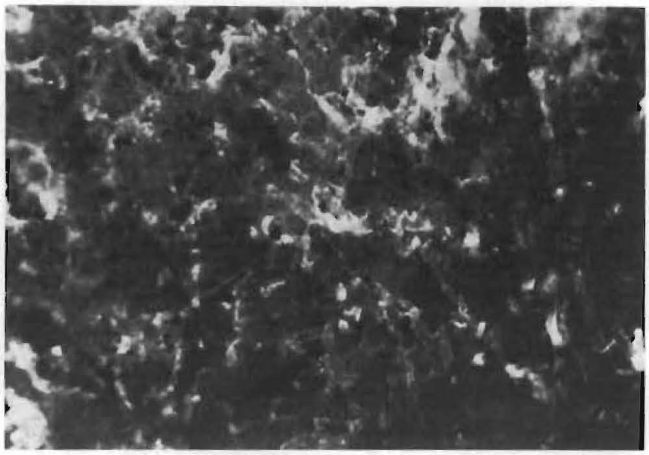

Fig. 12. Preparation similar to Fig. 11 showing negative staining when primary antibody is directed against human lambda light chains.

polymorphism and have verified the clonal status in many of these tumors by this technique (manuscripts in preparation).

In reviewing our cases it has become apparent that histologically monomorphous tumors are also monoclonal. Histologically polymorphous tumors may be either polyclonal or monoclonal. This latter finding underscores the limitation of routine histology in the analysis of these tumors. Indeed, in practice it is difficult to define the lower limit of polymorphism allowable before classifying a tumor as monomorphous. Clearly, more refined pathologic dissection of PTLDs is required before a final classification can be agreed upon.

Our current practice is to use the term PTLD as a generic diagnosis for a histologically verified diffuse lymphoproliferation occurring in a transplant recipient. The diagnosis is corroborated by identification of EBV within the lesion. The histologic diagnosis is further specified by the adjectives polymorphous or monomorphous as an estimate of the diversity of lymphocytes within the lesion. Likewise, the clonal designation of polyclonal or monoclonal is given based on immunophenotypic studies. This is then substantiated by immunogenotypic analysis, at which time the possibility of an oligoclonal tumor may also be revealed.

The relationship of histologic appearance to the pathogenesis of this disorder is considered in the discussion.

Response to therapy, patient survival and graft function

Kidney transplant recipients (Table 2): Nine out of the 10 kidney recipients with PTLD are alive. Of the 9, the tumors were monoclonal in 4, polyclonal alone in 2, and of unknown clonality in 3. Two of the patients with monoclonal tumors also had separate polyclonal tumors. The tenth patient had a monoclonal tumor that was not diagnosed until autopsy. Death in this patient was due to Pneumocystis carinii pneumonia and not tumor. In all surviving patients the diagnosis was made from biopsy specimens. Eight of the 9 survivors had in common the reduction or discontinuance of immunosuppression. Surgical intervention consisted of either resection or biopsy of visible tumor. Only 1 of the surviving patients was treated with acyclovir. Two patients were treated with multiple chemotherapeutic agents and another had 5400 rad cervical irradiation. In retrospect, this treatment was unnecessary and probably undesirable.

Five of the survivors had operations to relieve the complications of bowel involvement caused by PTLD. All had reduction of immunosuppression, and there has been no evidence of residual tumor. The renal grafts in 3 of the 9 survivors were rejected 1 week to 1 year after the reduction of immunosuppression. The kidneys of the other 6 recipients are functioning well.

Liver transplant recipients (Table 3): Ten of the 19 liver recipients with PTLD are alive. Three of the survivors had monoclonal tumors, 5 had polyclonal tumors, and in 2 patients the clonality is as yet undetermined. Of the 9 patients who did not survive, the diagnosis of PTLD was made at autopsy in four. One of these 4 had a polyclonal proliferation; clonality was indeterminate in the other 3. Five other patients who died received an antemortem diagnosis of PTLD. In this group, 1 case was monoclonal, 2 were polyclonal and 2 were of indeterminate clonality.

All 10 survivors had a reduction in immunosuppression, while 4 patients who had no adjustment in immunosuppression died. Two of 5 patients who received acyclovir died. One patient received radiation therapy and is alive, while another who received combination chemotherapy died of multiple organ failure. Three patients who underwent bowel resections are thought to be tumor-free. Two patients lost their grafts due to rejection after their immunosuppression was lowered, and both were successfully retransplanted. One patient has had several local recurrences of tumor over a 1 year period. He is currently doing well with no clinical evidence of tumor.

Heart and heart-lung recipients (Table 4): Two of the 7 heart or heart-lung recipients with PTLD are alive. These 2 patients had a significant reduction in immunosuppression. In 1 case the tumor was polyclonal, in the other, monoclonal.

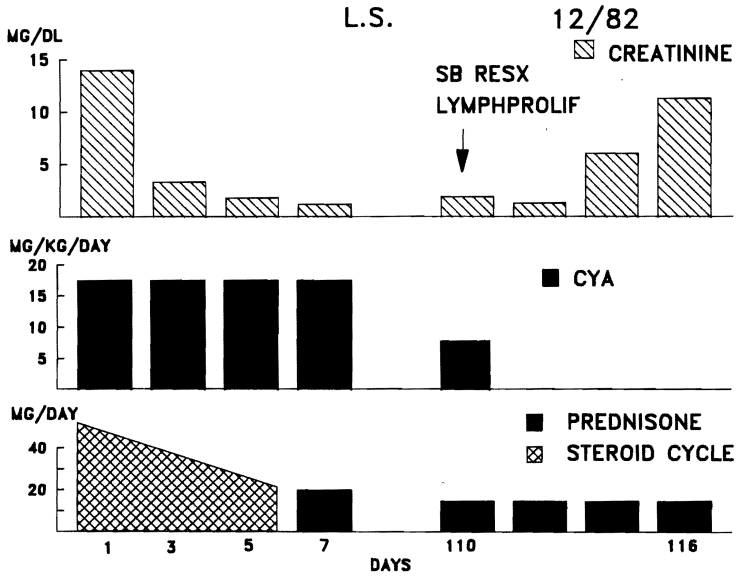

Fig. 13. Post-operative course of a 16-year-old male kidney transplant recipient who developed diffuse small bowel PTLD and perforation requiring emergent resection and cessation of cyclosporine therapy, resulting in complete resolution of disease but loss of the graft due to rejection.

Fig. 14. Representative pre-operative radiographic appearance of a small bowel PTLD in a 17-year-old male 5 months post liver transplant. Small bowel study shows submucosal masses with obstructive dilatation of the small bowel.

Neither patient received acyclovir and neither had problems with allograft rejection. Three other patients in whom the immunosuppression was reduced did not survive. One of these patients (case 4) died of abdominal sepsis after delayed diagnosis of a perforated PTLD of the ileum. This patient had already had a previous diagnosis of PTLD made on biopsy of enlarged cervical nodes. However, no response of the monoclonal PTLD to a reduction of immunosuppression was documentable in this patient. The 2 other patients died at 1 year and 18 months, respectively, following diagnosis of PTLD. In both cases the polyclonal tumors resolved following reduced immunosuppression and had not recurred. Both patients died of other, unrelated causes. A heart recipient who received chemotherapy, regional irradiation and acyclovir instead of reduction of immunosuppression died of widespread infection. The chemotherapy caused profound bone marrow depression. Residual foci of PTLD were found at autopsy.

Case histories

The following case histories are representative of the clinical presentation, diagnostic problems, pathologic considerations and management approach characteristic of the series of patients with PTLD at the University of Pittsburgh Health Center.

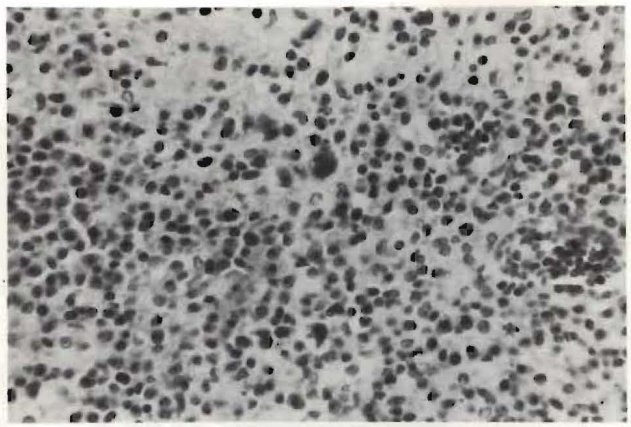

Fig. 15. Representative view of tumor from case 3. Polymorphic infiltrate with large atypical cell is apparent. Higher power showed plasmacytoid differentiation (H and E).

