Plasmablastic Extramedullary Plasmacytoma Associated with Epstein-Barr Virus Arising in an Immunocompetent Patient with Multiple Myeloma

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Abstract

We encountered a case of plasmablastic extramedullary plasmacytoma with multiple myeloma. Histological findings revealed that the extramedullary plasmacytoma of this patient was of the plasmablastic type, which was positive for λ-stain and EBV-encoded RNA. In contrast, bone marrow aspiration demonstrated a common-type multiple myeloma, which was positive for λ-stain and negative for EBV-encoded RNA. This was a rare case of plasmablastic extramedullary plasmacytoma associated with Epstein-Barr virus arising in an immunocompetent patient with multiple myeloma.

Key words: multiple myeloma, plasmablastic lymphoma, extramedullary plasmacytoma

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Introduction

Extramedullary involvement of multiple myeloma (MM) has been reported in 15-20% of patients at the time of diagnosis and in an additional 15% during the course of MM (1, 2). When MM is terminated owing to uncontrolled disease or chemotherapy resistance, cytological transformation into a high-grade lymphoma-like disorder has been recognized in association with prominent extramedullary involvement (3-5). In the present case, the tumor cells simultaneously showed two distinct morphologic appearances, typical myeloma cells in the bone marrow and plasmablastic cells in the extramedullary location. The histological characteristics of plasmablastic extramedullary plasmacytoma (EP) are similar to those of plasmablastic lymphoma (PBL).

PBL has recently been listed in the World Health Organization (WHO) classification as a subtype of diffuse large B-cell lymphoma and has a high incidence in Epstein-Barr virus (EBV)-positive, human immunodeficiency virus (HIV)-positive patients (6). It is difficult to distinguish between PBL and plasmablastic EP (7, 8), and therefore it is important to pay careful attention when making the differential diagnosis of PBL and EP. The presence of EBV infection is much more strongly associated with PBL than MM (7-10). However, EPs in the head and neck region and gastrointestinal tract have been occasionally associated with EBV in immunocompetent patients (10-12). These findings prompted us to study the effects of EBV on plasmablastic EP and MM. We describe here plasmablastic EP associated with EBV arising in an immunocompetent patient with MM.

Case Report

A 62-year-old Japanese man was referred to our hospital in September 2010 owing to a one-month history of left cheek discomfort. On physical examination, his left upper cheek was partially swollen. No abnormalities were found in the physical examination except the cheek lesion. Magnetic resonance imaging (MRI) showed a subcutaneous tumor that infiltrated the left maxillary sinus (Fig. 1A). ¹⁸F-fluorodeoxyglucose-potassium-positron-emission tomography (FDG-PET) demonstrated intense uptake in the left cheek, sternum, bilateral scapulas, left humerus, right forearm bone,
Figure 1. A. Magnetic resonance imaging showed a subcutaneous tumor that infiltrated the left maxillary sinus. The arrow indicates the subcutaneous tumor (→). B. The subcutaneous tumor was not detected after chemotherapy. C. 18F-fluorodeoxyglucose-positron-emission tomography demonstrated intense uptake in the left cheek, sternum, bilateral scapulas, left humerus, right forearm bone, left rib and right ilium.

Left rib and right ilium (Fig. 1C). As shown in Fig. 2A-G, histologic section with Hematoxylin and Eosin (H&E) staining of the subcutaneous tumor revealed diffuse proliferation composed of large tumor cells showing irregular nuclear contours with a few prominent nucleoli in the middle of the nuclei and a small-medium amount of amphophilic cytoplasm. Immunohistological study revealed that these tumor cells were positive for CD45 and CD56, and MIB1 labeling index was about 90%, and negative for CD3 and CD20. The result of in situ hybridization for EBV-encoded RNA (EBER) was positive in most of the tumor cells. At first, a diagnosis of non-Hodgkin’s lymphoma, extranodal NK/T-cell lymphoma, nasal type, was made on the basis of these findings. However, bone marrow aspiration revealed that myeloma cells were detected for 30% of nuclear cells. The cytoplasm of the myeloma cells was well developed and the nucleus eccentrically placed with a prominent hof (Fig. 3A). Flow cytometry (FCM) analysis of the myeloma cells using the CD38 gating method revealed that they were positive for CD138 (84.3%), MPC-1 (83.2%) and CD56 (97.6%), and negative for CD20 (1.2%), CD45 (2.0%) and CD49e (1.3%) (Fig. 3B). CD38 gating two-color FCM analysis of cytoplasmic light chains showed that the proportion of cytoplasmic kappa (κ)-positive/lamba (λ)-negative cells was 0% and that of κ-negative/λ-positive cells was 89.4%. Immunohistological study revealed that the MIB1 labeling index of these plasma cells was about 10%. Bone marrow cells revealed a normal karyotype. Neither t (8 ; 14), add (14) (q32), t (14 ; 18), nor t (4,14) was detected by fluorescent in situ hybridization of chromosomal analysis of bone marrow. The result of in situ hybridization for EBER was negative. Laboratory evaluation revealed a serum IgA level of 3,825 mg/dL, while IgG and IgM levels were suppressed. Monoclonal gammopathy was detected in both serum and urine, and serum immunoelectrophoretic pattern was IgA-λ. No Bence Jones protein was detected. Hemoglobin concentration was 12.2 g/dL. Biochemical analysis revealed the following: lactate dehydrogenase level 134 U/L, blood urea nitrogen 13.9 mg/dL, creatinine 0.97 mg/dL, uric acid 6.8 mg/dL, calcium 9.2 mg/dL and albumin 3.8 g/dL. In a peripheral blood smear, abnormal lymphoid cells were not observed. HIV antibody result was negative. IgG antibody to the viral capsid antigen (VCA-IgG) result was ×320, VCA-IgM result was <×10 and EBV antibody to nuclear antigen
Figure 2. Histological and immunohistochemical photographs of the subcutaneous tumor (original magnification×400 without Fig. 2B×1000). A, B. Hematoxylin and Eosin staining. C. Anti-CD56. D. Anti-CD138. E. Anti-CD20. F. MIB1. G. in situ hybridization for Epstein-Barr virus-encoded RNA. H. λ-stain. I. κ-stain. Photographs show diffuse proliferation composed of large tumor cells that are positive for CD56, CD138 and negative for CD20. MIB1 labeling index is about 90%. Epstein-Barr virus in situ hybridization result was positive in most of the tumor cells. Tumor cells of plasmablastic EP were predominantly positive for λ-stain but entirely negative for κ-stain.

