Risk Factors and Prognosis in T-Cell Posttransplantation Lymphoproliferative Diseases: Reevaluation of 163 Cases

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Background. Posttransplantation lymphoproliferative diseases (PTLD) are mainly Epstein-Barr virus (EBV)–associated disorders of B-cell origin. Due to the rarity of monomorphic T-cell PTLD (T-PTLD), knowledge about pathogenesis, risk factors, therapy, and prognosis relies predominantly on case reports and small series. Therefore, we aimed to provide an overview and a retrospective analysis of this rare PTLD subtype.
Methods. We analyzed all available articles on T-PTLD in the PubMed database as well as in our own databases (Institute of Pathology/Department of Paediatric Haematology and Oncology, Hannover Medical School) from 1988 to 2010. Reevaluated parameters were gender, age, transplanted organ, immunosuppressant regimen, time between transplantation and T-PTLD manifestation, T-PTLD subtype, virus positivity, localization, therapy, and follow-up.
Results. A total of 163 cases were evaluated. We found that hematopoietic stem cell transplantation was associated with early-onset T-PTLD, whereas late onset occurred after immunosuppression with steroids and azathioprine without administration of calcineurin inhibitors. The major independent favorable prognostic factors were T-PTLD of the large granular lymphocytic leukemia subtype, young age, and a combination of radiotherapy/radiochemotherapy and reduced immunosuppression, whereas the hepatosplenic T-cell lymphoma subtype and cases with involvement of bone marrow, the central nervous system, or graft had an adverse prognosis.
Conclusion. T-PTLD is a heterogeneous group of different aberrant T-cell proliferations and represents a significant complication following transplantation, showing a uniformly poor prognosis.

Keywords: Posttransplantation lymphoproliferative disease, PTLD, T cells, T-PTLD, Risk factor, Prognosis.

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Transplantation medicine is based on the stratification of the patients' individual risk profile, surgical techniques, intensive care, diagnostic monitoring, and drug-induced immunosuppression (*1, 2*). The latter inhibits graft rejection but also decreases the capability of the immune system to identify aberrant cells, which promotes the development of neoplasms after transplantation (*3, 4*). Posttransplantation lymphoproliferative diseases (PTLD), which are mainly Epstein-Barr virus (EBV)/human herpes virus-4–associated disorders, are a major complication. According to the World Health Organization (WHO) classification of 2008, PTLD are subclassified into early lesions (indistinguishable from lymphocytic hyperplasia or infectious mononucleosis), polymorphic PTLD (lymphocytic proliferation with histoarchitectural effacement but no lymphoma), and malignant lymphoma resembling monomorphic B- or T-cell PTLD and Hodgkin's-type PTLD (*5*). In contrast to the more than 90% of adult patients who are latently EBV positive, pediatric and juvenile patients are more often EBV naïve before transplantation and have their primary infection under immunosuppressive therapy, which puts them at a fourfold higher risk for PTLD manifestation (*3, 4*). The pathogenesis is based on the immunosuppression-associated reduction of $CD8^+$ T cells, resulting in an imbalance of EBV-positive B cells, virus-specific cytotoxic T cells, and regulatory T cells, which permits the EBV-positive B-cell population to proliferate and generate a PTLD phenotype (*3, 4*). Due to the EBV-associated

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pathomechanism, monomorphic PTLD are predominantly disorders of B lineage (B-PTLD), mainly high-grade B-cell non-Hodgkin's lymphomas.

The rarest forms of monomorphic PTLD are Hodgkin's lymphomas and PTLD of T lineage (T-PTLD). T cells do not usually express EBV receptor CD21; therefore, in most cases, the pathogenesis of monomorphic T-PTLD might not be based on EBV infection alone (*3, 4*). Due to the rarity of T-PTLD, prospective studies with large numbers of patients are not applicable and knowledge about risk factors, therapy, and prognosis relies predominantly on case reports and small series. Therefore, we aimed to provide a retrospective analysis of the rare monomorphic T-PTLD subtype to provide more general insights into this disease.

RESULTS

Frequency of T-Cell Posttransplantation Lymphoproliferative Diseases Among Monomorphic Posttransplantation Lymphoproliferative Diseases

Our own PTLD database comprises 117 monomorphic PTLD: 6 T-PTLD, 104 B-PTLD (80 diffuse large B-cell lymphomas, 10 Burkitt's lymphomas, and 14 other B-cell and plasma cell neoplasms), and 7 Hodgkin's PTLD. Therefore, in our cohort, the frequency of T-PTLD among all monomorphic PTLD is 5% (n=6 of 117).

