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CASE REPORT

Hodgkin's Lymphoma Developed after Autologous Stem Cell Transplantation for Multiple Myeloma

Transformation or coincidental appearance?

Istvan Kulcsar · Antonia Szanto · Laszlo Varoczy · Gabor Mehes · Margit Zeher

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Abbreviations

ABVD	Doxorubicin 25 mg/m2, bleomycin 10 mg/m2, vinblastine 6 mg/m2, dacarbazine 375 mg/m2
Anti-SSA	Anti-Sjögren's syndrome A (SSA)
Anti-SSB	Anti-Sjögren's syndrome B (SSB)
ASCT	Autologous stem cell transplantation
Bwkg	Body weight kilogramm
CA 19–9	Carbohydrate antigen 19–9
CD	Cluster of differentiation
EBV	Epstein-Barr virus
HL	Hodgkin's lymphoma
NHL	Non-Hodgkin lymphoma
PET-CT	Positron emission tomography—computed tomography
PTLD	Posttransplant lymphoproliferative disorder
SCT	Stem cell transplantation
VAD	Vincristine 2 mg i.v., doxorubicin 9 mg/m2 i.v. és dexamethasone 40 mg
WHO	World health organisation

I. Kulcsar (✉) · A. Szanto · L. Varoczy · M. Zeher
3rd Department of Internal Medicine,
University of Debrecen Medical and Health Science Center,
Móricz Zs. krt. 22,
4032 Debrecen, Hungary
e-mail: istvankulcsar@yahoo.com

G. Mehes
Institute for Pathology,
University of Debrecen Medical and Health Science Center,
Nagyerdei krt. 98,
4032 Debrecen, Hungary

Background

Lymphoproliferative disorders are well-known complications of solid organ or allogeneic stem cell transplantation [1–5]. Posttransplant lymphoproliferative disorders (PTLDs) are divided into the following groups by World Health Organisation (WHO): 1. Early lesions (reactive plasma cell hyperplasia and infectious mononucleosis-like lesions following transplantation in the early period and responding well for reduction of immunsuppressive therapy); 2. Polymorph PTLD (polyclonal or monoclonal); 3. Monomorph PTLD (classified according to WHO classification of non-Hodgkin's lymphoma); 4. Hodgkin's lymphoma (HL) and Hodgkin's lymphoma like PTLD [2, 3].

The incidence of PTLD in allogeneic bone marrow transplantation has been reported between 0.5% and 1.8%, with the majority (82%) occurring within the first year after transplantation [2]. Most of the PTLDs (85%) show B-cell origin, the role of Epstein-Barr virus (EBV) is presumed in more than 80–90% of the cases. The proportion of EBV negative disease is increased in late (>1 year) PTLDs [2]. Occurrence of Hodgkin's lymphoma is uncommon after transplantation [5]. Compared to the allogeneic setting, autologous stem cell transplantation carries a much lower risk of secondary developed lymphoproliferative disease [2]. To our knowledge, only three other cases of two authors have been reported about Hodgkin's lymphoma following autologous transplantation so far [4, 5].

