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RESEARCH

Histopathological Difficulties in an Adolescent Lymphoma Patient

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Abstract The B-cell lymphoma, unclassifiable, showing intermediate features typical for both diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (HL) is a novel category of diffuse large B-cell lymphomas (DLBCL/HL), which has been described by the WHO classification in 2008. This rare type of lymphomas, previously called as gray zone lymphoma presents peculiar clinical, morphological and immunophenotypical patterns. In December 2011 a 17-year old male was diagnosed with mixed cellularity subtype of classical HL. His clinical stage was IV/BXS (abdominal bulky) with unfavourable prognosis. Because of the unusally extended disease (nodal-extranodal-bulky) a histological revision was performed. After an incomplete course of ABVD chemotherapy the patient's symptoms disappeared and regression was detected in the size of peripheral lymph nodes. The diagnosis changed into DLBCL/HL, so the treatment was modified to R-CHOP-14 regimen. After the administration of 3 cycles of R-CHOP-14, he achieved a complete metabolic remission (CMR), which was confirmed by a ^{18}FDG-PET/CT scan. Receiving further 4 cycles of R-CHOP-14 therapy the patient was still in CMR, but a PET negative large mass (70× 30 mm) still remained visible in the abdominal region. Considering this residuum and the agressive subtype of lymphoma he was referred for an autologous hemopoietic stem cell transplantation (AHSCT). After 2 cycles of R-DHAP regimen, successful CD34 positive stem cell collection was performed in August 2012. In September 2012, he underwent a R-BEAM conditioning followed by AHSCT. The next ^{18}FDG-PET/CT still detected CMR 100 days after the AHSCT. The patient was in excellent clinical condition and also in complete remission 15 months after the AHSCT. Upon this case, it should be underlined that the diagnosis may need revision if a patient represents atypical clinical signs and behavior, and the importance of cooperation between clinicians and pathologists is also strongly emphasized.

Keywords B-cell lymphoma intermediate beetwen DLBCL and classical HL · 18FDG-PET/CT · R-CHOP · Agressive lymphomas

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Introduction

The recently used WHO classification of 2008 represents B-cell lymphoma, unclassifiable, showing intermediate features typical for both diffuse large B-cell lymphoma and classical Hodgkin's lymphoma, which was formerly referred to the heterogenous group of so-called gray-zone lymphomas. It mainly occurs in young or middle-aged males with a predominant invasion of mediastinal lymph nodes, representing the morphological, immunophenotypical and clinical features of both DLBCL and HL. The aetiology is unknown; however, the association with Epstein-Barr virus infection can be detected in 20 % of all cases [1]. The thymus origin of malignant B-cell is suggested; moreover, the plasticity of their genotype and gene expression may result in the development of primary mediastinal B-cell lymphoma (PMBL), Hodgkin's lymphoma and intermediate cell clones within the same patient [2]. Gene

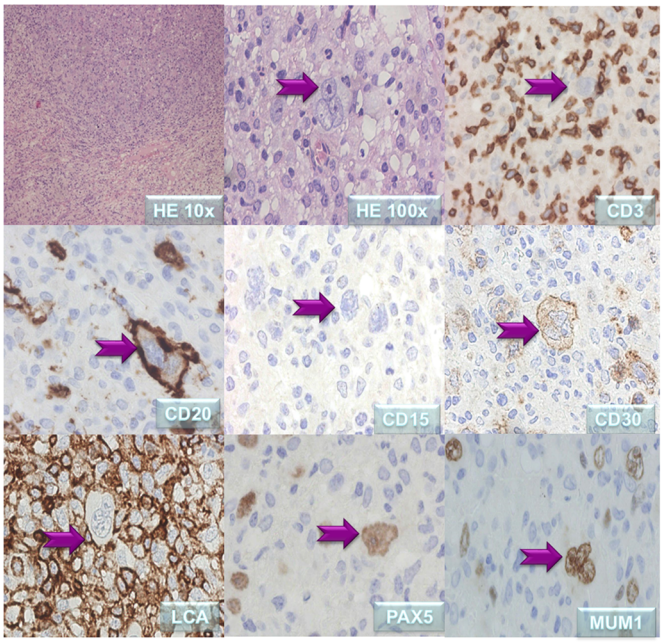
expression surveys revealed that PMBL and classical Hodgkin's lymphoma are similar in profile but completely different from DLBCL [3]. Common genetic (2p15 – Rel locus, 9p24 – jak locus) and complex molecular alterations (constitutive NF-kappaB pathway activation, JAK-STAT pathway activation, overexpression of TNF-receptor family members like CD30, TRAF-1, aberrant activation of tyrosine-kinase and PI3K/ATK pathways) can be detected [4], but no specific genetic marker has been found for DLBCL-HL intermediate lymphoma so far. The DLBCL-HL intermediate lymphoma is considered as a disorder of unfavorable prognosis which shows rapid progression without the immediate administration of polychemotherapy [1, 5].

