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ORIGINAL ARTICLE

Post-transplant lymphoproliferative disorders with naso- and oropharyngeal manifestation

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Summary

The nasopharyngeal/oropharyngeal lymphatic tissues represent the anatomical site of Epstein–Barr virus (EBV) entry. Post-transplant lymphoproliferative disorders (PTLD) are often associated with EBV, but little is known about the characteristics of nasopharyngeal/oropharyngeal mass-forming PTLD. Retrospective evaluation of our own PTLD database (n = 79) and the PubMed® database (n = 61) has been performed. Sinonasal/oro-/nasopharyngeal lymphatic masses were early lesions (n = 54/140, 38.5%), polymorphic PTLD (n = 32/140, 23%), monomorphic B-PTLD (n = 47/140, 33.5%) and T-PTLD (n = 7/140, 5%). One-fourth of lesions manifested as masses in the Waldeyer's ring, and in two-thirds of cases, swelling of tonsils was related to manifestation of benign early lesions. Tonsil infiltration by polymorphic PTLD and monomorphic PTLD was present in one-third of cases. Extratonsillar masses were mainly monomorphic PTLD. Meta-analysis of our data in combination with previously published data revealed that lung transplantation and young patients are at a higher risk for earlier manifestation of monomorphic PTLD. Therapy is similar to PTLD therapy strategies, in general reduced immunosuppression and chemotherapy for polymorphic and monomorphic PTLD, and diagnostic and therapeutic surgical gross tumour resection of tonsillar/adenoid lesions. In summary, it is relevant for the clinical differential diagnosis that oro-/nasopharyngeal aggressive PTLD manifested in ~30% as tonsillar masses and >90% at extratonsillar sites.

Introduction

Transplantation of allogeneic organs requires an immunosuppressive regimen to avoid rejection but also increases the risk for immunosuppression-associated complications. Post-transplant lymphoproliferative disorders (PTLD) are major complications which are often of B-cell phenotype and associated with Epstein–Barr virus (EBV; human herpes virus 4) [1–6]. EBV primary orally transmitted infection predominantly occurs in early childhood and leads to a lifelong persistency, and over 90% of the world's adolescent and adult population are carriers of EBV [7,8]. The lymphatic tissue of the nasopharynx and oropharynx represents the anatomical site of EBV entry. The virus is a lymphotropic pathogen which infects B lymphocytes and manipulates the cell cycle of the infected B cell which leads to proliferation of an EBV+ clone. Different EBV protein expression is associated with lytic and latent stages and leads to clinical presentation in terms of infectious mononucleosis of the tonsils or, in the majority of immunocompetent individuals, indolent latent infection [9,10]. The normal immune system can control the proliferation of EBV+ B cells by CD4+ and CD8+ T lymphocytes. Immunosuppression after organ transplantation affects

T-cell homeostasis, which may lead to aberrant B-cell proliferation with formation of a tumour mass. Therefore, risk factors for PTLD manifestation are high-dose immunosuppression and young age because children are more often EBV-naïve before transplantation and have their primary infection under immunosuppressive therapy [1,11–18]. According to the World Health Organization (WHO), PTLD include all benign and malignant lymphatic masses after transplantation and are subclassified into three groups [19]: (i) early lesions (plasmacytic/mixed lymphocytic hyperplasia and infectious mononucleosis-like lesions), (ii) polymorphic PTLD with mixed B and T cells and destructive tissue infiltration (not meeting the diagnostic criteria for an overt malignant lymphoma), (iii) monomorphic PTLD, which show phenotypes similar to malignant B- or T-cell lymphomas in nontransplanted patients (excluding low-grade lymphomas such as follicular and MALT lymphomas which are considered to be incidental in adults and very infrequent in children) [7,19–21]. Hodgkin-like PTLD are considered to be CD20+/CD30+/CD15- and resemble T-cell-rich high-grade B-cell lymphoma [19]. Hodgkin PTLD are CD20−/CD30+/CD15+ [19]. Although the WHO classifies early lesions as PTLD subtypes, these lesions are considered to be benign and are not usually designated as 'PTLD', because, for clinicians, the term implies the more aggressive polymorphic and monomorphic subtypes [1]. However, early lesions are clinically relevant because hyperplasia can also lead to formation of a tumorous mass. Without histopathological examination, benign early lesions cannot be discriminated from more aggressive PTLD [12,22]. All three lesions can occur at any anatomical site at any time after transplantation and clinical presentation is related to the tumour site but mainly unspecific. For example, tumour formation in the nasopharynx (adenoids) and oropharynx (tonsils) can lead to pain as well as breathing and swallowing problems. In these patients with suspected PTLD, basic diagnostic work-up includes conventional inspection of the oral cavity [23,24].

