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Case Report

Plasmablastic lymphoma involving the breast: report of a case and review of literature

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Abstract: Background: Plasmablastic lymphoma (PBL) is a rare entity of non-Hodgkin lymphomas that usually occurs in the oral cavity in immunocompromised patients. PBL involving the other sites have rarely been reported. Case report: Herein, we report a rare case of EBV-negative PBL in the left breast of an immunocompetent 56-year-old woman. During physical examination, she had left breast masses and left axillary lymphadenopathy. After surgical resection of the neoplasm, histological and cytological examinations were performed and the tumor was diagnosed to be primary PBL. Tumor cells expressed VS38c and some were MUM1-positive, but were negative for common leukocyte antigen CD45, pan-B cell markers CD20 and CD79a, plasma cell marker CD138, EMA, CD38, CD56, PAX5, ALK. Ki-67 immunostaining showed a proliferation index of 80%. Gene rearrangement analysis showed positive B lymphocyte gene IGH and IGK rearrangement in the bone marrow. Bone marrow biopsy was negative for marrow infiltration. Patient received modified CHOP chemotherapy after the surgery and was responding well. Conclusions: Accurate diagnosis of this PBL case relied on the histological morphology of the tumor cells, immunohistological markers and gene rearrangement tests. Despite the poor prognosis of PBL, surgical resection of the tumor combined chemotherapy maintains a stable state of the patient 6 months from the diagnosis. Accumulation of more cases could guide future diagnosis and treatment choices for this rare disease.

Keywords: Plasmablastic lymphoma, breast, non-Hodgkin lymphomas

Background

Plasmablastic lymphoma (PBL) is a rare entity of non-Hodgkin lymphomas which include follicular lymphoma, B-cell chronic lymphocytic leukemia, diffuse large B-cell lymphoma and other subtypes. PBL is considered a morphological variation of diffuse large B cell lymphoma [1, 2]. PBL often occurs in the oral mucosa which almost always accompanies the detection of Epstein Barr Virus (EBV) infection [3]. PBLs that involve other sites than oral cavity are rare. Here we reported a recently diagnosed case of PBL involving the breast and its pathological feature, antidiastole, treatment and prognostic factors were discussed. This will facilitate further understandings of this disease and accumulate clinical experiences for the diagnosis and treatment of PBL.

Case report

A 56-year-old woman was admitted to the breast surgery department in our hospital in July 2014 due to a palpable hard mess in the outer upper quadrant of the left breast for 3 weeks. The lump was about 2 cm diameter in irregular form, with unclear boarder, unsmooth surface, poor mobility, no tenderness, no skin surface depression and no adhesion with chest muscle or skin. A hard enlarged lymph node of about 2×2 cm was palpable in the left axilla. There was no palpable abnormity in her right breast, no lymphadenectasis in right axilla or in supraclavicular and infraclavicular regions. No other abnormality was found during physical examination. Breast B-ultrasound examination detected three hypoechoic nodules in the outer upper quadrant of the left breast, each measured 1.8×1.1 cm, 2.6×1.0 cm and 1.4×1.4 cm,

