

Lymphoma in Danon disease with chronic rhabdomyolysis treated with EPOCH-R

A case report

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Abstract

Rare disorders often represent a challenge for clinicians and require close collaboration of an interdisciplinary team.

We present the complex case of a 22-year-old male with Danon disease and late-onset of posttransplant lymphoproliferative disorder after heart transplantation. The critical aspects of his condition were: pre-existing rhabdomyolysis; infiltration of muscle and gut with lymphoma; advanced clinical stage with bulky disease; nonresponsiveness to the reduction of immunosuppression and rituximab monotherapy; expected cardiotoxicity of anthracyclines. Therefore, the patient was treated with the EPOCH-R protocol, which includes continuous administration of doxorubicin over 4 days, instead of R-CHOP, in which the anthracycline is given in a short single infusion. Complete remission was achieved after the third cycle; rhabdomyolysis did not increase and heart function was not affected. The patient received a total of 6 cycles and is still in metabolic complete remission.

We conclude that patients with Danon disease can be treated with anthracycline-containing chemotherapy and that continuous infusion of EPOCH-R does not exacerbate pre-existing rhabdomyolysis.

Abbreviations: BNP = B-type natriuretic peptide, CK = creatinine kinase, CR = complete remission, DH = double-hit, DLBCL = diffuse large B-cell lymphoma, EBV = Epstein–Barr virus, ERT = enzyme replacement therapy, HCMV = human cytomegalovirus, LAMP2 = lysosome-associated membrane protein-2, LDH = lactate dehydrogenase, LSD = lysosomal storage disease, MYC = v-myc avian myelocytomatosis viral oncogene homolog, PET-MRI = positron emission tomography–magnetic resonance imaging, PTLD = posttransplant lymphoproliferative disorder, R = rituximab.

Keywords: Danon disease, EPOCH-R, glycogen storage disease, LAMP2, posttransplant lymphoproliferative disorder, PTLD, rhabdomyolysis

1. Introduction

Danon disease is a rare X-linked lysosomal storage disease (LSD) characterized by an early onset of muscle weakness and severe cardiomyopathy sometimes, necessitating heart transplantation.^[1,2] The underlying defect is poorly understood, but is associated with a

mutation in the lysosome-associated membrane protein-2 (LAMP2) gene and modulations in autophagy.^[3] Elevated serum creatinine kinase (CK) levels are sometimes observed.^[1]

Posttransplant lymphoproliferative disorders (PTLDs) occur in up to 10% of organ transplant recipients with heterogeneous clinical manifestations ranging from indolent polyclonal proliferations of lymphocytes to aggressive lymphomas.^[4,5] Current treatment strategies recommend a sequential therapy including reduction of immunosuppression, use of rituximab (R), combination chemotherapy, and radiation.^[4–8] If chemotherapy is needed, anthracycline-based chemotherapy, that is the CHOP protocol (cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with R, is generally considered to be the most effective treatment especially in B-cell-derived PTLDs.^[6,7]

As far as our knowledge is concerned, the co-occurrence of Danon disease and PTLD has not been reported yet.

2. Case report

We report a unique case of Danon disease with PTLDs after heart transplantation.

In March 2015, a 22-year-old Caucasian male student who had undergone heart transplantation at the age of 12 due to hypertrophic cardiomyopathy associated with LAMP2-positive Danon disease was diagnosed with a non-Epstein–Barr virus (EBV)-associated PTLD.^[9] Histopathological examination showed diffuse large B-cell lymphoma (DLBCL) of centroblastic and germinal center type highly positive for BCL6, weakly for v-myc avian myelocytomatosis viral oncogene homolog, but negative for BCL2 protein (double hit score 0), with a proliferation index of 95%. Clinical manifestations included

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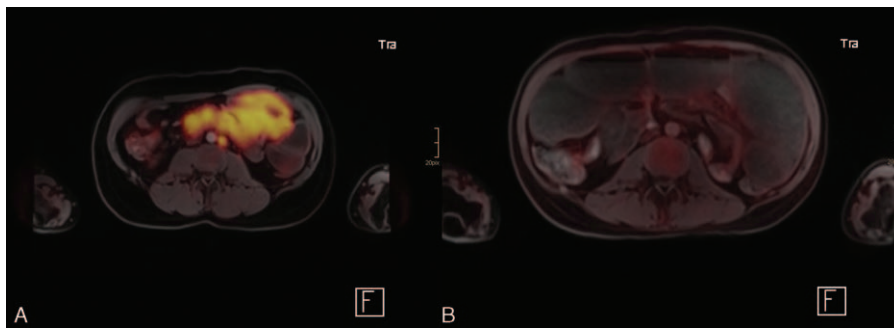