Although a common clinical differential diagnosis in transplanted patients, little is known about the characteristics of nasopharyngeal and oropharyngeal mass-forming lymphoproliferations. Most studies include case reports or small series of patients and are often restricted to a particular type of patient profile, for example regarding transplant organ or young age. Furthermore, most studies concentrate on polymorphic and monomorphic PTLD, but exclude the main differential diagnosis, the early lesions. In this analysis, we wanted to clarify some of these unsolved questions regarding post-transplant lesions in the nasopharynx and oropharynx: (i) What is the frequency and anatomical site of early lesions compared to PTLD? (ii) Which types of monomorphic PTLD are typically found? (iii) What are the risk factors and prognostic factors for this specific anatomical localization?

Material and methods

Data collection

We retrospectively evaluated our own PTLD database for the period between 1993 and 2013 (Institute of Pathology/Department of Paediatric Haematology and Oncology, Hannover Medical School). The local ethics committee has approved the retrospective evaluation of our archived files (#911–2011). These data were used for a general evaluation of the frequencies of different lymphoid tumour types at sinonasal, naso- and oropharyngeal sites in comparison with extracranial manifestations. In addition, we searched for all available articles on oral and/or nasopharyngeal PTLD in the PubMed® database (up to 2013) using the following keywords: post-transplant lymphoproliferative disorder, oral PTLD, nasopharyngeal PTLD, PTLD in oral cavity and PTLD in tonsils. Data from the literature on PTLD and our own cohort of PTLD were used for a specific characterization of polymorphic and different subtypes of monomorphic PTLD.

The following parameters were evaluated: gender, age, transplanted organ, immunosuppressant regimen, time between transplantation and PTLD manifestation, PTLD subtype, EBV status, localization, therapy after PTLD diagnosis, and follow-up.

Statistical analysis

All available data were statistically analysed with PRISM 5.0 (GraphPad Software, San Diego, CA, USA) and SPSS (IBM Corporation, New York, NY, USA). Log-rank/Mantel–Cox test and, for univariate analysis, two-tailed *t*-test/Mann–Whitney *U*-test were used for analysis of significance (PRISM). Multivariate analyses were also performed (SPSS). For risk analysis associated with PTLD manifestation, time of transplantation until first diagnosis of PTLD, and, for survival analysis, time of PTLD manifestation until last declared follow-up date were evaluated.

Results

More frequent early lesions than sinonasal, nasopharyngeal and oropharyngeal monomorphic/polymorphic PTLD

Our own PTLD database comprises 276 different cases: patients with monomorphic PTLD (n = 145/276, 52.5%), polymorphic PTLD (n = 27/276, 10%) and hyperplastic early lesions (n = 104/276, 37.5%). Details are summarized in Table 1.

Table 1. Characteristics of our own post-transplant lymphoproliferative disorders (PTLD) cohort with summary of anatomical site of mass formation.

n, %	Monomorphic PTLD	Polymorphic PTLD	Early lesions
Total, all anatomic localizations (276)	145/276, 52.5% (131/145 B-PTLD, 8/145 T-PTLD, 6/145 HL-PTLD)	27/276, 10%	104/276, 37.5%
Sinonasal (3/276, 1%)	1/145 (B-PTLD, maxillary sinus)	0	2/104
Nasopharynx and/or oropharynx (tonsils/adenoids/mucosa) (76/276, 28%)	12/145 (all B-PTLD: 4/12 mucosa, 8/12 tonsils)	12/27 (all tonsils)	52/104 (34/52 tonsils, 11/52 adenoids, 6/52 tonsils+adenoids, 1/52 tongue base)
Larynx (1/276, <1%)	1/145 (T-PTLD)	0	0
Oesophagus (1/276, <1%)	0	0	1/104
GI (53/276, 19%)	30/145 (all B-PTLD)	5/27	18/104
Tx-organ (19/276, 7%)	11/145 (all B-PTLD: 5/11 Tx-liver, 5/11 Tx-lungs, 1/11 Tx-haematopoiesis)	4/27 (2/4 Tx-lungs, 2/4 Tx-kidneys)	4/104 (Tx-lung, Tx-kidney, Tx-haematopoiesis, Tx-gut)
Nodal (93/276, 34%)	66/145 (57/66 B-PTLD, 4/66 T-PTLD, 5/66 HL-PTLD)	6/27	21/104
Extranodal (183/276, 66%)	79/145 (74/79 B-PTLD, 4/79 T-PTLD, 1/79 HL-PTLD)	21/27	83/104