We identified a total of 163 T-PTLD: 157 cases from the literature, for whom primary data were published, and the 6 cases in our own files. Our own cases comprise three children and three adults (Fig. 1; Tables 1 and 2). T-PTLD phenotypes were hepatosplenic T-cell lymphoma (HSTCL), peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), cutaneous T-cell lymphoma (CTCL; including mycosis fungoides, Sézary syndrome, primary cutaneous T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma), anaplastic large cell lymphoma (ALCL), adult T-cell leukemia/lymphoma (ATL), T-cell large granular lymphocytic leukemia (LGL), PTLD with natural killer cell phenotype, and T-PTLD with manifestation in the central nervous system. Approximately half of T-PTLD was either $CD4^+$ (n=32 of 60 [53%]) or $CD8^+$ (n=28 of 60 [47%]); full immunoprofile was not reported in all cases.

Among Patients With T-Cell Posttransplantation Lymphoproliferative Disease, Kidney Recipients Are Common

In patients in whom T-PTLD manifested, the most frequently transplanted organs were kidneys (n=107) (*6–78*, including two cases with additional pancreas transplantation (Table 2) (*27, 67*). In one case, the kidney transplant failed (*70*). Four patients had been retransplanted (*27, 51*).

Other solid organ transplants were heart (n=26) (*57, 71, 73, 79–94*), including one patient who received a liver transplant 4 months after heart transplantation and developed T-PTLD 5 months afterward (*87*); liver (n=17) (*95–105*); lung (n=3) (*105–107*), including one heart-lung (*107*); and multivisceral organ transplantation (n=1) (*108*). Hematopoietic stem cell transplantation comprised bone marrow–derived cells (n=6) (*109–111*), autologous peripheral blood–derived cells (n=2) (*112, 113*), and blood-derived cells after failed bone marrow transplantation (n=1) (*114*).

Epstein-Barr Virus Is Present in Approximately One-Third of T-Cell Posttransplantation Lymphoproliferative Diseases

T-PTLDY–associated viruses were EBV, cytomegalovirus/human herpes virus-5 (CMV), human T-cell leukemia virus (HTLV), and human herpes virus-6 (HHV-6), including coinfections with EBV/CMV and EBV/HTLV (see **Tables S1** and **S2**, **SDC**, http://links.lww.com/TP/A735). EBV status was reported in 126 T-PTLD cases: 46 of 126 (36.5%) were EBV-positive (none of our own cases were EBV-positive).

EBV was demonstrated in 41 of 46 tumor samples (*8, 11, 15, 17–19, 28, 35, 38, 39, 41, 44, 47, 48, 55, 58, 62, 63, 67, 73, 77, 81, 88, 91, 92, 94, 97, 99, 100, 103, 112, 113*), whereas, in 5 of 46 cases, only EBV seropositivity was present (*12, 23, 89, 90, 102*). In two of these five seropositive cases, no biopsy was performed (*90, 102*). Whereas, in two seropositive cases, the neoplastic cells were stated to be EBV-negative (*23, 89*), the presence of EBV-positive tumor cells was not reported in one seropositive case (*102*). Comparison of EBV-positive and EBV-negative cases (independent of coinfections) revealed no significant difference regarding the time between transplantation and T-PTLD manifestation (P=0.9) as well as no significant prognostic impact regarding survival (P=0.6), even if only cases with EBV-positive tumor cells were considered and EBV-seropositive cases were excluded.

The only T-PTLD subtype that was associated with a particular virus was ATL. HTLV was positive (mainly seropositive) in seven of eight ATL-PTLD cases (*28, 29, 31, 68, 70, 83*); however, this virus was not systematically tested in most other cases (see **Tables S1** and **S2**, **SDC**, http://links.lww.com/TP/A735).

Risk Factors for T-Cell Posttransplantation Lymphoproliferative Disease Manifestation: Hematopoietic Stem Cell Transplantation and Calcineurin Inhibitors

The earliest T-PTLD manifestation (early-onset PTLD <12 months) was found after hematopoietic stem cell transplantation (median, 5 months; range, 2–43 months), which was, according to Bonferroni-adjusted bivariate analysis, significantly earlier than after kidney (1–324 months) (*82*), heart (9–168 months) (*70*), or liver (2–180 months) (*46*) transplantation (Fig. 2A). Multivariate analysis confirmed these significant results for hematopoietic stem cell versus kidney, heart, and liver transplantation (P<0.05) and also showed a significant difference regarding underlying lung/heart-lung transplantation (32–108 months; P=0.0135 versus hematopoietic stem cell transplantation) (*64*). In one case, T-PTLD manifested 24 months after multivisceral organ transplantation (*108*), which was comparable with the time period between single-organ transplantation and disease manifestation.

