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Review

An elderly patient with primary cervical CD5-positive diffuse large B-cell lymphoma: a case report and review of the literature

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Summary

Objective: To increase our understanding of the clinical features, diagnosis and treatment, and prognosis of primary cervical CD5+ diffuse large B-cell lymphoma (DLBCL) in an elderly patient. *Materials and Methods:* We analyzed a case of an elderly patient with primary cervical CD5+ DLBCL and reviewed the literature. *Results:* The clinical features of this patient were not specific and were manifested as fever, significantly elevated LDH, normal blood test results, an unidentified fraction (6.5%) of cells shown by bone marrow puncture, unexpressed T-system and medullary system markers, and a primary lesion of the cervix found upon positron emission tomography-computed tomography (PET-CT). Cervical biopsy plus immunohistochemical staining showed a CD5+DLBCL, and the diagnosis was confirmed and R-CHOP therapy achieved a favorable therapeutic effect. *Conclusions:* The clinical manifestations of primary cervical CD5+DLBCL are not specific but PET-CT combined with cervical biopsy can clarify the diagnosis with R-CHOPas the preferred therapeutic regimen.

Key words: Elderly; Cervical; Diffuse large B cell lymphoma; CD5.

Introduction

Case reports of primary diffuse large B-cell lymphoma (DLBCL) of the cervix are rare, and the disease's incidence is low-especially among elderly women, where it is less than 1% of all cervical malignant tumors [1]. Reports in the literature have shown that patients with CD5+ DLBCL account for 5%-10% of all DLBCLs [2]. With reference to the literature and the diagnosis-as well as treatment-we analyzed the patient's primary CD5+ DLBCL of the cervix in the author's hospital in order to acquire a new perception of this disease.

Case Report

The patient (a 74-year-old female) was admitted to our hospital on October 17, 2017, due to fever and expectoration over 2 weeks. Two weeks prior to admission, the patient exhibited a fever of unknown cause, with her highest body temperature recorded at 38.6 °C; this was accompanied by shivering and slight productive coughing with white foam sputum. Cefaclor tablets (7 days) and moxifloxacin hydrochloride tablets (3 days) were self-administered, and the coughing and expectoration were alleviated; however, there was no significant improvement in fever. Loxoprofen sodium was than taken, which resulted in a reduction in body temperature, but this was followed by an intermittent fever. For further diagnosis and treatment, the patient visited our hospital. Since the onset of the health issues, the patient exhibited a depressed mood, night sweats, and a weight loss of 4 kg in the past year. The patient had previously been healthy, with regular menstrual cycles of 28-30 days. Menarche commenced at 18 years of age, with menses lasting for 4-5 days with no pain; and menopause began at 50 years of age. The patient had 3 successful pregnancies (G3P3). Physical examination showed no anemia, no yellowing of the sclera, no petechia or ecchymosis on the skin or mucosa, and no swelling of superficial lymph nodes; she produced coarse breath sounds in both lungs, but no dry or wet rales; she had a soft abdomen, no tenderness or rebound pain, no palpable abnormal mass, no involvement of the subcostal liver or spleen, and no edema of the lower limbs. Routine blood tests showed 4.42×10^9/L WBC (2.72×10^9/L N, 1.04×10^9/L L, 0.64×10^9/L M, 0.01×10^9/L E and 0.01×10^9/L B), 4.34×10^{12}/L RBC, a HGB of 124 g/L, PLT count of 169×10^9/L, LDH of 4529 U/L, FIB of 4.8 g/L, DD of 4.85 μg/mL, and FDPs of 17.79 μg/mL. Examination for acute infection showed the following concentrations: a PCT of 0.039 ng/mL, IL-6 of 26.34 pg/mL, and a hsCRP of 38.49 mg/L. EB viral DNA quantification showed 8.11×10^2IU. The antibodies against hepatitis indices, anti-HIV, and syphilis were negative. We detected no abnormalities in a routine urine test, routine stool test, liver or kidney function, electrolytes, blood culture, Widal and Weil-Felix reactions, or TORCH. Computed tomography (CT) of the chest showed that the right-middle and lower lung lobes and left lung revealed