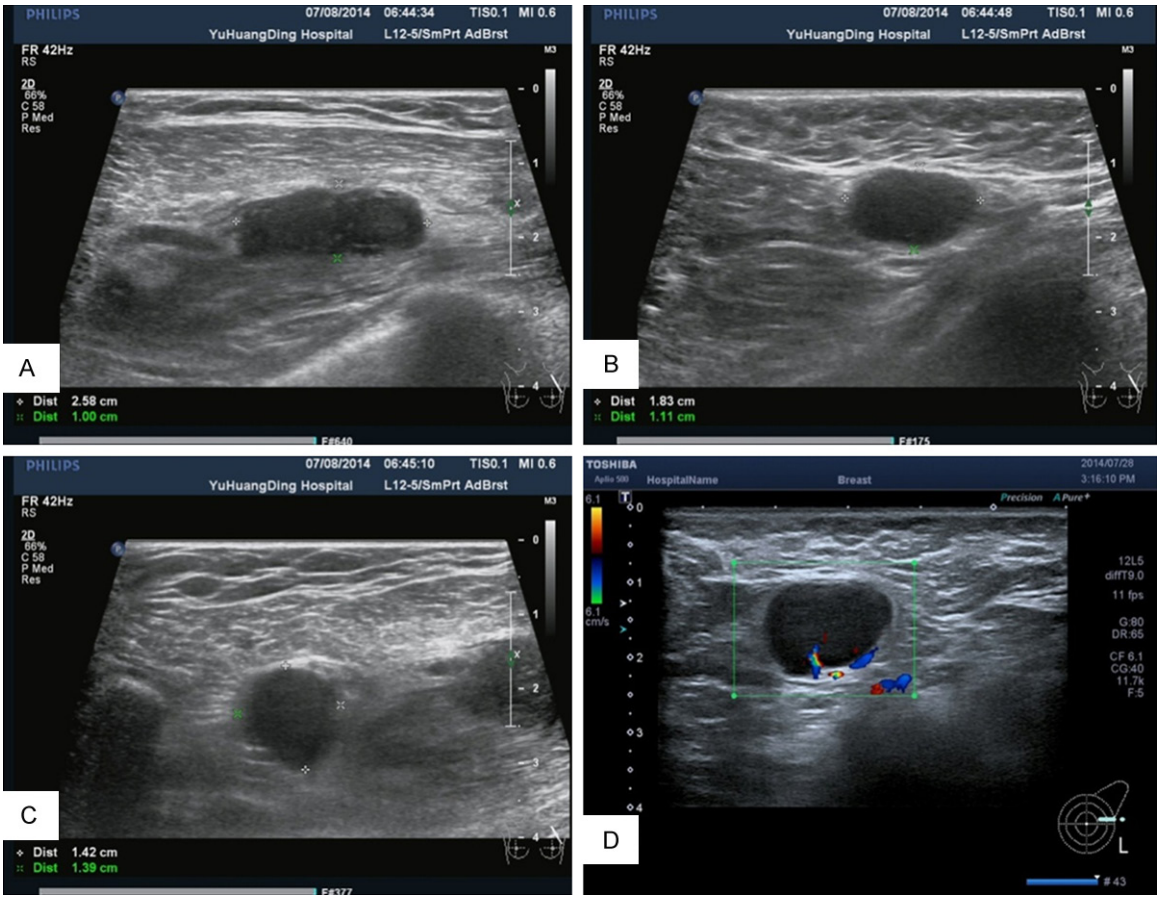

Figure 1. B-ultrasound imaging of the left breast masses. A-C. Three nodules in the left breast. D. Axillary nodule. Colored areas reflected blood flow.

and one hypoechoic nodule above the nipple, measured 0.7×0.5 cm. These nodules had clear boarders, uneven internal echo and rich blood flow signals (**Figure 1**). The patient was tested to be negative for HIV. Electrocardiographic examination showed she had ventricular premature beat (VPB). The patient denied any history of drinking, smoking, hypertension, cardiopathy, diabetes or cerebrovascular diseases. She denied any family history of malignancy or genetic disease but both her parents died of gastric carcinoma. The clinical diagnosis of left breast neoplasm was reached and she received surgical resection of the breast and axillary masses under general anesthesia at the end of July, 2014 after VPB was controlled. The patient reported no obvious discomfort post-surgery.

Histologic and cytological findings

Pathological examination showed the axillary mass to be reactive lymphoid hyperplasia. The resected breast mass measured 7×6×3 cm. A grey-white nodule was visible at the section plane, measured 1.8×1.0×1.0 cm, with unclear boundary and fine texture. Pathological examination showed heterotypic tumor cell infiltration in lymph tissues between the left nipple and left clavicle. The lobules of left mammary gland disappeared and were replaced by diffuse proliferation of tumor cells. Focal necrosis was also detected (**Figure 2A**). Tumor cells comprised mainly monocytes and occasionally binucleate cells. The tumor cells were large basicytes with enlarged vesicular nuclei, prominent nucleoli and numerous mitotic figures. More mature plasmocytes scattered among the large cells (**Figure 2B**). Immunohistochemical tests showed that the tumor cells express the plasmocyte marker VS38c (**Figure 2C**) and some cells were MUM1-positive. They were negative for markers CD45 (or LCA), CD20, CD79a, CD56, CyclinD1, AE1/AE3, EMA, CD30, ALK, CD117, MPO, CD38, CD138, S-100, C-myc,