T-PTLD manifestation-associated immunosuppressive drugs/drug combinations were evaluated (Fig. 2B). Bonferroni-adjusted bivariate analysis and multivariate analysis showed that T-PTLD developed earlier in patients who received tacrolimus (alone or with other drugs) than in patients with azathioprine therapy (alone or with other drugs, except cyclosporine A or tacrolimus; P<0.0001).

Pediatric/juvenile T-PTLD comprised only 13% of all T-PTLD (n=21 of 163; n=3 of 21 in our own cases) (*8, 71,*

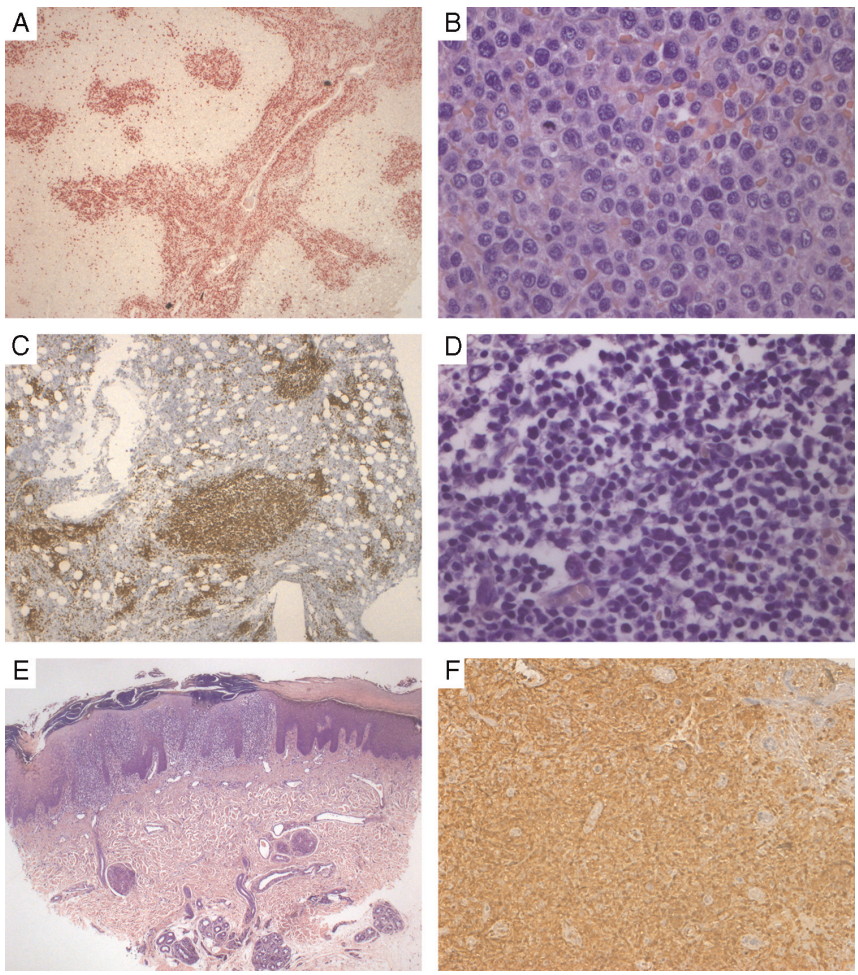

FIGURE 1. Variable histopathology of T-PTLD. A, patient #2 (see Table 1, PTCL, NOS): liver graft showed portal infiltration by $CD3^+/CD4^+$ small cells (CD4 is depicted; original magnification, ×25). In addition, an abdominal lymph node showed a similar infiltration (not depicted). Bone marrow was not involved. B, patient #4 (PTCL, NOS): specimen of the lung showed infiltration by blastoid, mainly moderately enlarged $CD3^+/CD8^+$ cells that revealed coexpression of granzyme B and TIA1 (Giemsa, ×400). C, patient #5 (PTCL, NOS): bone marrow showed interstitial and nodular infiltration by $CD3^+/CD4^+$ cells (CD3 is depicted; ×25) that partially coexpressed granzyme B and TIA1. Nonlymphoid hematopoiesis showed moderate hyperplasia. D, most cells were small, some were slightly enlarged, and nuclei showed dense chromatin (Giemsa, ×400). E, patient #6 (mycosis fungoides with unusual involvement of the pharynx): palmar skin specimen is depicted and shows dense epidermotropic and partially intraepithelial lymphoid infiltration (Giemsa, ×25). The small cells were predominantly $CD3^+/CD4^+$ and very few larger cells were $CD30^+$. F, similar atypical T-cell infiltrates were found in larynx tissue specimen (CD4 is depicted; ×100). PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; T-PTLD, T-cell post-transplantation lymphoproliferative diseases.

