Clinical Case Report

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Anemia and thrombocytopenia as initial symptoms of occult breast cancer with bone marrow metastasis

A case report

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Abstract

Rationale: Occult breast cancer (OBC) is a rare type of breast cancer without any symptoms in the breast and is often presented with initial symptoms of axillary lymph node metastasis or other metastases. The low incidence rates of OBC make it a great challenge to diagnose and cure.

Patient concerns: Our case was a 58-year-old female affected by dizziness and fatigue for nearly a month. Blood tests revealed anemia and thrombocytopenia, and pathological results of a bone marrow biopsy confirmed the metastatic carcinoma.

Diagnoses: It was diagnosed as an OBC based on the positive immunohistochemical staining of cytokeratin (CK) and gross cystic disease fluid protein-15 (GCDFP-15).

Interventions: Doctor advised her to check whether the bone metastases existed in order to choose an appropriate treatment. It is highly regrettable that the patient gave up all treatments and left the hospital.

Outcomes: Recently, we conducted a telephone follow-up and received that the patient only took tramadol and other painkilling drugs to alleviate the pain caused by cancer.

Lessons: The current case inferred that symptoms of anemia and thrombocytopenia should not be ignored for the diagnosis of OBC, and bone marrow biopsy is useful in reducing the rates of misdiagnosis and missed diagnosis of OBC.

Abbreviations: ALP = alkaline phosphatase, CK = cytokeratin, GCDFP-15 = gross cystic disease fluid protein-15, HB = hemoglobin, HE = hematoxylin and eosin, LYM = lymphocyte, MAHA = microangiopathic hemolytic anemia, MRI = magnetic resonance imaging, OBC = occult breast cancer, PLT = blood platelet, PNT = paroxysmal nocturnal hemoglobinuria, RBC = red blood cell, Ret = reticulocyte, WBC = white blood cell.

Keywords: anemia, bone marrow biopsy, mammograph, occult breast cancer, thrombocytopenia

1. Introduction

Occult breast cancer (OBC) is a rare type of breast cancer without a detectable primary cancer lesion in breast on a physical examination or imaging examination such as ultrasound and mammograph. Approximately 0.2% to 0.9% of breast cancer cases are occult.[1,2] The initial symptoms of OBC includes axillary lymph nodes metastasis, distant metastasis, nipple discharge, nipple dermatitis, papillary dermal edema, eczema, and skin retraction.[3] Anemia and thrombocytopenia as the first symptoms have never been reported. The low incidence rates of OBC create a difficult diagnostic and therapeutic challenge even with the increasing availability of modern investigative techniques, such as mammography, ultrasound, and magnetic resonance imaging (MRI).[4,5] MRI and mammography can be used to detect non-OBC sensitively, but they are not sensitive for the diagnosis of OBC cases.[6] However, immunohistochemical staining of tumor tissue using breast cancer-specific glycoprotein monoclonal antibodies is widely used for the diagnostic and prognostic evaluation of breast cancer in recent years.[7] Interestingly, this is a case report of a female patient with initial symptoms of anemia and thrombocytopenia, and the immunohistochemical staining of bone marrow biopsy gave the most important information to confirm the diagnosis of OBC, which was also different from cases reported before.

2. Case report

A 58-year-old female patient was admitted to the Affiliated Hospital of Jining Medical University (Jining, China) on March 2, 2016 with initial complaints of dizziness and fatigue for nearly a month. The patient never underwent any operation with no