Of these lesions, 79 of 276 (29%) were diagnosed in a sinonasal, nasopharyngeal or oropharyngeal site. Resected tumours of the tubal tonsils, as parts of the Waldeyer's ring, were not reported. Early lesions, mainly in terms of tumour-like nasopharyngeal or oropharyngeal swelling and rarely as hyperplasia inside a paranasal sinus, were the most frequent histopathological finding (n = 54/79, 68%). Polymorphic/monomorphic PTLD were found less frequently (n = 25/79, 32%).

Sinonasal and oropharyngeal monomorphic PTLD were relatively rare and comprised 5% of all lesions (n = 13/276) and 9% of all monomorphic PTLD (n = 13/145). Monomorphic PTLD were all of B-cell/plasmacytoid phenotype (n = 13/79, 17%) and manifested mainly in the tonsils as high-grade B-cell lymphomas (n = 8/13) and less often in the oropharynx (n = 4/13; two plasmoblastic/plasmocytic PTLD, one high-grade B-cell PTLD and one Burkitt PTLD) or in the tissue of the maxillary sinus (n = 1/13; plasmoblastic PTLD). A representative histopathology is depicted in Fig. 1a. While all other PTLD were first presentation lesions, the one oropharyngeal high-grade B-cell PTLD was the second occurrence of a PTLD in this given patient. Four months prior to oropharyngeal PTLD, another high-grade B-cell PTLD had developed in the supragluteal soft tissue, while the oropharyngeal B-cell PTLD manifested in the bone and the mucosal tissue around tooth 47. These two PTLD tumours showed different IgH rearrangements and were therefore classified as two independent PTLDs and not a recurrence of the initial PTLD.

Oropharyngeal manifestation of polymorphic PTLD was restricted to the tonsils and, in comparison with all polymorphic PTLD, relatively frequently (n = 12/27, 44%). Among all sinonasal, nasopharyngeal or oropharyngeal lesions, polymorphic PTLD were the rarest (n = 12/79, 15%).

Tonsils are the most frequent site of sinonasal/nasopharyngeal/oropharyngeal PTLD manifestation

In total, 71 of 276 (26%) lesions manifested as masses in the nasopharyngeal and oropharyngeal sites and of these 60 were located in the tonsils (n = 60/276, 22% of all lesions at any site; n = 60/71, 85% of all lesions in the Waldeyer's ring). Swelling of tonsils was mainly benign (early lesions, n = 41/60, 68%), while tonsil infiltration by polymorphic PTLD (n = 12/60, 20%) and high-grade monomorphic PTLD (n = 8/60, 12%) was rarer.

In contrast to oropharyngeal PTLD manifestation, sinonasal and laryngeal PTLD were rare (one B- and one T-PTLD). At least in this cohort, neither the nasopharynx nor the oesophagus was affected by polymorphic or monomorphic lesions. The frequency of monomorphic PTLD in biopsies from the gastrointestinal tract was more than double that in biopsies from the sinonasal/oropharyngeal region (n = 30/145 vs. 13/145 of all monomorphic PTLD; 21% vs. 9%).

Meta-analysis: characteristics of sinonasal/nasopharyngeal/oropharyngeal PTLD

To increase the number of cases, we combined our own data with data from the literature. From the literature, we identified a total of 61 reports on monomorphic B-PTLD (n = 34) [12,23,25–46], T-PTLD (n = 7) [6,26,34,47–50] and polymorphic PTLD (n = 20) [4,12,35,37,40,42,44,46,51–53] with sinonasal and/or oro-/nasopharyngeal manifestation. Therefore, including our cases, a total of 140 cases were evaluated (Table 2). The focus of these meta-analyses was the clinically relevant polymorphic and monomorphic PTLD cases from previously published reports and our own cohort.