TABLE 1. Summary of T-PTLD (our own cases)

Own patients	Transplant organ	Gender (F/M)	Age, yr	Time between transplantation and T-PTLD, mo	Diagnosis/T-PTLD subtype	Site of involvement	Follow-Up, mo
#1	Heart	F	<0.5	NA	ALCL	Lymph node	12 (dead)
#2	Liver	M	0.5	20	PTCL, NOS	Graft, lymph node	1 (dead)
#3	Liver	M	1	2	PTCL, NOS	Lymph node, pleural fluid	48 (alive)
#4	Kidney	M	30	312	PTCL, NOS	Lung	NA
#5	Kidney	M	43	96	PTCL, NOS	Bone marrow	NA
#6	Liver	M	53	21	Mycosis fungoides	Skin, larynx	29 (alive)

ALCL, anaplastic large cell lymphoma; NA, not available; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; T-PTLD, T-cell post-transplantation lymphoproliferative diseases.

TABLE 2. Total cohort of reevaluated T-PTLD cases

References and our own cases	Transplant organ (total n=163), n (%)	Gender, n (F/M/NA)	Age, yr	Time between transplantation and T-PTLD, mo	Diagnosis/T-PTLD subtype, n
(*6–78*) #4, #5	Kidney, 107/163 (65.5)	7/74/26	44 (12–75)	84 (1–324)	HSTCL, 17; PTCL, NOS, 35; CTCL, 20; ALCL, 13; LGL, 4; NK, 6; ATL, 7; CNS, 5
(*57, 71, 73, 79–94*) #1	Heart, 26/163 (16)	7/18/1	34 (<0.5–75)	72 (9–168)	HSTCL, 1; PTCL, NOS, 11; CTCL, 6; ALCL, 6; NK, 1; ATL, 1
(*95–104*) #2, #3, #6	Liver, 17/163 (10.5)	6/8/3	19.5 (0.5–63)	48 (2–180)	HSTCL, 2; PTCL, NOS, 9; CTCL, 2; ALCL, 2; LGL, 1; CNS, 1
(*109–111*)	Hematopoietic stem cells, 9/163 (6)	0/6/3	49 (13–60)	5 (2–43)	PTCL, NOS, 5; ALCL, 1; LGL, 3
(*105–107*)	Lung, 2/163 (1); heart+lung, 1/163 (0.5)	1/2/0	40 (3–43)	66 (32–108)	PTCL, NOS, 1; CTCL, 2
(*108*)	Multiorgan, 1/163 (0.5)	1/0/0	7	24	PTCL, NOS, 1

ALCL, anaplastic large cell lymphoma; ATL, adult T-cell leukemia/lymphoma; CNS, T-PTLD with manifestation in the central nervous system; CTCL, cutaneous T-cell lymphoma (including mycosis fungoides, Sézary syndrome, primary cutaneous T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma); HSTCL, hepatosplenic T-cell lymphoma; LGL, T-cell large granular lymphocytic leukemia; NK, PTLD with natural killer cell phenotype; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; T-PTLD, T-cell posttransplantation lymphoproliferative diseases.

73, 79, 81, 85, 91, 93, 95, 99, 100, 104, 105, 108, 114). Age less than 18 years (n=21; median, 12 years; range, <0.5–16 years) or age more than 60 years (n=18; median, 68.5 years; range, 61–75 years) (*6, 12, 15, 21, 35, 44, 54, 55, 70, 74, 83, 87, 88, 90, 92, 96, 101*) were not general risk factors.

Hepatosplenic T-Cell Lymphoma–Posttransplantation Lymphoproliferative Disease Has an Adverse Prognosis

In the bivariate (but not multivariate) analysis, juvenile patients had a significantly better survival than adult patients (Fig. 3A), and with regard to PTLD subtypes, the best prognosis was found for the LGL type (18 months median follow-up; range, 4–36 months; survival data from 7 of 8 cases, 6 of 7 alive in the follow-up period) (*21, 45, 109, 110*). Regarding this, patients with LGL-PTLD were all adults (median age, 48 years; range, 36–70 years); none of the pediatric/juvenile patients had an LGL-PTLD but PTCL, NOS (n=12; n=2 of 12 in our own cases) (*71, 73, 79, 81, 99, 100, 104, 105, 108*), ALCL (n=7; n=1 of 7 in our own cases) (*8, 71, 81, 91, 93, 114*), and CTCL (n=2) (*85, 95*).

Patients with $CD4^+$ or $CD8^+$ T-PTLD had a similar survival (P=0.4).

HSTCL-type PTLD had an adverse prognosis (4 months median survival; range, 0.5–12 months; n=19, all died during the follow-up period; Fig. 3B) and showed a significantly lower overall survival versus CTCL (bivariate and multivariate analysis) and LGL (only in bivariate but not multivariate analysis) (*10, 18, 33, 35, 42, 55, 58, 59, 64, 76, 83, 102*).