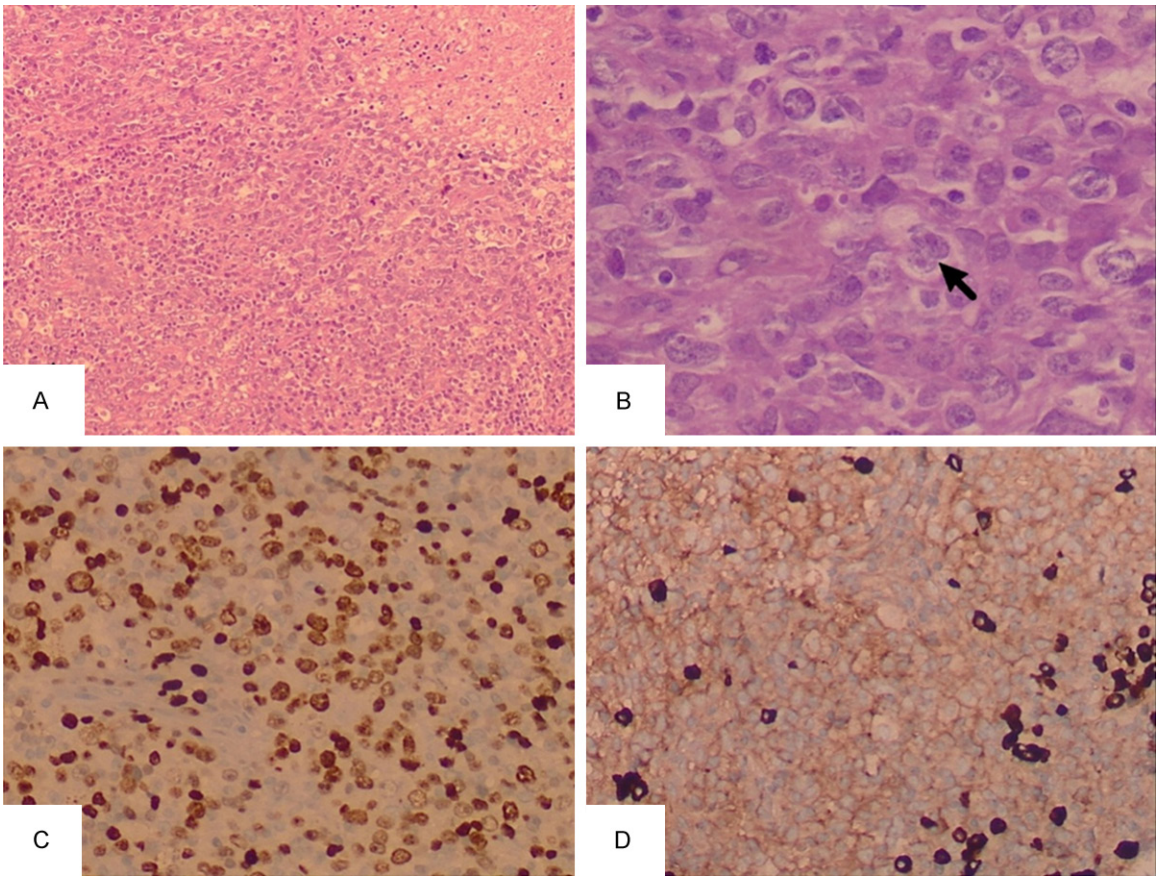

Figure 2. Histopathologic manifestations of PBL involving breast. A. Diffused distribution of the tumor cells with scattered plasmocytes and focal necrosis. B. Zoom-in picture showing large PBL cells with concentrated eosinophilic cytoplasm, enlarged vacuolated nuclei and abundant mitosis features. Arrow pointed at a binuclear tumor cell. C. Immunohistochemistry staining for VS38c marker. D. Ki-67 staining.