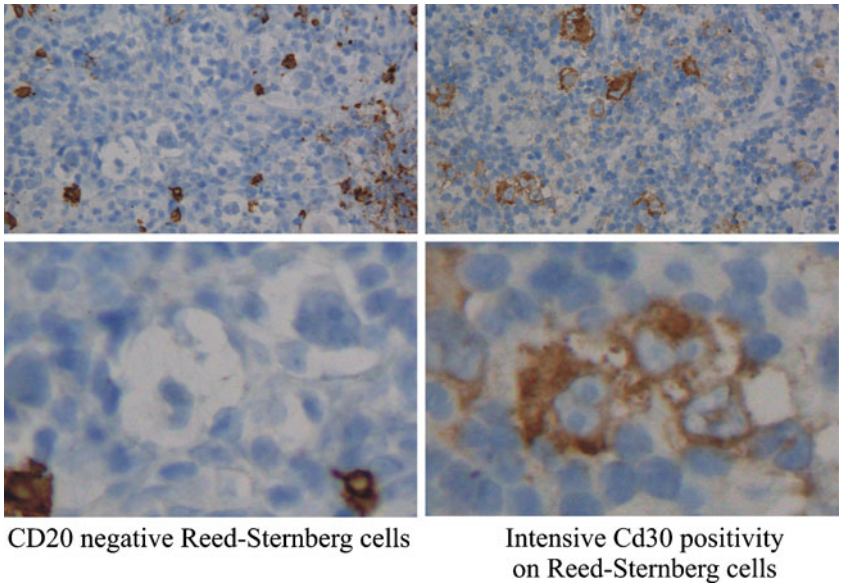

Fig. 1 Histological examination of mediastinal lymph node biopsy. Hodgkin's lymphoma (lymphocyte predominant type, stage II/B) was diagnosed, the large atypical cells showed CD30 antigen positivity, CD20 and LCA negativity during immunohistochemical examination

Case Presentation

In 1999, a 43-year old female without any previous remarkable disease was diagnosed with multiple myeloma (Immunoglobulin A kappa, stage III/A Salmon-Durie) in an other hospital. The amount of serum IgA kappa was 52.1 gram/litre, bone marrow biopsy showed 40% plasmacytoid infiltration. She received 3 cycles of VAD chemotherapy (vincristine 2 mg i.v., doxorubicin 9 mg/m2 i.v., dexamethasone 40 mg), peripheral stem cell harvesting was performed in the spring of 2000. For mobilization 6,800 mg cyclophosphamide was administered. After 6 more cycles of VAD in October 2000 she underwent autologous peripheral stem cell transplantation with 350 mg melphalan conditioning therapy. Maintenance interferon alpha-2A therapy was started at the dose of three million units three times a week, it discontinued because of side effects in 2003. She was in complete remission for 7 years.

In February 2007 she was begun to examine because of fever of onknown origin. In her laboratory results haematuria, hypersedimentation were found, normal serum elec-

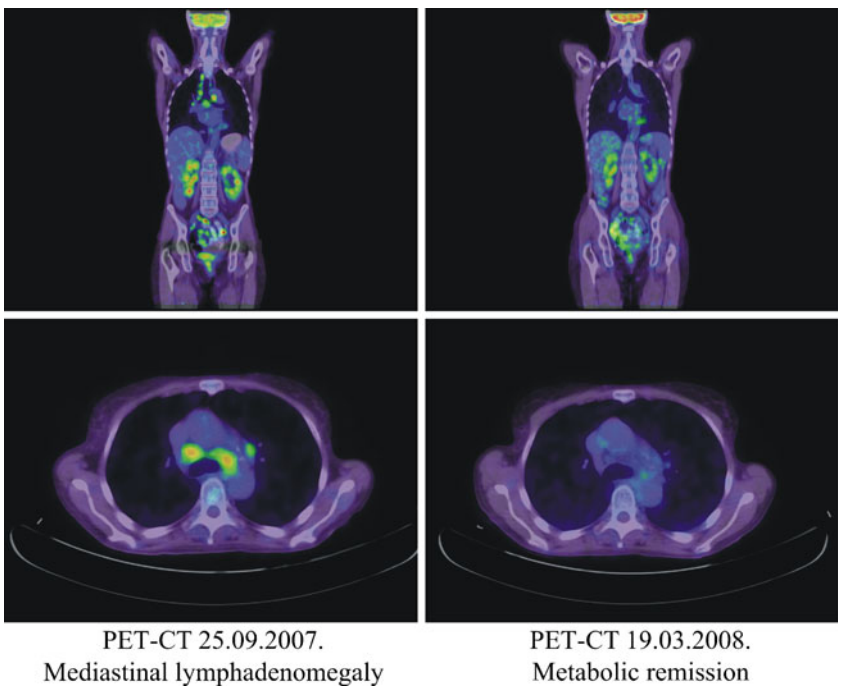

Fig. 2 PET-CT findings before and after administration of ABVD protocol and irradiation therapy. On 25.09.2007. PET-CT indicated mediastinal lymphadenomegaly. Administration of ABVD protocol and irradiation therapy resulted in complete metabolic remission, confirmed by interim PET-CT on 19.03.2008

