Pathol. Oncol. Res. (2008) 14:281–284
DOI 10.1007/s12253-008-9051-y

BRIEF COMMUNICATION

Prolonged Survival Using Anti-CD20 Combined Chemotherapy in Primary Prostatic Intravascular Large B-cell Lymphoma

Judit Csomor · Ilona Kaszás · Balázs Kollár · László Pajor · Zsolt Egyházi · Sándor Fekete · Miklós Egyed · Botond Timár

Received: 17 March 2008 / Accepted: 7 April 2008 / Published online: 21 May 2008

Abstract Here we report a case of a 73-year-old man with primary intravascular large B-cell lymphoma localized to the prostate. Total prostatectomy was performed due to a benign adenoma suggested by ultrasonography. The diagnosis of IVLBL was obtained incidentally from the prostatectomy specimen. Eight months after the initial R-CHOP chemotherapy a relapse was detected in the left inguinal lymph node, where histologic examination revealed common diffuse large B-cell lymphoma with minimal intravascular component. The second complete remission was achieved by R-IEV therapy. Five months later a second relapse occurred and the patient died in the widespread disease and pneumonia. Primary prostate IVLBL is extremely uncommon; to date only four cases have been described. This is a well documented case, where we also confirmed that the initial primary IVLBL and the secondary lymph node involvement are clonally related. Successful treatment depends on early diagnosis of IVLBL, aggressive chemotherapy and the fact that IVLBL should be considered as a generalized disease in spite of negative staging results.

Keywords DLBCL · Intravascular large B-cell lymphoma · Prostate · Rituximab

Abbreviations

BCL2	B-cell lymphoma 2 gene
CD	Clusters of differentiation
CT	Computer tomography
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
FDG-PET	Fluorodeoxyglucose positron emission tomography
FISH	Fluorescence In Situ Hybridization
IGH	Immunoglobulin Heavy Chain gene
IVLBL	Intravascular large B-cell lymphoma
LCA	antibody to leukocyte common antigen
MUM1	antibody to multiple myeloma oncogene-1
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-IEV	rituximab, ifosfamide, epirubicin and etoposide
VSC38	Plasma cell specific antibody
WHO	World Health Organization

The work described in this publication represents an original contribution. The manuscript has not been published previously and is not being considered concurrently for publication elsewhere. The authors report no potential conflict of interest. Prior to his death subject gave an informed consent to the scientific utilization of his specimens and research was conducted by the highest principles of human subject welfare.

J. Csomor (✉) · B. Timár
1st Department of Pathology and Experimental Cancer Research, Semmelweis University,
Üllői út 26,
1085 Budapest, Hungary
e-mail: csomor@korb1.sote.hu

I. Kaszás
Department of Pathology, Szt. Margit Hospital, Budapest, Hungary

B. Kollár · Z. Egyházi · M. Egyed
Department of Oncohematology, Kaposi Mór Teaching Hospital, Kaposvár, Hungary

L. Pajor
Department of Pathology, Medical School, University of Pécs, Pécs, Hungary

S. Fekete
Department of Hematology, Szt. László Hospital, Budapest, Hungary

Introduction

According to the current WHO classification intravascular large B-cell lymphoma (IVLBL) is a rare subtype of diffuse large B-cell lymphoma (DLBCL). It is characterized by the presence of lymphoma cells filling the lumen of small vessels, particularly capillaries. The estimated incidence based on the literature is less than one in a million, and there is no sex preference [1]. The majority of the cases present central nervous system and skin involvement, but it can occur primarily in almost any organ. The bone marrow and the lymph nodes are spared in most cases [1, 2]. Symptoms are highly variable since most are resulted from occlusion of small vessels by tumor cells in different organs. It is difficult to reach the diagnosis without specific symptoms, organomegaly or specific laboratory findings. Therefore the diagnosis is frequently made post mortem. The prognosis is poor due to the rapid and widespread dissemination and multi organ failure except in cases of primary cutaneous involvement with early diagnosis and treatment [2].

Prostatic lymphoma is extremely rare. In a large study series nearly half of the cases were diagnosed as secondary involvement of a systemic disease. Most of the primary lymphomas were of B-cell type, and half of the cases were DLBCL [3, 4]. Previously four primary prostatic IVLBL were reported [5–8]. Now we report the fifth, but well documented case, where the patient underwent various chemotherapies detailed below.

