Plasmacytoma-like post-transplant lymphoproliferative disorder, a rare subtype of monomorphic B-cell post-transplant lymphoproliferation, is associated with a favorable outcome in localized as well as in advanced disease: a prospective analysis of 8 cases

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ABSTRACT

Post-transplantation lymphoproliferative disorder (PTLD) with plasmacellular differentiation has been reported as a rare subtype of monomorphic B-cell post-transplant lymphoproliferation with histological and immunophenotypical features of plasmacytoma in the non-transplant population. Here we present clinical, laboratory and histopathological features, treatment and outcome of 8 patients from the German prospective PTLD registry. Clinically, extranodal manifestations were common while osteolytic lesions were rare and none of the patients had bone marrow involvement. Immunohistochemistry showed light chain restriction and expression of CD138 without CD20 expression in all samples. An association with Epstein-Barr virus was found in 3 out of 8 cases. We suggest that the Ann Arbor classification is most useful for this disease entity and report a generally good response to treatment including reduction of immunosuppression, surgery and irradiation in localized disease and systemic chemotherapy analogous to plasmacell myeloma in advanced disease.

Key words: plasmacytoma, plasmacell lymphoma, post-transplant lymphoproliferative disorder, CD138.

Citation: Trappe R, Zimmermann H, Fink S, Reinke P, Dreyling M, Pascher A, Lehmkuhl H, Gärtner B, Anagnostopoulos I and Riess H. Plasmacytoma-like post-transplant lymphoproliferative disorder, a rare subtype of monomorphic B-cell post-transplant lymphoproliferation, is associated with a favorable outcome in localized as well as in advanced disease: a prospective analysis of 8 cases. Haematologica 2011;96(7):1067-1071. doi:10.3324/haematol.2010.039214

Introduction

Post-transplantation lymphoproliferative disorder (PTLD), a spectrum of lymphatic diseases associated with the use of potent immunosuppressive drugs after transplantation,[1] represents one of the most common neoplastic diseases following solid organ transplantation.[2] Patients with PTLD commonly present with stage III or IV disease of varying histology, frequently involving extranodal sites.[3-10] Organ dysfunction, especially renal function impairment, is also a common feature at presentation. Initial therapy in PTLD is immunosuppression reduction (IR). This can result in complete remission (CR)[11,12] but overall response rates are low.[13] Additionally, IR is known to be associated with a high risk of graft rejection and graft loss. A rejection rate of 37% has recently been reported in a first prospective trial systematically evaluating IR in PTLD.[13] Common subsequent therapies in patients failing to respond to upfront IR are rituximab monotherapy in CD20-positive B-cell PTLD,[6-8] CHOP-like chemotherapy[14] and a combination of rituximab and CHOP, either synchronous or in sequence. Both options are highly effective in the treatment of PTLD after an initial failure of upfront IR. Overall response rates of about 40-60% for single agent rituximab[6-9] and up to 90% for sequential treatment with 4 courses of rituximab followed by 4 cycles of CHOP have been reported[9] leading to an improved overall survival. Thus, significant progress has been made in the treatment of CD20-positive B-cell PTLD. However, PTLD is not a homogeneous entity, neither in its clinical presentation nor in its pathological appearance. While the majority of monomorphic PTLD lesions resemble non-Hodgkin's lymphoma, specifically diffuse large B-cell lymphoma, rare forms have been identified, one of which is PTLD with plasmacellular differentiation. Plasma cell rich infiltrates in transplant recipients can be found in a

Funding: the PTLD D 2006-2012 registry is supported by grants from AMGEN, CLS Behring, Mundipharma GmbH and Roche Pharma AG. The German Study Group on PTLD (DPTLDSG) is a member of the German Competence Network Malignant Lymphomas (KML).
Manuscript received on December 20, 2010. Revised version arrived on March 1, 2011. Manuscript accepted March 18, 2011.
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spectrum of lesions comprising acute rejection, early PTLD lesions also known as plasmacytic hyperplasia and plasma cell rich polymorphic lymphoproliferations.[15] These plasma cells usually show neither light chain restriction nor clonal proliferation. In contrast, PTLD with plasmacellular differentiation has been reported as a rare monomorphic B-cell PTLD subtype with a histomorphology comparable to plasmacytoma in the non-transplant population, clonal immunoglobulin gene rearrangements and light chain restriction.[16] So far, only case reports and one retrospective series of 4 cases have been published on this disease entity.[17] Here, we present the first prospective case series, including clinicopathological features, treatment and treatment outcome.