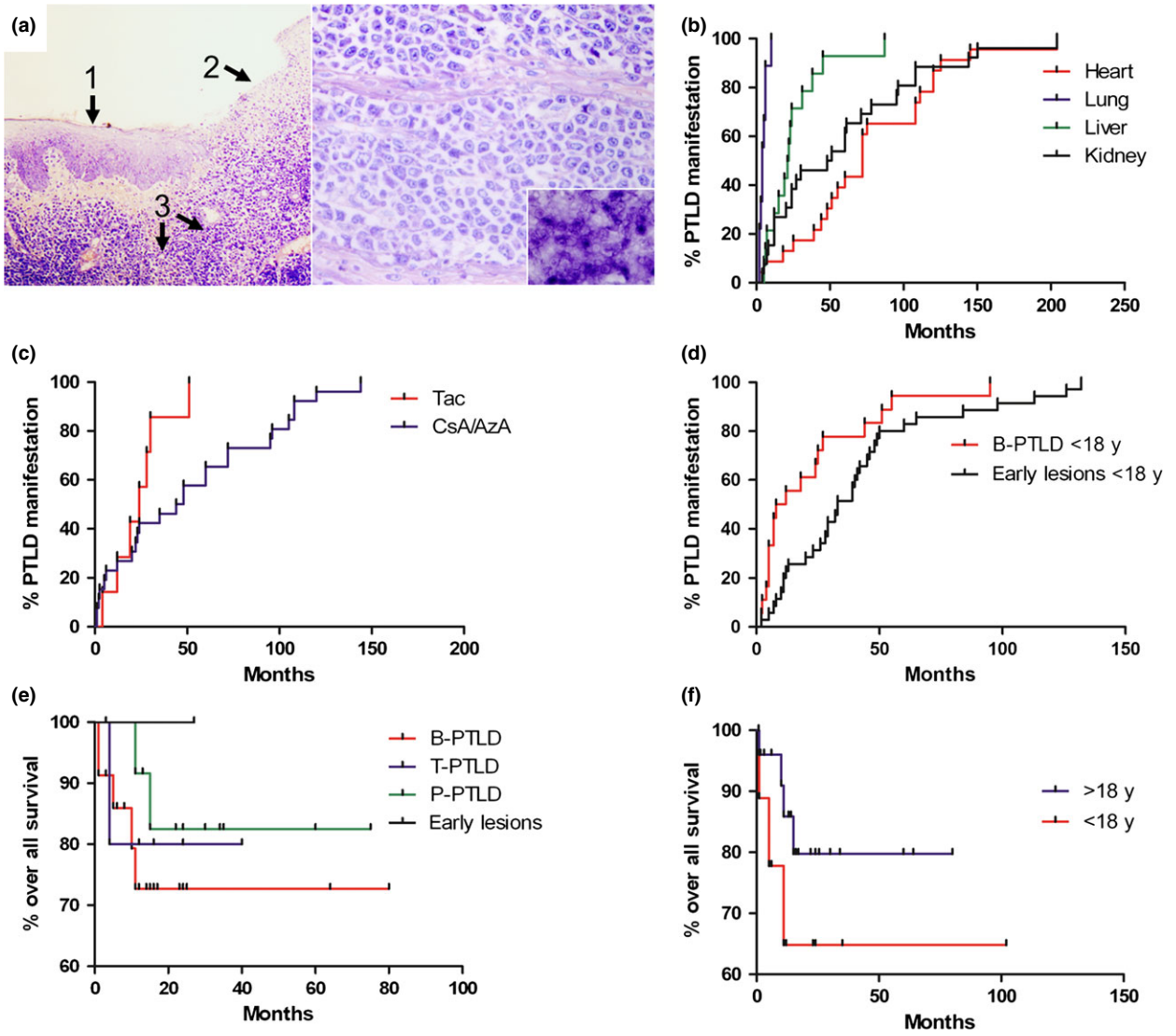

Figure 1 Risk factors and prognosis of post-transplant lymphoproliferative disorders (PTLD) with sinonasal, oro- and nasopharyngeal tumour mass formation. (a) Example of a mass-forming oral PTLD. The overview shows the oral squamous mucosa (arrow, 1) and ulceration (arrow, 2) secondary to a submucosal PTLD infiltration (arrows, 3; original magnification ×100, Giemsa stain). The higher magnification (×400, Giemsa) reveals a plasmablastic differentiation of the monomorphic PTLD with medium to large tumour cells with unipolar enlarged cytoplasms and large nuclei with prominent nucleoli. In the small insert, a positive EBER *in situ* hybridization of the tumour tissue is depicted (×400), indicating EBV-infected PTLD cells. (b) Analyses of risk profiles of polymorphic and monomorphic PTLD cases revealed that tumours manifested earlier in lung-transplanted patients (six B-PTLD and four polymorphic PTLD after lung transplantation). Early lesions are not included in the depicted image but developed earlier in a total of four lung-transplanted patients, too. It has to be taken into account that in only 14 of 140 cases under investigation, have lung transplantations been performed and that multivariate analysis could not confirm the significant result of the univariate analysis (most likely due to small number of cases). (c) A trend towards earlier polymorphic/monomorphic PTLD development was noted for patients with tacrolimus-based immunosuppression (Tac), but compared with azathioprine/cyclosporine A-treated patients (CsA/AzA), the difference was not statistically different. (d) Regarding the subgroup of children and adolescents (<18 years), we found that patients with high-grade B-PTLD manifested earlier tumour masses than patients with benign early lesions. (e) In comparison with sinonasal, oro- and nasopharyngeal early lesions, the histopathological diagnosis of monomorphic or polymorphic PTLD in the same localizations was associated with an adverse prognosis. (f) Compared to adults (>18 years) with polymorphic/monomorphic PTLD, younger patients (<18 years) with polymorphic/monomorphic tumours tended to have an adverse prognosis (uni- and multivariate statistically not significant).