In general and independent of the T-PTLD subtype, infiltration of the central nervous system (n=5) (*22, 65, 67, 70, 96*), bone marrow (n=24 nonhematopoietic stem cell transplanted cases; n=1 of 24 in our own cases) (*6, 10, 18, 27, 34, 39, 64, 76, 83, 84, 93, 98, 102, 104, 105*), and graft (kidney [n=6] (*12, 37, 55, 69, 71, 77*), liver [n=5; n=1 of 5 in our own cases] (*102, 103, 105*), hematopoietic stem cells [n=3] (*109, 110*), and multivisceral [n=1] (*108*)) was associated with a poor prognosis (significant in Bonferroni-adjusted bivariate analysis but not multivariate analysis; Fig. 3C).

Basis of Therapy: Reduced Immunosuppression

Therapy regimens were variable and were mainly based on radiotherapy and chemotherapy, corticosteroid administration, and reduction of immunosuppressants. Treatment protocol alterations (e.g., due to rescue efforts) were included. Chemotherapy and radiochemotherapy had been performed in 48 cases and immunosuppression (with or without cytoreductive therapy) had been reduced in 56 patients. Fifteen of 56 patients were treated solely with reduced immunosuppression (no additional therapy): 6 of 15 (40%) died after a median period of 2.5 months, whereas 9 of 15 (60%) were alive after a median of 13 months. Chemotherapy alone appears to be less efficient than other therapy strategies (e.g., reduced immunosuppression alone), but, in general, there was no significant difference (Fig. 3D). Eleven patients received no therapy (*6, 7, 15, 27, 28, 35, 55, 71, 83, 101*) mainly because of rapid progression or due to their refusal of therapy, and they succumbed to disease or

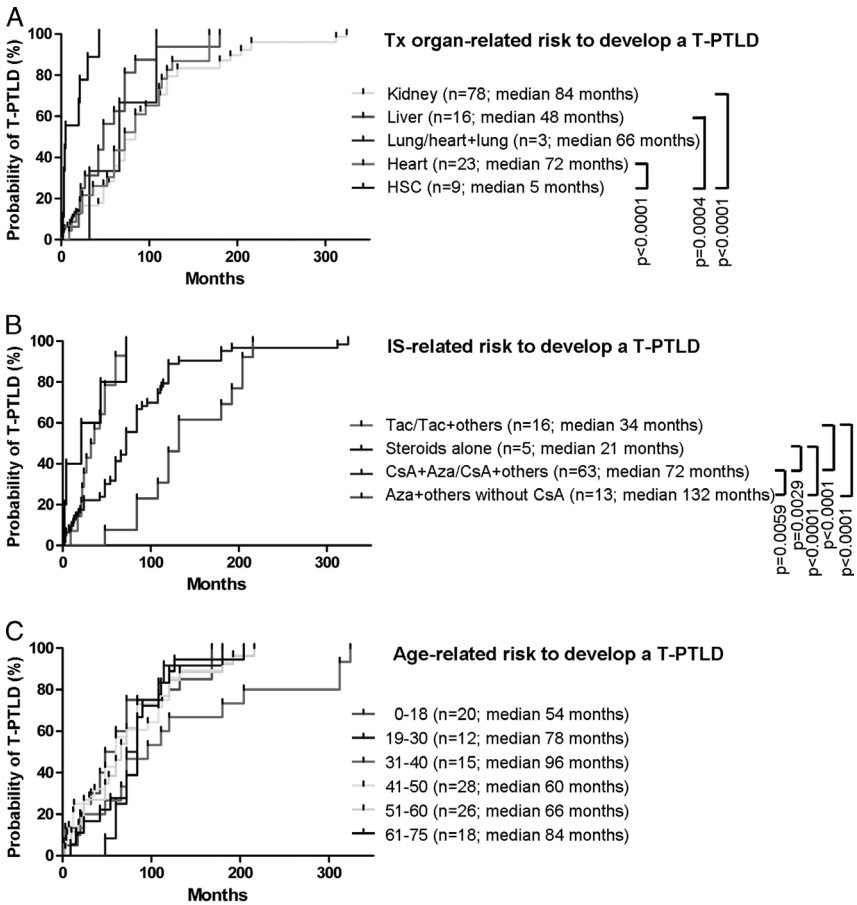

FIGURE 2. Predisposing risk factors in T-PTLD patients. For further details, see Table S3 (**SDC**, http://links.lww.com/TP/A735). Aza, azathioprine; CsA, cyclosporine A; HSC, hematopoietic stem cells; IS, immunosuppression; T-PTLD, T-cell post-transplantation lymphoproliferative diseases; Tx, transplant.

complications after a median of 3 weeks. As could be expected, these cases had a significantly low overall survival rate ($P<0.05$, bivariate and multivariate analyses).