Case Report

A 73-year-old man was referred to the urology department for total transvesical prostatectomy due to lower urinary tract obstruction caused by an enlarged prostate (5.5×4.5×4 cm). Ultrasonography and specific laboratory tests that showed only a slightly elevated prostate specific antigen level suggested adenoma. No other abnormal findings were detected. The prostate biopsy demonstrated typical benign nodular hyperplasia. Besides, relatively circumscribed microscopic focuses of dilated capillaries and thin walled small vessel proliferation were observed within the hyperplastic nodules. The lumina of the vessels were filled with large (~25 μm) lymphoid cells. Immunohistochemical staining of the tumor cells were positive for LCA and CD20 (Fig. 1). Fifty percent of the cells were positive for VSC38 and had a week partial CD79α expression. Five percent of the cells were positive for MUM1. All of the cells were negative for CD10, BCL-6, BCL-2, and CD5. A proliferation rate of nearly 90% was detected by Ki67. There was a dense, mixed B- and T-cell infiltrate in the stroma around the intraluminal B-cell proliferation.

Staging procedures (CT, blood and bone marrow flow cytometry, bone marrow biopsy) did not reveal extraprostatic manifestation. Eight cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy combined with CD20 antibody rituximab (R) was administered by conventional guidelines. After completing

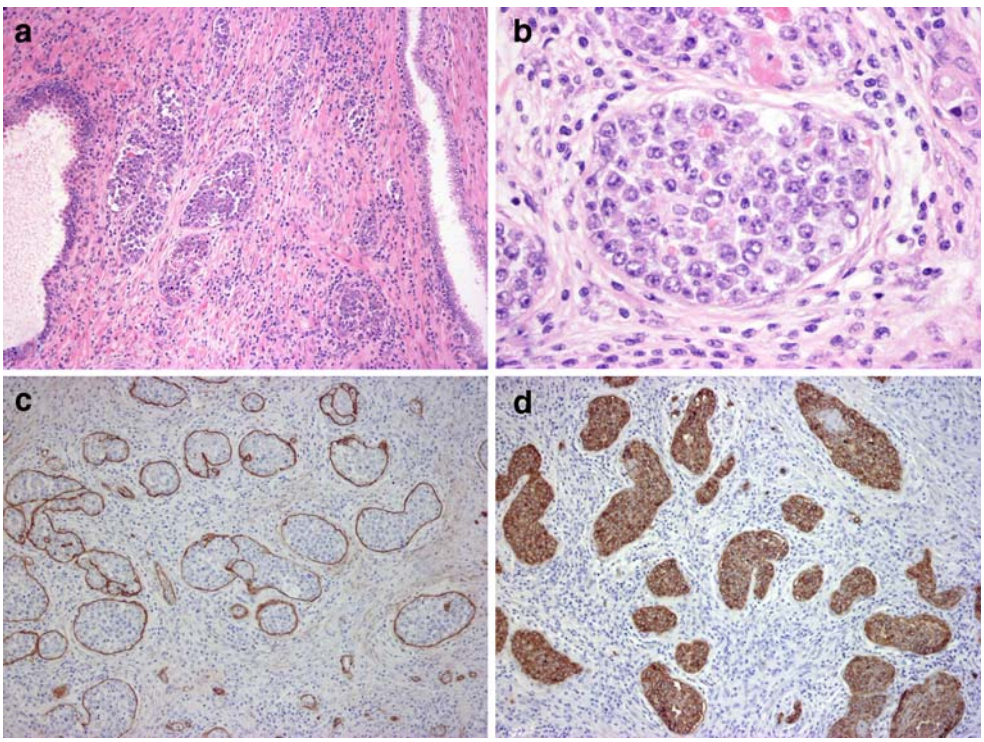

Fig. 1 **a** Prostate, H&E, 10×: In a hyperplastic nodule, small vessels can be seen filled with lymphoid cells between the dilated glands. **b** H&E, 60×: The lymphoid cells are large and have a centroblastic or immunoblastic character—open, round vesicular nucleus with multiplex peripheral or a single centrally located nucleolus, and a scanty basophilic cytoplasm. **c** CD34, 20×: The tumor cells are circumscribed by the CD34 labeled endothelial cells. **d** CD20, 20×: The large tumor cells have intense membrane staining meaning they are B-cells

the eight cycles, restaging by the procedures mentioned above proved to be negative.