Design and Methods

To assess the clinical features, treatment options and outcome of rare PTLD subtypes, a prospective PTLD registry was set up in Germany in 2006. Here we present our data on patients diagnosed with plasmacytoma-like monomorphic PTLD from 2006 to 2010. Follow-up data was reviewed for all patients up to December 2010. Tumor response to treatment was defined according to the World Health Organization criteria. In plasmacytoma-like PTLD definition of complete remission (CR) additionally required the absence of monoclonal gammopathy. Progression-free survival (PFS) was defined from start of therapy to disease progression or to death from any cause, while overall survival (OS) was defined from diagnosis of PTLD to death from any cause. Clinical data on the patients in the registry was collected before, during and at least at four weeks, six, 12 and 24 months after treatment. Additional data on patients' characteristics were retrieved from databases at the different transplant centers. The responsible local ethics committee approved the trial and patients gave written informed consent for non-anonymous documentation according to the Declaration of Helsinki.

The diagnosis of PTLD was based on the examination of histological material, obtained either by open biopsy or core needle biopsy. Diagnostic tissue samples were subsequently reviewed by a single expert pathologist (IA) and classified morphologically according to the WHO classification (2008). An association with the Epstein-Barr virus was confirmed by immunohistochemical staining for the latent membrane protein 1, Epstein-Barr nuclear antigen 2, Epstein-Barr ZEBRA antigen and/or by *in situ* hybridization for EBER-transcript detection. The extent of existing disease was determined through a complete patient history, physical examination, laboratory investigations (including full blood count, lactate dehydrogenase [LDH, upper limit 240U/l]), renal and liver function tests, as well as determination of the EBV DNA load in peripheral blood), bone marrow biopsy and computed tomography (CT) scans of the chest, abdomen and pelvis. All patients diagnosed with plasmacytoma-like PTLD had further blood tests to detect monoclonal gammopathy and an osteo-CT or osteo-MRI scan to detect local bone destruction. Patients for whom IR had provided no benefit received subsequent treatment as chosen by the treating physician. Treatment protocols included local irradiation and surgery for localized disease and systemic chemotherapy for disseminated PTLD.

Results and Discussion

By the end of 2010, 182 patients were reported to the German PTLD registry D2006-2010 from which 8 (4%) had a diagnosis of monomorphic plasmacytoma-like PTLD (6 male, 2 female). They had previously undergone solid organ transplantation of kidney (n=3), lung (n=1), liver (n=1), heart (n=2) or small intestine (n=1). The median age at diagnosis was 55 years (range 25-73). All patients received immunosuppressive treatment at the time of their PTLD diagnosis (Table 1A). In accordance with previously published data,[17] most cases were late-onset PTLD with a median time from transplant to diagnosis of PTLD of 8.3 years (range 3 months to 26 years). Only 2 cases were diagnosed within the first year after transplantation while 4 cases were diagnosed more than ten years after transplantation. There was no obvious association with an underlying disease (Table 1A).

All 4 cases with localized disease at diagnosis presented with exclusively extranodal manifestations. Out of the 4 patients with disseminated disease, one had only extranodal and another only nodal manifestations, while 2 patients had both. Of note, osteolytic lesions were rare (2 of 8) and none of the patients had bone marrow involvement (Table 2). This is in contrast to the 3 patients diagnosed with monomorphic multiple myeloma-like PTLD described by Sun *et al.* who all presented with osteolytic lesions and bone marrow involvement but without nodal or extranodal disease.[18]

The neoplastic plasma cell population was well-differentiated (Marschalko-type) in 7 of 8 cases and showed either lambda (2 of 8) or kappa (6 of 8) light chain restriction and positivity for CD138 (8 of 8), while CD20 was negative in all and CD56 in 7 of 8 cases. A paraprotein could be detected in all cases, but overall serum immunoglobulin levels were low compared to plasmacell myeloma (Table 3). An association with latent EBV infection was verified by EBER-ISH in 3 of 8 cases (Table 1B). EBV-associated plasmacytoma-like PTLD showed no expression of LMP-1 or EBNA-2 proteins, while the ZEBRA protein indicative for a transition from the lytic to the latent infection cycle was expressed in 2 of 3 cases. All 3 cases of EBV-associated PTLD showed remarkably elevated EBV DNA loads in their peripheral blood, while non-EBV associated cases often had no detectable blood levels of EBV DNA (Table 1B).