Figure 1. Imaging in a patient with Danon disease and posttransplant lymphoproliferative disorder 10 years after heart transplantation. Diffusion-weighted magnetic resonance imaging showing lymphoma burden (A) before treatment (B) after the third cycle of EPOCH-R.

extranodal lymphoma of the jejunum, mesentery, rectus abdominis muscle, and multiple lymph nodes (clinical stage III with bulky disease) (Fig. 1A). Physical examination revealed a large (5 × 6 cm) tumor in the abdominal wall. Lactate dehydrogenase levels (LDHs) had been elevated since childhood (range 450–1885 U/L) and was assumed to be associated with Danon disease. The patient’s family history did not include Danon disease,^[9] and was negative for malignant diseases. The patient’s medical history revealed chronic rhabdomyolysis, with CK levels around 1100 U/L, a retinopathy/myopia, and a human cytomegalovirus (HCMV) reactivation in 2007.

Initially, immunosuppression was modified (treatment with mycophenolic acid 900 mg/d was discontinued, whereas treatment with tacrolimus 2.5 mg/d was unchanged), and the patient received a total of 4 doses of rituximab weekly without sufficient response.^[4,6,10] Immunochemotherapy was therefore planned.^[4,6,10] Since we were concerned for an exacerbation of the rhabdomyolysis with short-term infusion of R-CHOP, we initiated treatment with reduced-dose EPOCH-R (1 m² instead of 1.68 m²; etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisone with rituximab).^[11,12] This was intended to reduce peak concentrations of doxorubicin, which can be associated with muscle damage and carry a higher risk for cardiotoxicity^[13,14]; and to enable immediate interruption of doxorubicin administration in case of severe myolysis. EPOCH-R was well-tolerated and CK levels even decreased during treatment (Fig. 2).

After the second cycle, the patient developed febrile neutropenia and reported abdominal pain, and was affected by enduring vomiting. A computed tomography (CT) scan showed distended intestinal loops, and also partial remission of the lymphoma. Our interdisciplinary team decided to use a conservative approach and to continue chemotherapy with EPOCH-R.

After the third cycle, a positron emission tomography–magnetic resonance imaging revealed complete metabolic remission (CR) of the lymphoma, but intestinal loops were still distended (Fig. 1B). A few days later, the patient developed clinical signs of a mechanical ileus due to adhesions that required surgical treatment. Histologically, no signs of malignancy were detected. After surgery, the patient received additional 3 cycles of EPOCH-R, which he tolerated well without any side-effects, and has been in CR since. Both the systolic function monitored by echocardiography and pro-B-type natriuretic peptide (pro-BNP) remained unaffected before, during, and after treatment.

3. Discussion

The LSDs are a heterogeneous group of rare inherited disorders with trafficking dysfunctions within the lysosome–endosome system leading to substrate accumulation in different organs.^[15] Long-term complications include prolonged local inflammation, activation of cell-death signaling, and dysregulation of autophagy. These pathologic conditions often induce irreversible organ dysfunction that require organ transplantation.^[15] Recently, LSDs were reported to be at increased risk for malignancies, including multiple myeloma and

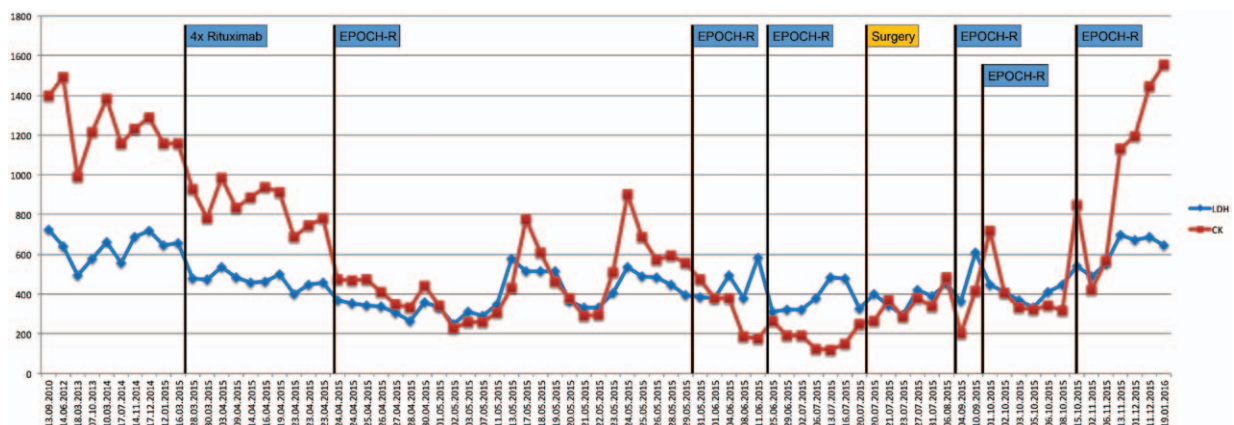


Figure 2. Course of serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels before, during, and after antilymphoma treatment.