Kappa, Lambda, CD68, PAX-5, HMB45, Bcl-2, Bcl-6, CD2, CD3, CD4 and CD7. Tumor cell immunostaining of Ki-67 showed a proliferation index of 80% (**Figure 2D**). *In situ* hybridization of EBV-EBER reported negative result. Gene rearrangement analysis of the immunoglobulin heavy chain (IGH), κ-light chain (IGK), γ-chain (IgL) and T-cell receptor β-chain (TCRB) and γ-chain (TCRG) using GeneScan fragment analysis to determine the clonality status of T cells and B cells revealed positive B lymphocyte gene IGH and IGK rearrangement in the bone marrow (**Figure 3**), while the TCRB Vβ-Jβ, TCRB Dβ-Jβ, TCRG Vγιf/Vγ10-Jγ, TVRG Vγ9/Vγ11-Jγ clonality analysis result was negative. Based on the histological patterns, staining results and clonality assay, the pathological diagnosis of the sample was PBL in the left breast. Subsequent bone marrow biopsy was negative for marrow infiltration.

Treatment

The patient received 3-week radiotherapy 1.5 month after the surgery. Bilateral multiple enlarged lymph nodes in the neck were found 2.5 month post-surgery. The patient then underwent two cycles chemotherapy consisting of Epirubicin 60 mg/m^2 (day 1), Vincristine 2 mg (day 1), Cyclophosphamide 750 mg/m^2 (day 1) and Prednisone 100 mg (day 1-5) (CEOP). Drugs were well tolerated and the neck lymph node enlargement disappeared. Up to date, the patient was in good general state 5 months after the initial diagnosis.

Discussion

PBL most often occurs in the oral cavity but could also grow in other parts of the body. Patients are often accompanied with HIV infection or other immunodeficiencies. The appear-