Figure 3. A. Morphological findings with May-Giemsa staining of the bone marrow confirmed that myeloma cells were detected for 30% of nuclear cells. The cytoplasm of the myeloma cells was well developed and the nucleus eccentrically placed with a prominent hof. B. Flow cytometry analysis of the myeloma cells using the CD38 gating method revealed that they were positive for CD138 (84.3%), MPC-1 (83.2%) and CD56 (97.6%), and negative for CD20 (1.2%), CD45 (2.0%) and CD49e (1.3%).

result was ×20, indicating past history of EBV infection. EBV DNA quantitative polymerase chain reaction was < 2.0×10^6 copies in 1×10^6 white blood cells both before and after treatment. Bone X-ray survey revealed no osteolytic lesion. Therefore, the patient was diagnosed with multiple myeloma (IgA-λ, Durie-Salmon stage IIA).

Since the bone marrow and laboratory evaluation results did not disagree with the histological findings of the subcutaneous tumor, we further examined the subcutaneous tumor by immunohistological analysis. The tumor cells were
strongly positive for CD138 and negative for T-cell restricted intracellular antigen-1 (TIA-1) (Fig. 2D). Tumor cells of plasmablastic EP were predominantly positive for \( \kappa \)-stain but entirely negative for \( \lambda \)-stain (Fig. 2H, I). As a result, a final diagnosis of MM with EP composed of plasmablastic cells was made. In the present case, since we expected a poor response with conventional chemotherapy for MM owing to the plasmablastic phenotype and since the patient’s performance status was good, he was treated with intensive chemotherapy consisting of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC chemotherapy). After the first course of chemotherapy, the subcutaneous tumor was not detected on MRI (Fig. 1B) and the serum IgA level had markedly decreased from 3,850 mg/dL to 655 mg/dL. Bone marrow aspiration revealed that plasma cells decreased to 1% of nuclear cells. He is now scheduled to receive the second course of chemotherapy.

**Discussion**

MM is a plasma cell neoplasm commonly found in the middle-aged and elderly. The median survival is approximately 3 years from diagnosis. Extramedullary involvement of MM has been reported in 15-20% of patients at the time of diagnosis and in an additional 15% during the course of MM (1, 2). In general, MM terminating as an uncontrolled disease or chemotherapy resistance frequently develops as a form of plasma cell leukemia. Furthermore, cytological transformation into a high-grade lymphoma-like disorder has been recognized in association with prominent extramedullary involvement (3-5). Although the present case was diagnosed as having both MM and plasmablastic EP simultaneously, there are several interesting points concerning the diagnosis.

Myeloma cells of bone marrow in the present case exhibited cytoplasm that was well developed and nucleus that was eccentrically placed with a prominent hof and MPC1+ CD49e- CD45-. Plasmablastic cytomorphicologic features in aspirated smears were not observed. In aspirate smears, plasmablastic features were defined for equal to or greater than 2% of blasts in accordance with the criteria of Greipp et al (13). These findings indicate mature MM in accordance with previous reports (10, 13-15). In contrast, the extramedullary tumor revealed diffuse proliferation composed of monomorphic large tumor cells showing irregular nuclear contours with a few prominent nucleoli in the middle of the nuclei and a small-medium amount of amphiphilic cytoplasm. The proliferative rate with MIB1 labeling index was extremely high, suggesting morphologic features of PBL rather than those of plasmablastic EP because Vega et al (8) reported that PBL was characterized by a monotonous proliferation of plasmablasts and/or immunoblasts, with rare or no obvious plasmacytic cells. However, in H&E-stained sections, plasmablastic features were defined as equal to or greater than 30% of blasts (16). In fact, plasmacytic cells were frequently seen in plasmablastic MM (8). However, there are some subtle differences in the morphology between PBL and plasmablastic MM (8). Thus, evidence of morphologic features is insufficient to differentiate between PBL and plasmablastic EP, which is a progression from underlying MM. Moreover, cytogenetic/molecular studies such as in situ hybridization for EBER and clonality are needed to make the distinction.

