Case Report

Diagnosis and management of a patient with plasmablastic lymphoma of the stomach: report of own experience and review of literature

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Received October 28, 2015; Accepted December 25, 2015; Epub February 1, 2016; Published February 15, 2016

Abstract: Plasmablastic lymphoma (PBL) is a very rare B-cell lymphoproliferative disorder with an aggressive clinical behavior. Although PBL is most commonly observed in the oral cavity of human immunodeficiency virus (HIV)-positive patients, it can also be observed at extra-oral sites in HIV-negative patients. PBL is significantly associated with condition of immunodeficiency, particularly HIV infection and Epstein-Barr virus (EBV) infection. Immunohistochemical staining is imperative to differentiating PBL from other malignant tumors. Here, we present a case of PBL of the gastric in a 39-year old HIV-negative female. Our case highlights the possibility of PBL in the gastric, with EBV, HBsAg, HIV and hepatitis C virus negative. The related literature review summarized the differential diagnosis and treatment status of PBL.

Keywords: Plasmablastic, lymphoma, gastric, stomach

Introduction

Plasmablastic lymphoma (PBL) is a rare type of progressive and almost fatal lymphoma with plasmablastic features that predominantly occurs in the oral cavity of human immunodeficiency virus (HIV)-positive patients. Despite improvements of the biology, it is still a challenge from the diagnostic and therapeutic perspectives for us. PBL is characterized by high rates of relapse and short median survival. The optimal treatment of PBL is still undefined. This kind of lymphoma has also been reported in HIV-negative individuals, particularly those who have immunosuppression. Although PBL is most commonly observed in the oral cavity of human immunodeficiency virus (HIV)-positive patients, it can also be observed at extra-oral sites in HIV-negative patients. Here, we present a PBL case of gastric in an immunocompetent female which intensive regimens were given, provided a remarkable response without severe side effects.

Case report

A 39-year-old female presenting with an epigastric discomfort was admitted to the outpatient clinic of the First affiliated hospital of Henan college of traditional Chinese medicine (Henan, China) on October 11, 2014. She also complained of epigastric discomfort for half a year, suffering from no stomachache, abdominal tympany, night-sweat, low-grade fever, and significant weight reduction. Her past history was unremarkable except for planning cesarean surgery about 5 years ago. There were no definite conditions associated with immunosuppression in the past, having no a history of alcohol consumption, tobacco smoking and drug use. The examination biopsy of the stomach by gastroscopy was taken mimicking poorly differentiated adenocarcinoma of gastric fundus and body in morphology in primary hospital.

Then the patient was admitted to the department of general surgery in the affiliated tumor hospital of Zhengzhou University on October 14, 2014. On physical examination, there were no enlarged and palpable lymph nodes in the bilateral neck, axilla and groin. Laboratory examination on admission to our hospital revealed a normal serum biochemical profile. Routine hematological examinations were car-
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A patient with plasmablastic lymphoma of the stomach. SYN(-), CK(-), epithelial membrane antigen (EMA(-), CEA(-), ALK(-), CD20(-), Pax-5(-), CD10(-), BCL-6(-), CD30(-), EBER(-). B cell antigen receptor (BCR) gene rearrangement was positive. It didn't reveal bone marrow involvement by bone marrow aspirate examination. Finally, the patient was diagnosed as PBL IE2 of stomach achieved complete response according to Lugano staging after operation. Then the patient was treated with 2 cycles chemotherapy of CHOP 21 regimens. AIM to increased antitumor effect intensive chemotherapy was carried. Following two courses of CHOP chemotherapy, two cycles of EPOCH (VP16, prednisone, adriamycin, vincristine and cyclophosphamide) chemotherapy, two cycles of DICE (Platinum Dichlorodiamine, ifosfamide, dexmethasone, and VP16) chemotherapy were administered due to the refractory clinical characteristics. After sixth courses of chemotherapy, the tumor sustaining with a complete response and all the discomforts disappeared. To date, the patient still maintains complete response.

Discussion

PBL is a rare type of progressive and almost fatal lymphoma with plasmablastic features, exclusively occurring the oral cavity in HIV-positive patients, which has been described latterly entity of large-cell lymphoma by WHO. PBLs account for approximately 2.6% of all HIV-related non-Hodgkin lymphoma (NHL) [1]. HIV-
positive patients were significantly younger than those who were HIV-negative (median 42 vs. 58 years) [2, 3], showing a predilection for elderly individuals and affecting more males than females (M:F, 2.2:1) [3]. Recently, sporadic cases of PBL in extraoral locations of HIV-negative patients have been reported. Uptonow, only limited HIV-negative cases have been reported that have frequently been found in patients with an underlying immunosuppressive status [4]. The stomach is a rare extraoral site of PBL patients, 15.79% of HIV-negative PBL patients involved the gastrointestinal tract. To the best of our knowledge, there are only a few papers to report PBL of stomach without any condition of immunosuppression [5].