DISCUSSION

Monomorphic B-PTLD mainly comprises two types of high-grade lymphomas: diffuse large B-cell lymphoma and Burkitt's lymphoma (*2–5, 115*). In contrast, T-PTLD manifest in a variety of aberrant T-cell proliferations. The pathogenesis of B-PTLD is mostly based on virus-infected B lymphocytes. Although it is generally appreciated that T lymphocytes do not express the EBV receptor CD21, some T-PTLD might show aberrant T cells, which are positive for CD21 and EBV (*58*). CD21 was not tested in most cases and only one-third of T-PTLD reevaluated in this study were positive for EBV. In contrast, B-PTLD are more frequently associated with EBV (>70%) (*3, 4, 115*). Although children are at a fourfold higher risk to develop a PTLD because they are more frequently EBV-naïve at the time of transplantation (*3*), the rarity of T-PTLD in young patients had been recognized earlier (*105*). In this review of a large number of cases, 13% pediatric/juvenile T-PTLD were identified; young age was associated with a better survival. Other detectable viruses were CMV (*8, 17, 21, 47, 80, 99–101, 109, 110*), HTLV (*28, 29, 31, 68, 70, 83*), and HHV-6 (*42*). Some T-PTLD patients were even coinfected with EBV and CMV (*8, 17, 47, 99, 100*) or EBV and HTLV (*28*), whereas coinfection of tumor cells has not been shown in these cases (non-EBV viruses were mainly detectable in the serum but have not been systematically analyzed in tumor samples). Virus seropositivity, however, might be associated with immunosuppression rather than necessarily being the initiating cause in all T-PTLD; for example, in two EBV-seropositive patients, the PTCL tumor cells were EBV-negative (*23, 89*). Overt primary immune disorders are, similar to PTLD, frequently associated with EBV-positive B-cell lymphomas but rarely with T-cell lymphomas (*5*). Furthermore, in nontransplanted immunocompetent patients, high-grade lymphomas are more frequently of B rather than of T lineage, indicating a different predisposition of these two lymphocytic differentiations to generate an aberrant clonal proliferation. However, the molecular basis of monomorphic PTLD is partially different from sporadic malignant lymphomas, as could be demonstrated by gene expression profiling (*116*). The relatively long latency between transplantation and T-PTLD onset may be explained by molecular events:

