

ORIGINAL ARTICLE

Lymphoproliferative disorders in Oxford renal transplant recipients

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Background: Increased cancer incidence, particularly lymphoproliferative disease, is a complication of immunosuppression in organ transplantation. Non-Hodgkin's lymphomas (NHLs) occur frequently during the first year after transplantation, more so in North America than in Europe.

Methods: This study audited and correlated the demographic, clinical, pathological, and outcome features of post-transplant lymphoproliferative disorders (PTLDs) in a large centre in Oxford, and assessed whether the time of onset fitted more with the European or North American pattern.

Results: There were 1383 renal transplants in the study period and 27 patients developed lymphoma: 26 NHLs and one Hodgkin's disease (1.95%). Four of the patients never received cyclosporin. The mean time of diagnosis after transplant was 46 months. Most tumours (21/27) presented extranodally. Management included reduction of immunosuppression, surgical excision, antiviral treatment, radiotherapy, and chemotherapy. Three patients presented in the first post-transplant year—0.34% of cyclosporin managed patients—similar to the North American incidence, although the incidence of extranodal late PTLDs was also high (mean onset, 36 months v 15 months international mean). Post-transplant lymphomas were the most common malignancy associated with death in transplant patients.

Conclusions: PTLDs occurred in 2% of renal transplant patients, presenting both in the first year in association with cyclosporin use, as in North America, but also in subsequent years, giving an overall presentation time later than the international mean. The disease usually presented extranodally, accounting for the wide range of symptoms and signs. Despite awareness and active management, the disease contributed to death in more than 50% of patients with PTLDs.

The risk of non-Hodgkin's lymphoma (NHL) or post-transplant lymphoproliferative disease (PTLD) in organ transplant recipients has long been recognised to be high, and is a complication of immunosuppressive treatment.¹ A multicentre study reported in 1993 that the NHL rate was especially high during the first post-transplant year among kidney transplant patients and that the first year incidence was higher in North America than in Europe, the major centres available for comparison in the study.²

Detailed clinicopathological studies, particularly from the USA,^{3,4} have described the location, clonality, biological nature (in particular, Epstein-Barr virus (EBV) status), and responsiveness to management of these lymphoproliferative disorders. Relatively few detailed studies of this transplant complication have been undertaken outside of the USA and in particular in the UK.

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The aim of our study was to describe the essential demographic, clinicopathological, and outcome features of PTLDs in a European, and in particular a UK, transplant centre. We wanted to find out whether the UK experience of this disease was comparable to other descriptions and, in particular, whether our patients showed the European pattern as opposed to the prominent first year incidence found in the USA.²

MATERIALS AND METHODS

Patient population

The Oxford Transplant Centre undertook 1383 renal transplants from January 1975 until May 1996. From the start, the awareness of increased malignancy in transplant patients led to careful examination for, and the prospective documentation of, neoplastic complications.⁵ The prospectively maintained tumour register included 27 patients in whom the diagnosis of lymphoma or post-transplant lymphoid proliferation had been made. This included one patient with the diagnosis of Hodgkin's disease, the remainder being categorised as non-Hodgkin's lymphoma.

Histological evaluation

Formalin fixed, paraffin wax embedded histological sections from all 27 patients were available for review by three pathologists: WDB, MAD, and KCG. Immunocytochemical stains were performed to establish the lymphoid nature of the lesions (leucocyte common antigen); the type of cell—B cell (L26, JCB117) or T cell (CD3); the distinction between Hodgkin's and non-Hodgkin's disease using antibodies to CD15 (By87a) and CD30 (BerH₂), respectively; and to establish the EBV status of the tumours (latent membrane protein; CS 1–4). In most cases κ and λ light chain staining was performed to help evaluate clonality but, like others, we found that these stains were seldom helpful and we have not included the results.

Abbreviations: CNS, central nervous system; CyA, cyclosporin; EBV, Epstein-Barr virus; NHL, non-Hodgkin's lymphoma; PTLD, post-transplant lymphoproliferative disease; REAL, revised European-American lymphoma