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history of infective diseases and family genetic disease. Blood tests provided by the local hospital indicated thrombocytopenia and anemia of unknown reason; thus she was admitted to hematology department of our hospital for diagnosis and further treatment. A physical examination revealed that the patient's lymphadenopathy and antiadoncus were not observed and bilateral breast were normal on palpation. No sternal tenderness was found, and heart and lung auscultation were normal. Abdominal wall was soft. Liver and spleen were not palpable. Blood tests indicated thrombocytopenia and anemia (white blood cell [WBC] count, 8.10×10^9 L^{-1} [normal, $3.5–9.5 \times 10^9$ L^{-1}]; red blood cell [RBC] count, 2.63×10^{12} L^{-1} [normal, $4.3–5.3 \times 10^{12}$ L^{-1}]; hemoglobin [HB] level, 88 g/L [normal, 130–175 g/L]; blood platelet [PLT] count, 51×10^9 L^{-1} [normal, $100–300 \times 10^9$ L^{-1}]; reticulocyte [Ret] count, 115.2×10^9 L^{-1} [normal, $24–84 \times 10^9$ L^{-1}]; percentage of reticulocytes, 4.38% [normal, 3.0–6.0%]; lymphocyte [LYM] count, 4.23×10^9 L^{-1} [normal, $1.0–3.8 \times 10^9$ L^{-1}]; percentage of LYMs, 52.20% [normal, 18.7–47.0%]; and elevated alkaline phosphatase [ALP] levels, 268 U/L [normal, 40–150 U/L]). No obvious abnormal changes were found among the other tests, including comprehensive serology and screening for autoimmune antibodies, myocardial enzymes, routine coagulation, and liver and renal function. A bone marrow puncture of the right posterior iliac crest was a dry tap. Peripheral blood samples and bone marrow aspirate smears were stained with Wright-Giemsa (Beijing Leagene Biotech Co., Ltd., Beijing, China) for morphological evaluation (Olympus L100 S600; Olympus, Tokyo, Japan). Bone marrow smears showed that the proliferation of granulocytes and erythrocytes were reduced, thrombocytopenia and no cancer nests were found (Fig. 1A). Peripheral blood smears presented large granular LYMs (Fig. 1B), nucleated and teardrop-shaped RBCs (Fig. 1C). Bone marrow aspiration was repeated in sternum, the result was similar to iliac crest. Tests of paroxysmal nocturnal hemoglobinuria (PNT) and Coombs were performed at the discretion of the managing clinician to exclude other diseases, and the result was normal. These results excluded the possibility of aplastic anemia, but made us consider myelofibrosis initially.

To confirm the diagnosis, a bone marrow biopsy of the right posterior iliac crest was performed. The resected tissues were formalin-fixed, paraffin-embedded, and cut into sections (2–4 μm) using a RM2235 rotary microtome (Leica, Wetzlar, Germany). Formalin-fixed specimens were stained with hematoxylin and eosin (HE) (Beyotime Institute of Biotechnology, Shanghai, China) and reticular fiber for histological evaluation. Proliferation of collagen fibers was observed in most mesenchymal regions (Fig. 2A) while a type of abnormal cells with medium size, less cytoplasm, and light-stained nuclei existed (Fig. 2B). Immunohistochemical analyses were performed to identify the abnormal cells according to the manufacturer's protocol. The following mouse monoclonal primary antibodies were used: CK (ab88247, abcam), GCDFP-15(ab86721, abcam), and CD20 (ab7753, abcam). Following incubation with the primary antibodies at 4°C overnight, sections were incubated with a monoclonal biotin-conjugated goat anti-mouse IgG secondary antibody (Kit-9710, Fuzhou Maixin Biotech) at 37°C for 30 minutes, followed by peroxidase-labeled streptavidin and diaminobenzidine chromogen (Ventana UltraView Universal DAB Detection Kit; Ventana Medical Systems, Inc) incubation. Evaluation was then performed using an Olympus BX51 microscope (Olympus Corporation, Tokyo, Japan). All immunostaining was performed using a BenchMark XT automated immunostaining device (Ventana Medical Systems, Inc). Immunohistochemical staining indicated that the abnormal cells were positive for CK (Fig. 2C) and GCDFP-15 (Fig. 2D), which helped confirm the diagnosis of breast carcinoma metastasis. We considered the patient was OBC and suggested she go to department of breast and thyroid surgery for further diagnosis.

On March 15, the patient was evaluated with a complete physical examination, bilateral mammography and ultrasonography of the breasts in the department of breast and thyroid surgery of our hospital. The patient presented with completely negative physical examinations of lymph nodes and breasts. Breast ultrasonography (Fig. 3A) also did not reveal any abnormalities, but the mammography of the left breast (Fig. 3B) showed multiple abnormal signals which were considered adenomatous hyperplasia and multiple small mammary gland adenomas. Thereby the patient was finally diagnosed with OBC. As this patient has bone marrow infiltration phenomenon, doctor advised her to check whether the bone metastases exists and find an appropriate treatment option. It is highly regrettable that the patient has not conducted PET/CT and any other diagnostic procedure to rule out bone metastases for