Case 1: A 2½-year-old female with biliary atresia and a history of a failed Kasai procedure and revision, underwent uneventful orthotopic liver transplantation. Her post-operative course is depicted in Fig. 5. Her recovery was prolonged because of a severe ischemic injury to the donor liver. This eventually resolved with excellent final function on discharge, 6 weeks later. Two months after discharge, she developed a fever of unknown origin, anorexia, malaise, cervical and inguinal lymphadenopathy, and tonsillar enlargement of such a magnitude that

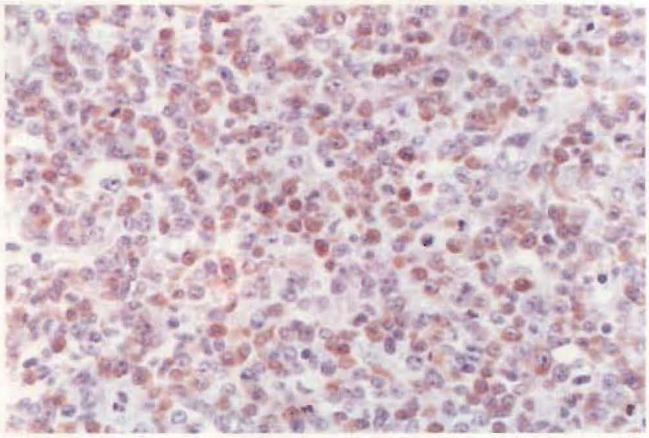

Fig. 16. Immunoperoxidase stain for intracytoplasmic lambda light chain in case 3. Plasmacytoid features facilitate interpretation. Note positive staining of immunoblasts (Avidin-biotin complex immunoperoxidase, diaminobenzidine development).

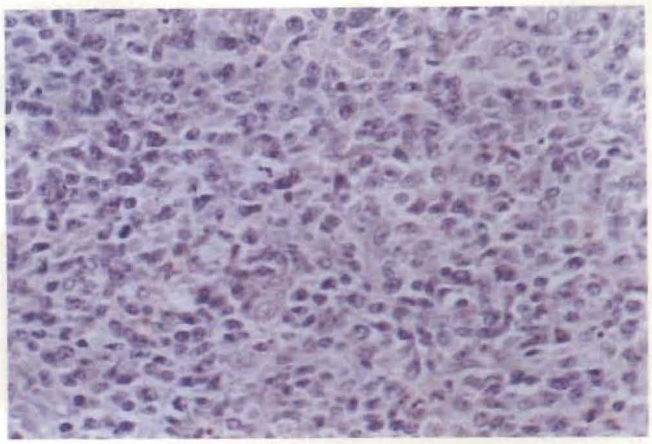

Fig. 17. Similar preparation as in Fig. 16 using antibody stain directed against kappa light chain. No intracytoplasmic staining is evident.

upper respiratory impairment developed (Fig. 6 represents a radiographic illustration of a similar finding in another patient in our series). This required emergency tracheotomy. At the same time, a tonsillectomy and an inguinal lymph node biopsy were performed (Fig. 2 represents the histology taken from the tonsil and Fig. 7 from the inguinal node). The tonsil showed confluent areas of necrosis (cf. Fig. 1) with a florid, diffuse, polymorphous proliferation of lymphocytes, plasmacytes, plasmacytoid cells, immunoblasts and Reed-Sternberg-like cells. A lesser degree of plasmacytic proliferation was observed in the lymph node, with good retention of underlying architecture. The process was judged to be polyclonal on the basis of immunoperoxidase staining for immunoglobulin light chains.

The patient's immunosuppressive therapy was reduced, cyclosporine from 15.5 to 7.75 mg/kg/day and prednisone from 10 to 5 mg/day (Fig. 5), and she received a full course of intravenous acyclovir. The patient recovered promptly, and she is currently well 2 years later, with normal hepatic function and receiving relatively reduced immunosuppression.

Case 2: A 21-year-old female underwent emergency orthotopic liver transplantation for fulminant hepatic failure following right hepatectomy for fibrolamellar hepatoma. Her original liver disease was congenital tyrosinemia and macronodular cirrhosis. At the time of liver transplantation, it was found that her portal vein had been ligated at the time of partial hepatectomy. This necessitated the use of a venous graft for portal vein reconstruction. Her post-operative course was quite uneventful and she was discharged with normal hepatic function (Fig. 8). She was re-admitted 6 months later with elevation of liver enzymes. During her work-up an

Fig. 18. Low power photomicrograph of bowel wall from case 3 showing resolving lesion. Notice flattened regenerating epithelium covering upper portion of bowel wall. The extent of remaining infiltrating cells is estimable at this power. Notice involvement of submucosa, muscularis propria and serosal aspect (H and E).

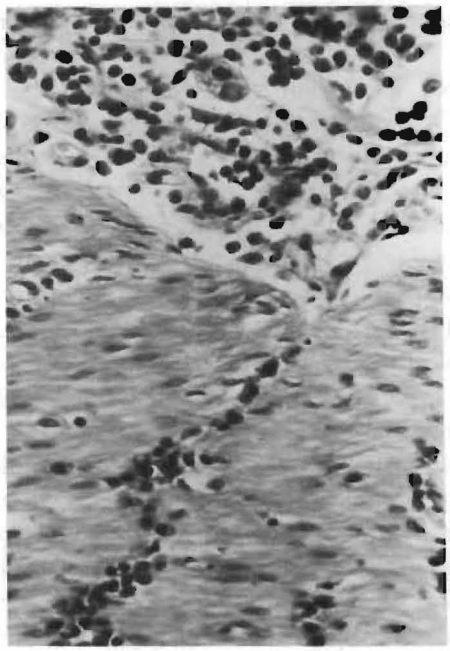

Fig. 19. Close-up of muscularis propria shown in Fig. 18. Infiltrating cells are small mature plasma cells (H and E).

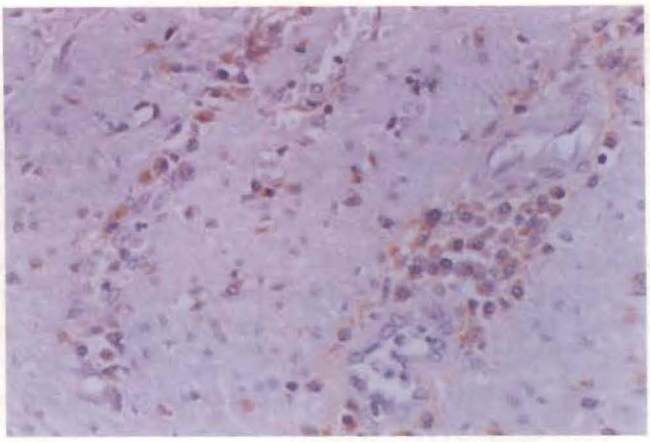

Fig. 20. Immunoperoxidase stain of intracytoplasmic lambda light chains in plasma cells infiltrating muscularis propria in patient 3 (cf. Figs. 18, 19). Note crisp granular intracytoplasmic staining of the cells in question (Avidin-biotin complex immunoperoxidase, diaminobenzidine development).

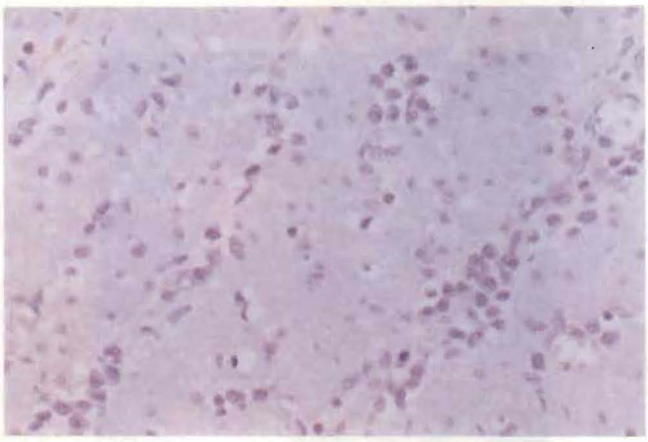

Fig. 21. Immunoperoxidase preparation similar to Fig. 20 with antibody directed against kappa light chain. No staining of plasma cells is evident.