Table 1 Patient population and tumour incidence

Patient	Age at 1st transplant	Sex	CyA	ATG	OKT3	Months to lymphoma
<i>Alive</i>						
1	13	M	Yes	No	No	43
2	51	F	Yes	Yes	No	42
3	42	F	Yes	No	No	12
4	60	M	Yes	No	No	17
5	38	M	Yes	No	No	33
6	25	F	Yes	No	No	5
7	29	M	Yes	No	No	39
8	49	F	Yes	No	No	12
9	26	F	Yes	No	No	52
10	41	M	Yes	Yes (1+2 Tx)	No	79
<i>Dead</i>						
11	53	M	Yes	No	No	68
12	56	F	Yes	Yes (1+2 Tx)	Yes	7
13	51	M	No	No	No	14
14	60	M	Yes	No	No	67
15	26	M	Yes	No	No	70
16	62	M	Yes	No	No	72
17	52	M	No	No	No	93
18	53	M	Yes	No	No	17
19	54	M	Yes	No	No	105
20	47	M	Yes	Yes (1 No 2Tx)	No	16
21	39	F	Yes	No	No	13
22	64	F	Yes	No	No	8
23	34	M	No	No	No	232
24	65	F	Yes	Yes	No	50
25	57	M	Yes	No	No	38
26	57	M	Yes	Yes	No	37
27	54	M	No	No	No	15

ATG, antithymocyte globulin; CyA, cyclosporin; OKT 3, anti-CD3 monoclonal antibody; Tx, transplant.

Clinical and demographic evaluation

A range of demographic, clinical, and outcome information was obtained from the patients' transplant folders. In common with other centres, a variety of therapeutic interventions were applied to these patients over the time span of this retrospective study, reflecting in part the uncertainty regarding the natural history and response of these tumours.

RESULTS

Patient population and tumour incidence

There were 18 male and nine female patients (M:F ratio, 2:1). The age at first transplant ranged from 13 to 65 years, with a mean of 46 years and a median of 51 years (table 1).

Immunosuppressive protocols

Twenty three of the 27 patients received initial immunosuppression based on the use of cyclosporin (CyA), whereas four patients had never received CyA (table 1). (Before 1980, patients (498) were treated with an azathioprine based protocol, after which CyA was gradually introduced, and by 1984 CyA was used routinely, often in combination with prednisolone. From 1995 onwards a uniform triple treatment regimen with CyA, azathioprine, and prednisone was used.) Six patients had also been treated with antithymocyte globulin (ATG), two of these with both their first and second transplants, the lymphoma developing with the second transplant. One patient had ATG with the first transplant but not the second when the lymphoma presented. One patient

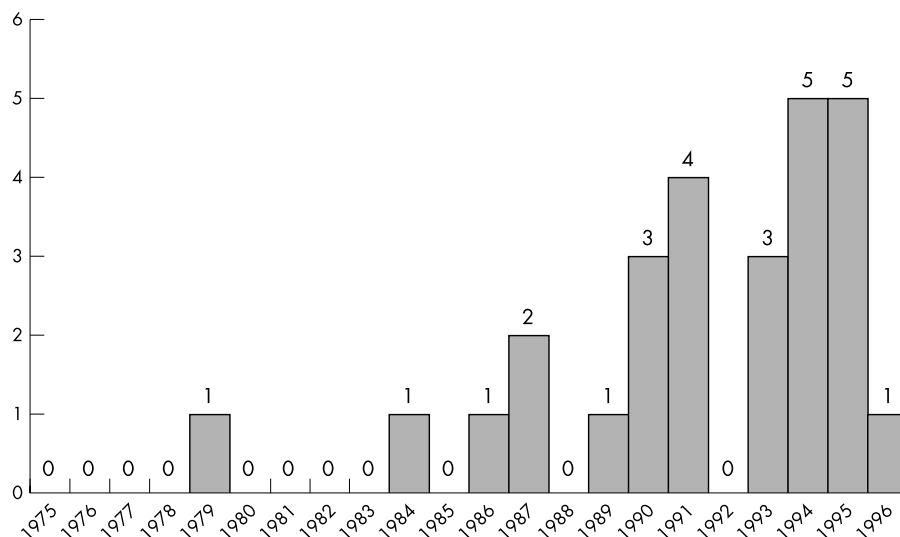


Figure 1 Lymphomas by year of diagnosis.

Table 2 Clinical presentation

Patient	Clinical presentation	Site	Group
<i>Alive</i>			
1	Pyrexia/lymphadenopathy	Neck	LN
2	Ulcerating skin lesion	Behind ear	Skin
3	Headache/personality change	CNS	CNS
4	Abdominal pain/mass	Ileum, caecum	Abd
5	Weight loss/lymphadenopathy	Inguinal LN	LN
6	Soft tissue swelling	Neck	Skin/ST
7	Facial pain/nasal blockage	Nasal cavity	Head
8	Fever/night sweats	Lung	Lung
9	Skin/soft tissue swelling	Neck	Skin/ST
10	Haemoptysis/melaena	Small bowel	Abd
<i>Dead</i>			
11	Enlarging lymph node	Neck	LN
12	Headache/visual and memory problems	CNS	CNS
13	Lung mass on routine chest x ray	Lung	Lung
14	Neck swelling	Laryngeal	Head
15	Enlarging lymph node	Neck	LN
16	Purple skin lesion	Forehead	Skin
17	Weight loss/diarrhoea	Small bowel	Abd
18	Fever/abdominal pain	Adrenal	Abd
19	Weight loss/epigastric pain	Para-aortic LN	LN
20	Necrotic skin lesion	Chest wall	Skin
21	Confusion/fever	CNS	CNS
22	Nerve deafness	CNS	CNS
23	Fever/abdominal mass	Sigmoid colon	Abd
24	Weight loss/confusion/pneumonia	Lung	Lung
25	Fatigue/lymphadenopathy	Neck	LN
26	Unwell/flank pain	Psoas muscle	Deep ST
27	Cough/wheeze	Lung	Lung

