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Case report

Intravascular large B cell lymphoma

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ABSTRACT

Intravascular large B cell lymphoma (IVBCL) is a rare type of extranodal large B cell lymphoma characterized by selective growth of lymphoma cells within the microvasculature. We present an illustrative case of intravascular B cell lymphoma suspected by the presence of a very small monoclonal B cell population identified by immunophenotype and polymerase chain reaction in bone marrow. The diagnosis was confirmed by skin biopsy.

1. Introduction

Intravascular large B cell lymphoma (IVBCL) is a rare type of extranodal large B cell lymphoma characterized by selective growth of lymphoma cells within the microvasculature. We present an illustrative case of IVBCL suspected by the presence of a very small monoclonal B cell population identified by immunophenotype and polymerase chain reaction in bone marrow. The diagnosis was confirmed by skin biopsy.

A 72 year-old man was referred to our Hematology service with a history of four months of recurrent fevers, sweats, weight loss, headache, proximal limb girdle pain and mild cough. Physical examination was normal. He had no neurological deficit, and cardiovascular, respiratory and abdominal examinations disclosed no significant abnormalities. On laboratory analysis creatinine, alanine aminotransferase, aspartate aminotransferase and immunoglobulin levels were within normal range. However, lactate dehydrogenase 901 UI/L (reference range 230–480 UI/L), gamma-glutamyl transferase 210 UI/L (reference range 10–71 UI/L), Beta-2 microglobulin 4.1 mg/L (reference range 1.1–2.5) and reactive C protein 219 mg/L (reference range 0–10 mg/L) were raised. He also had anemia (Hb 8.4 g/dL) and a leukocyte count of 10.900/μl with normal differential count; platelet count was 304,000/μl. Autoimmunity was negative. Blood, sputum, synovial fluid, bone marrow, urine and stool cultures, serological determinations and cultures for various microorganisms (*Mycobacterium tuberculosis* (*Bone Marrow and sputum culture*), *Leishmania sp* (*bone marrow culture*), *Brucella sp*, *Syphilis*, *Toxoplasma gondii*, *human immunodeficiency virus*, *Hepatitis B virus*, *Hepatitis C virus*, *Epstein Barr virus and Cytomegalovirus*) gave repeated negative results.

Polymyalgia rheumatica and temporal arteritis were suspected, and glucocorticoids were administered, leading to some improvement in the patient's symptoms. However, a temporal artery biopsy yielded no significant findings.

Since the patient still had fever of unknown origin and headache, a computer tomography (CT) and a cranial MRI were performed.

Whole-body CT only showed mild splenomegaly (14 cm) and an enlarged iliac lymph node (1.5 × 3 cm). Cranial MR yielded no specific findings.

To check for a possible tumor, Positron emission tomography (PET-CT) was performed. PET-CT showed increased FDG uptake in the adrenals (Suv max 6.7) and spleen (Suv max 3.1). A lymphoproliferative disorder was suspected and a bone marrow biopsy/aspiration was performed. Examination of a bone marrow biopsy specimen should rule out the possibility of macroscopic infiltration by lymphoma or leukemia. However, infiltration of 2% of monoclonal B cells was detected by immunophenotypic analysis in bone marrow. The neoplastic cells expressed lambda chain, CD19+, CD20+, CD11c+, CD79b+, CD27+, CD5+, CD43+, IgM+, BCL-2+, CD44+ and CD22+, CD103−, CD25−, CD38−, Cyclin-D1 negative, CD23−, CD123−, FMC7− and CD34−. Cytogenetic analysis revealed a normal 46 XY karyotype, and FISH analyses were negative for BCL-1, BCL-2, BCL-6. Polymerase chain reaction (PCR)

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demonstrated B cell clonality (CDR2 and CDR3). Demonstration of immunoglobulin gene rearrangement by PCR in the histological negative bone marrow sample suggested the presence of intravascular lymphoma, and a decision was made to repeat PET-CT and perform a biopsy in any organ with increased FDG-uptake.

In the meantime, the patient was given Rituximab. He received 375 mg/m^2 of Rituximab per week, but after the third dose the patient rapidly developed shock and abdominal pain. With the suspicion of septic shock, the patient received empirical antibiotic treatment with Meropenem and Vancomycin. Despite aggressive treatment in the intensive care unit his condition deteriorated progressively. At this stage, violaceous skin lesions appeared on his back and shoulders.