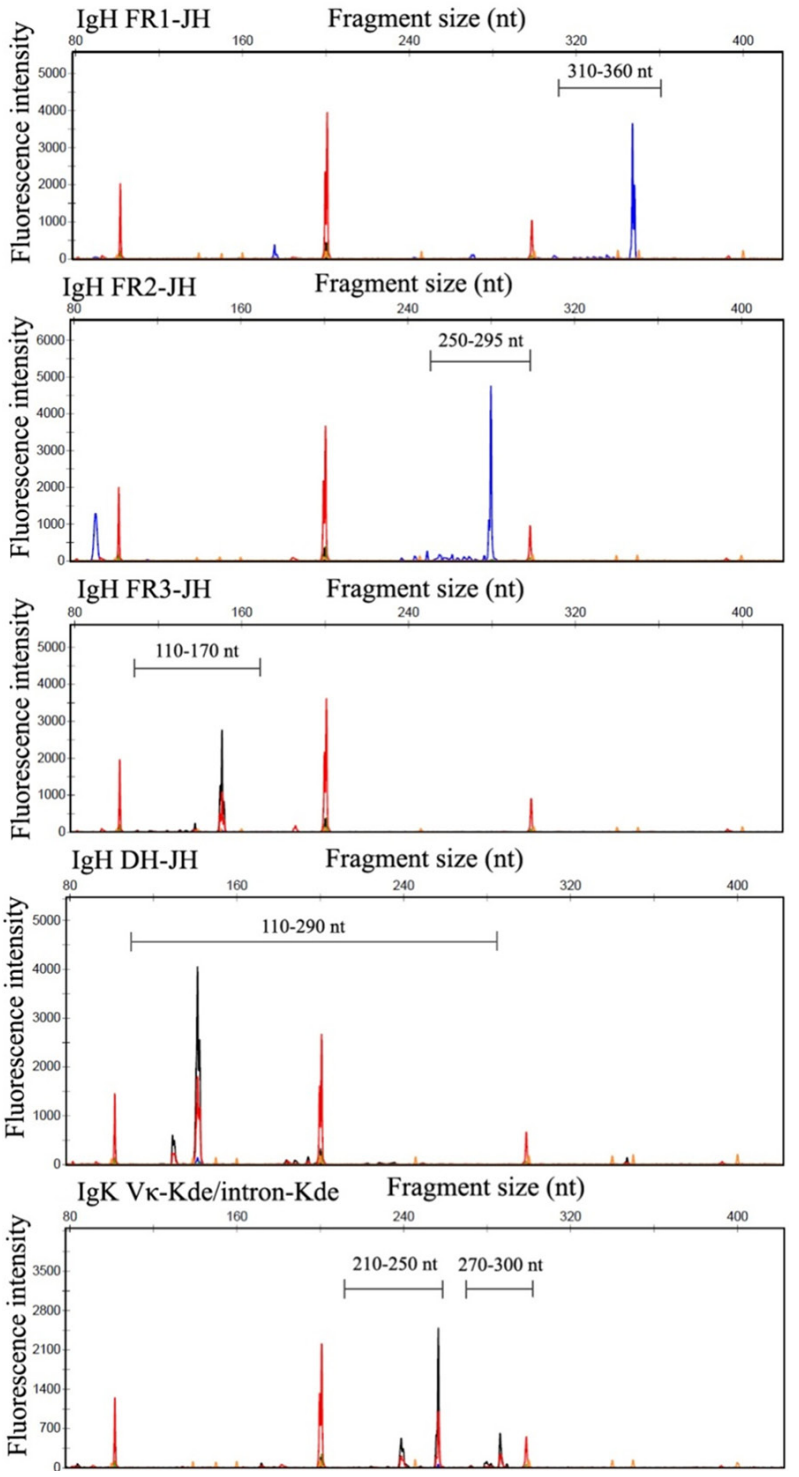

Figure 3. Gene rearrangement assay of the bone marrow. Presence of fluorescence signal for IGH FR1-JH, IGH FR2-JH, FR3-JH, IGH DH-JH and the IgK Vκ-Kde/intron-Kde gene by GeneScan fragment analysis positively indicated B lymphocyte rearrangement in the bone marrow. Red: marker. Blue: sample. Black: overlapping signal of marker and sample.

ance of PBL cells resembles the immunoblasts, with plasma cell differentiation. They are normally CD20 and PAX5 B-cell immune marker negative. 50%-85% of the patients express CD45, CE38, CD138, CD79a and MUM1 but not CD56 and CyclinD1 [4]. The proliferation rates are usually high (> 80%). PBL is highly invasive. Most PBL patients are also diagnosed with EBV infection with the survival time being less than 1 year [5, 6]. PBL is rarely seen involving the breast and only four cases have been reported previously [7-10] (**Table 1**). Including our case, the breast PBL patients aged between 36 and 56 years old. Two of the patients were HIV-positive and only one had EBV infection. Immunolabelling results of these cases showed varied results, however PAX5-, CD20-, CD79a- and CD3- were shared features. PBL patients tend to have very poor prognosis. Among these 5 cases, two of them died within 2 months after diagnosis. One case achieved a complete remission of the disease after numerous cycles of chemotherapy and stem cell transplantation. In our case the patient responded well to refined chemotherapy after tumor resection and is still surviving.

Definite diagnosis of PBL is important for choosing the appropriate therapeutic principles and determining prognoses. The main differential diagnosis of PBL is plasma cell myeloma (PCM) with plasmablastic differentiation. Although they share similar histological patterns and immunolabelling (both express VS38c), the

Table 1. Summary of published cases of plasmablastic lymphoma involving the breast