Abd, abdominal; CNS, central nervous tissue; LN, lymph node; ST, soft tissue.

had ATG with the first transplant and ATG in addition to OKT 3 (anti-CD3 monoclonal antibody) with the second transplant.

Time to tumour onset

The time interval between renal transplantation and lymphoma diagnosis ranged from five to 232 months, with a mean of 46 and a median of 38 (table 1). The fact that the earlier patients did not receive CyA meant that the patient with the longest interval (232 months), who received azathioprine and steroids, raised the overall mean of the non-CyA group (14, 15, 93, 232) to 88.5 months. Cases presenting within the first year of transplant only occurred after the introduction of CyA (three cases).

Year of diagnosis

It can be seen that in the first decade of renal transplantation at Oxford during which time 479 transplants were carried out, only two patients presented with PTLT (fig 1). During the following 11 years, with naturally many more long term survivors, the disease presented more often, with five cases in both 1994 and 1995. Figure 1 shows the number of cases of lymphoma for each year.

Clinical presentation

The presentations included a wide range of symptoms and signs, reflecting the range of tissues and organs involved by lymphoproliferative disease (table 2). The effects included constitutional symptoms, in addition to those linked more directly to the site of involvement (table 2).

As recommended by Nalesnik,³ an attempt was made to categorise the patients according to the predominant site of the initial symptoms. The most striking finding, linked to the diversity of presentation, was that most of the lesions (21 of 27) were extranodal. Six of the lesions were in the skin and soft tissues, five in the abdomen (two each in small and large bowel), four in the central nervous system (CNS), four in the lung, and two in the head and neck area. The six nodal pres-

entations comprised four in cervical nodes (including the Hodgkin's disease case), one inguinal, and one para-aortic.

Pathological features of lesions

Gross pathology

These post-transplant lymphoid lesions may appear as a solid tumour, diffuse infiltrates of parenchymal organs, or enlargement of native lymphoid tissue.³ They are similar to lymphomas at a macroscopic level. Some lesions in this series were described as having fleshy white cut surfaces and in the larger lesions necrosis was frequently seen. The psoas tumour (case 26) was described as a "caseating mass".

Microscopic pathology

The microscopic appearance of PTLT is that of a diffuse proliferation of lymphoid cells. Attempts have been made to characterise the lesion on the basis of the presence or absence of lymphocyte heterogeneity. In many lesions, the entire range of recognisable B cell forms is seen, in varying proportions. These can include small lymphocytes, small and large cleaved and non-cleaved lymphocytes, immunoblasts, plasmacytoid cells, and plasma cells.

Monomorphic PTLTs are composed of uniform lymphoid cells, overwhelmingly at one stage of differentiation, usually small or large non-cleaved lymphocytes. In general, plasma cell differentiation is not a feature of such lesions and the appearance is that of typical NHL.

We attempted to classify the lesions by the Pittsburgh³ and Minnesota⁶ systems, in addition to the revised European-American lymphoma (REAL) classification (table 3).⁷

The case of Hodgkin's disease, initially diagnosed elsewhere, was confirmed both by haematoxylin and eosin morphology, and by the positive staining in Reed-Sternberg type cells for CD15 and CD30. It was viewed as the mixed cellularity form.

The remaining 26 cases were all B cell positive (either or both of L26 and JCB117) and in 24 of the 27 cases, including the Hodgkin's disease case, tumour cells were positive for EBV.