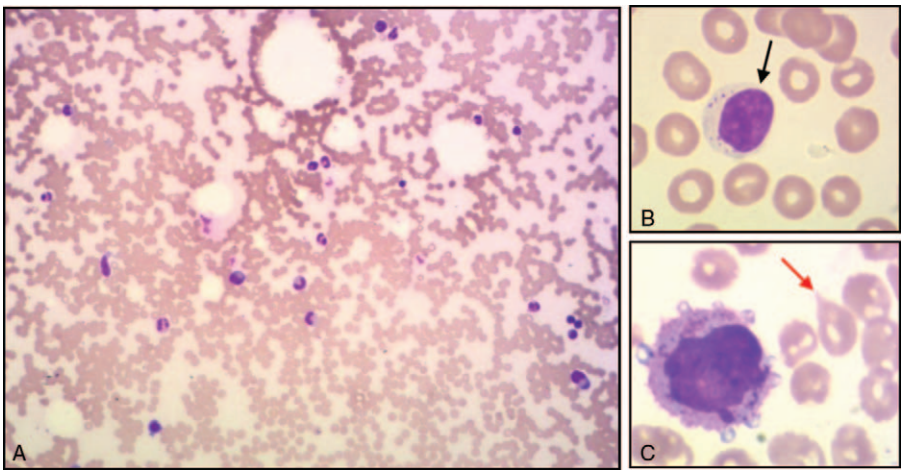

Figure 1. Peripheral blood and bone marrow morphology. (A) Bone marrow biopsy sections showed reduced myeloproliferation, and no cancer nests were found. (B, C) Peripheral blood smear presented large granular lymphocytes (LYMs) (B, black arrow) and teardrop-shaped red blood cells (RBCs) (C, red arrow).

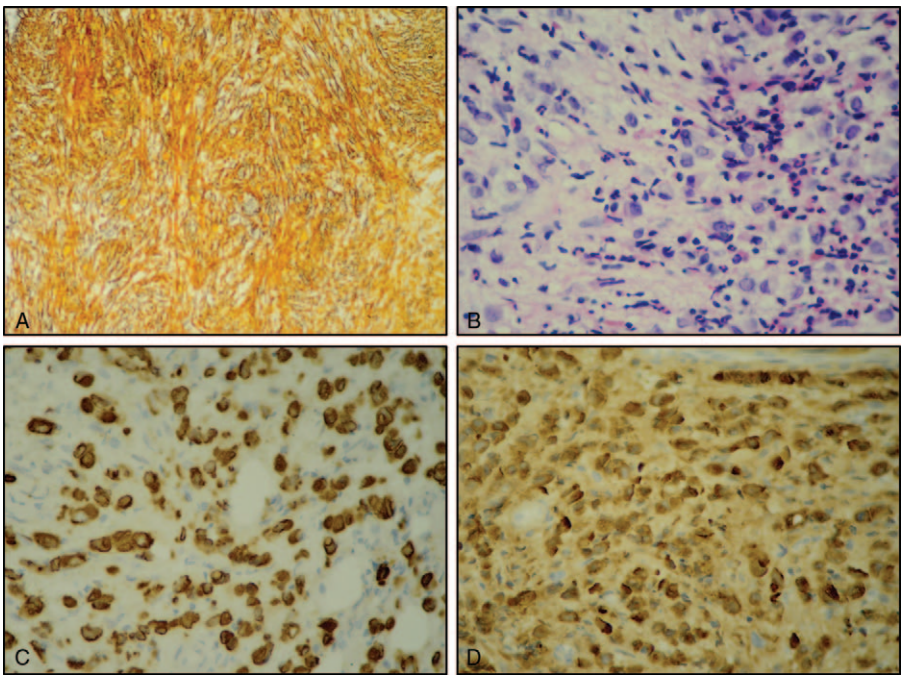

Figure 2. Histopathological and immunohistochemical features of the bone marrow biopsy. Images of the bone marrow biopsy showed involvement of myelofibrosis and metastases cells. (A) Formalin-fixed specimens were treated with Comori staining (magnification, 200×); proliferation of collagen fibers was observed in most mesenchymal regions. (B) With hematoxylin and eosin (HE) staining (magnification, 400×), a type of abnormal cells with medium size, less cytoplasm, and light-stained nuclei existed in specimens. (C, D) Immunohistochemical analyses were performed; the abnormal cells were positive for CK (C) (magnification, 400×) and GCDFP-15 (D) (magnification, 400×). CK = cytokeratin; GCDFP-15 = gross cystic disease fluid protein-15.

economic reasons. Then the patient gave up all treatments and left the hospital. Recently, we conducted a telephone follow-up on March 20, 2017. The patient only took tramadol and other painkilling drugs to alleviate the pain caused by cancer. We will continue to focus on the development of this case, and provide more clinical information for subsequent OBC.