trophoresis and bone marrow biopsy did not confirm myeloma recidiva, no pathological enrichment was detected by bone scan and RES scintigraphy.

Gastroenterological examination procedure began because of elevated carbohydrate antigen 19–9 (CA 19–9) tumormarker level, but solid neoplasm was excluded. In a local hospital, additional laboratory tests showed uncertain anti-Sjögren's syndrome A (anti-SSA) and anti-Sjögren's syndrome B (anti-SSB) autoantibody positivity and elevated immunocomplex levels. As presence of a systemic autoimmune disease was supposed, 0,5 mg/body weight kilogramm (bwkg) methylprednisolon and 2 mg/bwkg azathioprine were administered. As her symptoms persisted, she was sent to our hospital with the suspicion of systemic autoimmune disease in the autumn of 2007. That was the first time that we had seen the patient. At admission, leukopenia was detected which had resolved spontaneously after abstaining from azathioprine. Repeated immunoserological examination and the clinical aspect did not support the presence of systemic autoimmune disease. Positron Emission Tomography—Computed Tomography (PET-CT scan) indicated mediastinal lymphadenomegaly (Fig. 2). Targeted mediastionscopy and biopsy were performed, histological examination diagnosed Hodgkin's lymphoma—lymphocyte predominant type, stage II/B (Fig. 1). The immunohistochemical test revealed large atypical cells showing CD30 antigen positivity, CD20 and LCA negativity. Intensive positivity was detected with the Mib-1 proliferation marker. 5 cycles of ABVD chemotherapy (doxorubicin 25 mg/m2, bleomycin 10 mg/m2, vinblastine 6 mg/m2, dacarbazine 375 mg/m2) were administered, then 36 Gray dose tangential field irradiation therapy of the mediastinum was performed. In March 2008, interim PET-CT demonstrated complete metabolic remission (Fig. 2).

Written informed consent was obtained from the patient for participation in this case report.

Discussion

In this report we present a case of Hodgkin's lymphoma developed after ASCT for multiple myeloma. ASCT plays an important role in the standard therapy of multiple myeloma. [6, 7] The association of Hodgkin's lymphoma and B-cell non-Hodgkin lymphomas has been described in non-transplant setting, common clonal origin of the neoplastic cells was confirmed in most cases. [8–10]

Posttransplant lymphoproliferative disorders are well-known complications of solid organ and allogeneic stem cell transplantation [1–5]. PTLDs usually occur within the first year after transplantation, most of them showing B-cell origin and the majority is EBV associated [2]. Immunosuppression may contribute to the development of PTLDs, in

Table 1 Hodgkin's lymphoma developing after ASCT reported in the literature (*CHOP*: cyclophosphamide, hydroxydoxorubicin, vincristine, prednisone; *IAPVP-16*: iphosphamide, cytarabine, VP-16 (etoposide); *G-CSF*: Granulocyte colony stimulating factor; *MTX*: methotrexate)

