Plasmacytoma-Like Post-Transplantation Lymphoproliferative Disease Occurring in a Cardiac Allograft: A Case Report and Review of the Literature

Case Report

A 33-year-old woman with a history of an orthotopic heart transplantation in 2006 for a left anterior descending artery dissection presented 5 years post-transplantation with intermittent palpitations and light headedness for 2 months. The patient had multiple episodes of acute and chronic rejection since her transplantation, and her immunosuppression consisted of prednisone 5 mg per day, mycophenolate mofetil, tacrolimus, and rapamune at the time of presentation. Telemetry monitoring revealed a new onset of sinus pauses. An echocardiogram showed normal biventricular function with left ventricular hypertrophy and biatrial enlargement. Myocardial magnetic resonance imaging of the heart demonstrated patchy areas of delayed contrast enhancement that mostly involved the left ventricular infe-

rior and lateral wall (Fig 1A, arrow), foci within the inferior septum (Fig 1B, arrow), and the right ventricular free wall and apex, which indicated a pattern not typical of ischemic disease and most compatible with an infiltrative process. An endomyocardial biopsy revealed sheets of plasma cells (Figs 2A and 2B; hematoxylin and eosin stain; original magnifications: A, $\times 20$; B, $\times 100$) that were CD138+ (Fig 2C; immunohistochemical stain for CD138; original magnification $\times 40$) and light chain restricted (Fig 2D; in situ hybridization stain for kappa light chains; original magnification $\times 20$), with only occasional light-chain positivity (Fig 2E; in situ hybridization stain for lambda light chains; original magnification $\times 20$). Epstein-Barr virus (EBV)-encoded RNA in situ hybridization stain was negative (Fig 2F; original magnification $\times 40$). Diffuse lymphocytic infiltrates of the myocardium were found in the background, which were consistent with grade 1R cellular rejection according to the International Society for Heart and Lung Transplantation criteria.¹ This presentation was consistent with plasmacytoma-like monomorphic B-cell post-transplantation lymphoproliferative disease (PTLD) occurring in the setting of graft rejection.

Fig 1.

Fig 2.

An additional staging workup was performed. Serum protein electrophoresis demonstrated a possible abnormal λ -restricted peak in the γ region of 0.2 g/dL, which was inconsistent with the endomyocardial biopsy that demonstrated a κ restriction. Subsequent testing before and after therapy did not confirm the presence of an abnormal restricted peak. β -2 microglobulin was slightly increased at 2.8 mg/L. Serum-free κ and λ light chains were within normal ranges at 1.49 mg/dL (normal range, 0.33 to 1.94 mg/dL) and 0.85 mg/dL (normal range, 0.57 to 2.63 mg/dL), respectively; however, the κ : λ ratio was slightly increased to 1.75 (normal range, 0.26 to 1.65). Urine electrophoresis and immunofixation were unremarkable. A whole-body [^{18}F]fluorodeoxyglucose positron emission tomography scan revealed increased right myocardial [^{18}F]fluorodeoxyglucose uptake, likely as a result of PTLD (Fig 3, arrow). A bone marrow biopsy, computed tomography scans of the chest, abdomen, and pelvis, and skeletal surveys did not reveal any evidence of systemic involvement of the PTLD.

The decision was made to reduce immunosuppression despite evidence of low-grade chronic rejection. Mycophenolate mofetil was discontinued, but the patient continued to receive tacrolimus, rapamune, and low-dose prednisone. Repeat endomyocardial biopsies after 1 and 2 months showed grade 2R acute cellular rejection and

persistent, although decreased, involvement by plasmacytoma-like PTLD. With evidence of ongoing acute rejection, it was felt that the immunosuppression of the patient could not be safely reduced further, and she was given subcutaneous bortezomib at a dose of 1.3 mg/m² per day on days 1, 4, 8, and 11 of a 28-day cycle. After three cycles of bortezomib, a repeat magnetic resonance imaging of the heart showed a modest interval decrease in the left-ventricle contrast enhancement (Figs 1C and 1D, arrows). After four cycles of bortezomib, the chronic palpitations of the patient improved subjectively. Her treatment is ongoing.

Discussion

Post-transplantation lymphoproliferative disorders (PTLDs) consist of a variety of lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in the setting of solid organ or bone marrow transplantation. PTLDs remain rare but are one of the most morbid complications after solid organ transplantation. The frequency of PTLDs varies from less than 1% in patients with renal transplantation to more than 5% in heart or lung transplantation recipients.² Monomorphic PTLDs most commonly resemble diffuse large-B-cell lymphoma or Burkitt's lymphoma, whereas plasmacytoma-like PTLDs are much less common and account for

Fig 3.

less than 4% of PTLDs.³ In addition, PTLDs are usually found in the lymph nodes, gastrointestinal tract, kidney, and liver and much less commonly in an allograft. Allograft involvement is often found in early lesions in patients who are EBV positive. Cardiac allograft involvement, as found in our patient, is exceedingly rare. According to the WHO classification, PTLDs can be divided into the following three main categories: early lesions, polymorphic, and monomorphic PTLDs.² The first category is characterized by lymphoid proliferations with preserved architecture of the involved tissues with plasmacytic hyperplasia and infectious mononucleosis-like features. In the latter two categories, architecture effacement of involved tissues is seen. Monomorphic PTLDs are often clinically indistinguishable with the corresponding lymphomas or plasma-cell dyscrasias in immunocompetent hosts.