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scattered stripes of blurred shadows, which we suspected to be inflammation. Color Doppler ultrasonography of uterine appendages showed an enlarged uterus with a volume of approximately 14.0 × 8.3 × 4.6 cm, a thickened appearance shape, and regular edges. On October 24, 2017, CTPA and plain CT scanning along with enhanced scanning were performed on the nasopharynx, oropharynx, laryngopharynx, submandibular glands, parotid glands, chest, and the entire abdomen, revealing 1) an uneven thyroid density with multiple, small, patchy, low-density shadows, 2) multiple small lymph nodes in the neck and submandibular region, 3) a right renal cyst, 4) an enlarged uterus with uneven density, and a small amount of effusion in the uterine cavity, 5) stripes of blurred shadows in the right-middle and lower lung lobes and left lower lobe, which were suspected to be inflammation, and 6) deficient pulmonary artery filling in the medial and lateral segments of the right middle lobe; the lateral, medial, and posterior basal segments of the right lower lobe; and the lateral segment of the left lower lobe-with small stripes of low-density shadows, which were considered to constitute a pulmonary embolism. After admission, anti-infective treatment using cefoperazone sulbactam sodium was administered for 1 week, while low-molecular-weight heparin calcium treatment was provided continuously. Body temperature however, was not significantly attenuated, and therefore we considered bone marrow puncture plus culture. Bone marrow images on October 25, 2017, showed that granulocytes, erythrocytes, and megakaryocytes proliferated actively; megakaryocytes matured poorly; and 6.5% of the cells were unidentifiable (primarily suspected to be lymphocyte-derived cells). We observed no abnormalities in bone marrow culture. Bone marrow biopsy in the Hematological Hospital of the Chinese Academy of Medical Sciences showed normal proliferation (about 40%) and a class of large heteromorphic cells with reticular fibers staining as grade MF-1; and bone marrow histopathology showed a class of large heteromorphic cells. Bone marrow immunohistochemistry revealed that the cells were CD20+, weak CD5+, CD3-, CD117-, CD4-, CD8-, CD56-, CD138-, CyclinD1-, and CD10-; and based on these indices, the patient's condition was diagnosed as B-cell lymphoma invading bone marrow and CD5 positive large B-cell lymphoma (Figure 1). For flow cytometry, bone marrow puncture was conducted at the replacement site on November 1, 2017. Bone marrow cytology of this site presented with reduced bone marrow hyperplasia, decreased granulocytic hyperplasia, and erythroid hyperplasia; megakaryocytes were only seen occasionally, and there were no unidentifiable cells. Simultaneous flow cytometric results revealed no lymphocytes with obvious phenotypic abnormalities. In order to find the primary lesion, positron emission tomography-computed tomography (PET-CT) was performed on November 3, 2017, and this demonstrated enlargement of the cervix accompanied by increased metabolism, which was suspected to be cervical cancer; and uterine body and bottom enlargement combined with increased metabolism, which was suspected to be an invasion by cervical cancer. Thickening of the upper vaginal wall was discovered, accompanied by increased metabolism, which was considered to be invasion. On the left side of the pelvis, multiple lymph nodes were enlarged in the hepatic hilar region, and the protuberance was combined with increased metabolism, which was considered to be metastasis. Hypermetabolic lesions were found in the left clavicle, left first anterior rib, left femoral head, sacrum, right greater trochanter of the femur, and tubular bone marrow cavity of the extremities, which were suspected to be metastases. Gynecologic consultation and medical examination were suggested and showed that the cervix was obviously hypertrophic; the surface was smooth, exhibiting no erosion or papillary or cauliflower-like substance; the texture was soft; and no bleeding was observed when touched. An HPV nucleic acid test revealed no infection. A cervical pathologic biopsy was carried out on November 20, 2017, that suggested no neoplastic lesions in epithelial components, while atypia was present on the free cells in interstitial vessels and coagulation tissues. Immuno histochemistry of cells showed the following: CD20 (+), C-MYC (+), BCL-2 (+), BCL-6 (foci +), CD5 (+), CD10(+), CD31 (vessels +), CD34 (vessels +), CD45RO (+), LCA (+), pax-5 (+), mum-1 (+), P53 (partially +), Ki67 (80%), CD3 (-), CD23 (-), CD56 (-), and CK (-). Therefore, on the basis of these findings, we diagnosed CD5 + DLBCL. Combined with the aforementioned data, a more definite diagnosis of primary CD5 + DLBCL of the cervix (stage IV group B; IPI score, 4) was provided. A R-CHOP chemotherapy regimen was started on November 22, 2017, which included rituximab (600 mg/d1) + cyclophosphamide (1.1 g/d1)+vincristine (4 mg/d1) + epirubicin hydrochloride (80 mg/d1)+prednisone (100 mg, d1-d5), after which the patient's body temperature returned to normal. On December 13, 2017, Color Doppler ultrasonography of uterine appendages was reviewed, showing that the size of the uterus was approximately 8.1 × 5.0 × 3.6 cm, the shape was normal, the margin was regular, and the uterus was obviously reduced in size. From December 14, 2017, to December 18, 2017; January 4, 2018, to January 8, 2018; and January 30, 2018, to February 3, 2018, 3 courses of R-CHOP regimen were administered, and the chemotherapy was suc cessful. During this period, lumbar puncture and intrathecal injection were conducted 3 times (5 mg of dexamethasone, 33 mg of cytarabine, and 12.5 mg of methotrexate). After 4 courses of the treatment, we performed a comprehensive evaluation and observed that routine blood tests returned to normal: 5.82 × 10^9/L WBC (3.99 × 10^9/L N, 1.14 × 10^9/L L, 0.53 × 10^9/L M, 0.14×10^9/L E, and 0.02 × 10^9/L B) 5.01×10^{12}/L RBC, a HGB of 151 g/L, and PLT count of 268 × 10^9/L. LDH was also normal (189 U/L). PET-CT showed that the volume of the uterus was reduced, the density was uniform, the outline was smooth, and no obvious space-occupying lesions or hypermetabolic lesions were found in the vagina. Multiple enlargements of lymph