Case report

A 17-year-old male presented with fever of unknown origin, weight loss, night sweating and lymphadenomegaly in the left inguinal region in November 2011. Laboratory tests highlighted normochromic, normocytic anaemia, high ESR rate, elevated ALT, AST and cholestatic enzyme levels (Table 1). Serological tests revealed former Epstein-Barr and Cytomegalovirus infections, HIV, hepatitis B and C results were all negative. Abdominal ultrasound detected hepatosplenomegaly and several enlarged lymph nodes in the pelvic and retroperitoneal regions, which was confirmed by a CT examination as well. A lymph node biopsy was perfomed in December 2011 and the histological examination revealed classical Hodgkin's lymphoma, mixed cellularity subtype. Immunohistochemical tests represented CD15 negative, CD20 and CD30 positive B-cells with high Ki-67 proliferation rate. No pathological B-cells were found in the bone marrow sample and no IgH, TCRg gene rearrangement was detected in the peripheral blood sample. A primary staging ^{18}FDG-PET/CT (Fig. 2a) examinaton showed advanced disease with bulky-size lymph nodes in the abdominal region (120×50 mm) as well as radiopharmacon enhancement within the bones and the spleen (SUVmax: 18). Considering the unfavorable prognostic factors – male gender, stage IV disease, anaemia, lymphopenia -, it was planned to administer 6–8 cycles of ABVD chemotherapy (doxrubicine, bleomycine, vinblastine and dacarbazine) with adequate supportive treatment including allopurinol, antacides, antiemetics and low molecular weight heparin. In January 2012 he was administered an incomplete coursele of ABVD treatment and as a result, his B-symptoms disappeared and the regression of the peripheral lymphadenomegaly could be found upon physical examination. However, the revision of the primary histological diagnosis was indicated considering the advanced, disseminated abdominal and extranodal disease which is not typical in Hodgkin's lymphoma. The result of the histological revision was B-cell lymphoma, unclassifiable, showing intermediate features typical for both diffuse large B-cell lymphoma and classical Hodgkin's lymphoma. Upon this second immunohistochemical examination B-cells with CD30, LCA, Pax5, Mum-1 positivity, but CD3, CD4, CD8, CD15, CD79a, CD138 and ALK1 negativity were detected (Fig. 1). Clinical staging and prognostical factors were reviewed and the disease was found stage IV/BXS (abdominal bulky tumor, osseal and splenic manifestation) with unfavorable prognosis. The treatment was changed to R-CHOP-14 protocol (rituximab, cyclophosphamide, doxorubicin, vincristin, prednisolon administered every 14 days). Pegfilgastrim primary prophylaxis was administered because of more than 20 % risk of febrile neutropenia. He received 3 cycles of R-CHOP-14 chemotherapy until February 2012. The interim ^{18}FDG-PET/CT examination showed complete metabolic and acceptable morphological remission of the disease (Fig. 2b). He was administered 4 further cycles of R-CHOP-14 treatment. In May 2012, a 70×30 mm sized, PET negative residual mass was still visible on the next PET-CT scan (Fig. 2c). Radiation therapy was not recommended because of the expected side effects and the unfavorable localization of the mass. Considering the agressive, intermediate-type lymphoma, the patient was referred for autologous hemopoietic stem cell transplantation. In August 2012, 7.5×10^6/body weight kilogram CD34+ stem cells were harvested after the administration of R-DHAP (rituximab, cisplatina, cytosin-arabinosid, dexamethasone) chemotherapy. In September, R-BEAM (rituximab, BCNU, etoposide, cytosin-arabinosid, melphalan) conditioning chemotherapy was followed by a succesful autologous stem cell transplantation. In January 2013, the fourth PET-CT scan detected further regression of the abdominal tumor mass (53×26 mm); however, a 10 mm nodule appeared in the upper lobe of the left lung (Fig. 2d). Most likely, it could have been the manifestation of a symptomless fungal infection; however,