Table 3 Pathological classification

Patient	REAL	Pittsburgh	Minnesota	B cell	EBV LMP-1
<i>Alive</i>					
1	LC	MM	5	Positive	Positive
2	LC	MP	5	Positive	Positive
3	LC	MM	4	Positive	?
4	LC	MP	4	Positive	Positive
5	LC	MP	4	Positive	Positive
6	LC	MP	5	Positive	Positive
7	LC	MM	4	Positive	Positive
8	LC	MP	4	Positive	Positive
9	LPC	P	2	Positive	Positive
10	LC	MM	4	Positive	Negative
<i>Dead</i>					
11	LC	MP	4	Positive	Positive
12	LC	MP	4	Positive	Positive
13	LC	MM	4	Positive	Positive
14	LC	MM	4	Positive	Positive
15	HD MC	HD MC	HD MC	Positive	Positive
16	LC	MP	4	Positive	Positive
17	Marginal zone	P	2	Positive	Positive
18	LC	MP	4	Positive	Positive
19	LC	MM	5	Positive	?
20	LC	MP	4	Positive	Positive
21	HG ? type	MM	4	Positive	Positive
22	LC	MM	4	Positive	Positive
23	LC	MM	5	Positive	Positive
24	LPC	P	2	Positive	Positive
25	LPC	P	2	Positive	Positive
26	LC	MM	5	Positive	Positive
27	LC	MP	4	Positive	Positive

REAL: HG ? type, high grade lymphoma of uncertain type; LC, large cell; LPC, lymphoplasmacytic. Pittsburgh: MM, monomorphous; MP, minimally polymorphous; P, polymorphous. Minnesota: 2, polymorphous diffuse B cell hyperplasia; 4, polymorphous B cell lymphoma; 5, immunoblastic sarcoma. EBV LMP-1, Epstein-Barr virus latent membrane protein 1; HD MC, Hodgkin's disease, mixed cellularity subtype.

Most of the NHLs (21 of 26) were large cell lymphomas according to the REAL classification; when the Pittsburgh classification was used, 11 were monomorphous, 11 minimally polymorphous, and four were polymorphous, whereas using the Minnesota categorisation 16 were polymorphous B cell lymphomas, six were immunoblastic sarcomas, and four were polymorphous diffuse B cell hyperplasia.

Analysis of tumour clonality

Although staining for κ and λ light chains was carried out in all cases, the results were seldom unequivocal and have therefore been excluded. It would be of value and interest to pursue the clonality of these lesions by more reliable techniques. (It should be emphasised that this is not easy and the results thus far are not clear cut or of obvious clinical value.)³

Clinicopathological correlation: clinical presentation, and extent of tumour

The manner of presentation of each individual patient provided a guide to the site of predominant pathology. The presence of constitutional symptoms and the difficulty of excluding infections in locations such as the lung complicated these correlations and sometimes led to delays. It was not clear from our data whether any location was better or worse than others, but factors such as time of presentation and extent of disease may have complicated the issue.

Management

Table 4 details the management of the patients. Of the 27 patients, four had resections of the lesions (in three cases bowel and one lung wedge resection), one had the diagnosis made on initial pleural cytology, followed by necropsy, whereas the remainder had biopsies which in some cases were also excisions. In 20 patients, immunosuppression was initially reduced, usually as the first line of treatment, and in four patients immunosuppression was stopped. (In one patient it was later started again.) Acyclovir (an antiviral drug) was

used in 13 patients, and it was attempted in one other patient, who was unable to tolerate it. Radiotherapy was used in 13 patients and various forms of polychemotherapy in nine, including three patients who also had radiotherapy. Of those alive in September 1996, our end point, only three had not had specific antilymphoma treatment; namely, patient 2 with a small skin lesion that was excised, patient 4 with ileum and caecum resected, and patient 9 with neck skin/soft tissue/lymph node lesions.

Four of the five patients who survived less than one month did not really have the opportunity for planned management. In patients 24 and 27 the diagnosis was made when they were in a terminal condition, patient 23 was known to have extensive lymphoma intra-abdominally postoperatively, and patient 26 was also too ill for specific treatment. Patient 25 was given a short course of chlorambucil in addition to decreasing immunosuppression.

Response to treatment and outcome

Table 5 details the response to treatment and outcome in the 27 patients. At the end point of this study (September 1996), 10 of the patients were still alive, nine with functioning grafts and eight with no evidence of residual disease. Two patients had suffered graft failures as a result of reduced immunosuppression; one was on dialysis, whereas the other had undergone a second transplant 60 months after the first had been allowed to fail. The second transplant was still working well. (Since the end of the study period, in November 1996, a further patient lost his graft as a result of reduced immunosuppression.)

Of the 17 patients who had died, 14 were assessed to have died of their lymphoma, or at least with their lymphoma still clinically relevant. In eight patients, the time interval from diagnosis to death was less than two months, despite awareness of this disease and careful and regular patient follow up.