Biopsies of skin lesions were performed. Given the strong suspicion of intravascular lymphoma, the patient agreed to receive treatment with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) without histological confirmation. After CHOP treatment the patient developed a myocardial infarction and heart failure despite of having a previously normal left ventricular ejection fraction. Skin biopsies confirmed the clinical suspicion of intravascular B cell lymphoma (Fig. 1). B cell clonality was demonstrated in both skin and bone marrow by PCR, immunophenotypic analysis and/or immunostaining pattern. The patient's clinical condition progressively improved. We decided to change the chemotherapy regimen to avoid anthracyclins and the patient received four cycles of Rituximab–Gemcitabine–Oxaliplatin (R-GEMOX) with a partial response and improvement in cardiac function, which returned to normal. For this reason we continued the treatment with seven cycles of R-CHOP. At present, the patient is in complete remission according to PET-CT, and random skin biopsy; however, persistent bone marrow minimal residual disease (MRD+) was detected by immunophenotypic analysis in June 2013. The patient is receiving Rituximab as maintenance in an attempt to eradicate the MRD+ and prevent relapse.

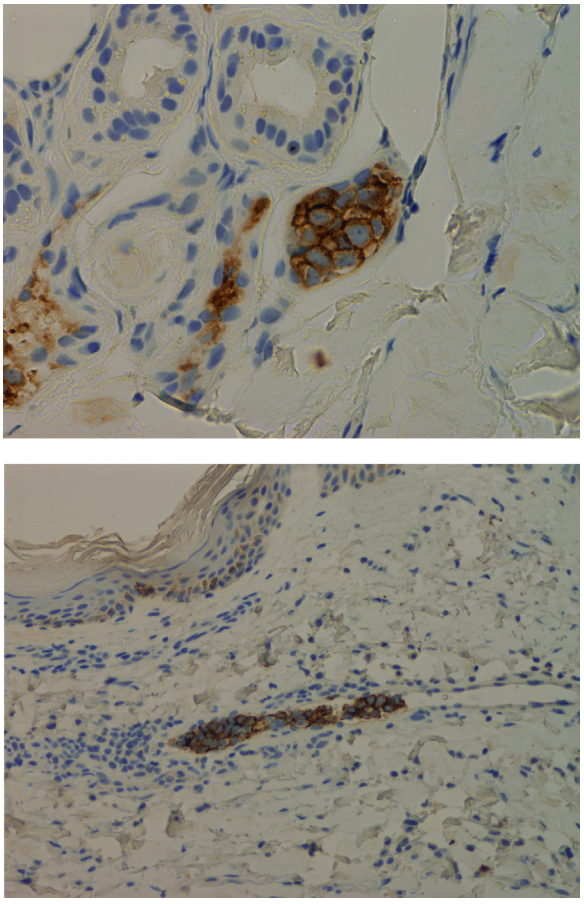

Fig. 1. CD20 positive intravascular neoplastic B cells occupy the vessel lumina.

2. Discussion

The clinical diagnosis of IVBCL may be difficult, and in several reported cases the diagnosis has been made at autopsy [1–3]. In this case, intravascular B cell lymphoma was suspected because of the presence of a very small monoclonal B cell population indentified by immunophenotype and polymerase chain reaction in bone marrow [4] and then confirmed by skin biopsy. Patients can present with a confusing complex that reflects organ dysfunction secondary to vascular obstruction or systemic symptoms such as unexplained fever [5–7]. Two major patterns of clinical presentation have been recognized a Western form characterized by symptoms related to involvement of the central nervous system and skin [8–14] and an Asian variant in which the patients present with multiorgan failure, hepatosplenomegaly, pancytopenia and hemophagocytic syndrome [15]. However, the lymphoma is usually widely disseminated in extranodal sites including bone marrow, spleen, liver, lungs, skin, nervous system and rarely in blood [14,16–23]. The diagnosis of IVBCL is made by demonstrating the presence of large lymphoma cells within small to medium blood vessels [24]. As far as diagnosis is concerned, biopsies of diseased skin or random biopsies of "normal" skin without any obvious abnormality may be diagnostic [25]. If this does not yield a diagnosis, biopsy of other sites of suspected involvement may be undertaken in the appropriate clinical setting.