ERCP was performed, which demonstrated a stricture of the common bile duct. The patient developed severe pancreatitis and adult respiratory distress syndrome as a complication of the ERCP. The patient's condition was further complicated by gastrointestinal hemorrhage from an undetermined site. As soon as she was stable enough, she was taken to the operating room for exploration, with the intention of revising her biliary tree. She was found to have multiple tumors involving the

terminal ileum, ascending and transverse colon (Fig. 9). An extended right hemicolectomy was performed, as well as a Roux-en-y choledochojejunostomy revision of the bile duct. A total of 27 cm of terminal small bowel and 30 cm of adjacent colon was resected. This portion of bowel contained a total of 16 separate tumors, most of which had yellow-green, necrotic appearing bases (Fig. 9). Several tumors grossly involved the entire thickness of bowel wall. Microscopically a focus of extra-intestinal tumor extension was seen. Eight regional lymph nodes were negative for tumor. The intestinal tumors were extensively necrotic (cf. Fig. 1) and contained a generally polymorphous population of lymphoid cells and occasional large atypical cells (Fig. 10). At least one of the tumors was judged to be monoclonal on the basis of strongly positive immunofluorescence staining for kappa light chain (Fig. 11) and concomitant negative staining for lambda light chain (Fig. 12).

Her post-operative management consisted of a significant reduction of immunosuppression to approximately one-third previous levels, CsA from 13 to 5 mg/kg/day and prednisone from 10 to 7.5 mg/day (cf. Fig. 8). Her recovery was

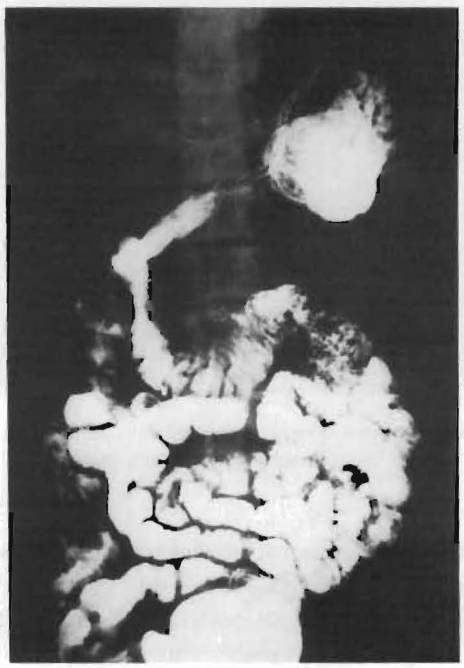

Fig. 22. Follow-up small bowel study in case 3 at approximately 3 months after allograft nephrectomy demonstrating no evidence whatsoever of GI tract involvement.

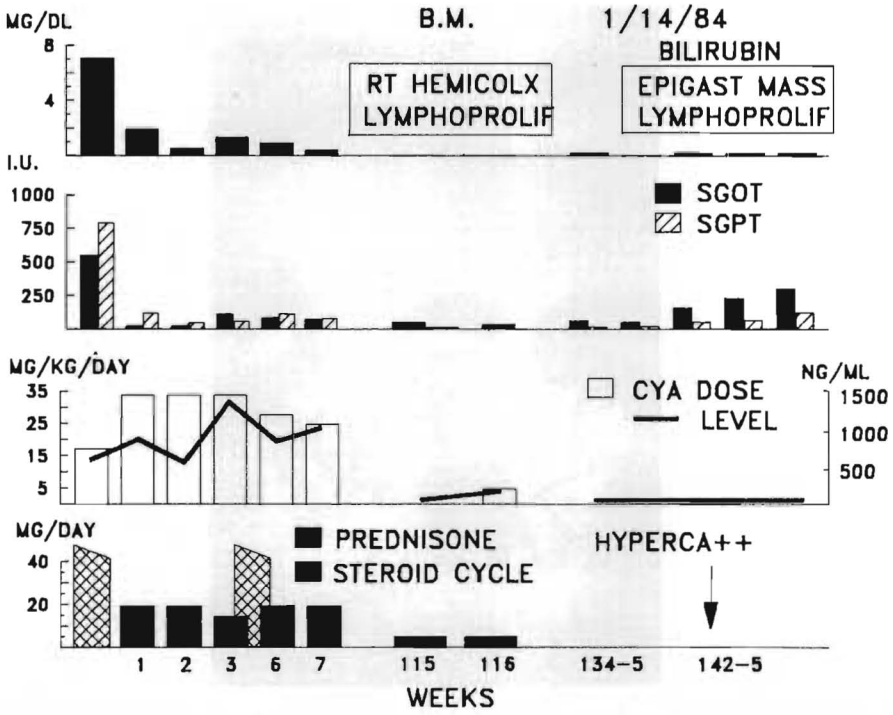

Fig. 23. Post-operative course of a 4-year-old male liver transplant recipient who presented with terminal ileal PTLD, and then developed 2 large epigastric recurrences which each required resection and cessation of immunosuppression for control.

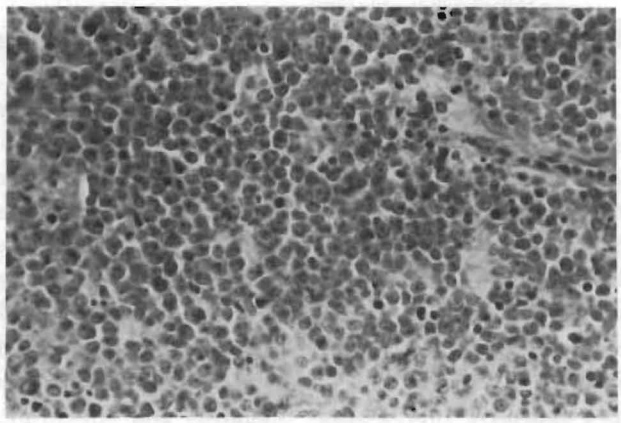

Fig. 24. Representative section of tumor from case 4. Monomorphous proliferation of small noncleaved cells are admixed with smaller dark cells representing examples of individual cell necrosis. Several recurrences of this tumor showed an identical pattern with no morphologic evidence of tumor cell maturation.

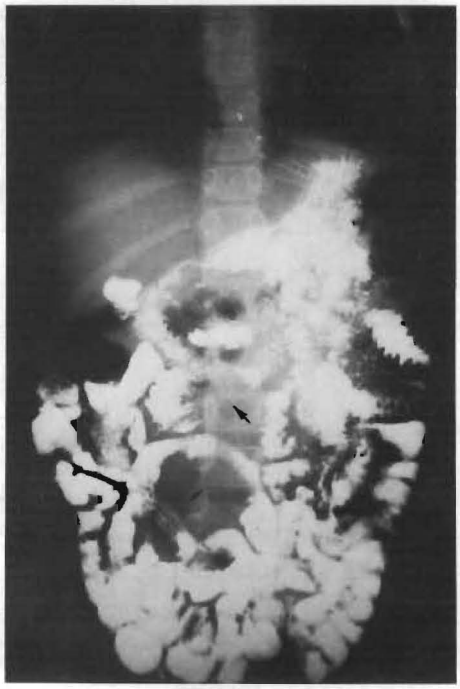

Fig. 25. Small bowel study to investigate the first appearance of recurrent PTLD in the epigastrium. Radiograph demonstrates displacement of small bowel by large anterior epigastric mass (arrows), but with apparently no invasion of the small bowel mucosa.

rapid, and she is alive and well with normal liver function approximately 3 years later.

Case 3: This 16 year old male with Lawrence-Moon-Biedl syndrome underwent a cadaveric renal transplant for end-stage renal disease secondary to his primary disorder. His post-operative course was smooth and he was discharged in 4 weeks (Fig. 13). He presented 2 months later with severe diarrhea and guaiac positive stools. After being observed in the hospital for 3 days, the patient developed an acute abdomen secondary to a perforated hollow viscus. He was explored immediately and was found to have multiple tumors involving the ileum and the hepatic flexure of the colon, with 3 areas of obvious small bowel perforation. The gross appearance was similar to that described in Fig. 9 for Case 2. (Fig. 14 represents the pre-operative radiographic diagnosis and appearance of a small bowel PTLD in a different patient with similar findings). Segmental resections of the small bowel and colon with primary anastomoses were performed to remove only some of the tumors. Fig. 15 represents the histology of 1 of the primary

lymphoproliferations in this patient. These were in general polymorphous with plasmacytoid differentiation. Immunoperoxidase staining of cytoplasmic lambda and kappa light chains is shown in Figs. 16 and 17, respectively. Of 13 tumors so stained, 11 were monoclonal with lambda: kappa ratios of up to 116:1. Although the regional lymph nodes were not involved, all of the tumors could not be removed. Post-operatively the patient's CsA dose was discontinued completely and his prednisone was maintained at 15 mg/day. He made a surprisingly smooth recovery, except for repeated episodes of lower gastrointestinal tract bleeding and the rapid development of intractable rejection which required allograft nephrectomy approximately 5 weeks after the initial exploration. At the time of allograft nephrectomy, the patient's peritoneal cavity was again explored and appeared to be totally tumor-free except for an area of small bowel adjacent to an anastomosis which felt thickened. This area was resected with a primary anastomosis (Fig. 18 displays a regenerating mucosal epithelium with residual cells throughout the bowel wall in the specimen taken during the second resection procedure). The plasmacytic nature of the cells is seen in Fig. 19. Again, immunoperoxidase staining of intracytoplasmic immunoglobulins from 3 separate sites revealed marked restriction of the mature plasma cells to expression of lambda light chain (Figs. 20, 21). The process was interpreted pathologically as resolving lymphoproliferative lesions, both grossly and microscopically. Immunosuppression was obviously stopped completely at this time due to allograft nephrectomy and the patient recovered uneventfully. Five years later he remains well and free of tumor (Fig. 22)