PBL is significantly associated with condition of immunodeficiency, particularly HIV infection [6]. The EBV infection has also been identified and observed in 70%-74% of HIV-positive PBL patients [2, 7], and demonstrated to play an important role in the tumorigenesis of HIV-positive PBL [8]. EBER was positive in 45-58% of HIV-negative patients [3, 4], and EBV infection appears to be weaker than HIV infection to HIV-positive PBL patients [4, 9]. In addition, Herpesvirus-8 (HHV-8) infection was rare being positive in only 7.55% of the HIV-negative patients [3]. Other causes of immunodeficiency, may also be predisposing factors for PBL [4, 7]. Besides, Cases without a history of immunodeficiency have also been reported [10].

The underlying mechanism of PBL remains poorly understood. The Genetic abnormality of MYC gene rearrangement (located 8q24) was first discovered in PBL cells [11]. MYC rearrangements were identified in 49-67% PBL [2, 12], and the immunoglobulin (IG) genes were the partners in most PBL [2, 12]. MYC RNA was expressed in all PBL patients, and MYC protein was expressed in 80% analyzed PBL tumors [13]. The expression increased of BCL2, BCL6, MALT1, or PAX5 were detected in 31% to 41% PBL [12]. Twelve of the 40 PBL could be investigated multiple simultaneous gains in 3 or more loci. Those indicated that PBL are genetically characterized by frequent IG/MYC translocations and gains in multiple chromosomal loci.

In Vega F’s paper, most cases of PBL virtually lossexpression profile of tumor suppressor gene (p16 and p27), having overexpression of p53 and Ki-67 proliferation index [14]. Comparative genomic hybridization (CGH) array and FISH analysis were performed to identify the involved chromosomal translocations in a cell lines of PBL, who was immunologically competent including negative human immunodeficiency virus (HIV) serology [15]. The results show that the protein was loss of p16 by chro-
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mosomal translocation of t(9;13) and upregulation of MDR-1 by t(4;7) [15]. To a certain extent that, these studies reveal resistance mechanisms of PBL [15]. Besides, a combination of immunohistochemical immunophenotype and flow cytometric techniques was used on 9 cases of PBL. Nearly complete loss of B-cell-associated markers and uniform expression of Notch1 are found in PBL cases [16]. The expression of mTOR targets eukaryotic initiation factor 4E-binding protein 1 (86%) and phosphorylated ribosomal protein S6 (100%) were observed in most cases [16]. That indicated there is a concurrent activation of the mTOR pathway. These findings suggest that activation of Notch1 may be involved in mechanism of loss of B-cell phenotype in PBL. Thus, there might be a role for the Notch1 and mTOR pathways in the pathogenesis and therapy of PBL [16]. Chapman, J. et al [13] identified 645 genes as differentially expressed between PBL and DLBCL, 257 highly expressed in PBL, and 388 lower in PBL.

Morphologically, PBL is characterized by a monomorphic proliferation of large cells resembling immunoblasts or plasmablasts morphology, high proliferation rate and immunophenotypic evidence of terminal B cell differentiation [8, 17]. The immunophenotypic features of PBL are negative for the typical B-cell antigens (CD20, CD19, PAX5) and T-cell antigens (CD2, CD3, CD5, CD7), positive for plasma cell markers (CD138, MUM1, CD38 and CD79a) [10, 18, 19]. Almost all the PBL patients exhibit a high rate of proliferation index (Ki-67). Characteristically, the proliferation index in 67% of HIV-negative PBL patients is higher than 80% [3, 4].

Differentiating PBL from other malignant diseases, including gastrointestinal stromal tumors (GIST), poorly differentiated carcinomas, MM (multiple myeloma), DLBCL, anaplastic large cell lymphoma (ALCL) and Burkitt’s lymphoma, is difficult. The differentiating between these neoplasms is critical, because of the treatments for these diseases are significantly different. CD20 negativity facilitates with differentiating PBL from Burkitt’s lymphoma and DLBCL. GIST is a common mesenchymal tumor of gastrointestinaltract, which is usually characterized by CD117 (c-Kit) and CD34 expression. The tumor cells of ALCLE are consistently immunoreactive for CD30 and usually immunoreactive for ALK and CD3, and the tumor cells of poorly differentiated carcinomas are usually positive for Cytokeratin. The distinction between PBL and MM is frequently dependent on their clinical presentations, including the expression of monoclonal light chains and the M protein in the urine and blood, renal function dysfunction lytic bone lesions, anemia and hypercalcemia. In the present case, a high Ki-67 proliferation index and positivity for MUM-1 and CD56 reduced the likelihood of a diagnosis of MM. In this case, poorly differentiated adenocarcinoma was diagnosed just by histomorphology which was identified by immunohistochemistry; consequently, immunohistochemical staining are imperative to differentiating PBL from other malignant tumors.