Table 4 Management

Patient	Bx excision	Decreased immunosuppression	Acyclovir	RT/ Chemotherapy
<i>Alive</i>				
1	Ex Bx	Yes later stopped	Yes	C
2	Ex Bx	No	No	No
3	Bx	Yes	Yes	RT
4	Resection	Yes	Yes	No
5	Bx	Yes	Yes	RT+C
6	Bx	Yes	Yes	RT
7	Bx	Yes later stopped	Yes	RT
8	Wedge resection	Yes	Yes	RT
9	Ex Bx	Yes	Attempted	No
10	Resection	Yes	No	C
<i>Died</i>				
11	Ex Bx	Yes	Yes	RT+C
12	Bx	Yes	No	RT
13	Bx	Yes stopped+No	Yes	C
14	Bx+PM	Yes	Yes	RT
15	Bx+PM	?	?	RT
16	Bx	No	No	RT
17	Resection	Yes ?not initially	No	No
18	Bx	Yes	Yes	C
19	Bx	Yes	Yes	C
20	Bx	No	No	RT
21	Bx	Yes	No	RT+C
22	Bx	Yes	No	RT
23	Bx	Stopped	Yes	No
24	Cytology+PM	No	No	No
25	Bx	Yes	No	C
26	Bx	Yes	No	No
27	Bx+PM	No	No	No

Bx, biopsy; C, chemotherapy; Ex, excision; PM, postmortem examination; RT, radiotherapy.

The Starzl group categorised the response of 43 PTLDs into groups showing regression with reduced immunosuppression,

resolution, no evaluable response, no response, and postmortem diagnosis only. There are many uncertainties involved in

Table 5 Response to treatment and outcome

Patient	Follow up post-transplant (months)	Outcome	Follow up (months)	Response to treatment
<i>Alive</i>				
1	152	NED	108	RES
2	122	NED	80	RES
3	46	NED CaB	34	RES
4	46	NED	29	RES
5	61	?	28	PTR
6	31	NED	26	RES
7	61	NED GF	22	RES
8	31	NED	19	RES
9	62	NED	10	REG
10	85	?	6	PTR
<i>Died</i>				
11	125	T 91	57	PTR
12	55	T 94	48	PTR
13	50	?87	36	PTR
14	91	95	24	RES
15	92	T 93	22	PTR
16	89	92	17	RES
17	106	T 88	13	PTR
18	24	T 95	7	NR
19	110	T 94	5	NR
20	18	T 90	2	NR
21	15	T 93	2	NR
22	9	T 91	1	NR
23	232	T 95	0	NT
24	50	T 95	0	NT
25	38	T 91	0	NT
26	37	T 90	0	NT
27	15	T 79	0	NT

Outcome: CaB, carcinoma of breast; GF, graft failure; NED, no evidence of disease; T 94 (other number), patient died in 1994 (other year) of/or with lymphoma; ?87, not clear about role of lymphoma in death of patient. Response to treatment: NR, no response; NT, necropsy or terminal diagnosis; PTR, partial tumour resolution; REG, regression; RES, resolution.

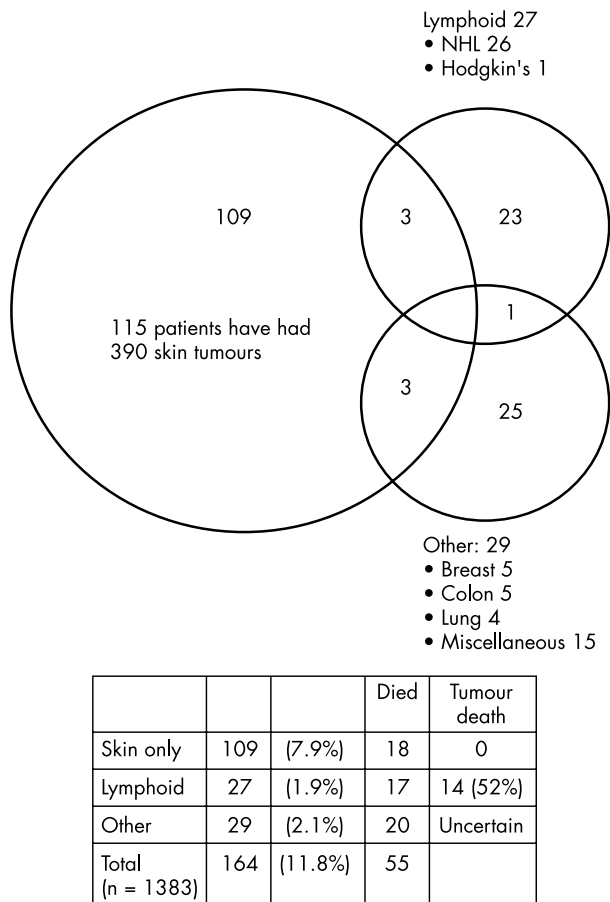


Figure 2 Oxford post-transplant malignancies. NHL, non-Hodgkin's lymphoma.

trying to categorise our patients into such broad response categories. Only one of our 27 patients has shown regression (case 9), nine have shown resolution, seven showed partial or temporary resolution or response, five showed little or no response, whereas five were essentially terminal or postmortem diagnoses (table 5).