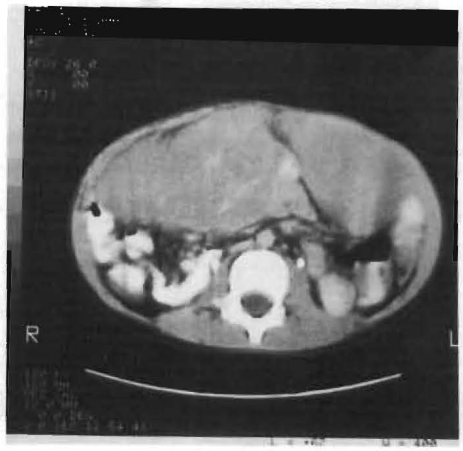

Fig. 26. CT scan investigation of the epigastric mass depicted in Fig. 25, further defining a large, solid, non-invading mass anteriorly in the epigastrium. CT studies proved to be an excellent method of following the lesion.

and awaits a new kidney transplant after having been placed back on our candidate list.

Case 4: This 4-year-old male underwent an uneventful orthotopic liver transplant for biliary atresia with failed Kasai procedure. His post-operative course was smooth and he left the hospital with excellent function 7 weeks later (Fig. 23). Two years thereafter he presented to his local hospital with a painful and tender right lower quadrant mass which was suspected of being a periappendiceal abscess. At exploration he was found to have a PTLD involving the terminal ileum. All grossly visible tumor was completely resected. Pathologic studies revealed a monomorphous proliferation of predominantly small noncleaved lymphoid cells (Fig. 24). Neither large atypical cells nor areas of plasmacytoid differentiation were seen. The tumor was monoclonal lambda by immunocytochemistry.

Post-operatively his CsA was decreased from 5.2 mg/kg/day to no drug for 7 days and then resumed at 2.5 mg/kg/day. Prednisone was decreased from 20 to 5 mg/day. He did well initially, but 5 months later he developed a large epigastric mass involving the small bowel mesentery. Radiographic studies are presented in Figs. 25 and 26. All immunosuppression was completely stopped for 3 months. The

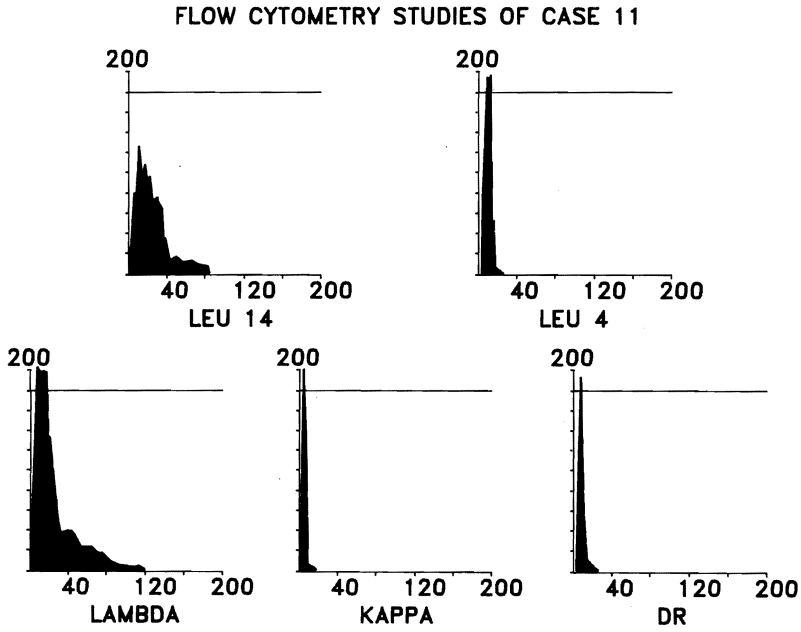

Fig. 27. Schematized representation of flow cytometric analysis of case 4. Leu 14-positive cells represented 62.8% of the population. Leu 4 (11.6%), lambda (38.4%), kappa (6.0%), and Dr (19%) antigens are also represented.

patient developed a refractory hypercalcemia (17 mg/dl) and there was no change in tumor size. At 8 months after the initial diagnosis of PTLD was made, he underwent an almost complete excision of the large epigastric PTLD, which was favorably situated on the mesentery. Histopathology showed a lesion identical to the first occasion. Flow cytometry (Fig. 27) showed the tumor to again demonstrate clonal restriction for lambda light chain. Currently, at about 1 month following his latest resection, he is normocalcemic and progressing well, off all immunosuppression, with no gross evidence of tumor and with very reasonable liver functions.

Case 5: This 34-year-old male underwent an orthotopic liver transplant for end-stage liver disease secondary to sclerosing cholangitis associated with Crohn's disease. He promptly recovered and was discharged in 4 weeks. Approximately 5 months after transplantation, the patient returned complaining of malaise, anorexia and fever (Fig. 28). Work-up revealed marked inguinal and retroperitoneal lymphadenopathy (Fig. 29). Operative biopsies revealed a polymorphous PTLD characterized by areas of necrosis and numerous atypical large cells, some resembling Reed-Sternberg cells. The cellular background contained

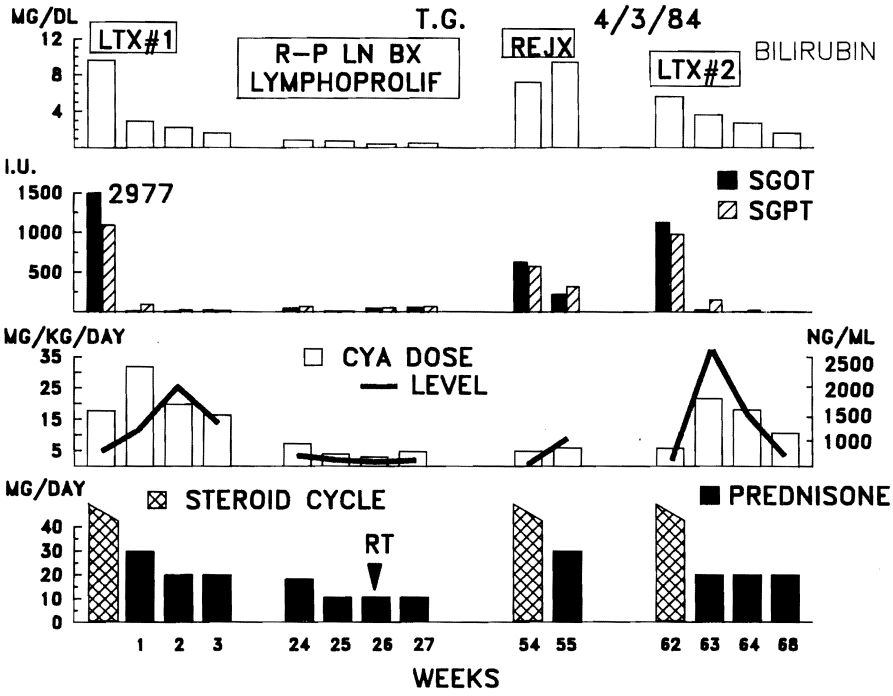

Fig. 28. Post-operative course of a 32-year-old male liver transplant recipient who presented with generalized lymphadenopathy and Hodgkin's-type PTLD, requiring marked reduction in immunosuppression and radiation for control, and who rejected his liver requiring retransplantation.

significant numbers of lymphocytes and eosinophils, leading to a diagnosis of Hodgkin's disease. EBV genome was demonstrated within the tumor by DNA hybridization. Immunocytochemical analysis of immunoglobulins revealed a polyclonal pattern. Whether this represents a bona fide case of Hodgkin's disease or is a variant of PTLD is currently under investigation.

The patient's immunosuppression was significantly reduced, CsA from 7.5 to 3.3 mg/kg/day and prednisone from 17.5 to 10 mg/day. No response was observed and he subsequently received a course of radiotherapy. Remission followed immediately, but the patient underwent severe rejection requiring retransplantation. There was no evidence of residual tumor at the time of his second liver transplant. He remains well, with normal liver function and no evidence of tumor almost 2 years later.