PBL was first described as an aggressive lymphoma presenting in the oral cavity of patients with HIV (17). PBL is currently listed by WHO as a rare subgroup of diffuse large B-cell lymphoma. PBL was also characterized by diffuse growth of large tumor cells with a high MIB1 labeling index, as well as positivity for CD38 and CD138 and negativity for CD19 and CD20. The test result for EBER is frequently positive (6). These findings share many morphological and immunophenotypic features with the present case. Vega et al found that the only significant difference between MM and PBL was the presence of EBER, which was positive in all PBL cases and negative in all MM cases (8). In contrast with Vega et al (8), although the presence of EBV infection is much more strongly associated with PBL than MM (7-10), Chang et al reported that EBER+ plasmablastic MM and plasmacytomatas, although rare, existed in immunocompetent patients (10). For diagnostic purposes in immunocompetent patients, EBER+ transcripts in tumor cells seemed to be of little value when the differential diagnoses were between PBL and plasmablastic MM (10). Thus, in cases of immunocompetent patients such as the present case, the presence of EBER does not enable differentiation between plasmablastic EP and PBL. In addition, since Suzuki et al reported that only one patient (10%) was HIV-positive among 9 Japanese cases with PBL (18), the presence or absence of HIV infection is also insufficient to differentiate between these neoplasms. In practice, the distinction between PBL and plasmablastic MM frequently depends on the clinical correlation (19). Since the two distinct lesions of extramedullary and bone marrow simultaneously occurred in the present case, to make the distinction between plasmablastic EP and PBL, it is very important to determine the relationship between plasmablastic EP and MM in terms of their clonal origin. Tumor cells of plasmablastic EP were significantly positive for \( \kappa \)-stain compared to \( \kappa \)-stain although they were not strongly stained. And these cells were positive for CD45 and CD56 although the neoplastic cells of PBL usually express negativity for CD45 and CD56 (6, 20). These findings were consistent with the FCM analysis of cytoplasmic light chains of MM. Therefore, we established the diagnosis of plasmablastic EP arising from MM against coexistence of PBL and MM. Moreover, to confirm the clonality, heavy chain gene rearrangement including CDR3 analysis should be employed; however, we could not perform the analysis owing to a lack of specimens.

EPs in the head and neck region and gastrointestinal tract were found to be occasionally associated with EBV in immunocompetent patients (10-12). Aguilera et al reported that EP of the head and neck in patients not known to be im-
munosuppressed showed a small number of EBV-positive cases (11), and Tomita et al also reported a close association of EBV and Korean gastrointestinal tract plasmacytoma in patients without findings suggestive of the presence of immunodeficiency (12), suggesting that the possibilities of a relationship of EP from these anatomic regions and the effects of EBV should be considered even in immunocompetent patients. In the present case, given that in situ hybridization for EBER of bone marrow was negative and EBV DNA level was <2.0×10^6 copies in 1×10^6 white blood cells, we postulated that reactivation of EBV might have been important for the development to plasmablastic EP, which resulted in two distinct morphologic appearances in MM and EP at diagnosis. Interestingly, EP may have been driven by EBV to obtain the plasmablastic features irrespective of MM, even if the present case was immunocompetent.

EBV-positive lymphoma is frequently resistant to combination chemotherapy, and EBV association results in poorer clinical outcome (21, 22). In particular, the effects of EBV association on the prognosis of MM have not been well clarified. One of the mechanisms of chemoresistance is the overexpression of the multidrug resistance gene products, which cause both drug efflux from cells and decreased intracellular accumulation of drugs such as adriamycin and vinca alkaloids. Nakazato et al reported that there was no response to VAD (adriamycin, vinca alkaloids and dexamethasone) in a case of plasmablastic-type myeloma with multiple EPs (23). Thus, we expected a poor response with conventional chemotherapy as VAD chemotherapy for MM and therefore chose DeVIC chemotherapy, which is an intensive chemotherapy not only including high-dose dexamethasone but also without adriamycin and vinca alkaloids, and for which adverse effects are mild compared with those of various intensive regimens for aggressive lymphomas (24). After informed consent was obtained, we planned to use Bortezomib immediately if DeVIC chemotherapy was not effective, the patient was treated with DeVIC chemotherapy and had a significant response. The clinical course was good. In such cases, following the course, autologous peripheral blood stem cell transplantation should also be a concern. However, the effects of EBV association on the prognosis of plasma cell neoplasms should be analyzed and the most suitable chemotherapy for plasma cell neoplasms composed of plasmablastic cells should be determined in a larger series.

In summary, plasmablastic EP associated with EBV arising in an immunocompetent patient with MM is reported to be extremely rare. The present case indicates that the occasional development of plasmablastic features associated with EBV from extramedullary locations is possible, even in immunocompetent patients.

The authors state that they have no Conflict of Interest (COI).

References


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