Series	Age	Clinical presentation	HIV/EBV detection	Immunohistochemical findings	Treatment	Follow-up (months)	Status
Wang J et al 2008 [7]	47	Painful bilateral breast lumps and multiple enlarged cervical and axillary lymph nodes	+/-	CD45+, CD138+; CD20-, CD79a-, PAX5-, CD10-, Bcl6-, CD30-, ALK-, CD2-, CD3-, CD4-, CD5-, CD8-, AE1/AE3-; Ki-67=80-90%	NA	NA	NA
Valera A et al 2010 [8]	42	Monomorphic PBL	+/-	NA	NA	1	DOD
Matikas A et al 2014 [9]	36	Bilateral multiple masses of breast, worsening left thoracic and abdominal pain	-/-	CD45+, CD20+, MUM1+, Clg (κ)+; CD3-, CD45 (RO)-, CD138-, CD79a-, EMA-; Ki-67=80%	CHOP×8, COP×3, stem cell transplantation	96	ANED
Fan G et al 2014 [10]	53	NA	-/+	CD45+, CD79a+, CD38+, CD138+, MUM1+; CD20-, PAX5-, CD56-, CD10-, CD30-	CHOP×1	1.9	DOD
Present case	56	Multiple left breast masses	-/-	VS38c+, MUM1+; CD45-, CD20-, CD79a-, CD56-, AE1/AE3-, EMA-, PAX5-, CD30-, ALK-, CD38-, CD138-, CD2-, CD3-, CD4-; Ki-67=80%	CEOP×2	6	AWD

NA: not applicable; COP: Cyclophosphamide, Vincristine (Oncovin®), Prednisone; CHOP: COP and Doxorubicin (Hydroxydaunomycin); CEOP: COP and Epirubicin; DOD: dead of disease; ANED: alive with no evidence of disease; AWD: alive with disease.

patient's clinical manifestations differ. Patients with a history of immunodeficiency, extranodal lesions, high proliferation index and EBER-positive are more inclined to be diagnosed with PBL. PCM is often coupled with multiple osteolytic damages and raised immunoglobulin. Moreover, PBL usually expresses CD45 but not CD56 or CyclinD1 while most PCMs are CD56+ and some are CyclinD1+ [11]. In our case, the patient's extranodual pathogenic site, high proliferation index, uneventful bone marrow biopsy and normal immunoglobulin level confirmed the PBL diagnosis.

Other neoplasms that are likely to be confused with PBL include the unspecified diffuse large B cell lymphoma (DLBCL), ALK-positive large B cell lymphoma, histiocytic sarcoma, malignant melanoma and myeloid sarcoma. ① Unspecified DLBCL is a histologic type of lymphoma mostly occurred in the breast with diffuse proliferation. The tumor cells have similar histologic form to PBL due to their large shapes, enlarged nuclei and prominent nucleoli. However, unspecified DLBCL abundantly expresses B-cell antigen CD20 while PBL does not [12]. ② ALK-positive large B cell lymphoma mainly affects the youth. It is mostly characterized with intranodal aggressions. Although ALK+ large B cell lymphoma is VS38c+, unlike PBL, it is also ALK+ and EMA+, CD45 weakly positive or negative [13]. ③ Histiocytic sarcoma cells diffuse infiltratively destruct the tissue structure. Sinus infiltrations are observed in the liver, spleen and lymph nodes. Tumor cells are large with abundant eosinophilic cytoplasm which can be confused with PBL. Histiocytic sarcoma mostly affects the extranodal intestine, skin and soft tissue of the elderly. The cell nucleus appears circular or ovoid and lacks features for Hallmark cell nucleus. Immunohistochemistry marking shows CD68+, VS38c-, ALK-, CD30-, and EMA- [14]. ④ Malignant melanoma cells have various histologic forms, all with large and prominent nucleoli. Melanin granules are visible in the cytoplasm. Malignant melanoma cells express Melan A, S-100 and HMB45 in immunohistochemistry tests while PBL does not. ⑤ Myeloid sarcoma originates from myeloid blast cells and locates in extramedullary site. Tumor cells are MPO+, CD34+, CD117+, CD138-, VS38c- which can be distinguished from PBL [15]. Therefore, the immunohistochemistry markers appear to be the major index in the diagnosis of PBL.

In summary, herein we reported a very rare case of PBL involving the breast. We focused on the definitive diagnosis of this disease. The patient was first diagnosed with breast neoplasm and received surgical operation. Histologic examination combined cytologic analysis helped distinguishing PBL from other types of tumors. The patient responded well to chemotherapy at the time of writing. More cases need to be accumulated to instruct the diagnosis and treatment of PBL.