Out of the 6 patients who received a reduction of immunosuppression as the initial therapeutic intervention, 2 responded while 4 patients showed progressive disease. All 3 evaluable patients with localized disease achieved sustained lymphoma control (including CR after IR and CR after surgery). The 3 patients with disseminated disease and PD after IR received systemic chemotherapy analogous to plasmacell myeloma (Table 3) which was remarkably well tolerated with supportive treatment including GCSF. All 3 responded to treatment (including one CR after PAD). None of the patients received rituximab, as staining for CD20 was negative in all cases.

The group of 8 adult patients presented here included different types of solid organ transplant recipients under immunosuppressive therapy. The small number of patients does not allow any conclusions to be drawn as to whether either transplantation of a particular organ or a specific immunosuppressive drug is linked to the development of plasmacytoma-like PTLD. It is likely that the total amount of immunosuppression plays an important role, as it does in other PTLD.[19]

Like other monomorphic PTLD subtypes, EBV-association is present in half of the lymphomas.[9] This is in con-

trast to classical plasmacytoma in non-transplant patients in whom EBV is rarely present. The fact that LMP-1 and EBNA-2 expression was negative in all cases underscores the importance of EBER *in situ* hybridization. With positive PCR results for EBV DNA in peripheral blood in all patients with EBV-associated plasmacytoma-like PTLD, monitoring of EBV copy numbers might provide a potential further method for monitoring treatment in these patients.[20-23] However, a careful interpretation of EBV loads is necessary.[24]

As bone marrow involvement and lytic bone lesions are rare, and most patients suffer from impaired renal function

Table 1A. Baseline characteristics.

N.	Sex	Age at diagnosis of PTLD (years)	Transplant	Disease resulting in solid organ transplantation	Time from transplantation to PTLD (days)	Immunsupression at diagnosis of PTLD		
						CNI	anti-metabolite	steroid
1	male	56	Kidney	ESRD	3921	CyA	MMF	yes
2	female	51	Lung	alpha1-antitrypsin deficiency	5037	CyA	AZA	no
3	male	66	Liver	Hepatocellular carcinoma/liver cirrhosis	107	CyA	no	no
4	male	53	Heart	Dilative cardiomyopathy	2118	FK	no	no
5	male	72	Kidney	Chronic glomerulonephritis	9427	CyA	no	no
6	male	24	Small intestine	Chronic intestinal pseudo-obstruction	102	FK	MMF	yes
7	female	39	Kidney	Polycystic kidney disease	6616	CyA	AZA	yes
8	male	68	Heart/ kidney	Dilatative cardiomyopathy/ ESRD	1439/ 419	CyA	AZA	yes

ESDR: end-stage renal disease.

Table 1B. Baseline characteristics.

N.	Diagnosis	Histology	Bartl Grade	CD56	Light chain restriction	Expression of EBVs LMP-1, EBNA-2 and ZEBRA	EBER-ISH: percentage of EBER-positive cells	EBV DNA-load in peripheral bood (copies/mL)
1	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	lambda	LMP-1: negative EBNA-2: negative ZEBRA: negative	negative	negative
2	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	kappa	LMP-1: negative EBNA-2: negative ZEBRA: negative	80%	110
3	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	kappa	LMP-1: negative EBNA-2: negative ZEBRA: negative	negative	n.d.
4	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	kappa	LMP-1: negative EBNA-2: negative ZEBRA: negative	negative	negative
5	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	kappa	LMP-1: negative EBNA-2: negative ZEBRA: negative	negative	380
6	monomorphic, plasmacytoma-like PTLD	predominantly mature plasma cells atypical forms: none increased number of mitotic figures: yes nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	negative	lambda	LMP-1: negative EBNA-2: negative ZEBRA: negative	negative	negative
7	monomorphic, plasmacytoma-like PTLD	predominantly asynchronous increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Intermediate (asynchronous)	negative	kappa	LMP-1: negative EBNA-2: negative ZEBRA: single positive cells	90%	6940
8	monomorphic, plasmacytoma-like PTLD	predominantely mature plasma cells atypical forms: none increased number of mitotic figures: no nuclear/cytoplasmic inclusions: none	Low (Marschalko type)	positive	kappa	LMP-1: negative EBNA-2: negative ZEBRA: positive	60%	4900*1 24400*2

**1 at diagnosis, *2 at relapse*

due to their underlying disease or the use of calcineurin inhibitors even before the diagnosis of plasmacytoma-like PTLD, neither the Durie and Salmon classification nor the ISS classification seem appropriate to predict prognosis. The presentation with mass lesions and successful therapy of localized disease with surgery and irradiation make the Ann Arbor classification appear most useful. In this respect, plasmacytoma-like PTLD behaves similarly to extramedullary plasmacytoma in immunocompetent patients.