Because of their rarity, there is a paucity of literature on plasmacytoma-like PTLDs. All articles have been case reports or small case series.⁴⁻²⁷ A summary of all published cases found in PubMed up to November 2011, and modified from the table by Richendollar et al,⁴ is presented in Table 1. Thirty-seven cases were included. All cases occurred after a solid organ transplantation. The majority of cases involved skin and lymphoid tissues, and only three cases involved an allograft (one kidney and two livers). The median age of patients was 56 years old; 22% of patients (eight of 37) were below the age of 40 years at diagnosis, whereas 30% of patients (11 of 37) were more than 60 years of age. Eighty percent of patients were men. Fifty-three percent of cases (17 of 32) were EBV positive, and 49% of cases (17 of 35) were λ restricted. Unlike lymphoma-like PTLDs, which usually present within 1 to 2 years after transplantation, plasmacytoma-like PTLDs typically demonstrated a delayed onset. Only six patients developed disease within 1 year, and the majority of other patients developed disease after more than 3 years, with the longest instance being almost 26 years post-transplantation.¹⁰ No apparent correlations were identified among the type of protein restriction (κ or λ), the sites of involvement, or EBV positivity.

Among the 33 patients with available treatment records, 31 patients had a reduction of immunosuppression and/or radiation ther-

apy as initial treatment, which indicated that they remained the mainstay of treatment for plasmacytoma-like PTLDs. Chemotherapy was added in 15 cases for refractory or progressive diseases. One patient achieved complete remission with autologous stem-cell transplantation.¹⁸ Allogeneic stem-cell transplantation was done in another patient without significant benefits.²¹ Treatment responses were unclear in six patients. Among the remaining 31 patients, 17 patients (55%) were free of disease at the last follow-ups, although 28 patients (90%) had at least partial responses at some point. These results were consistent with the favorable outcome demonstrated by a recently published prospective registry series.¹⁰ However, publication biases may have contributed to these positive results. In addition, the follow-up in most cases was relatively short (within 2 years).

To our knowledge, this is the first report of plasmacytoma-like PTLD that occurred within a cardiac allograft. PTLD occurred five years after the transplantation, which was consistent with the delayed onset seen in the literature with this disease. The EBV-encoded RNA in situ hybridization of the patient was negative. The proportion of EBV-negative PTLDs is on the increase in the past decade (up to 50% to 60% in some series), although the proportion varies widely among studies.^{2,28} This type of PTLD usually occurs later after transplantation, with a median of 50 months post-transplantation compared with 10 months in patients with EBV-positive PTLD.²⁸ EBV-negative PTLDs are typically monomorphic and carry a poor prognosis.²⁸ Because of the location of the disease of our patient (endomyocardium), radiation therapy was contraindicated. Although immunosuppression was tapered in this patient, the development of acute rejection precluded the additional reduction needed to treat her PTLD. Chemotherapy regimens, such as vincristine, doxorubicin, and dexamethasone, melphalan, and cyclophosphamide plus prednisone, have been reported in the literature as treatments for plasmacytoma-like PTLDs with various degree of success.^{4,7,10,12,22} In recent years, bortezomib, which is a proteasome inhibitor, has become a mainstay for plasma-cell dyscrasia. From our experiences in this case, we feel that bortezomib represents a feasible treatment option with low toxicity for plasmacytoma-like PTLDs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Table 1. Summary of Plasmacytoma-Like PTLDs in the Literature