Case 6: This 43-year-old male was admitted with end-stage liver disease secondary to Laennec's cirrhosis and hepatorenal syndrome. He underwent orthotopic liver transplantation, followed by an extremely stormy post-operative course. This was characterized by severe renal failure, fungemia, several episodes of rejection and, in general, very slow recovery. However, he slowly improved and was discharged from the hospital with good hepatic and renal function (Fig. 30). Six months after transplantation, the patient was admitted to his local hospital with shortness of breath and a productive cough. Pneumocystis carinii pneumonia (PCP) and disseminated cytomegalovirus (CMV) infection were diagnosed (Fig. 31). CsA therapy was stopped (5.5 to 0 mg/kg/day) and prednisone was decreased from 7.5 to 5 mg/day (Fig. 30). He also received trimethoprim sulfamethoxazole therapy, required ICU care and intubation with respiratory support. He slowly improved and his chest picture resolved significantly except for a persistant, peculiar nodular infiltrate which was evident on chest X-ray (Fig. 32) and CT scan (Fig. 33). He underwent an open lung biopsy of one of the suspicious areas which revealed a monomorphous PTLD (cf. Fig. 4). Immunosuppression was completely stopped and the patient's chest pathology resolved completely (Fig. 34). He was discharged on low maintenance immunosuppression, and at the present time, approximately 7 months later, he is stable, clinically tumor-free and maintains good liver function.

Kaposi's sarcoma

Introduction

Kaposi's sarcoma is a rare form of tumor in the general population, particularly in the Western hemisphere, although its incidence is higher in populations of

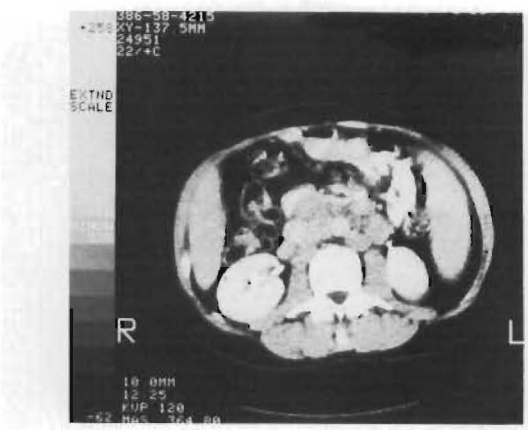

Fig. 29. CT scan of the abdomen demonstrating periaortic enlarged nodes as part of the generalized lymphadenopathy of this patient's presentation.

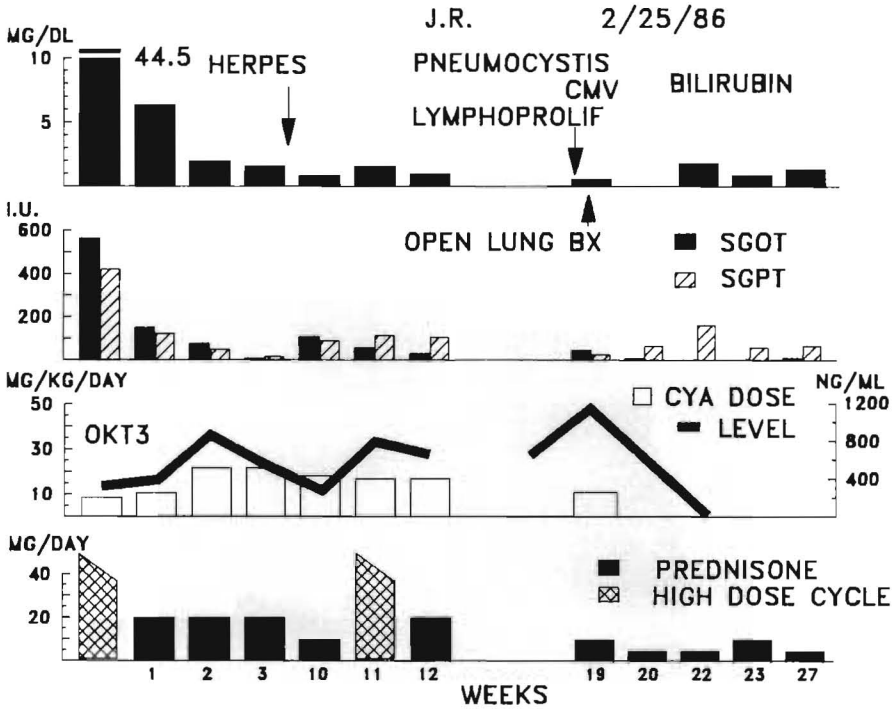

Fig. 30. Post-operative course of a 43-year-old male liver transplant recipient who presented with PCP and generalized CMV infection and respiratory failure with PTLD of the lung diagnosed by open lung biopsy. This required cessation of immunosuppression for complete resolution.

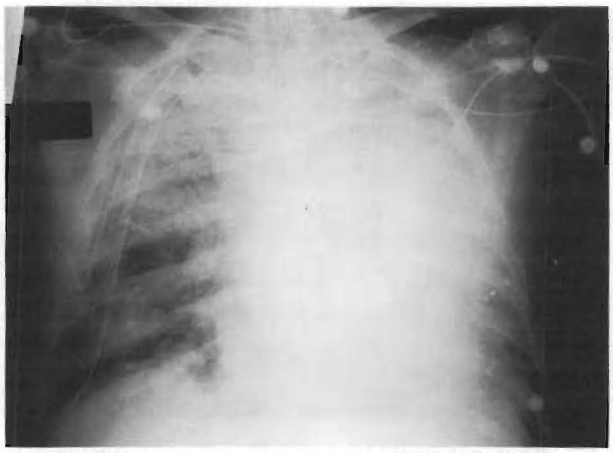

Fig. 31. Chest x-ray demonstrating severe white-out of the lungs representing PCP, CMV pneumonitis and PTLD of the lung with respiratory failure.

Mediterranean and Jewish ancestry and in certain regions of Africa (40). In the last decade there has been a sharp increase in the incidence of this tumor as a result of the spread of AIDS (41).

Another group that is at high risk for development of Kaposi's sarcoma is represented by the allograft transplant population. This lesion has been seen with

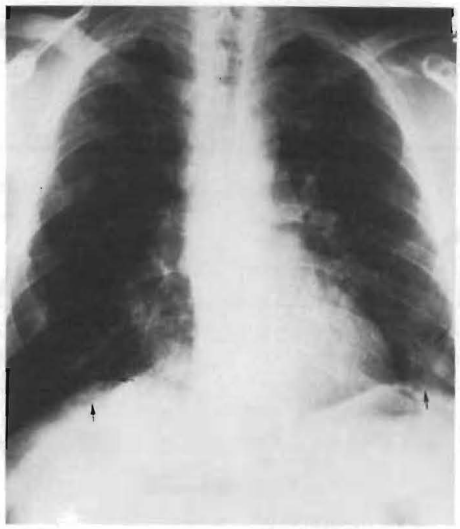

Fig. 32. Chest x-ray demonstrating a persistent, peculiar nodular infiltrate which was diagnosed as PTLD on open lung biopsy.

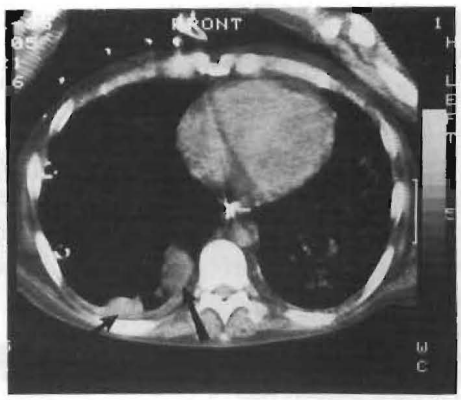

Fig. 33. CT scan of chest further demonstrating and delineating these peculiar, persistent lesions seen on chest x-ray.

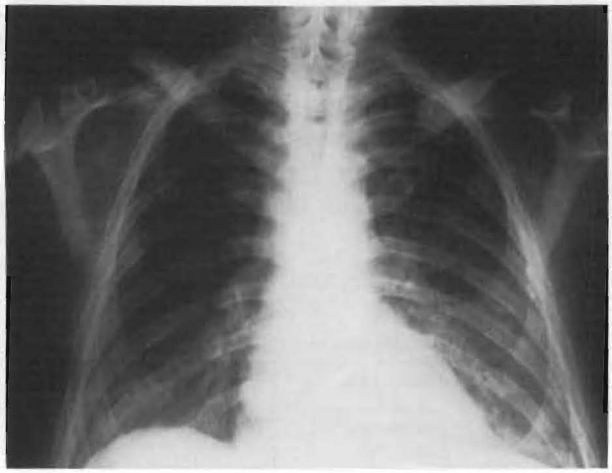

Fig. 34. Chest x-ray prior to patient's discharge demonstrating complete resolution of the PTLD of the lung.

much less frequency than PTLDs in our series. Nevertheless, striking similarities in therapeutic response lead us to believe that analogous host mechanisms may be at work in both types of disorders.