Table 1 Laboratory findings at the diagnosis

2011. December	Laboratory findings	Normal values
Hemoglobin	105 g/L	130–165 g/L
White blood cell count	4.32 G/L	4.7–6.1 G/L
Lymphocytes#	0.44 G/L	0.9–4.44 G/L
GOT	76 U/L	<40 U/L
GPT	233 U/L	<40 U/L
AP	1,223 U/L	40–115 U/L
GGT	571 U/L	7–50 U/L
LDH	608 U/L	135–220 U/L
Se-B2 microglobulin	4.5 mg/l	1.2–2.5 mg/l
Erythrocyte sedimentation rate	100 mm/h	<20 mm/h



Immunhistological examination	
CD3	Negative
CD15	Negative
CD20	Positive
CD30	Positive
LCA	Positive
MUM1	Positive
PAX5	Positive

Fig. 1 B-cell Lymphoma, unclassifiable, showing intermediate features typical for both diffuse large B-cell lymphoma and classical Hodgkin's lymphoma. Histological images were stained with hematoxilin-eosin (HE). The pathological B-cell signed by arrows

lymphoma progression could not be excluded as well. Considering the patient's good clinical condition, watchful waiting was chosen. In May 2013, he was still symptomless and the fifth PET-CT scan (Fig. 2e) detected complete metabolic remission and further morphological reduction of the abdominal mass (33×15 mm). The nodule of the lung was not detected on this PET/CT examination, so the laesion might have been the result of a previous inflammatory, fibrotising process. 15 months after the transplant he lives a normal life and no relapse of the lymphoma has been noticed.

Discussion

The DLBCL-HL intermediate type lymphoma is a rare disease of B-cell origin which occurs mainly in young males. It commonly affects the mediastinal lymph node region; however, peripheral lymph node manifestation is rare. It is a borderline disorder between classical Hodgkin's lymphoma (mainly nodular sclerosis subtype) and diffuse large B-cell lymphoma (mainly primary mediastinal subtype) as it bears the morphological, immunophenotypical and clinical signs of both lymph node tumors [1, 6]. The diagnosis should be based on thorough histological and immunohistochemical examinations. PET-CT scan has got a high importance in the initial staging, the detection of extranodal localizations and finding the proper site for biopsy in some difficult cases. After the discontinuation of the chemotherapy, a so-called restaging PET-CT scan has to be performed to evaluate the efficacy of treatment as well as to detect any residual tumor mass. However, the rate of false positive results is very high [13]. There is no consensus on the optimal treatment protocol; nevertheless, most of the authors agree that the disease must be treated as an agressive lymphoma [4, 5, 8]. It was an interesting finding when Cazels-Hatem et al. published in a retrospective study that the 5 years' event-free survival (EFS) of intermediate-type lymphoma patients was significantly lower when treated with NHL protocol than of those treated with Hodgkin-like chemotherapy (54 % vs 77 %), however, there was no significant difference in the overall survival (OS) results (81 % vs 77 %) [10]. Reduced-dose ABVD might be a palliative treatment modality in elderly patients with no mediastinal bulky disease [11]. So far, only a few case reports have described the efficacy of rutiximab containing chemotherapy (DA-EPOCH-R: dose-adjusted etoposide, vincristine, doxorubicine, cyclophosphamide, rituximab) and complementary radiation treatment in CD20 positive mediastinal gray zone lymphoma (MGZL), therefore no evidence-based data are available. It was found that both overall and event-free survival data are more favorable in PMBL than in MGZL patients at 4 years (OS: 100 % vs. 75 %, EFS: 95 % vs. 45 %) [7]. In 2012 Vassilakopoulos et al. reported favorable results with R-CHOP-21 (with or without mediatinal irradiation) protocol in PMBL patients, the 5 years' OS was 89 % and the progression-free survival (PFS) was 81 % [12]. Patients having mediastinal bulky disease can be administered involved field radiation after chemotherapy; however, the role of radiation therapy should be further investigated [9]. Patients who do not respond well to conventional chemotherapy and radiation treatment might be candidates for high-dose therapy followed by autologous stem cell transplantation. The survival of transplant-uneligible patients is only a couple of months if administered salvage treatment (second-line chemotherapy +/