To date, the optimal treatment of PBL is still undefined because of the rare incidence of tumor. However, the most commonly administered chemotherapy regimen is still CHOP [20, 21]. HIV-negative patients have a poor response to chemotherapy and a reduced survival time compared with HIV-positive patients. A review of 70 HIV-positive patients treated with CHOP or CHOP-like regimens chemotherapy showed the overall response rate (ORR) was 77% [4], while in 42 HIV-negative patients at least 69% achieved a PR [9]. However, despite a good response to chemotherapy, the median overall survival (OS) was 12 months [22] and the 2-year OS rates of in HIV-negative and HIV-positive PBL patients was 45.3% [3] and 43% [23], respectively.

It is difficult to do prospective studies in patients with PBL; hence, these recommendations are only based on consensus derived from small case series and case reports. CHOP regimen seems not adequate, intensive regimens were recommended to treat PBL in the recently updated National Comprehensive Cancer Network guidelines (NCCN), such as CODOX-M (cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate)/IVAC (ifosfamide, etoposide and high dose cytarabine), Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone), or DA-EPOCH. However, there was no statistical difference between 35 patients treated with CHOP or CHOP-like regimens and 16 patients treated with more intensive regimens (18 vs. 16 months, respectively; P = 0.84) from 70 HIV-associated PBL patients [10]. In a recent study,
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patients who received CHOP chemotherapy tended to have better OS compared with those who received hyper-CVAD [2]. Liang, R. et al [24] reported a patients of PBL with multiple organ involvement, achieved rapid and CR after three rounds of CHOP chemotherapy, followed by hyper-CVAD and ESHAP.

Novel approaches are needed because of intensive regimens seeming no benefits and the most PBL patients dying of disease progression [25]. Agents borrowed from the plasma cell myeloma therapy, such as bortezomib, lenalidomide, and hematopoietic stem cell transplantation (HSCT) prove to be of value in PBL [25]. However, limited clinical evidence of bortezomib was reported in PBL, with only six cases identified in a review of the literature by 2014 [26, 27]. Two of the 6 patients succumbed to infectious complications and one succumbed to cardiopulmonary failure, while the remaining patients die of rapid disease progression. Ruben et al [28] found three patients treated with bortezomib plus standard CHOP (V-CHOP) every 21 days, receiving concurrent combination antiretroviral therapy (cART) and prophylaxis with acyclovir and trimethoprim/sulfamethoxazole, achieved CR (complete remission). Castillo JJ et al [29] reported three patients with PBL who treated with the combination of bortezomib and dose-adjusted EPOCH (V-EPOCH). All three patients obtained a durable CR to V-EPOCH with survival times of 24, 18 and 12 months respectively. Sylvain Carras et al [30] reported a patients with HIV-negative PBL of stomach defining a complete response unconfirmed (CRu) after 3 months introduced at a low dose lenalidomide as monotherapy (10 mg/day, 21 days in 28).

The data available on HSCT in PBL are rather scant; however, a potential benefit in patients obtaining a first complete remission cannot be discarded. Liu et al [9] present a series of nine patients with a pathological diagnosis of HIV-negative PBL, and suggest that HSCT in first remission could get better outcomes, achieving a median survival of 27.5 month at their institution [9]. Chiara Cattaneo et al [31] evaluated that the 2-year OS after translation of PBL is 53%, and auto-HSCT was recommended to be further explored as consolidation for first-line and salvage therapy of PBL.

In the present case, the patient received surgery and chemotherapy. And the patient sustained complete remission after surgery, two courses of CHOP, two courses of EPOCH and two courses of DICE chemotherapy. More intensive regimens are given to PBL, as it is a highly aggressive neoplasm and CHOP does not seem to be an optimal chemotherapy.

Its predominant predilection for history of HIV infection, the oral cavity, male, and EBER expression are features that may be helpful for its differential diagnosis. However, a female patient with extraoral location and HIV- and EBER-negative hinder the clinical diagnosis. To our knowledge, there were only a few case of gastric PBL presented in HIV- and EBER-negative patients. The findings in this case suggest that, PBL must be considered when unexplained gastroduodenal ulcers are exhibited, even with immunocompetent and HIV-and EBER-negative. Furthermore, CHOP does not appear to be an optimal treatment regimen for PBL and novel approaches may improve the prognosis of patients. Understanding the rare disease would benefit patients by representing earlier correct diagnosis and taking appropriate therapeutic strategies. A large scale study with novel approaches is needed.

Disclosure of conflict of interest

None.

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References

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