Etiology

The etiology of this unusual form of sarcoma is still unknown, although an ever expanding body of knowledge seems to suggest certain associated factors. Several

studies performed in various centers around the world have shown a correlation between the development of Kaposi's sarcoma and depressed immune system states. The T4/T8 ratio is depressed in these patients, although this does not appear to be a prerequisite for the development of this tumor (41). The presence of CMV infection as documented by serologic studies is almost the rule (41). The infection does not necessarily need to be de novo. Previous exposure with reactivation of "dormant" virus seems to be the case in a good number of patients (41). The scenario that is most often postulated is that of a debilitated immune system attacked by CMV, with the virus somehow inducing or contributing to the formation of Kaposi's sarcoma.

Presentation and course

Kaposi's sarcoma may present as characteristic purplish, raised, firm and non-tender skin lesions. A more widespread form of the disease may involve the gastrointestinal tract, lungs, and/or lymph nodes. The skin lesions are normally asymptomatic, but the gastrointestinal involvement may cause such severe symptoms as nausea, vomiting, abdominal pain, loss of appetite or hemorrhage. Fever and weight loss may also occur. Concomitant infections, particularly with candida, are not infrequent. Left alone, the disseminated form of the disease will progress to cachexia and death.

Table 6. Kaposi's sarcoma in kidney transplant recipients.

Case	Sex	Age (yr) at Tx	Date of Tx	Time (Mo) of onset of sarcoma after Tx	Involvement	Clinical presentation	CMV infection
1	M	59	Nov. 2, 1981	3	Diffuse cutaneous	Skin lesions of arms, legs and penis	Reactivation
2	M	51	Dec. 3, 1982	10	Diffuse cutaneous	Skin lesions of forearm + penis	Reactivation
3	M	34	Sept. 22, 1985	6	Diffuse cutaneous, diffuse GI	Skin lesions arising initially around operative incision and then diffuse; severe GI symptoms	Reactivation

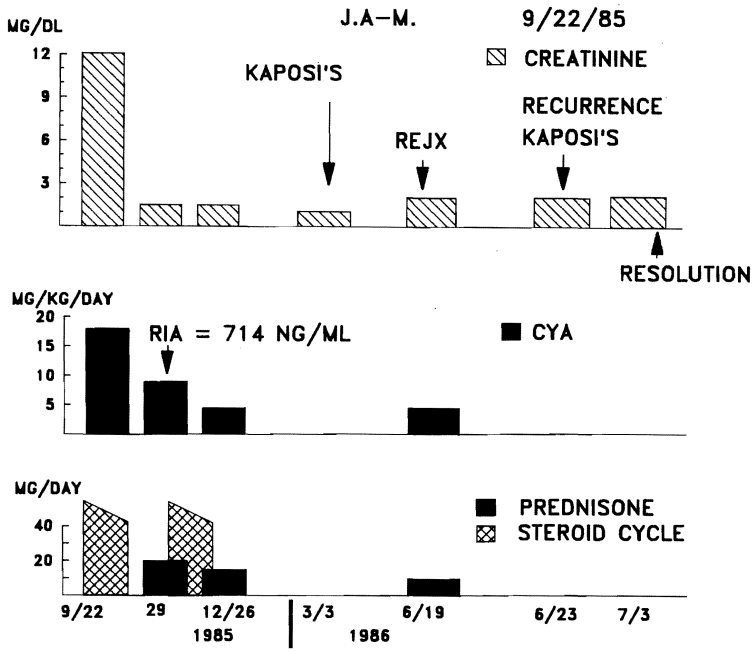

Fig. 35. Post-operative course of a 35-year-old male kidney recipient who developed diffuse Kaposi's sarcoma of the skin and GI tract requiring complete cessation of immunosuppression for relative tumor control although the kidney is being slowly rejected.

Contemporaneous infection	Original immunosuppression	Change in immunosuppression		Other anti-tumor treatment	Fate of patient	Graft function
		CsA (mg/kg/d)	Prednisone (mg/d)			
None	CsA, Pred	14–1.35	10–10	None	Died 5/16/86, after Re-KTx (Systemic TB and Listeria meningitis)	Rejected, Re-KTx
None	CsA, Pred	9.8–2.5	15–10	Radiation	Alive with new skin lesions; receiving low dose CsA	Retained to date
None	CsA, Pred	4.2–0	15–0	None	Alive in complete remission;-re-institution of low dose CsA + prednisone led to rapid tumor recurrence which resolved when CsA discontinued.	Retained to date; but slowly being rejected

Fig. 36. Typical skin lesions of Kaposi's sarcoma around the transplant scar.

Patient population

We have identified 3 patients (0.1%) in our entire transplant population who have developed Kaposi's sarcoma following kidney allografting (Table 6). Thus, Kaposi's sarcoma accounts for 7.7%, and PTLD for 92.3% of our total tumor population. This proportion is in keeping with recent published figures (17).

All 3 patients were male, received kidney transplants, and were Saudi Arabian in origin. All 3 had evidence of reactivated CMV infection.

Case Report of Kaposi's sarcoma patient

This 35-year-old Saudi male underwent a cadaveric kidney transplant for end-stage renal disease (Fig. 35). The allograft had immediate and sustained function. Prior to transplantation, he had been found to be PPD positive and had received prophylactic anti-tuberculin therapy. Post-transplant he developed schistosomiasis of the bladder and epididymitis, both of which were satisfactorily treated. Six months post-transplant, he developed purplish, raised skin lesions around the transplant scar (Fig. 36), with subsequent dissemination to the chest and upper arms (Fig. 37). A skin biopsy of one of the allograft scar lesions demonstrated Kaposi's sarcoma. He rapidly developed severe gastrointestinal symptoms and was found to have diffuse involvement of the GI tract by UGI series (Figs. 38, 39). This was confirmed by endoscopic biopsy. Histologic examination of the biopsy showed

Fig. 37. Typical skin lesions of Kaposi's sarcoma on the arm. These lesions were diffuse.

Fig. 38. Small bowel series demonstrating diffuse widespread involvement of GI tract with Kaposi's sarcoma (biopsy proven). Arrows demonstrate thick, infiltrated rugal folds with tumor.

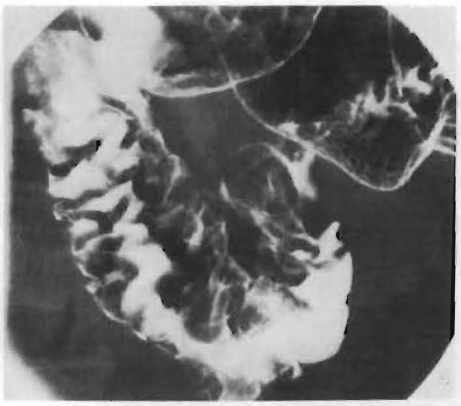

Fig. 39. Close-up of small bowel series above, demonstrating the prominent folds in stomach infiltrated with tumor.

a characteristic proliferation of spindle cells which formed vascular slits containing erythrocytes (Fig. 40). The appearance was similar to that of the skin biopsy.

Complete cessation of immunosuppressive therapy (Fig. 35) led to rapid resolution of the lesions, evidenced most dramatically in the GI tract (Fig. 41). A reduction of the number and size of the skin lesions also occurred. The patient maintained relatively good renal function even without immunosuppression. An attempt to restart low dose immunosuppression with CsA and prednisone led to a

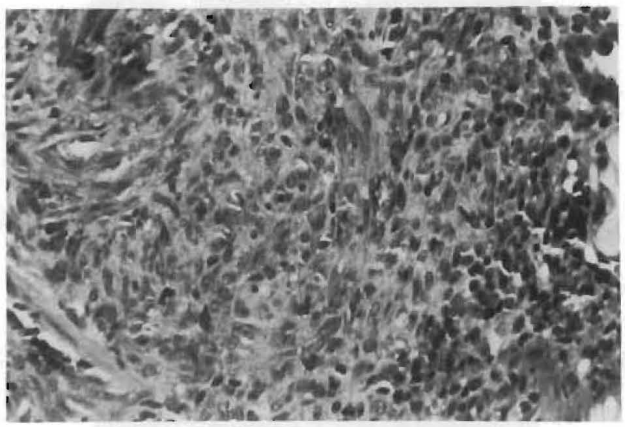

Fig. 40. Kaposi's sarcoma in a gastric biopsy of the kidney transplant recipient. A proliferation of spindle cells forms vascular slits which contain red cells. In one end of the photograph glandular epithelium is present (H and E).

Fig. 41. Follow-up GI series after complete discontinuation of immunosuppression and resolution of GI symptoms demonstrates normal mucosal pattern and no evidence of Kaposi's sarcoma.

rapid reappearance of the skin lesions and GI symptoms. Consequently, the immunosuppression was again terminated, again with resolution of the lesions.