Despite a relatively high proportion of false negatives, experts recommend staging work up with contrasted whole-body computerized tomography scan, contrasted whole-brain magnetic resonance imaging, peripheral blood smear, cerebrospinal fluid cytology and biochemical examination and bone marrow biopsy [24]. [18F] FDG-positron emission tomography may also be useful for the early diagnosis of IVBCL and can guide biopsies of affected organs [26–29]. Accurate and timely diagnosis of IVBCL is still a problematic issue, and many cases are diagnosed at autopsy. However, in recent years, the heightened awareness of IVBCL with appropriate investigations has resulted in more patients being diagnosed during life.

Delays in diagnosis due to the subtlety and focal nature of the intravascular infiltrates often lead to a terminal disease with death before chemotherapy is initiated. R-CHOP plus CNS prophylaxis is the treatment of choice in patients [30,31] without nervous system involvement. CNS involvement and recurrence is still challenging despite the improvement in clinical outcomes induced by Rituximab plus chemotherapy.

CNS prophylaxis is strongly recommended because CNS recurrence at 3 years is still as high as 25% [32,33]. The fact that several patients have CNS involvement at diagnosis or relapse supports the recommendation to use chemotherapy combinations containing drugs with high CNS bioavailability such as high dose Methrotrexate and high dose Cytarabine in these patients.

Even though high-dose chemotherapy supported by autologous stem cell support (HDC/ASCT) seems to be a useful option in younger patients with unfavorable features [34], the main indication for HDC/ASCT remains consolidation in chemosensitive relapsing disease, as is the case for other diffuse large B cell lymphomas in a small proportion of patients.

References

[1] Nakamura S, Ponzoni M, Campo E. Intravascular large B cell lymphoma. In: Swerdlow SH, Campo E, Lee Harris N, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed.. Lyon, France: International Agency for Research of Cancer; 2008. p. 252–3.