Case	Age at ASCT (year)	Gender	Primary disease	Therapy of primary disease	Latency after ASCT	Clinical presentation of HL	Histology of HL, Stage	Therapy of HL	Outcome
This case	44	Female	Multiple myeloma	VAD, ASCT	7 years	Mediastinal lymphadeno-megaly	Lymphocyte predominant type, Stage II/B	ABVD	Complete metabolic remission
F. Fend (2002) Case 1 [4]	60	Male	Mantle cell lymphoma	CHOP, IAPVP-16, ASCT	3 years	Supraclavicular lymphadenomegaly, liver and bone marrow involvement	Mixed cellularity	ABVD	Nosocomial pneumonia, Exitus letalis
F. Fend (2002) Case 2 [4]	53	Male	B-CLL	CHOP, ASCT	2 years	Compression of the extrahepatic bile duct Mediastinal and abdominal lymphadenopathia	Mixed cellularity	–	Rapid progression Infection, pseudomembranous colitis, nosocomial pneumonia, Exitus letalis
A. Zambelli (2005) [5]	60	Male	Anaplastic astrocytoma	Resection, cyclo-phosphamid, G-CSF, MTX, thiotepa, ASCT, irradiation, dexa-methason	105 days	Hilar lympadenopathia, cutan laesion	nodular sclerosis, Stage I/A	Radical surgical excision	Relaps of glioma and HL, Exitus letalis

some cases good response can be reached with reduction of immunosuppressive therapy [2]. Considering Hodgkin's lymphoma, two groups were distinguished among allograft recipients: Hodgkin-like PTLD (HL-PTLD) and the usually late-onset true Hodgkin's lymphoma with good prognosis. [11] The large cells of HL-PTLD react strongly for CD20 and/or CD79a, express CD30, but are usually negative for CD15 and have few mitoses. The atypical Reed-Sternberg-like cells of true Hodgkin's lymphoma contain numerous mitoses, do not have CD20 or CD79a reactivity, have CD15 and CD30 staining [11, 12].

Compared to the allogeneic setting, autologous SCT carries a much lower risk of secondary developing lymphoproliferative disease, Hodgkin's lymphoma appearing after ASCT is particularly rare, only three cases were reported by two authors in the literature (Table 1) [2, 4, 5].

ASCT was performed for malignant glioma in the case reported by Zambelli and for B-cell non-Hodgkin's lymphoma in both cases of Fend. Less than half a year after the ASCT for anaplastic astrocytoma, nodular sclerosis type of Hodgkin's lymphoma developed, and contributed to the death of patient in a short time together with the relapse of astrocytoma. The case was interpreted as an early onset post-transplant EBV-negative Hodgkin's lymphoma by the authors: the treatment administered for malignant glioma, consisting of immuno-suppressive procedures played a role in immunologic derailment and exposed the patient to a high risk of PTLD [5]. In both cases of Fend, mixed cellularity type of Hodgkin's lymphoma appeared in 2 and 3 years following ASCT, and patients died of infectious complications in a few months. Analysis of rearranged immunoglobulin genes from the primary B-cell neoplasm and the secondary HL provided evidence of separate clonal origins of the two tumours in both patients, thus excluding secondary transformation of the original B-cell clone. In both cases, the large atypical cells were positive for CD15 and CD30, negative for T- and B-cell antigens. The molecular findings and the relatively long latency period referred to a true secondary neoplasm [4].

Considering the autologous form of SCT, the lack of continuous immunosuppressive therapy, the immunohistochemical findings and the long follow-up-time, our case does not correspond to a real PTLD. However, different immunological characteristics exist in the background, our case shows similar clinicopathological features to late onset HL arising in allogeneic post-transplant settings [12]. However, transformation of the primary multiple myeloma clone into secondary Hodgkin's lymphoma could not be excluded, considering the long latency period it is less possible. Comparison of rearranged immunoglobulin sequences could provide an opportunity for us to declare the clonal relation of the two lymphoproliferative diseases.

The development of primary multiple myeloma and secondary classic Hodgkin's lymphoma in the presented patient suggests the coincidental appearance of two independent lymphoproliferative diseases, as well.

Although stem cell transplantation is suitable to result in permanent remission, continuous haemato-oncological follow-up is essential in such cases.

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Competing Interests The author(s) declare that they have no competing interests.

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