The kidney graft continues to function 10 months later, but an increase in the allograft size and creatinine indicate slow, progressive renal rejection. The patient remains relatively well with minimal remaining lesions of the skin and no evidence of gastrointestinal lesions.

Discussion

The spectrum of lymphoproliferations occurring in post-transplant immunosuppressed patients and associated with the Epstein-Barr virus has been recognized for several years. PENN has recently estimated that PTLDs constitute 41% of all tumors occurring in patients immunosuppressed with CsA, in contrast to 12% of tumors in conventionally immunosuppressed allograft recipients (17). Our current report is based on the largest single series of CsA-immunosuppressed individuals to date.

The favorable outcome of a significant number of these cases in response to modulation of immunosuppression has raised the challenge, of defining both host and tumor variables that characterize the mechanisms and limitations of immune controls in this system. We have presented evidence that most polyclonal and many monoclonal tumors remain subject to host control mechanisms if immune function is allowed to recover at least partially by a reduction of immunosuppressive therapy. This observation indicates that a diagnosis of monoclonal lymphoproliferation in and of itself is not equivalent to a diagnosis of malignant lymphoma in these patients.

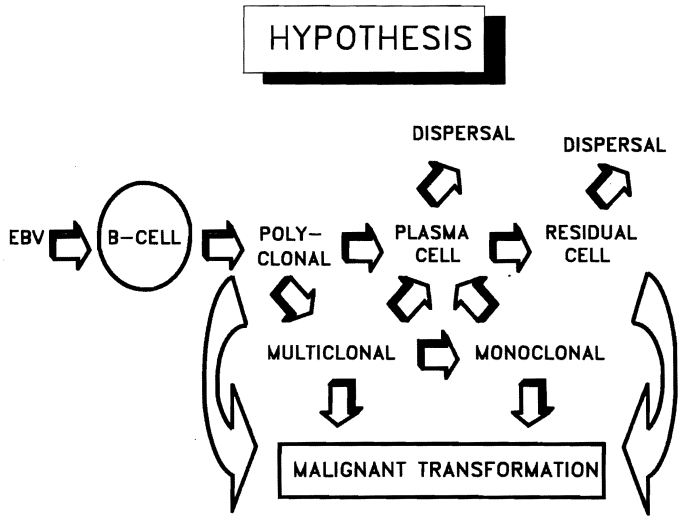

Fig. 42. Suggested pathogenetic sequence of PTLDs. See text for Discussion.

Our current concept of the pathogenesis of this disorder is indicated in Fig. 42. This represents an extension from that previously published (42). EBV infects the B-lymphocyte and causes a polyclonal proliferation of cells. In cases of infectious mononucleosis occurring in non-immunosuppressed hosts, this normally leads to very early plasmacytic maturation, induced by a variety of lymphokines. The fate of these cells is currently unknown. They are dispersed early from the circulation and in their place are seen infected cells that do not display the appearance of plasma cells. These are designated as residual cells in the diagram and are themselves dispersed by a variety of mechanisms, in particular by cytotoxic T-cells. Again, the extent and range of long-term survival of this residual cell type is poorly characterized.

In immunosuppressed transplant recipients, a similar sequence of events may occur. Indeed, it is likely that some of our patients sustain an illness identical to normal or subclinical infectious mononucleosis, since the frequency of primary and reactivation infection exceeds the number of PTLDs. In other cases, iatrogenic immunosuppression may allow time for clonal selection processes to operate. This may result in the overgrowth of one or several clones, resulting in a multiclonal or monoclonal proliferation. Whether this process represents a response to external antigenic stimulation or events indigenous to the cell clone in question is not at present answerable. Both processes appear equally likely.

This form of monoclonal proliferation, although poorly controlled and histologically invasive, is probably still amenable to reconstituted host immune control mechanisms. We suggest that clinical regression is accompanied by a maturation of cells into plasma cells with subsequent dispersal and organ repair. This would appear to be the sequence of events followed by the tumor in case 3. We have observed similar clinical behavior in other monoclonal tumors restricted to gut or lungs. It is possible that monoclonal tumors restricted to single organs are especially responsive to immunomodulation.

It is not yet clear at what point, if any, reconstitution of the immune system can no longer switch off tumor growth. Deaths both of patients with polyclonal and monoclonal tumors have seemed more related to the lateness of diagnosis than to any other factor. It is possible but difficult to prove at the moment that some of the patients who died had tumors which had sustained an irreversible change or changes conferring complete autonomy and metastatic potential (Fig. 42) but at present, the specific critical change remains undefined.

One example of a tumor which we consider to be more than a benign lesion but somewhat less than a fully developed malignancy is that of case 4. This recurrent neoplasm manifested a karyotypic translocation and has not completely regressed in the absence of immunosuppression (NALESNIK et al., manuscript in preparation). Despite its large size and multiple recurrences, it has not demonstrated metastatic potential. The prolonged survival of this patient as compared to similar cases in the literature argues that the therapeutic dilemma has been successfully handled to date.

We consider polyclonal proliferations to be at the more benign end of the spectrum of PTLDs. However, occasional patients exhibit an explosive onset of widespread polyclonal lymphoproliferation with an acute course that often leads to death before the diagnosis can be established. At our current level of knowledge we presume that this represents an exaggerated host defect in the handling of the Epstein-Barr virus infection.

The instinctive approach to the treatment of the PTLDs would be chemotherapy. However, based on our clinical results the more logical initial

therapy appears to be manipulation of the immune system. A drastic reduction or even complete cessation of immunosuppressive therapy elicits a rapid response in those cases amenable to this therapy. Interestingly enough, rejection did not occur in some of our cases even if the immunosuppression was reduced to up to 75% of the initial dose (18). Therefore, in practice we generally assess the clinical response to a 50% reduction of immunosuppressive therapy. The remission is usually complete and the immunosuppressive regimen may later be resumed at previous or reduced levels. The temptation to treat with chemotherapy should be resisted since this would further reduce the host immune response, causing an even worse exacerbation of PTLD. In those monoclonal and monomorphous tumors which do not respond to a reasonable trial of reduced immunosuppression, aggressive antilymphoma therapy may be unavoidable. In practice, these unfortunate patients are usually moribund at the outset, have a very rapid downhill course, and often die with multiple infections. Add to this the fact that there is still no absolute a priori pathologic indicator of which tumors will and which will not respond to host immune restoration in a given patient, the case for immunosuppressive dose modulation as an initial therapy appears complete.

Comments regarding Kaposi's sarcoma must be even more preliminary, considering the low frequency of this lesion in our population. Based on the behavior of this tumor in our series, the possibility exists that this condition may also represent an as yet unrecognized spectrum of disorders. The hypothesis that Kaposi's sarcoma may be a reversible hyperplasia has long been suspected (13, 24, 27, 43). This argument is based on the following observations: 1) the lesion has a male: female ratio of 15:1, implying a hormone-responsive factor in pathogenesis, 2) the lesion often appears in "crops", a behavior unusual for de novo neoplasms, 3) an 84% rate of regression in transplant patients following reduction of immunosuppression is claimed, 4) no well-defined cluster of neoplastic cells is observed in early lesions, 5) tumor emboli are not seen in sites of presumed metastases, 6) sites of extracutaneous involvement are readily predictable. The persistence of skin lesions in our case, accompanied by the disappearance of histologically identical gastrointestinal lesions, indicates that our current classification of this disorder is inadequate.

Many basic questions regarding oncogene activation, viral integration into host genome, specific host immune defects, etc. remain to be answered. Continued analysis of these lesions in our patients and in similar patients from other institutions, as well as animal model studies, will continue to lead to important insights into these interesting disease processes.

References

(1) EHRLICH, P.: In: HIMMELWEIT, F. (ed.): The collected papers of Paul Ehrlich. Vol. 11. Pergamon Press, London 1957.

(2) THOMAS, L.: Discussion of paper by P. B. Medawar (1957). Reactions to homologous tissue antigens in relation to hypersensitivity, March 12 and 13, 1957, New York City. (Symposium No. 9, New York Academy of Science). In: LAWRENCE, H. S. (ed.): Cellular and Humoral Aspects of the Hypersensitive States; p. 530. Paul Hoeber, Inc., New York 1959.

(3) BURNET, F. M.: Cancer: A biological approach. Brit. Med. J. *1:* 779 and 841 (1957).

(4) BURNET, F. M.: The concept of immunological surveillance. Progr. Exp. Tumor Res. *13:* 1 (1970).

(5) STUTMAN, O.: Immunologic surveillance revisited. In: Immunity to Cancer; pp. 323–345. Academic Press, New York 1985.