[2] Sanna P, Bertoni F, Roggero E, et al. Angiotropic (intravascular) large cell lymphoma: case report and short discussion of the literature. Tumori 1997;83:772–5.
[3] Lachance DN, Louis DN. Case Records of the Massachusetts General Hospital. Weekly clinicopathological excercises. Case 31-1995 A 43 year-old man with multifocal neurologic problems and confusion. N Engl J Med 1995;333:992–9.
[4] Diss TC, Peng H, Wotherspoon AC, et al. Detection of monoclonality in low grade B cell lymphomas using the polymerase chain reaction is dependent of primer selection and lymphoma. J Pathol 1993;169:291–5.
[5] DiGiuseppe JA, Nelson WG, Seifter EJ, et al. Intravascular lymphomatosis: a clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol 1994;12:2573–9.
[6] Detsky ME, Chiu L, Shandling MR, Sproule ME, Ursell MR. Clinical problem-solving. Heading down the wrong path. N Engl J Med 2006;355:67–74.
[7] Fredericks RK, Walker FO, Elster A, et al. Angiotropic intravascular large-cell lymphoma (malignant angioendotheliomatosis): report of a case and review of literature. Surg Neurol 1991;35:218–23.
[8] Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood 2007;109:478–85.
[9] Chapin JE, Davis LE, Kornfeld M, Mandler RN. Neurologic manifestations of intravascular lymphomatosis. Acta Neurol Scand 1995;91:494–9.
[10] Detsky ME, Chiu L, Shandling MR, et al. Clinical problem-solving. Heading down the wrong path. N Engl J Med 2006;355:67–74.
[11] Shimada K, Murase T, Matsue K, et al. Central nervous system involvement in intravascular large B cell lymphoma: a retrospective analysis of 109 patients. Cancer Sci 2010;101:1480–6.
[12] Orwat DE, Batalis NI. Intravascular large B cell lymphoma. Arch Pathol Lab Med 2012;136:333–8.
[13] Zuckerman D, Seliem R, Hochberg E. Intravascular lymphoma: the oncologist's "great imitator". Oncologist 2006;11:496–502.
[14] Masaki Y, Dong L, Nakajima A, et al. Intravascular large B cell lymphoma: proposed of the strategy for early diagnosis and treatment of patients with rapid deteriorationg condition. Int J Hematol 2009;89:600–10.
[15] Yagappan S, Coupland R, Arber DA, et al. Angiotropic lymphoma: an immunophenotypically and clinically heterogeneous lymphoma. Mod Pathol 2001;14:1147–56.
[16] Miura Y, Matsui Y, Sugino N, et al. Intravascular large B cell lymphoma in the bone marrow smear preparation. Br J Haematol 2010;152:234–44.
[17] Ferreri AJ, Dognini GP, Campo E, et al. Variations in clinical presentation, frequency of hemophagocytosis in different geographical regions. Haematologica 2007;92:486–92.
[18] Raza M, Qayyum S, Raza S, et al. Intravascular B cell lymphoma: an elusive diagnosis. J Clin Oncol 2012;30:144–5.
[19] Yu H, Chen G, Zhang R, et al. Primary intravascular B cell lymphoma of lung: a report of one case and review. Diag Pathol 2012;7:70.
[20] Yamashita H, Suzuki A, Takahashi Y, et al. Intravascular large B cell lymphoma with diffuse FDG uptake in the lung by (18)FDG-PET/CT without chest CT findings. Ann Nucl Med 2012;26:515–21.
[21] Cobcroft R. Diagnosis of angiotropic large B cell lymphoma from a peripheral blood film. Br J Haematol 1999;104:429.
[22] Meyer GS, Hales CA, Amrein PC, Sharma A, Kradin RL. Case records of the Massachusetts General Hospital. Case 25-2007 – a 61-year-old man with recurrent fevers. N Engl J Med 2007;357:807–16.
[23] Pless ML, Chen YB, Copen WA, Frosch MP. Case records of the Massachussetts General Hospital. Case-9-2010. A 37-year-old woman with parestesias and ataxia. N Engl J Med 2010;362:1129–38.
[24] Ponzoni M, Ferreri AJ, Campo E, et al. Definition, diagnosis, and management of intravascular large B cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol 2007;25:3168.
[25] Asada M, Odawara J, Kimura S, et al. Use of random skin biopsy for diagnosis of intravascular large B cell lymphoma. Mayo Clin Proc 2007;82:1525.
[26] Shimada K, Kosugi H, Shimada S, et al. Evaluation of organ involvement in intravascular large B cell lymphoma by 18F-fluorodeoxyglucose position emission tomography. Int J Hematol 2008;88:149–53.
[27] Hoshino A, Kawada E, Ukita T, et al. Usefulness of FDG-PET to diagnose intravascular lymphomatosis presenting as fever of unknown origin. Am J Hematol 2004;76:236–9.
[28] Miura Y, Tsudo M. Fluorodeoxyglucose-PET-CT for diagnosis of intravascular large B cell lymphoma. Mayo Clin Proc 2012;85:e56–7.
[29] Odawara J, Asada N, Aoki T, et al. 18F-Fluorodeoxyglucose positron emission tomography for evaluation of intravascular large B cell lympoma. Br J Haematol 2007;136:684.
[30] Ferreri AJ, Dognini GP, Bairey O, Szomor A, Montalban C, Hovarth B, et al. The addition of Rituximab to anthracycline based chemotherapy significantly improves outcome in "Western" patients with intravascular large B cell lymphoma. Br J Hematol 2008;143:253–7.
[31] Ferreri AJ, Dognini GP, Govi S, Crocchiolo R, Bouzani M, Bollinger CR, et al. Can Rituximab change the usually dismal prognosis of patients with intravascular large B cell lymphoma? J Clin Oncol 2008;26:5134–6.
[32] Shimada K. Treatment strategy for central nervous system involvement in intravascular large B cell lymphoma. Brain Nerve 2011;63:467–72.
[33] Matsue K, Hayama BY, Iwama K, Koyama T, Fujiwara H, Yamakura M. High frequency of neurolymphomatosis as a relapse disease of intravascular large B cell lymphoma. Cancer 2011;117:4512–21.
[34] Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factor in a series of 38 cases, with special emphasis on the cutaneous variant. Br J Haematol 2004;127:173–83.