In conclusion, patients with plasmacytoma-like PTLD in this case series had a relatively good treatment outcome,

Table 2. Clinical presentation.

N.	Organ involvement	Lymph node involvement	BM	Osteolytic lesions	IF	IgG mg/dL	IgA mg/dL	IgM mg/dL	LDH (U/L)	Ann Arbor
				localized disease						
1	mucosa-associated gastric lesions	none	no	none	l-lambda	1107	269	105	178	IE
2	right main nasal cavity, right sinus frontalis, right sinus ethmoidalis, right sinus maxillaries	none	no	none	IgG-kappa	1730	250	170	171	IE
3	liver transplant	none	no	none	IgG-kappa	1582	257	163	253	IE
4	retroperitoneal mass	retroperitoneal mass	no	none	IgG-kappa	1010	110	300	203	IE
				disseminated disease						
5	None	cervical, retroperitoneal inguinal	no	none	IgG-lambda	3080	620	70	184	III
6	liver, peritoneal lymphomatosis	retroperitoneal, mesenterial, inguinal	no	none	IgM-kappa	1246	463	1534	507	IVE
7	skin, peritoneal lymphomatosis, m. psoas	none	no	three	IgG-kappa	2212	473	174	207	IVE
8	skin, pleura*1 skin, pleural effusion*2	mediastinal, abdominal*1 inguinal*2	no	multiple	IgG-kappa *1 negative*2	1138*1 1308*2	25*1 218*2	10*1 30*2	416*1 208*2	IVE

*1 at diagnosis, *2 at relapse, IF: immune fixation; BM: bone marrow involvement.

Table 3. Treatment.

N.	Reduction of immunosuppression	Response	Subsequent treatment	Response	Relapse/ progression	PFS (days)	OS (days)	Cause of death
			localized disease					
1	MMF reduced to 33% of initial dose CyA/steroid doses unchanged	CR	none		no	554	554	squamous cell carcinoma
2	Unchanged	→	involved field irradiation: 50,4 Gy	SD	no	>270	>300	alive
3	CyA reduced to 50% of initial dose	PD	retransplantation (bridging to transplantation by application of 3# dexamethasone + 1# dose-reduced CHOP*1)	CR	no	>459	>635	alive
4	Tacrolimus stopped	→	involved field irradiation started	not yet evaluable	no	not yet evaluable	not yet evaluable	alive
			disseminated disease					
5	CyA stopped	PR	none		no	>116	>116	alive
6	MMF stopped FK/steroid doses unchanged	PD	4# PAD*2	CR	no	>640	>660	alive
7	All immunosuppressants stopped	SD for 187 days	2# PAD*3 followed by local irradiation of skin lesions and 3# oral cyclophosphamid (5x200mg/m²/day)	PR	no	>83	>273	alive
8	AZA and steroid stopped CyA doses unchanged	PD	4# VAD*4 4# bendamustin*5 1# bortezomib*6	PR PR PD	yes yes →	301 110 10	428	PTLD-progression

*1 dexamethasone 40 mg days 1-4; cylophosphamide 500 mg/m² day 1, doxorubicin 25 mg/m² days 1; vincristin 1 mg. *2 doxorubicin 8 mg/m² days 1-4; bortezomib 1.3 mg/m² days 1, 4, 8, 12; dexamethasone 40 mg days 1, 8, 15; 6mg PEG-GCSF day 5; *3 doxorubicin 8mg/m² days 1-4; bortezomib 1.3 mg/m² days 5,10,14; dexamethasone 40 mg days 1,8,11; no GCSF prophylaxis; *4 vincristin 0.2 mg/m² days 1-4, doxorubicin 8 mg/m² days1-4; dexamethasone 40 mg days1-4; GCSF prophylaxis starting day 5; *5 100 mg/m² days1+2; no G-CSF prophylaxis; *6 bortezomib 1.3 mg/m² days 1, 4, 8.

with only one patient dying from progressive disease. As in the case of conventional PTLD, reduction of immunosuppression was an effective and potentially curative therapy in 2 out of 7 patients[11,12] and patients with localized disease responded well to localized treatment such as surgery and irradiation. In more advanced disease, anti-plasma cell chemotherapy including treatment with the proteasome inhibitor bortezomib could induce disease remission.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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