Oxford post-transplant malignancy experience

To place the frequency and mortality of the post-transplant lymphomas in perspective the available data on the tumour registry with regard to other malignancies were analysed. The data confirm that even in the relatively northern latitude of Oxford, skin malignancy is the most frequent form, with 115 patients having had 390 skin tumours by April 1996 (fig 2). Most of these were squamous cell carcinomas, with fewer basal cell carcinomas and in situ carcinomas.⁵ All the patients had at least one squamous or basal cell carcinoma. Eighteen of the 115 patients who had skin malignancies had died, but none was considered to have died of the skin malignancy.

The other major group of cancers was non-skin, non-lymphoid cancer, where a total of 29 were registered. Breast, colon, and lung were the main types, accounting for half of the malignancies (table 6). Of the 29 patients in this group, 20 had died by September 1996. The overall mortality rate in this group of 20 of 29 (69%) is similar to the lymphoma group of 17 of 27 (63%).

DISCUSSION

One of the earliest reports of de novo malignancy after cadaveric renal transplantation was of two fatal extranodal lymphomas found in the liver and CNS.⁸ In a subsequent early

Table 6 Non-skin, non-lymphoid malignancies

Type	N
Breast	5
Colon	5
Lung	4
Hepatocellular carcinoma	1
Seminoma	1
Melanoma	1
Haemangioendothelioma	1
Prostatic adenocarcinoma	1
Sebaceous carcinoma	1
Anal carcinoma	1
Renal cell carcinoma (one recurrence of pretransplant tumour)	2
Ovarian cystadenocarcinoma	1
Oesophagus (adenocarcinoma)	1
Bladder	1
Adenocarcinoma metastases (primary uncertain)	3
Total	29

multicentre report of post-transplant malignancies, lymphomas constituted approximately 40% of all non-skin tumours, with a predilection for the CNS.⁹ In time, the diagnosis of other non-skin malignancies, usually appearing later, reduced the proportion made up by lymphomas. By 1991, the Cincinnati transplant tumour registry was noting a lymphoma frequency of 21% compared with 5% in the general population when non-melanoma skin cancers and in-situ carcinoma of the cervix were excluded.¹⁰ In Australia and New Zealand, with a large comprehensive post-renal transplant tumour registry, the 54 lymphomas constituted 12% of the non-skin cancers by 1991.¹¹ It is of interest that no Hodgkin's disease had been diagnosed in this group of 459 malignancies and that 16 of the 54 lymphomas were cerebral. Sheil has emphasised that since the introduction of CyA a similar pattern of incidence in these new cohorts could occur, and a recent publication from the Oxford group, which specifically examined this point, was in broad agreement.¹²

In patients treated with CyA, lymphomas have again constituted almost 40% of non-skin malignancies. Because the proportion of lymphomas fell progressively in the pre-CyA era, it is possible that a similar reduction could occur in the CyA era.¹¹

Penn noted that several features of the lymphomas in the overall CyA group were different from those seen in the azothiaprime group.¹⁰ Since the introduction of CyA, first Penn, and then Opelz, recorded an increased frequency of lymphoproliferative disease.^{2 10} Our group of 498 patients who had taken azothiaprime after transplantation included only four PTLD cases, despite a long follow up period (four of 498; 0.8%), in contrast with 22 of 885 (2.4%) since the introduction of CyA, with shorter follow up. In addition, the CyA group internationally showed earlier occurrence, at 15 versus 48 months post-transplantation. In Oxford, presentation within the first year after transplantation has only occurred since the introduction of CyA (patients presenting at five, seven, and eight months), with two further patients presenting at 12 months.

Three of 885 (0.34%) CyA managed patients developed PTLD in the first post-transplant year, similar to the incidence seen in North American. However, the relatively high incidence in subsequent years gave a later mean onset for the Oxford CyA group of 36 months versus the 15 month international mean.