aberrant myelopoiesis, but further studies are urgent.^[16,17] Due to the rare co-occurrence of LSDs and malignancies, and since drug metabolism and side-effects may differ, there is an urgent need to report cases like ours to improve management of these patients. Therapeutic approaches in LSDs are currently being investigated in preclinical and clinical trials. Evidence for administration of immunomodulating agents such as R has been reported in cases in which patients developed IgG antibodies after treatment with enzyme replacement therapy (ERT).^[15]

Initially, the reduction of immunosuppression and treatment with R alone—according to the international recommendations and to our local standard operating procedures for patients with PTLD—seemed to be a safe option for our patient.^[4,6,7] Although CK and LDH levels began to decrease upon treatment initiation, the lymphoma did not sufficiently respond to therapy. Complicating circumstances were: the underlying Danon disease that had already affected the heart requiring heart transplantation; cardiac toxicity as a well-known side-effect of anthracyclines, particularly when administered with high peak concentrations^[13]; lack of literature and local experience with respect to administration of chemotherapy in patients with pre-existent chronic rhabdomyolysis and considerable muscle infiltration.

In nontransplant-associated DLBCL, continuous administration of EPOCH-R showed high efficiency in high-risk cases such as double-hit (DH) lymphomas,^[11] and treatment with EPOCH has been reported in a few PTLD cases.^[18,19]

Given that this form of anthracycline infusion might be less cardiotoxic and might have other advantages, especially the presented, we decided to start therapy with reduced dose (1 m²) EPOCH-R.^[11,13] Treatment was generally well-tolerated with rapid response and without severe side-effects, and left ventricular systolic function remained unaffected.

We conclude that the EPOCH-R protocol might have an advantage over R-CHOP, especially in more complex cases with higher risk of therapy-induced complications, and also shows high efficacy in PTLDs.

References

- [1] D'Souza RS, Levandowski C, Slavov D, et al. Danon disease: clinical features, evaluation, and management. *Circ Heart Fail* 2014;7:843–9.
- [2] Danon MJ, Oh SJ, DiMauro S, et al. Lysosomal glycogen storage disease with normal acid maltase. *Neurology* 1981;31:51–7.
- [3] Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature* 2000;406:906–10.
- [4] Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTL-1 trial. *Lancet Oncol* 2012;13:196–206.
- [5] Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. *Curr Hematol Malig Rep* 2013;8:173–83.
- [6] Murukesan V, Mukherjee S. Managing post-transplant lymphoproliferative disorders in solid-organ transplant recipients: a review of immunosuppressant regimens. *Drugs* 2012;72:1631–43.
- [7] Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients: BCSH and BTS guidelines. *Br J Haematol* 2010;149:693–705.
- [8] Singavi AK, Harrington AM, Fenske TS. Post-transplant lymphoproliferative disorders. *Cancer Treat Res* 2015;165:305–27.
- [9] Regelsberger G, Hoftberger R, Pickl WF, et al. Danon disease: case report and detection of new mutation. *J Inher Metab Dis* 2009;32(Suppl 1):S115–22.
- [10] Jagadeesh D, Woda BA, Draper J, et al. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol* 2012;13:122–36.
- [11] Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med* 2013;368:1408–16.
- [12] Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol* 2015;170:504–14.
- [13] Conway A, McCarthy AL, Lawrence P, et al. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. *BMC Cancer* 2015;15:366.
- [14] Hayward R, Hydock D, Gibson N, et al. Tissue retention of doxorubicin and its effects on cardiac, smooth, and skeletal muscle function. *J Physiol Biochem* 2013;69:177–87.
- [15] Boustany RM. Lysosomal storage diseases: the horizon expands. *Nat Rev Neurol* 2013;9:583–98.
- [16] Astudillo L, Therville N, Colacios C, et al. Glucosylceramidases and malignancies in mammals. *Biochimie* 2016;125:267–80.
- [17] Sgambato JA, Park TS, Miller D, et al. Gaucher disease-induced pluripotent stem cells display decreased erythroid potential and aberrant myelopoiesis. *Stem Cells Transl Med* 2015;4:878–86.
- [18] Davis CL, Wood BL, Sabath DE, et al. Interferon-alpha treatment of posttransplant lymphoproliferative disorder in recipients of solid organ transplants. *Transplantation* 1998;66:1770–9.
- [19] Radeski D, Hoehn D, Montanari F, et al. The impact of immunophenotypic subtypes and treatment regimens on patient outcomes in monomorphic post-transplant lymphoproliferative disorders (diffuse large B-cell lymphoma). *Blood* 2014;124:4449–14449.