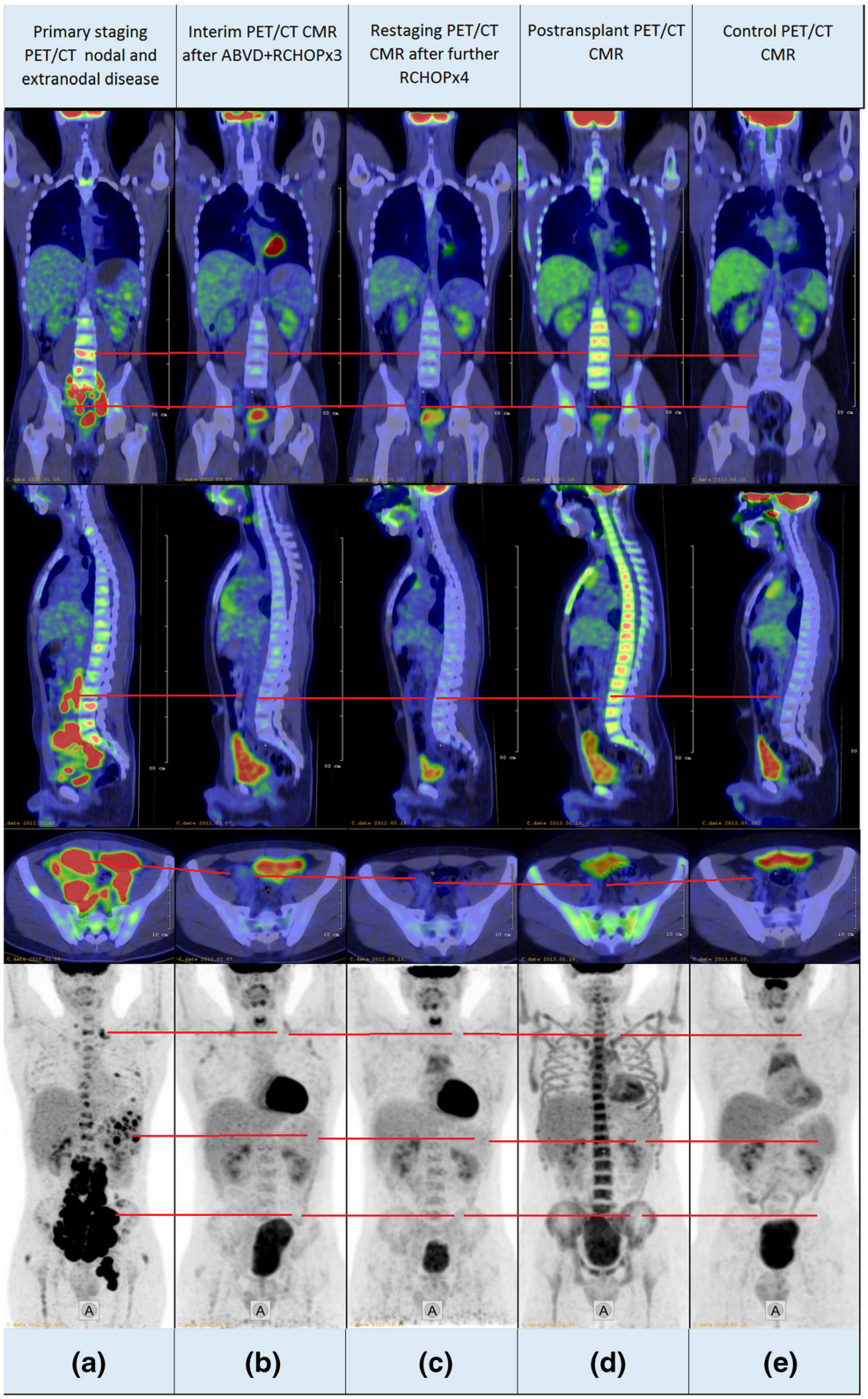


Fig. 2 ^{18}FDG-PET/CT examinations. From the top: coronal, sagittal, axial slices and maximum intensity projection (MIP) images. **a** Primarystaging PET/CT nodal and extranodal disease. **b** Interim PET/CT CMR after ABVD+RCHOP×3. **c** Restaging PET/CT CMR after further RCHOP×4. **d** Postransplant PET/CT CMR. **e** Control PET/CT CMR

− irradiation) [5, 9]. In our patient, Hodgkin's lymphoma was diagnosed at first; however, the B-symptoms and the advanced, disseminated disease with extranodal manifestation and abdominal tumor mass prejudiced the possibility of an agressive non-Hodgkin's lymphoma, which was confirmed by the histological review as well. The treatment modality was changed to R-CHOP-14 protocol which was found to be effective as complete metabolic and acceptable morphologic

remission was detected on the PET-CT scan. Later on, autologous hemopoietic stem cell transplant was performed considering the agressive lymphoma subtype and the PET-negative abdominal tumor mass. Our patient has achieved complete remission and is in excellent condition more than 1 year after the AHSCT. This case highlights that histological revision and modification of treatment strategy should be considered if the clinical picture is unusual in a lymphoma patient.

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