In the CyA group studied by Penn, lymph nodes were more frequently involved (39% v 23%). The Oxford group of 26 B cell lymphomas included five nodal and 21 extranodal tumours. All four patients who had never received CyA presented extranodally, whereas five of the 22 in the CyA group had

lymph node involvement only. In the CyA group described by Penn, the CNS was less frequently involved (15% *v* 38%). Our experience of four nodal lymphomas out of 22 B cell non-Hodgkin's lymphomas fits well with the general CyA experience. It should be emphasised that one of the earliest multicentre reports on lymphomas found a high CNS frequency in patients treated with azathioprine.⁹

A central question is whether these lesions are really lymphomas and should be classified and managed as such. Although it was clear from the start that they could be fatal like other lymphomas, there has also been the suggestion, with some evidence, that they may be different with different management leading to a far better prognosis. An early paper from Starzl *et al* in 1984¹³ suggested that these lesions usually had a good outcome with reduction or discontinuance of immunosuppression, strongly questioning whether they needed to be viewed as seriously as normal lymphomas. However, many of their initial patients had other treatments, including surgery, cytotoxic drugs, and radiotherapy, making it difficult to ascribe improvement only to the reduction in immunosuppression.¹³ The clinical advisory committee of the new World Health Organisation classification of neoplastic diseases of the haemopoietic and lymphoid tissues maintains that although a separate classification is not needed for immunodeficiency associated lymphomas, a separate classification of PTLDs would be useful, because of their distinctive biological and clinical features.¹⁴ This classification of PTLDs has four groups:

- (1) Early lesions such as reactive plasmacytic hyperplasia.
- (2) PTLD—polymorphic.
- (3) PTLD—monomorphic (which they suggest should be classified according to current lymphoma classification—for example, the REAL classification system).
- (4) Other types, such as Hodgkin's disease.

As a good illustration of the evolution of understanding of these lymphoid lesions and the management of these patients, it is interesting that in subsequent publications from the Starzl group,³ a broader, more complex perspective had developed, and of 43 PTLDs only nine were categorised as regressing in response to reduction of immunosuppression only, with or without acyclovir. They had also decided to preclude patients from this category if there had been surgical resection of all grossly evident tumour (as in five of eight of the original series of renal transplant patients),¹³ or if they had received chemotherapy or radiotherapy. These patients were placed in a group termed tumour resolution (including the above mentioned cases)—a large and encouraging group of 20 of 43. The remaining patients were in the categories of no evaluable response and no response (eight of 43) or post-mortem diagnosis only (six of 43).

It can be seen from table 5 that follow up of the lymphoma was only longer than 36 months in two patients who were still alive in September 1996. Therefore, it seems appropriate to be cautious about the apparent resolution or regression of disease in patients 3 to 10. It can be seen that two of those who died of lymphoma survived more than 36 months after that diagnosis.

"All involved with possible tumours in the post-transplant context should have a high index of suspicion for lymphoma"

Two of these cases were not diagnosed as lymphoid proliferations on initial histological examination, the diagnosis being altered during this review. One was the first Oxford patient who presented preterminally with respiratory symptoms and in whom a small bronchial biopsy was diagnosed as undifferentiated carcinoma. The patient died away from

Oxford a few days later and at necropsy a widespread lymphoma affecting the lungs was diagnosed. In this case, the correct diagnosis would probably have made little or no difference to management and outcome.

In the second patient, a small bowel lesion was resected and diagnosed as Crohn's disease 11 months before presentation with documented lymphoma in the vicinity of the sub-mandibular gland. In retrospect and with lymphoid and EBV markers the earlier small bowel lesion was PTLD. This diagnosis may well have altered management, with possible immunosuppression reduction after the surgical excision and greater clinical suspicion of subsequent recurrence or lymphoma development.

It seems clear that all involved with possible tumours in the post-transplant context should have a high index of suspicion for lymphoma. In our experience—for example, this diagnosis is as likely as all the other non-skin malignancies together in a patient who has undergone renal transplantation. Although this may be a temporary situation and many other centres have a lower proportion of lymphomas it remains a frequent and important diagnosis with considerable morbidity and mortality.

Two UK studies have described the overall experience of post-renal transplant malignancy at the Hammersmith Hospital in London and in Leeds.^{15, 16} Our series comprised more patients and documented more lymphoproliferative disorders, which constituted a larger proportion of the non-skin malignancies (49%), compared with 18% and 27% in the other two series. The median time of appearance of 38 months was also shorter in our group.

We report a relatively high overall tumour incidence and an apparently high lymphoma frequency, in particular, in relation to non-skin, non-lymphoid lesions. In contrast to the Australian and New Zealand transplant cancer registry of 459 non-skin malignancies, where the 54 lymphomas were 12% of the total,¹¹ our 27 lymphomas constitute almost half of the total number of malignancies (27 of 55). These figures were noticeably affected by the appearance of 10 lymphomas in 1994 to 1995, at least eight or nine years after the initial routine use of CyA. Whether these patients represent an unfortunate statistical variation or a real alteration in frequency or response is not yet clear. It is also uncertain to what extent the prospectively maintained tumour registry and careful follow up may contribute to the apparently high overall tumour figures at Oxford. It should be noted that the Leeds group emphasised how difficult it was to gather retrospective clinical and pathological records of malignancies in transplant patients.¹⁶

In the home country of the first author, South Africa, lymphoid tumours appear to be a less frequent risk of transplant immunosuppression. Uterine cervical neoplasms and Kaposi's sarcoma are two malignancies not seen in our group, which are relatively frequent in South African renal transplant patients.^{17, 18}

PTLDs are relatively infrequent, but because of uncertainty regarding their most appropriate management and their contribution to transplant recipient morbidity and mortality, they constitute an important ongoing challenge in transplantation.