Eight months later the patient developed severe B symptoms (fever, weight loss, and anemia) and left inguinal lymph node enlargement. Lymph node biopsy revealed DLBCL with centroblastic morphology and minimal perinodal intravascular component (Fig. 2a). The immunophenotype was similar except that the MUM1 and VSC38 expression level of tumor cells were higher (MUM1 30%, VSC38 100%), and there was an additional BCL-2 expression. Interphase FISH was performed on nuclei extracted from paraffin embedded tissue of both samples using LSI IGH/BCL2 Dual Color, Dual Fusion Translocation probe (Vysis). The tumor cells showed no fusion signal, however we detected an atypical signal pattern with extra signals. These extra signals may refer to gene amplification or tumor cell polysomy. Identical signal patterns in the prostate and lymph node biopsy imply that the tumor in the two samples is clonally related (Fig. 2b, c). Following the third cycle of chemotherapy and radiotherapy, restaging revealed a marked regression in lymph node diameter; however the B symptoms became more aggressive. R-IEV (rituximab, ifosfamide, epirubicin and etoposide) salvage therapy was given. The pronounced B symptoms disappeared after completing the third cycle of the R-IEV regimen. Following the sixth cycle of chemotherapy—25 months after the initial diagnosis—he was in complete remission, symptom free and in WHO-ECOG 0 stage. Five months after the last chemotherapy the patient developed B symptoms again. Lymph node involvement was detected by CT. He was enrolled in a study using pixantrone but after the second cycle his disease progressed, neutropenia occurred and died from bilateral pneumonia.

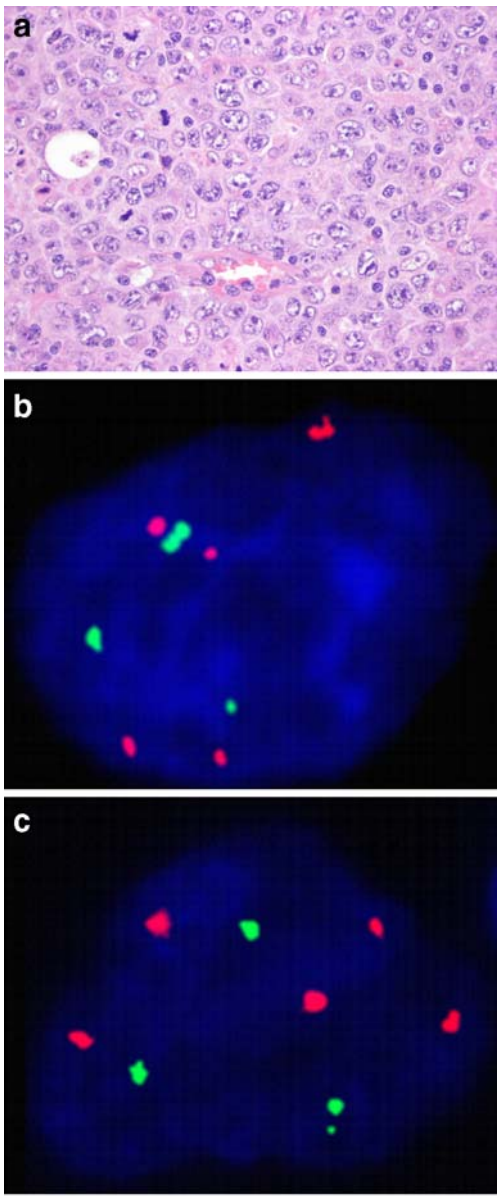

Fig. 2 **a** Inguinal lymph node. H & E, 40×: The figure shows a characteristic DLBCL with centroblastic features. FISH using LSI IGH/BCL2 DC DF translocation probe on the prostate (**b**) and lymph node (**c**) biopsy shows atypical but identical signal pattern. The normal pattern would be 2 green (IgH) and 2 red (BCL-2) signals. We see two additional green and three additional red signals. The extra signals may refer to gene amplification, numerical chromosome aberration or a split gene translocating to other partners

Discussion

IVLBL is a rare aggressive subtype of DLBCL. The problem of selective intravascular localization of tumor cells has widely been investigated, without firm conclusions. Endothelial cells express CD54 and CD106. Tumor cells express CD11a, CD49d and lack expression of CD29 and CD54. These markers may play a role in tumor cell trafficking, transvascular migration and adhesion to endothelial cells [9]. Our case proved to be unique because the relapse was a common DLBCL localized in the inguinal lymph node with minimal intravascular component. After R-CHOP therapy the tumor cells have lost their behavior growing in the lumen of small vessels. An interesting and not fully understood finding is that prostatic acid phosphatase, a marker of prostatic cancer, is suggested as a useful marker for screening disease activity in the non-prostatic form of IVLBL [10].