3. Discussion

Breast cancer is the most common malignancy in women and the number one cause of death in women between the ages of 45 and 55 in the world,[8] and approximately 0.2% to 0.9% of breast cancer cases are OBC.[1,2] For these patients, their diagnosis and treatment were often delayed because of no significant symptoms and lack of awareness of such a possibility.[9] This is the first case report of OBC initially manifested as anemia and thrombocytopenia, of which the pathological results showed bone marrow infiltration with metastatic carcinoma. Bone marrow metastasis can frequently occur following development of metastatic breast cancer.[10,11] However, anemia and thrombocytopenia as the herald of breast cancer are not typically seen. Cases of breast cancer related microangiopathic hemolytic anemia (MAHA) has been reported, albeit rarely.[12–14] In those cases, the anemia and thrombocytopenia raised concern for bone marrow metastasis and indicated poor prognosis, but its pathophysiology remains largely unknown. Someone speculated it as paraneoplastic

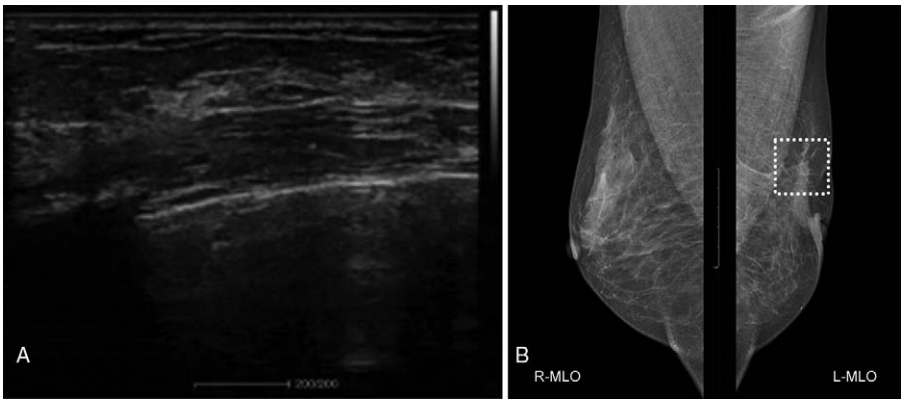

Figure 3. Radiography images of lymph nodes and breasts. (A) Ultrasonography examination of the lymph nodes and breasts did not reveal any abnormalities. (B) The mammography of the left breast (R-MLO) showed multiple abnormal signals compared with the normal one (L-MLO), which is considered adenomatous hyperplasia and multiple small mammary gland adenomas.

phenomenon. Paraneoplastic syndromes are defined as disorders caused by cancers, but not a direct result of cancer invasion of the affected organ or tissue.[15,16] In this case, anemia and thrombocytopenia may occur as a rare paraneoplastic phenomenon. Patients with an occult primary malignancy may cause changes in blood due to paraneoplastic phenomenon.[17,18] In addition to bone marrow metastases, anemia and thrombocytopenia in a patient with cancer can result from malignancy induced bone marrow fibrosis,[14] which was consistent with this patient's condition. Although the exact pathogenesis of anemia and thrombocytopenic is not yet delineated, we present this case to supplement the early symptoms of OBC. It is highly regrettable that the patient has not conducted any diagnostic procedure to rule out bone metastases and gave up all treatments. We did not get more valuable clinical and treatment information. In the future, we wish patients with the similar symptoms of this case can accept more detailed examinations to make more accurate and more detailed diagnosis.

OBC has a characteristically low incidence, and the lack of typical symptoms and clinical findings in the breast has brought great difficulties to its diagnosis.[6] Attention should be given to perform systematic relevant physical and imaging examination to find the primary lesion and avoid misdiagnosis. For this patient, hematologic work-up including bone marrow biopsy and immunohistochemistry revealed the presence of both CK and GCDFP-15 and gave the most important information to confirm the diagnosis of OBC by ruling out other primary cancers. This case inspired us to combine bone marrow biopsy with imaging techniques for early diagnosis of OBC.

4. Summary

This case highlights that bone marrow examination with appropriate and accurate immunohistochemical techniques is invaluable in establishing the diagnosis of OBC patients with rare initial symptom, particularly in patients presenting with hematological symptoms of anemia and thrombocytopenia. Thus, physicians should be aware of the importance of a structured approach that includes correlation with an accurate clinical history and examination, relevant radiological investigations, and peripheral blood and bone marrow histology.

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