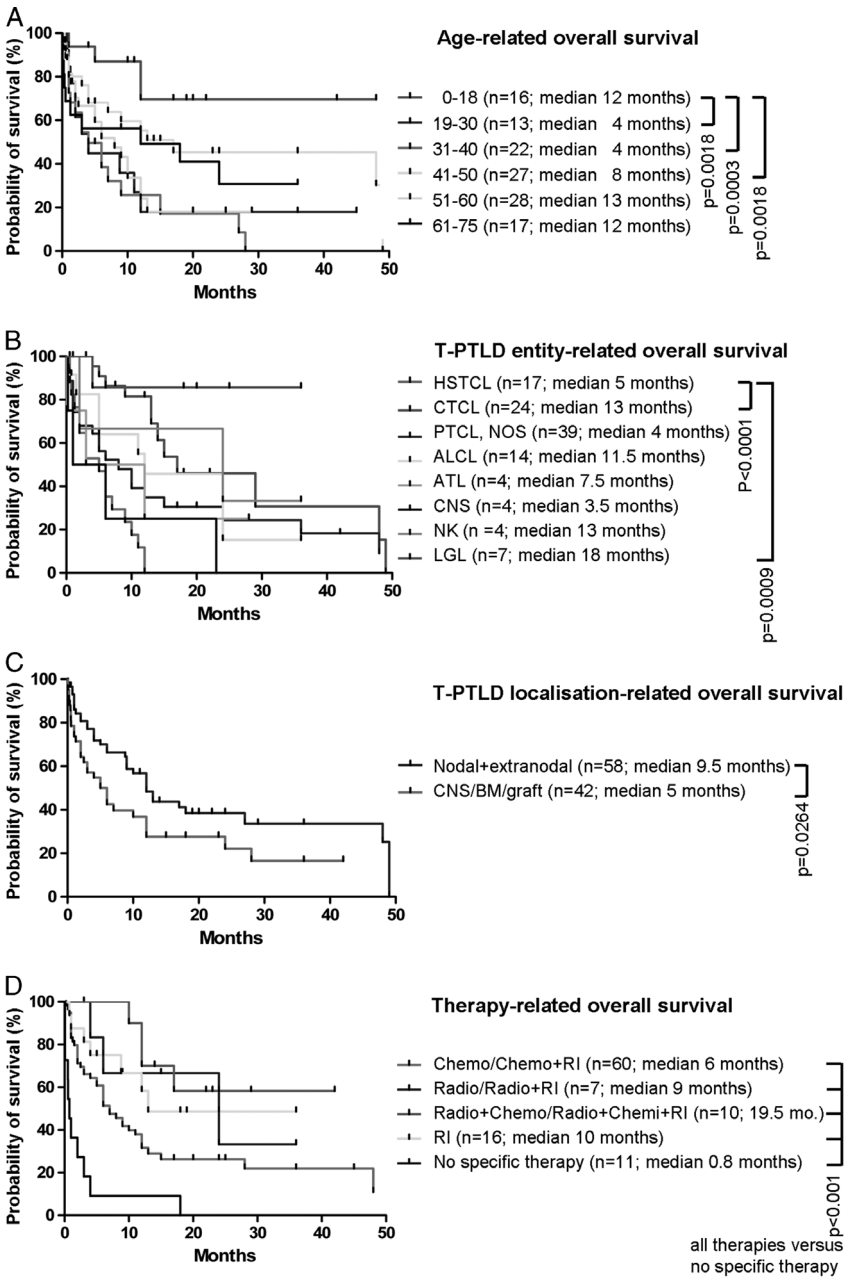

FIGURE 3. Prognostic factors in T-PTLD patients. For further details, see Table S4 (**SDC**, http://links.lww.com/TP/A735). ALCL, anaplastic large cell lymphoma; ATL, adult T-cell leukemia/lymphoma; chemo, chemotherapy; Chemo/Chemo+RI, chemotherapy alone and chemotherapy with immunosuppression; CNS, T-PTLD with manifestation in the central nervous system; CNS/BM/graft, T-PTLD with infiltration of the central nervous system, bone marrow, and graft; CTCL, cutaneous T-cell lymphoma (including mycosis fungoides, Sézary syndrome, primary cutaneous T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma); HSTCL, hepatosplenic T-cell lymphoma; LGL, T-cell large granular lymphocytic leukemia; NK, PTLD with natural killer cell phenotype; nodal+extranodal, lymph node infiltration without documented other extranodal involvement and extranodal infiltration, except bone marrow, the central nervous system, or graft showed similar overall survival and were therefore combined; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; Radio, radiotherapy; Radio/Radio+RI, radiotherapy alone and radiotherapy with immunosuppression; Radio+Chemo/Radio+Chemo+RI, radio-chemotherapy and radio-chemotherapy with immunosuppression showed no significant difference and were therefore combined; RI, reduced immunosuppression alone; T-PTLD, T-cell posttransplantation lymphoproliferative diseases.

whereas EBV infection and transformation is an early event after transplantation, typical molecular alterations such as ALK translocations in ALCL may occur later. In our reevaluation, we found that ALK status was documented only in a small subfraction of T-PTLD. Three cases were ALK-positive (*87, 93, 96*), whereas five ALCL were ALK-negative (*8, 55, 78, 91, 101*).

Furthermore, in this small number of cases, the ALK status showed no significant prognostic impact.

We found that immunosuppressive regimens with azathioprine but without administration of calcineurin inhibitors were associated with a later manifestation of T-PTLD (dose-dependent associations could not be performed). In contrast, calcineurin inhibitors, particularly tacrolimus and to a lesser extent cyclosporine A, were associated with early-onset T-PTLD. This does not imply that calcineurin inhibitors generally increase the risk to develop T-PTLD but only that the disease manifests earlier among T-PTLD patients. Combinations other than steroids and azathioprine without calcineurin inhibitors were too heterogeneous to draw a meaningful conclusion, although these patients showed the earliest T-PTLD manifestation.

Similar to B-PTLD, the transplant organ with the highest number of monomorphic T-PTLD is the kidney (*3*). However, it must be taken into account that kidney transplantation is more frequently performed than any other organ transplantation. PTLD can manifest as early as a few weeks after transplantation but, as could be demonstrated for B-PTLD, early-onset PTLD are not associated with a specific organ (*117*). We found that hematopoietic stem cell transplantation was a predisposing risk factor for the development of early-onset T-PTLD. The reason might be that, in these patients, a subfraction of defective endogenic hematopoietic stem cells remained after transplantation or even that the donor's hematopoietic stem cells have occult defects and that this aberrant reservoir generates the early-onset PTLD (*109, 118*). Alternatively, late PTLD may not occur in hematopoietic stem cells recipients, because immunosuppressive medication is usually tapered and immunocompetence normalizes over time in this patient population. Because of the large number of donor periportal lymphocytes, liver transplants are thought to be more often associated with donor-derived PTLD, mainly polymorphic PTLD, whereas monomorphic B-PTLD are more often recipient derived (*117, 119*).