Most of the IVLBL cases progress rapidly, is often generalized at time of diagnosis and ultimately lethal. Aside from cutaneous manifestation, the localized cases, as our case, are recognized incidentally. Standard lymphoma staging procedures might give false negative results. Imaging techniques have limited value due to the intravascular localization of the tumor that is without visible mass. Bone marrow involvement is rare (~30%), therefore a bone

marrow biopsy has also limited value in the diagnosis and staging [1, 2]. In our case, despite the negative staging, it is possible that the pronounced B symptoms were caused by the undetectable intravascular tumor. Recently FDG-PET has been demonstrated to be useful in staging [11].

Median survival is 24 months for the cutaneous variant, and less than 13 months for the disseminated form [1]. There is no standard chemotherapeutic approach for this uncommon disease. Most frequently anthracyclin based therapy is administered [12]. The poor prognosis is resulted from either the late diagnosis, or chemotherapy resistance of the tumor cell clone. Recent papers report better results after using monoclonal antibody (anti-CD20) combined with chemotherapy (R-CHOP) [13]. Despite these promising results, in our case R-CHOP regimen resulted only a short remission, and was not effective in the treatment of the relapse. Salvage therapy was necessary because of the pronounced B symptoms and a rapid remission was achieved. The patient reached the second remission 25 months after the initial diagnosis. Disease progression and death occurred after 32 months thus giving the patient an extended overall survival. In conclusion the clue for successful treatment remains to reach an early diagnosis of IVLBL, aggressive chemotherapy and the consideration that IVLBL should be treated as a generalized disease in spite of negative staging results.

References

1. Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds) (2001) World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC, Lyon
2. Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A et al (2004) Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol 127(2):173–183
3. Bostwick DG, Iczkowski KA, Amin MB, Discigil G, Osborne B (1998) Malignant lymphoma involving the prostate: report of 62 cases. Cancer 83(4):732–738
4. Chu PG, Huang Q, Weiss LM (2005) Incidental and concurrent malignant lymphomas discovered at the time of prostatectomy and prostate biopsy: a study of 29 cases. Am J Surg Pathol 29(5):693–699
5. Yin XR, Liu H, Chen HQ (2005) Intravascular lymphomatosis of the prostate gland. Zhonghua Bing Li Xue Za Zhi 34(3):189–190, Chinese
6. Alfaro J, Espinoza A, Manŕiquez M, Moyano L, González N, Larrondo M, Figueroa G (2004) Intravascular lymphoma treated with anti CD20 monoclonal antibodies. Report of one case. Rev Med Chil 132(11):1403–1406, Spanish
7. Quintini G, Barbera V, Franco V, Florena AM, Spadola V, Mariani G (2003) Uncommon presentations of non-Hodgkin's lymphoma: case 1. Intravascular large B-cell lymphoma: diagnosis on prostate biopsy. J Clin Oncol 21(3):564–565
8. Chim CS, Loong F (2002) Intravascular lymphomatosis of the prostate gland. Br J Haematol 119(1):2
9. Ponzoni M, Arrigoni G, Gould VE, Del Curto B, Maggioni M, Scapinello A et al (2000) Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol 31(2):220–226
10. Kishi Y, Kami M, Kusumi E, Mineyama T, Kato D, Hamaki T et al (2004) Prostatic acid phosphatase: a possible diagnostic marker of intravascular large B-cell lymphoma. Haematologica 89 (5):ECR13
11. Odawara J, Asada N, Aoki T, Yamakura M, Takeuchi M, Ohuchi T et al (2007) 18F-Fluorodeoxyglucose positron emission tomography for evaluation of intravascular large B-cell lymphoma. Br J Haematol 136(5):684
12. Bouzani M, Karmiris T, Rontogianni D, Delimpassi S, Apostolidis J, Mpakiri M et al (2006) Disseminated intravascular B-cell lymphoma: clinicopathological features and outcome of three cases treated with anthracycline-based immunochemotherapy. Oncologist 11(8):923–928
13. Ohno T, Sakamoto T, Mizumoto C, Miyoshi T, Ueda M, Takeoka T et al. (2006) Leukemic and meningeal relapse of CD5+ intravascular large B-cell lymphoma with down-modulation of CD20 after rituximab therapy. Int J Hematol 84(1):74–78