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Take home messages

- In Oxford, the overall incidence of post-transplant lymphoproliferative disorders (PTLDs) in renal transplant patients was 2%
- PTLDs presented both in the first year in association with cyclosporin use, as in North America, but also frequently in subsequent years, giving an overall presentation time later than the international mean
- Tumours usually presented extranodally, which accounts for the wide range of symptoms and signs encountered
- Despite awareness and active management, the disease contributed to death in more than half of patients with PTLDs.

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REFERENCES

- 1 Penn I, Hammond W, Brettschneider L, et al. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969;1:106–12.
- 2 Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993;342:1514–16.
- 3 Nalesnik MA, Jaffe R, Starzl TE, et al. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporin A–prednisone immunosuppression. *Am J Pathol* 1988;133:173–92.
- 4 Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology workshop. *Semin Diagn Pathol* 1997;14:8–14.
- 5 Liddington M, Richardson AJ, Higgins RM, et al. Skin cancer in renal transplant recipients. *Br J Surg* 1989;76:1002–5.
- 6 Frizzera G, Hanto DW, Gajl-Peczalska KJ, et al. Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. *Cancer Res* 1981;41(11 Pt 1):4262–79.
- 7 Harris NL, Jaffe ES, Stein H, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. *Blood* 1994;84:1361–92.
- 8 Doak PB, Montgomerie JZ, North JD, et al. Reticulum cell sarcoma after renal homotransplantation and azathioprine and prednisone therapy. *BMJ* 1968;4:746–8.
- 9 Schneck SA, Penn I. De-novo brain tumours in renal-transplant recipients. *Lancet* 1971;1:983–6.
- 10 Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991;23(1 Pt 2):1101–3.
- 11 Sheil AG, Flavel S, Disney AP, et al. Cancer development in patients progressing to dialysis and renal transplantation. *Transplant Proc* 1985;17:1685–8.
- 12 Libertiny G, Watson CJ, Gray DW, et al. Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients. *Br J Surg* 2001;88:1330–4.
- 13 Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin–steroid therapy. *Lancet* 1984;1:583–7.
- 14 Harris NL, Jaffe ES, Diebold J, et al. The World Health Organisation classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the clinical advisory committee meeting, Airlie House, Virginia, November 1997. *Histopathology* 2000;36:69–86.
- 15 Gaya SB, Rees AJ, Lechler RI, et al. Malignant disease in patients with long-term renal transplants. *Transplantation* 1995;59:1705–9.
- 16 London NJ, Farmery SM, Will EJ, et al. Risk of neoplasia in renal transplant patients. *Lancet* 1995;346:403–6.
- 17 Margolius L, Stein M, Spencer D, et al. Kaposi's sarcoma in renal transplant recipients. Experience at Johannesburg Hospital, 1966–1989. *S Afr Med J* 1994;84:16–17.
- 18 Moosa MR, McBryne A. The development of malignancies in renal allograft recipients: the Tygerberg Hospital experience. *S Afr J Surg* 1997;35:156–64.

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Blood culture bottles are the best test for sterility in cornea banks

Patients having corneal transplants could be saved from serious inflammation within the eye if cornea banks switched to blood culture bottles for screening organ culture media for microbial contamination, researchers have found. This method is quicker too.

The researchers spiked sterile standard organ culture medium for storing corneas with type cultures of 14 bacterial species and three fungal species commonly associated with such infection. After two days' incubation they tested the cultures for microbial growth during 14 days by three methods: turbidity and colour change in the medium; conventional subculture in bacterial and fungal media; and subculture into blood culture bottles (one each for aerobic and anaerobic bacterial species, and one for fungi).

The original medium contained two antibacterial and one antifungal antibiotics. These effectively stopped subsequent growth on subculture in five bacterial species. Residual contamination was shown with blood culture bottles for all (30/30) 12 remaining species compared with 77% (23/30) by conventional subculture and 70% (21/30) by the visual method. Final subcultures confirmed no external contamination of the samples. Results were available in under eight hours in 40% (12/30) of samples using blood culture bottles.

Most European cornea banks use organ culture medium containing antibiotics to store corneas and have a 10–12 day quarantine time for tests to ensure sterility. Blood culture bottles are particularly suitable for testing when microbes are present in small numbers or when antibiotics are present—so it made sense to test them in this context.

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