Early lesions were included, too, but it has to be taken into account that all of these cases were derived from our cohort which limits the comparability with the metadata sets.

EBV has not been analysed/reported in all cases, but EBV association was documented in 31 B-PTLD, 5 T-PTLD and 17 polymorphic PTLD. In 10 PTLD, no EBV was found (7

Table 2. Combined summary of our own cohort and patients from the literature with sinonasal and/or oro-/nasopharyngeal post-transplant lymphoproliferative disorder (PTLD) manifestation.

	B-PTLD	T-PTLD	P-PTLD	Early lesions
Total number (*n*, own cases + literature/references)	47/140, 33.5% (13 + 34 [12,23,25–46])	7/140, 5% (0 + 7 [6,26,34,47–50])	32/140, 23% (12 + 20 [4,12,35,37,40,42,44,46,51–53])	54/140, 38.5% (54 + 0)
Female/male/not reported	17/28/2	1/6	17/15	20/34
Age (years)	41 (<1–71)	31 (27–65)	8 (<1–68)	2.5 (<1–59)
Heart/heart+lungs	17/1	1/1	8/0	7/0
Lungs	6	0	4	2
Liver/liver+kidney	9/0	0/0	5/0	22/1
Kidney	11	5	15	18
HSC or other organs	3	0	0	3
Sinonasal	2	0	3	2
Nasopharynx and/or oropharynx	45	7	29	52
Time between transplantation and mass formation (median, range, months)	24.5 (1–204)	49.5 (1–120)	45 (4–150)	33 (2–132)
Follow-up time (median, range, months) reported death	13 (0.5–80), 5 deaths	14 (4–40), 1 deaths	22 (1–103), 2 deaths	27 (1–180), 0 deaths

B-PTLD, 1 T-PTLD, 2 polymorphic PTLD). Therefore, the estimated frequency of EBV association is 84%.

Patients suffering from T-PTLD (n = 7; all adults) or B-PTLD (n = 19/47, 40% children/adolescents) were older than those with polymorphic PTLD (n = 21/32, 66% children/adolescents; P = 0.01 and 0.03, respectively). Patients with early lesions (90% <18 years) were younger than in each of the three PTLD subtypes (each $P < 0.05$), but it has to be taken into account that, in general and independent of preceding transplantation, tonsillitis is more common in young individuals.

In the small group of T-PTLD, more male patients were reported (14% females/86% males). A similar male predominance was not observed in B-PTLD (38% females/62% males) and polymorphic PTLD (53% females/47% males). Early lesions (37% females/63% males) were distributed similarly to those in B-PTLD.

In polymorphic/monomorphic PTLD and early lesions, the transplanted organs were mainly heart and/or lungs (n = 38/140, 27%) and kidneys (n = 31/140 22%) and, to a lesser extent, livers (n = 14/140, 10%) or other organs.