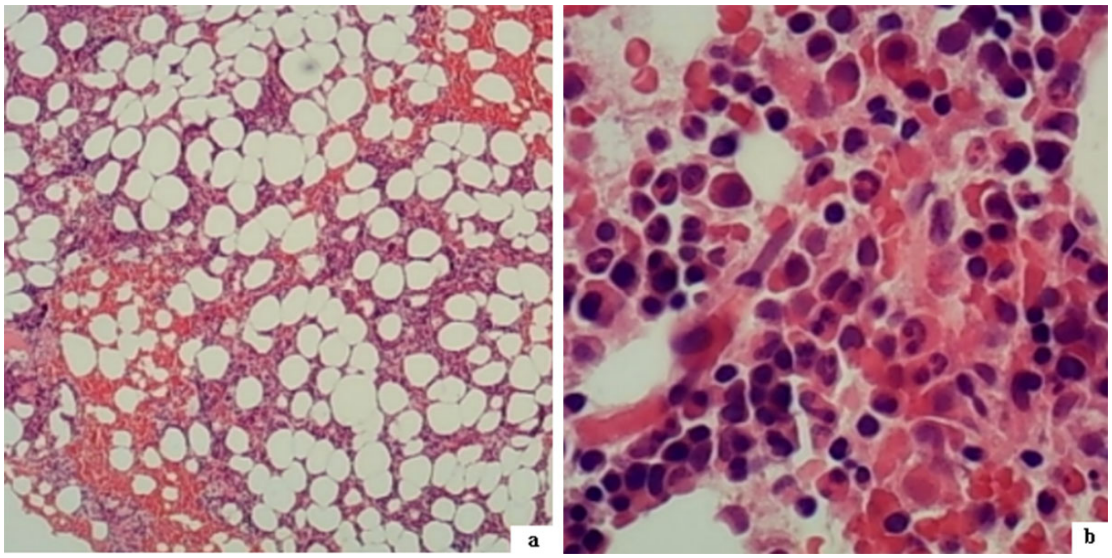

Figure 1. — A class of large heteromorphic cells observed in the detected bone marrow (a H&E ×4; b H&E ×40).

nodes were detected in the left side of the original pelvic cavity, hepatic hilar region, and a protuberance accompanied by increased metabolism, which was suspected to be the inhibition of major tumor activity. Multiple hypermetabolic lesions were found in the original left clavicle, left first anterior rib, left femoral head, sacrum, right greater trochanter of the femur, and tubular bone marrow cavity of the extremities. No metabolic increase or bone destruction was found at this time, suggesting that the activity of the tumor was inhibited. We uncovered no abnormalities were found in other parts and there was no abnormality in bone marrow puncture as well. Evaluation of minimal residual diseases showed no abnormal B lymphocytes, and the patient was determined to be in complete remission (CR). Afterward, 2 additional R-CHOP regimens were added, for a total of 6 courses. After chemotherapy, the patient refused to undergo a regular assessment at the author‘s hospital and did not complain of any discomfort at the follow-up phone call.

The patient was fully aware of the possible risks and benefits involved in publishing her case, and hereby gave written informed consent to publish her case (including any related images).