Case and Reference No.	Age (years)*	Sex	Transplantation Type	Time Since Transplantation	Site	Monoclonal Light-Chain Ig	EBER	Treatment	Responses
1 ⁴	17	M	Heart	9.5 years	Adenoids	λ	Neg	ROI	CR, NED at 2.3 years
2 ⁵	56	M	Heart	5.5 years	Skin	κ	NA	XRT	CR at 1 month, progression to MM at 2 months, DOD at 6 months
3 ⁶	61	F	Heart	9 years	Skin	λ	NA	NA	NA
4 ⁷	63	M	Heart	8 years	Skin	κ	Neg	ROI, VAD, XRT	CR at 5 months
5 ⁸	57	M	Heart	10 years	Skin	λ	Pos	XRT, excision	Multiple relapses, died as result of heart failure
6 ⁸	54	M	Heart	8 years	Skin	λ	Pos	ROI	CR
7 ⁹	56	F	Heart	3 years	Peritoneum	λ	NA	NA	NA
8 ¹⁰	53	M	Heart	5 years, 10 months	Retroperitoneum	κ	Neg	ROI, XRT	NA
9 ¹¹	58	M	Lung	9 years	Skin, mouth	λ	Pos	XRT	PR, DOD at 6 months
10 ¹⁰	51	F	Lung	13 years, 10 months	Nasal cavity/sinuses	κ	Pos	XRT	SD at > 9 months
11 ¹²	55	F	Liver	0.5 years	Pleura, kidney	λ	Neg	ROI, Mel, P	PR, DOD
12 ⁴	37	M	Liver	4 years, 11 months	Lymph node	λ	Neg	ROI	CR, relapse, DOD at 8 years
13 ⁴	48	M	Liver	6 years, 5 months	Lymph node	κ	Pos	ROI, R, T	CR, relapse at 5 years, CR again
14 ⁸	58	M	Liver	8 years	Skin	λ	Pos	ROI	CR, NED at 2 years
15 ¹³	66	M	Liver	2 months	Liver allograft	λ	Pos	ROI	CR at 4 months
16 ¹⁰	66	M	Liver	3.5 months	Liver allograft	κ	Neg	ROI, D, CHOP, retransplantation	CR
17 ¹⁴	52	M	Liver/kidney	1 year, 5 months	Abdomen and bladder	κ	Pos	ROI, XRT	CR, NED at 24 months
18 ¹⁵	33	M	Kidney	9 years	Lymph node	κ	Neg	NA	NA
19 ¹⁶	59	NA	Kidney	7 years	Kidney allograft	κ	Neg	ROI, resection	CR, NED at 12 months
20 ¹⁷	63	M	Kidney	6 years	Tonsil	λ	Neg	NA	NA
21 ¹⁸	52	M	Kidney	11 months	Left flank	κ	NA	ROI, XRT, R, ESHAP, mini-BEAM, auto-HSCT	Multiple relapses, CR after HSCT, NED at 31 months
22 ¹⁹	10	M	Kidney	5 years	Left groin	λ	Pos	ROI	CR, NED at 20 months
23 ²⁰	59	M	Kidney	12 years	Thigh, scalp, abdomen	κ	Pos	ROI, C, P, XRT	CR, died at 2 months as result of infection
24 ²¹	65	M	Kidney	13 years	Nasal tissue	κ	Pos	ROI, XRT, CVP, allo-HSCT, MTX	PR, progression, DOD at 8 months
25 ²²	36	F	Kidney	8 years	Bladder, small bowel, peritoneum	λ	Neg	ROI, VAD	CR, relapse at 10 months, DOD at 1 year
26 ⁴	52	M	Kidney	7 years, 2 months	Skin	λ	Pos	ROI R, C, P	CR, relapse at 3.3 years
27 ²³	63	M	Kidney	16.5 years	Nose	λ	Pos	XRT, C, P, resection	PR at 10 months
28 ²⁴	64	M	Kidney	7 years	Skin	κ	Neg	XRT, chlorambucil ROI	CR, NED at 8 years, died as result of other reason
29 ²⁵	66	M	Kidney	4 years	Skin	κ	Neg	ROI, XRT	CR, NED at 2 years
30 ²⁶	41	M	Kidney	0.5 years	Ileum	NA	NA	None	Died of sepsis and liver failure
31 ²⁷	55	M	Kidney/pancreas	5 years	Skin	κ	Pos	XRT	CR, NED at 1 year
32 ⁸	25	F	Kidney	8 years	Skin	NA	Pos	R	CR
33 ¹⁰	56	M	Kidney	10 years, 9 months	Stomach	λ	Neg	ROI	Unclear, died as result of SCC at 1.5 years
34 ¹⁰	72	M	Kidney	25 years, 10 months	Lymph nodes	κ	Neg	ROI	PR at 4 months
35 ¹⁰	39	F	Kidney	18 years, 1 month	Skin, peritoneum	κ	Pos	ROI, PAD, XRT, C	PR at 9 months
36 ¹⁰	68	M	Kidney/heart	1 year, 2 months/4 years	Skin, pleura	κ	Pos	ROI, VAD, benda, B	Progression, DOD at 14 months
37 ¹⁰	24	M	Small intestine	3.4 months	Liver, peritoneum	λ	Neg	ROI, PAD	CR

Abbreviations: B, bortezomib; BEAM, carmustine, etoposide, cytarabine, melphalan; benda, bendamustine; C, cyclophosphamide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; CVP, cyclophosphamide, vincristine, prednisone; D, dexamethasone; DOD, died as result of disease; EBER, Epstein-Barr virus–encoded RNA; ESHAP, etoposide, methylprednisolone, cisplatin, cytarabine; HSCT, hematopoietic stem-cell transplantation; Ig, immunoglobulin; Mel, melphalan; MM, multiple myeloma; MTX, intrathecal methotrexate; NA, not available; NED, no evidence of disease; Neg, negative; P, prednisone; PAD, bortezomib, doxorubicin, dexamethasone; Pos, positive; PR, partial response; PTLDs, post-transplantation lymphoproliferative disorders; R, rituximab; Ref, reference; ROI, reduction of immunosuppression; SCC, squamous cell carcinoma; SD, stable disease; T, Epstein-Barr virus–specific cytotoxic T-cell infusion; VAD, vincristine, doxorubicin, dexamethasone; XRT, radiation therapy.

*Age at diagnosis of post-transplantation lymphoproliferative disease.

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