Meta-analysis: risk factors for PTLD manifestation

Compared to all other transplant organs, monomorphic/polymorphic PTLD manifested significantly earlier in lung-transplanted patients (10 cases with PTLD after lung transplantation; Fig. 1b). Similar to monomorphic/polymorphic PTLD, early lesions manifested earlier in lung-transplanted individuals (four cases). The earliest monomorphic PTLD manifestation (early onset PTLD <12 months) was found in two patients 1 month after combined lung and heart transplantation (one B-PTLD and one T-PTLD). The earliest polymorphic PTLD developed in two other patients, each 4 months after lung and kidney transplantation, respectively. Early lesions were reported as early as 2 months after kidney transplantation.

In general, patients with tacrolimus-based immunosuppression tended to develop PTLD earlier than patients with azathioprine/cyclosporine A therapy (P = 0.07, Fig. 1c). However, the time period between transplantation and manifestation of polymorphic/monomorphic PTLD and early lesions was similar.

Regarding age as a potential risk factor (</>18 years), we found that B-PTLD manifested earlier after transplantation in children and adolescents than in adults with B-PTLD (P = 0.004), T-PTLD (P = 0.05; borderline significance) or polymorphic PTLD (P = 0.05; borderline significance). The difference was also significant when compared with children/adolescents with polymorphic PTLD (P = 0.005) and even early lesions (P = 0.02; Fig. 1d). However, multivariate analyses revealed no independent risk factor.

Comparison of EBV+ and EBV− PTLD showed no significant difference regarding the time between transplantation and tumour manifestation (P = 0.6).

Meta-analysis: prognostic factors in patients with PTLD

Therapy regimens were variable and were mainly based on reduction of immunosuppressive agents and/or immuno-/chemotherapy. No significant difference in overall survival was found in 25 evaluable polymorphic/monomorphic PTLD cases between reduction of immunosuppressant alone or in combination with chemotherapy (P = 0.5). Because of missing data (either on therapy or follow-up or both), the remaining cases could not be evaluated.

A total of five B-PTLD patients died 0.5–11 months after diagnosis, one T-PTLD patient after 4 months and two patients with polymorphic PTLD after 11 and 15 months (Fig. 1e). Three of these patients with fatal outcome had EBV− tumours which resulted in a generally poorer prognosis of EBV− versus EBV+ PTLD ($P = 0.01$ univariate analyses but no independent prognostic factor in multivariate analysis). Patients with early lesions all survived and had a better prognosis than patients with polymorphic or monomorphic PTLD but, due to the low number of early lesion follow-up data, the difference was not significant. Furthermore, compared to adults, younger patients with polymorphic/monomorphic PTLD tended to have a poorer overall survival rate, but again, the difference was not significant (Fig. 1f).

Discussion

The nasopharyngeal and oropharyngeal mucosa-associated lymphatic tissue is the main anatomical site of EBV entry and infection of B cells [54]. EBV+ tonsillitis, EBV+ malignant lymphomas and EBV+ nasopharyngeal carcinomas are typical virus-associated diseases of the naso- and oropharynx [54–56]. In organ-transplanted patients, in particular in children, swelling of the mucosal tissue always leads to the differential diagnosis of polymorphic/monomorphic PTLD manifestation versus benign early lesions [57,58]. It has to be taken into account that, most likely, early lesions are under-represented in other research studies because they are considered to be less relevant than high-grade lesions.

Most patients were transplanted after organ failure of hearts, livers or kidneys and only few after terminal lung dysfunction. However, the highest risk to develop an early onset PTLD in the naso- or oropharynx was associated with lung transplantation. It has to be taken into account that, due to the overlaps between polymorphic/monomorphic PTLD on the one hand and early lesions on the other hand, the type of transplant organ and the time of tumour mass formation after transplantation were not reliable indicators for predicting the type of lesion. Furthermore, when considering all ages, the time period between transplantation and polymorphic/monomorphic PTLD or early lesions was also similar, but we found that in children, B-PTLD manifested earlier than early lesions. We do not have enough data on pretransplant EBV status in these children but, in general, EBV-naïve children are at higher risk of PTLD manifestation [11,24]. As could be expected from the EBV-related pathogenesis in transplant patients, we identified adenoids and in particular tonsils as the most frequently affected anatomical site. The likelihood that a tonsillar mass is not a benign early lesion but a more aggressive PTLD is roughly ~30%. Sinonasal tumours were rare and tumour formation outside the Waldeyer's ring was infrequent but predominantly caused by monomorphic PTLD. This general finding, that extratonsillar masses are most likely aggressive PTLD, is relevant for the clinical differential diagnosis and has not been reported before.