Discussion

Primary cervical lymphoma primarily occurs in postmenopausal women [3], with a median age of 44 and a range of 27-80 years [4]. The most common histologic type is DLBCL, followed by follicular lymphoma [5]. The clinical manifestations of primary DLBCL of the cervix are nonspecific with the most common symptom being abnormal vaginal bleeding. Other symptoms include abdominal or pelvic pain, vaginal discharge, dyspareunia, and urinary symptoms. B symptoms (e.g., fever, night sweats, and weight loss) are rarely seen [6]. This patient had no gynecologic symptoms as mentioned above, but the principal manifestation was the B symptom of tumors. Although uterine enlargement was shown by B-mode ultrasonography, this was prone to a missed diagnosis because of older chronologic age and no corresponding clinical manifestations. Only with the aid of PET-CT was the cervix finally uncovered as the primary lesion. The diagnosis of primary DLBCL of the cervix is difficult in that it is rare, and the clinical manifestations are similar to those of squamous cell carcinoma. Therefore, the differential diagnosis is extremely important. In a gynecologic examination, cervical cancer shows erosion-like changes and polypoid and cauliflower-like vegetation in the exogenous type, which not only is very delicate in texture and bleeds easily but also shows a cervical canal enlargement with a hard texture in the endogenous type. Testing for HPV DNA is often positive. Histologic diagnosis is the basis for the diagnosis and unidentifiable squamous cells are often discovered through cervical cytology. However, the superficial epithe lium of primary DLBCL of the cervix remains mostly intact and therefore it cannot always be diagnosed with cervical cytology. Only deep cervical biopsy and immunohistochemical staining can provide a correct diagnosis [7]. Our patient showed only obvious cervical hypertrophy upon gynecologic examination and no HPV infection with HPV nucleic acid testing. Combining the physical and imaging examinations, cervical biopsy, and immunohistochemical results, our diagnosis of primary DLBCL of the cervix was supported.

There is no standard treatment for primary DLBCL of the cervix. In the past, CHOP combined with moderate-dose of radiotherapy was considered to be the optimal treatment for the disease while R-CHOP is now considered to be the preferred treatment. The application of rituximab was confirmed by using the GELA test which showed that adding rituximab improved the overall survival (OS) rate of patients [8]. However, for patients with $CD5^{+}$DLBCL,

this is not the case as primary $CD5^+$DLBCL has its own unique clinical and pathologic features [9]. $CD5^+$DLBCL always occurs in elderly women and is often accompanied by increased LDH activity, multiple extranodal lesions, and early involvement of bone marrow, liver, spleen, and CNS. Most of the patients are in advanced stages (Stage III-IV) upon initial diagnosis and exhibit a poor physical condition, high international prognostic index score [10], invasiveness, and a poor prognosis. This patient was an elderly woman with significantly elevated LDH at the time of admission. Extranodal lesions involved the cervix, vagina, uterus, and skeleton and the bone marrow was invaded at the first diagnosis in stage IV (IPI score, 4). These characteristics were consistent with those reported in the literature. Studies have shown that regardless of whether rituximab was included in the treatment regimen, the early response to treatment was favorable [11], but the long-term prognosis was poor, and the recurrence rate was not attenuated [12-13]. When Niitsu *et al.* [12] allocated 102 patients with $CD5^+$DLBCL treated with CHOP or R-CHOP regimens to groups for observation, their results showed that the 4 year progression-free survival (PFS) rate in the rituximab group was higher than that for the CHOP group. Our regimen containing rituximab improved PFS, although the OS rate remained unchanged and we adopted the R-CHOP regimen 4 times and achieved CR, without obvious adverse reactions. Then, 2 additional courses of treatment were added and after chemotherapy, the early treatment achieved satisfactory results—with no complaints from our patient regarding any discomfort in the follow-up phone call.

In conclusion, the R-CHOP regimen remains the best regimen for the treatment of primary $CD5^+$DLBCL of the cervix in elderly women. The debate regarding operative treatment is still ongoing and some studies in the literature indicate that surgical treatment should be avoided [14], although cervical biopsy is the basis for a definite diagnosis. Unfortunately, there is no uniform treatment standard for CD5+DLBCL. Rituximab combined with intensive chemotherapeutic regimens may benefit such patients, and future targeted therapy for CD5 may be a potential therapeutic approach to improving the cure rate [15]. However, how to improve the clinical cure rate while reducing recurrence in such patients requires urgent investigation.

Ethics approval and consent to participate

Informed consent was obtained from the patient for publication of this case Report.

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Conflict of interest

The authors declare that they have no competing interests.

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