We and others could previously show that infiltration of bone marrow, the central nervous system, and graft is an unfavorable prognostic factor in B-PTLD (*120, 121*). The HSTCL subtype and infiltration of these organ sites were also associated with a poor prognosis in T-PTLD. Favorable prognostic factors were young age and LGL-PTLD. None of the young patients had LGL-PTLD, indicating two independent factors.

An effective therapy for T-PTLD must account for the individual's age, constitution, and compliance (*3*). Therefore, it is difficult to suggest an optimal protocol for the treatment of heterogeneous T-PTLD subtypes based on retrospective data from multiple hospitals with different treatment modalities. Reduction of immunosuppression is usually the first measure if PTLD occurs. Patients receiving no further treatment will represent either the best (''cured'') or the worst (''no other treatment tolerable'') prognostic group. In our analysis, most patients with reduced immunosuppression survived. In contrast to B-PTLD, where monoclonal antibody treatment has become a well-tolerated standard of care during the last decade, T-PTLD usually requires intensive chemotherapy and radiotherapy treatment. Our analysis indicates that, similar to de novo malignancies, patients with T-PTLD may benefit from addition of radiotherapy to chemotherapy and, similar to B-PTLD, reduction of immunosuppression. A prospective study is, of course, mandatory to verify these retrospective results. To the best of our knowledge, due to the rarity of T-PTLD, no such prospective study has yet been conducted. However, we could provide the first evaluation of a large number of T-PTLD.

There are several previously described issues in this current evaluation, but it has to be taken into account that until now our knowledge on rare T-PTLD has been based mainly on findings derived from single case reports that have not been systematically compared with other case reports or extrapolation/transmission of B-PTLD–derived findings to T-PTLD. The impact of this analysis is not simply reporting additional cases of T-PTLD, but we aimed to provide a clinically relevant general overview on this rare PTLD subtype. In summary, T-PTLD is a heterogeneous group of different aberrant T-cell proliferations and represents a significant complication following transplantation, showing a uniformly poor prognosis. Unfavorable prognostic factors are the HSTCL subtype and involvement of bone marrow, the central nervous system, and graft. Hematopoietic stem cell transplantation is associated with early-onset T-PTLD, whereas a late onset was found after immunosuppression with azathioprine without administration of calcineurin inhibitors. The major independent favorable prognostic factors are LGL-PTLD, young age at diagnosis, and the combination of radiotherapy/radiochemotherapy with reduced immunosuppression.

MATERIALS AND METHODS

Data Collection

According to the WHO classification, T-PTLD is defined as a monomorphic lesion that comprises all T-cell lymphomas as well as natural killer cell lymphomas, which can be found in nontransplanted patients (*5*).

We searched for all available articles on T-PTLD in the PubMed database using the keywords posttransplantation lymphoproliferative disease, PTLD, T cell, and T-PTLD as well as in our own databases (Institute of Pathology/Department of Paediatric Haematology and Oncology, Hannover Medical School) for the time period between 1988 and 2010. The local ethics committee has approved the retrospective evaluation of our archived files and tissue samples that have been taken during the routine diagnostic procedure (formalin-fixed and paraffin-embedded samples; registration code #911-2011).

PTLD not fulfilling the WHO criteria for T-PTLD *(5)* were excluded (''polymorphic T-PTLD'') (*115, 122*).

The following parameters were reevaluated: gender, age, transplanted organ, immunosuppressant regimen, time between transplantation and T-PTLD manifestation, T-PTLD subtype, virus positivity, localization, therapy after T-PTLD diagnosis, and follow-up.

To determine the frequency of T-PTLD, we used our own PTLD databases (Institute of Pathology/Department of Paediatric Haematology and Oncology, Hannover Medical School), which comprise early lesions (n=79), polymorphic PTLD (n=21), and monomorphic PTLD (n=117).

Statistical Analysis

All available data were statistically analyzed with Prism 5.0 (GraphPad Software, San Diego, CA) and SAS 9.3 (SAS Institute, Cary, NC). Kaplan-Meier analysis was used for survival analysis and calculation of the corresponding hazard ratio was performed with Prism. Log-rank/Mantel-Cox test and, for bivariate analysis, two-tailed *t* test/Mann-Whitney test with Bonferroni adjustment of *P* values were used for analysis of significance (Prism). Multivariate analysis was performed with the Breslow method for ties (SAS). For risk factor analysis associated with T-PTLD

manifestation, the time of transplantation until first diagnosis of T-PTLD and, for survival analysis, the time of T-PTLD manifestation until last follow-up date was evaluated.

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