Ethics, consent and permissions

This study was approved by the Ethics Committee of Yantai Yuhuangding Hospital. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Disclosure of conflict of interest

None.

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References

[1] Al-Malki MM, Castillo JJ, Sloan JM, Re A. Hematopoietic cell transplantation for plasmablastic lymphoma: a review. Biol Blood Marrow Transplant 2014; 20: 1877-1884.

[2] Vaubell JI, Sing Y, Ramburan A, Sewram V, Thejpal R, Rapiti N, Ramdial PK. Pediatric plasmablastic lymphoma: a clinicopathologic study. Int J Surg Pathol 2014; 22: 607-616.

[3] Choi SY, Cho YA, Hong SD, Lee JI, Hong SP, Yoon HJ. Plasmablastic lymphoma of the oral

cavity in a human immunodeficiency virus-negative patient: a case report with literature review. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 117: e115-120.
[4] Castillo JJ, Winer ES, Stachurski D, Perez K, Jabbour M, Milani C, Colvin G and Butera JN. Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma. Leuk Lymphoma 2010; 51: 2047-2053.
[5] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008. pp. 256-257.
[6] Liu JJ, Zhang L, Ayala E, Field T, Ochoa-Bayona JL, Perez L, Bello CM, Chervenick PA, Bruno S, Cultrera JL, Baz RC, Kharfan-Dabaja MA, Raychaudhuri J, Sotomayor EM, Sokol L. Human immunodeficiency virus (HIV)-negative plasmablastic lymphoma: a single institutional experience and literature review. Leuk Res 2011; 35: 1571-1577.
[7] Wang J, Hernandez OJ, Sen F. Plasmablastic lymphoma involving breast: a case diagnosed by fine-needle aspiration and core needle biopsy. Diagn Cytopathol 2008; 36: 257-261.
[8] Valera A, Balagué O, Colomo L, Martínez A, Delabie J, Taddesse-Heath L, Jaffe ES, Campo E. IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas. Am J Surg Pathol 2010; 34: 1686-1694.
[9] Matikas A, Kanellis G, Papadimitriou C, Papadaki T, Kotsakis A, Dimopoulos MA, Georgoulias V. Plasmablastic lymphoma of the breast in an immunocompetent patient: long-lasting complete response induced by chemotherapy and autologous stem cell trasplantation. Anticancer Res 2014; 34: 5111-5115.
[10] Fan G, Liu Y, Wen L, Wang Y, Wang L, Zhang Y, Wang Z, Yan Q, Yang L, Guo Y. The clinicopathological features of plasmablstic lymphoma. J Modern Oncol 2014; 22: 2690-2694.
[11] Cha JM, Lee JI, Joo KR, Jung SW, Shin HP, Lee JJ, Kim GY. A case report with plasmablastic lymphoma of the jejunum. J Korean Med Sci 2010; 25: 496-500.
[12] Aviv A, Tadmor T, Polliack A. Primary diffuse large B-cell lymphoma of the breast: looking at pathogenesis, clinical issues and therapeutic options. Ann Oncol 2013; 24: 2236-2244.
[13] Onciu M, Behm FG, Downing JR, Shurtleff SA, Raimondi SC, Ma Z, Morris SW, Kennedy W, Jones SC, Sandlund JT. ALK-positive plasmablastic B-cell lymphoma with expression of the NPM-ALK fusion transcript: report of 2 cases. Blood 2003; 102: 2642-2644.
[14] Nangal JK, Kapoor A, Narayan S, Singhal MK, Beniwal S, Kumar HS. A case of CD68 negative histiocytic sarcoma of axilla masquerading as metastatic breast cancer. J Surg Case Rep 2014; 2014.
[15] Toumeh A, Phinney R, Kobalka P, Mohamed I. Bilateral myeloid sarcoma of the breast and cerebrospinal fluid as a relapse of acute myeloid leukemia after stem-cell transplantation: a case report. J Clin Oncol 2012; 30: e199-201.