(6) STUTMAN, O.: The immunological surveillance hypothesis. In: Basic and Clinical Tumor Immunology; pp. 1–81. Martinus Nijhoff, Boston 1983.

(7) PAGE, A. R., A. E. HANSEN, R. A. GOOD: Occurrences of leukemia and lymphoma in patients with agammaglobulinemia. Blood *21:* 197 (1963).

(8) PENN, L., W. HAMMOND, L. BRETTSCHNEIDER, T. E. STARZL: Malignant lymphomas in transplantation patients. Transplant Proc. *1:* 106 (1969).

(9) STARZL, T. E., I. PENN, C. W. PUTNAM, C. G. GROTH, C. G. HALGRIMSON: Iatrogenic alterations of immunlogic surveillance in man and their influence on malignancy. Transplant Rev. *7:* 112–145 (1971).

(10) FILIPOVICH, A. H., D. ZERBE, B. D. SPECTOR, J. H. KERSEY: Lymphomas in persons with naturally occurring immunodeficiency disorders. In: MAGRATH, I. T., G. T. O'CONNOR (eds.): Pathogenesis of Leukemias and Lymphomas: Environmental Influences; pp. 225–234. Raven Press, New York 1984.

(11) ZIEGLER, J. L., J. A. BECKSTEAD, P. A. VOLBERDING, D. I. ABRAMS, A. M. LEVINE, R. J. LUKES, P. S. GILL, R. L. BURKES, P. R. MEYER, C. E. METROKA, J. MOURADIAN, A. MOORE, S. A. RIGGS, J. J. BUTLER, F. C. CABANILLAS, E. HERSH, G. R. NEWELL, L. J. LAUBENSTEIN, D. KNOWLES, C. ODAJNYK, B. RAPHAEL, B. KOZINER, C. URMACHER, B. D. CLARKSON: Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. N. Eng. J. Med. *311:* 565–570 (1984).

(12) BORING, C. C., R. K. BRYNES, W. C. CHAN, N. CAUSEY, H. R. GREGORY, M. R. NADEL, R. S. GREENBERG: Increase in high-grade lymphomas in young men. Lancet *1:* 857–859 (1985).

(13) PENN, I.: Tumors arising in organ transplant recipients. Adv. Cancer Research *28:* 31–61 (1978).

(14) PURTILO, D. T.: Defective immune surveillance in viral carcinogenesis. Lab. Invest. *51:* 373–385 (1984).

(15) SHEIL, A. G. R., S. FLAVEL, A. P. S. DISNEY, T. H. MATHEW: Cancer development in patients progressing to dialysis and renal transplantation. Transplant Proc. *17:* 1685–1688 (1985).

(16) PURTILO, D. T., J. P. S. YANG, C. K. CASSEL, P. HARPER, S. R. STEPHENSON, B. H. LANDING, G. F. VAWTER: X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). Lancet *1:* 935 (1975).

(17) PENN, I.: Cancers following Cyclosporine Therapy. Transplantation *43:* 32–35 (1987).

(18) STARZL, T. E., M. A. NALESNIK, K. A. PORTER, M. HO, S. IWATSUKI, B. P. GRIFFITH, J. T. ROSENTHAL, T. R. HAKALA, B. W. SHAW, R. L. HARDESTY, R. W. ATCHISON, R. JAFFE, H. T. BAHNSON: Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. Lancet *8377:* 583–587 (1984).

(19) FRIZZERA, G., D. W. HANTO, K. J. GAJL-PECZALSKA, J. ROSAI, R. W. MCKENNA, R. M. SIBLEY, K. P. HOLAHAN, L. L. LINDQUIST: Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. Cancer Research *41:* 4262–4279 (1981).

(20) HANTO, D. W., K. J. GAJL-PECZALSKA, G. FRIZZERA, D. C. ARTHUR, H. H. BALFOUR, K. MCCLAIN, R. L. SIMMONS, J. S. NAJARIAN: Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation. Ann. Surg. *198:* 356–369 (1983).

(21) Hanto, D. W., G. Frizzera, K. J. Gajl-Peczalska, R. L. Simmons: Epstein-Barr virus, immunodeficiency, and B-cell lymphoproliferation. Transplantation *39:* 461–472 (1985).
(22) Starzl, T. E., I. Penn, C. G. Halgrimson: Immunosuppression and malignant neoplasm. N. Engl. J. Med. *283:* 934 (1970).
(23) Iwatsuki, S., W. P. Geis, Z. Molnar, J. L. Giacchino, T. S. Ing, J. E. Hano: Systemic lymphoblastic response to antithymocyte globulin in renal allograft recipients. An initial report. J. Surg. Res. *24:* 428–434 (1978).
(24) Brooks, J. J.: Kaposi's sarcoma: A reversible hyperplasia. Lancet *2:* 1309–1310 (1986).
(25) Penn, I.: Kaposi's sarcoma in renal transplant recipients. Report of 20 cases. Transplantation *27:* 8 (1979).
(26) Zisbrod, Z., M. Haimov, H. Schanzer, E. Ambinder, L. Burrows: Kaposi's sarcoma after kidney transplantation. Report of complete remission of cutaneous and visceral involvement. Transplantation *30:* 383 (1980).
(27) Al-Suleiman, M., A. Haleen, A. Al Khader: Kaposi's sarcoma after renal transplantation. Transplant Proc. *1:* 2243–2244 (1987).
(28) Marker, S. C., N. L. Ascher, J. M. Kallis, R. L. Simmons, H. H. Balfour: Epstein-Barr virus antibody responses and clinical illness in renal transplant recipients. Surgery *85 (4):* 433–440 (1979).
(29) Klein, G., D. Purtilo: Summary: Symposium on Epstein-Barr virus induced lymphoproliferative diseases in immunodeficient patients. Cancer Res. *41:* 4302–4304 (1981).
(30) Nemerow, G. R., R. Wolfert, M. E. McNaughton, N. R. Cooper: Identification and characterization of the Epstein-Barr virus receptor on human B lymphocytes and its relationship to the C3d complement receptor (CR2). J. Virol. *55:* 347–351 (1985).
(31) Miller, G.: Epstein-Barr virus. In: Fields, B. N. et al. (eds.): Virology; pp. 563–587. Raven Press, New York 1985.
(32) Robinson, J. E., D. Smith, J. Niederman: Plasmacytic differentiation of circulating Epstein-Barr virus-infected B lymphocytes during acute infectious mononucleosis. J. Exp. Med. *153:* 235–244 (1981).
(33) Rosen, A., P. Gergely, M. Jondal, G. Klein, S. Britton: Polyclonal Ig production after Epstein-Barr virus infection of human lymphocytes in vitro. Nature *267:* 52–54 (1977).
(34) Brewster, F. E., K. S. Byron, J. L. Sullivan: Immunoregulation during acute infection with Epstein-Barr virus: Dynamics of interferon and 2'5'-oligoadenylate synthetase activity. J. Infect. Dis. *151:* 1109–1115 (1985).
(35) Ioachim, H. L.: Lymph node Biopsy; p. 42–48. J. B. Lippincott, Philadelphia 1982.
(36) Warnke, R. A.: Lymphomas in cardiac transplant recipients: Immunological phenotype. In: Malignant Lymphomas; pp. 231–238. Academic Press, New York 1982.
(37) Cleary, M. L., R. Warnke, J. Sklar: Monoclonality of lymphoproliferative lesions in cardiac transplant recipients. Clonal analysis based on immunoglobulin gene rearrangements. N. Engl. J. Med. *30:* 477–482 (1984).
(38) Cleary, M. L., J. Sklar: Lymphoproliferative disorders in cardiac transplant recipients are multiclonal lymphomas. Lancet *2:* 489–493 (1984).
(39) Nalesnik, M. A., T. E. Starzl, K. A. Porter, J. Sklar, M. L. Cleary: Genotypic analyses of Cyclosporine-associated lymphoproliferations. Transplantation *43:* 592–593 (1987).
(40) Dorfman, R. F.: Kaposi's sarcoma revisited. Hum. Pathol. *15:* 1013–1017 (1984).
(41) Safai, B., K. G. Johnson, P. L. Myskowski, B. Koziner, S. Y. Yang, S. Cunningham-Rundles, J. H. Godbold, B. Dupont: The natural history of Kaposi's sarcoma in the Acquired Immunodeficiency Syndrome. Ann. Int. Med. *103:* 744–750 (1985).
(42) Bird, A. G.: Cyclosporin A, lymphomata and Epstein-Barr virus. In: White, D. J. G. (ed.): Cyclosporin A; pp. 307–315. Elsevier Biomedical Press, Amsterdam 1982.
(43) Harwood, A. R., D. Osoba, S. L. Hofstader et al.: Kaposi's sarcoma in recipients of renal transplants. Am. J. Med. *67:* 759–765 (1979).