In our cohort, monomorphic PTLD were all diffuse large B, plasmablastic or plasmacytoid cell phenotypes. In other studies, in addition to B-PTLD, T-cell phenotypes have also been reported, but no CD30+/CD15+ Hodgkin lymphoma types [6,26,34,47–50]. In general, both T-PTLD and Hodgkin PTLD are rare PTLD subtypes, while high-grade B-PTLD comprise ~80–90% of all monomorphic lesions [6,11,59,60]. The majority of naso-/oropharyngeal PTLD were EBV-associated which was expectable because, in general, up to 80% of all PTLD are EBV+ [10,61]. As the putative EBV+ founder B cell most likely originated from the naso- or oropharynx, it could be expected that this would result in a frequent B-PTLD manifestation at this cranial submucosal site. Furthermore, it could be expected that preceding early lesions would mediate a local vulnerability in terms of a precursor lesion for a subsequent high-grade PTLD at the same oropharyngeal site. In contrast, early lesions were not risk factors for a subsequent local polymorphic/monomorphic PTLD, and oral B-PTLD tumours were infrequent while extra-oral PTLD were common. Therefore, the term 'early' does not imply an oral precursor lesion, for example in the tonsils, and at least in children and adolescents, polymorphic/monomorphic PTLD manifested earlier in the oral cavity than early lesions. It could be possible that the aberrant founder cell acquires the EBV infection in the oral cavity and afterwards migrates/circulates, which leads to neoplastic tumour formation at other anatomical sites of the lymphatic tissues. Lymph nodes, as the natural environment for lymphatic cells, are clearly a vulnerable location for aberrant lymphoproliferation. It is not clear why homing of tumour cells is more likely at extracranial mucosa-associated lymphatic tissues such as the gastrointestinal tract. We and others found a few PTLD in the oral cavity and simultaneously or sequentially in other anatomical sites [4,25,39]. As, in general, these cases are rare and IgH analysis often shows two clonally independent diseases, naso- or oropharynx PTLD is not related to a higher risk of tumour spreading [25].

In our retrospective evaluation, we found that, depending on the subtype, therapy is based on surgical debulking, reduced immunosuppression and immuno-/chemotherapy. Reduced immunosuppression alone could lead to remission of PTLD in some cases [4,25,26,51]. Absence of EBV was associated with an adverse prognosis, which was not related to age, PTLD subtype or therapy. EBV− PTLD are thought to represent either tumours which have lost the initially acquired viral genome during evolution or which are based on more severe genetic defects which do not require EBV as

a driver of neoplastic transformation [62]. Both models would indicate tumour biological more advanced stages which could explain the more aggressive clinical behaviour [62,63]. However, it must be emphasized that not all PTLD were evaluated for EBV and that details of therapeutic regimes were not always reported or available. Thus, due to the retrospective analysis of relatively few EBV− PTLD and the lack of complete reports on therapies and follow-up data, these results must be confirmed by prospective studies, for example the ongoing Ped-PTLD study.

In summary, post-transplant tumour masses at sinonasal, nasopharyngeal or oropharyngeal sites occur in ~30% of all patients and are mainly localized in the tonsils. Two-thirds of these masses are early lesions, and one-third are polymorphic or monomorphic PTLD. Therefore, ~30% of tonsillar masses are caused by polymorphic or monomorphic PTLD. Extratonsillar masses are infrequent but likely to be high-grade B-cell PTLD.

Monomorphic PTLDs of the oral cavity are almost all of B cell/plasma cell type and rarely T-cell subtypes. CD30+/CD15+/CD20− Hodgkin PTLD have not been reported.

Lung-transplanted and young patients are at higher risk for earlier PTLD manifestation in the oral cavity. However, in individual patients, there is no reliable indicator or risk factor for predicting the type or onset of these cranial mucosa-associated lesions. Therefore, the final diagnosis is based on pathological evaluation. Therapy is similar to PTLD therapy strategies in general: reduced immunosuppression and chemotherapy for polymorphic and monomorphic PTLD, diagnostic and therapeutic surgical gross tumour resection of tonsillar/adenoid lesions.

Authorship

AA, CT and KH: designed research study. AA, CT, JL, BMK, HK and KH: collected data. AA and KH: analyzed data, AA, CT, JL, BMK, HK and KH: wrote paper.

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