

B-cell lymphoma as well as breast cancer contributes to the development of hemophagocytic lymphohistiocytosis: A rare case report

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Case Report

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Abstract

Background

Hemophagocytic lymphohistiocytosis (HLH), which is also known as hemophagocytic syndrome (HPS), can be caused by various factors leading to the reactive proliferation of lymphocytes as well as tissues and cells and the release of inflammatory cytokines, which then impair vital organs. Hemophagocytic lymphohistiocytosis, especially malignancy-associated HLH, which is difficult to differentiate from other diseases in the early stage because of its nonspecific and overlapping manifestations, has a high mortality rate once it occurs. Cases of hemophagocytic lymphohistiocytosis triggered by both solid tumors and lymphomas have rarely been reported before. There is still no consensus regarding the first-line treatment for HLH in adults. More attention should be paid to its early diagnosis and treatments.

Case presentation

A 55-year-old woman who had undergone thyroidectomy in 2014, left mastectomy for left breast cancer in 2013 and twelve rounds of chemotherapy had continuous fever approximately twenty days prior to admission. Tumor cells were found in her right axillary lymph node aspiration smear in the hospital on January 23. The patient was first diagnosed with pneumonia and treated with antibiotics, with little effectiveness. The etiology of fever remained unclear after a series of examinations, which excluded infection and rheumatic diseases and led us to consider noninfectious fever. Continuous hyperpyrexia, pancytopenia and continuous decreases in blood platelets and plasma albumin were suggestive of HLH. Then, bone marrow puncture confirmed this finding and indicated B-cell lymphoma invading the bone. Unexpectedly, during this time, the disease progressed rapidly, culminating in the patient's death, and no examinations or treatments were performed in time.

Conclusions

Secondary hemophagocytic lymphohistiocytosis can be caused by various factors. Malignancy-associated HLH (M-HLH), as a kind of secondary HLH, is difficult to distinguish from primary cancer due to its nonprominent clinical manifestation, thus leading to misdiagnosis and delayed treatment.

Background

Hemophagocytic lymphohistiocytosis is an overreactive disease of the mononuclear macrophage system and is thought to be the clinical manifestation of immune dysregulation with an overactivation of macrophages and a reduction in cytotoxic T cells and natural killer (NK) cell function. Lymphocytes and macrophages that are activated by the disease secrete high levels of pro- and anti-inflammatory cytokines, chemokines, and other substances, leading to abnormal clinical and laboratory findings¹. Hemophagocytic lymphohistiocytosis can be generally divided into two groups: familial forms of HLH and acquired forms of HLH². Secondary or acquired HLH has a wide range of causes, including malignancies, infections, metabolic diseases, autoimmune diseases, and acquired immune deficiencies.

Malignancy-associated HLH (M-HLH), as a kind of secondary HLH, can be difficult to differentiate from malignancy due to their similar clinical manifestations. In this case report, we present a rare M-HLH-related case caused by both solid cancer and B-cell lymphoma.

Case Presentation

A 55-year-old female patient who had breast cancer in 2013 and received 12 cycles of chemotherapy after mastectomy had continuous fever with cough and expectoration approximately twenty days prior to admission. A computed tomography (CT) scan of her chest acquired before admission showed nodules in the lung and enlargement of the right axillary and mediastinal lymph nodes. A biopsy of the right axillary mass indicated metastatic carcinoma (Figure 1), and a biopsy of the right breast mass in the hospital demonstrated hemorrhage and adipose tissue. Before admission, she was treated with cefoperazone, sulbactam and etimicin. At first admission, her physical examination showed that her right breast was swollen and hard to palpate, with no tenderness and marked swelling of the left upper limb. Breast ultrasound showed a right breast lesion after left mastectomy and right axillary lymph node enlargement. Thyroid ultrasound showed postoperative thyroid echogenicity, a lesion in the right lobe, and thyroiditis, and abdominal ultrasound showed fatty liver and cholecystolithiasis. The laboratory examination results at first admission were as follows: blood biochemical parameters: aspartate aminotransferase (AST), 39.6 IU/L (13-35 IU/L); lactate dehydrogenase, 769.0 L/IU (90-245 IU/L); and albumin, 31.0 g/L (40-55 g/L) an abnormal white blood cell examination: neutrophils%, 84% (50-70%); human lymphocyte%, 8% (20-40%); C-reactive protein, 94.60 mg/L (0-7 mg/L); hemoglobin, 108 g/L (115-150 g/L); and platelet count, $92 \times 10^9/L$ (125-350/L). Several days later, virus type B was weakly positive (+-) in the respiratory pathogen series, and the following results were observed: serum ferritin assay, 655.9 ng/mL (13-232 ng/mL); CEA, 42.7 ng/mL (0-6 ng/mL); CA125, 69.4 U/mL (0-35 U/mL); and NSE, 13.09 ng/mL. Moxifloxacin and oseltamivir were applied until discharge. Physical examination revealed uneven ecchymosis in multiple punctures on both the upper limbs and the right breast when she was readmitted to the hospital 3 days after discharge because of uncontrolled hyperpyrexia. At second admission, the platelet count was $71 \times 10^9/L$, complement C3 and C4 were normal, and fungal d-glucan was >5000 pg/mL. The results of the rheumatism series, ANCA, t-spot, GM test, the detection of giant cells and Epstein Barr virus, and epidemiological examination showed no abnormalities. After the patient was transferred to the oncology department, she continued to develop hypoalbuminemia, and the platelet count dropped to a critical value. Routine blood tests indicated the following: WBC count, $2.80 \times 10^9/L$; neutrophil%, 86.80%; hemoglobin, 85 g/L; platelet count, $37 \times 10^9/L$; glutamine transaminase (AST), 35.7 IU/L; albumin, 31.7 g/L; and TG, 4.17 mmol/L (0.3-1.8 mmol/L). At second admission, the computed tomography (CT) scan of her chest showed nodules in the lung and enlargement of the right axillary and mediastinal lymph nodes (Figure 2). However, meropenem, vancomycin, fluconazole, and other antibiotics were successively applied as anti-infection drugs but had little effect according to CT. Cardiac ultrasonography was performed to exclude infective endocarditis and showed no abnormalities. Breast ultrasound showed a solid mass in the right axillary region and subcutaneous soft tissue edema and effusion of the right breast. During treatment, the patient had continuous fever of more than 39.0°C over

7 days and pancytopenia. She gradually exhibited uneven ecchymosis on her body, and her blood platelets and plasma albumin continued to decrease. Based on her unusual medical history and abnormal physical examination, a hematological disease was considered. Then, bone marrow puncture was performed for confirmation. Hemophagocytes were found in the bone marrow smear (Figure 3A), indicating hemophagocytic syndrome. Moreover, 4.5% of the identified cells were not of uniform size, so tumor cells were suspected (Figure 3B). The histopathological examination of the bone marrow aspiration sample indicated the possibility of B-cell lymphoma (Figure 4). To test for the existence of lymphoma and determine the exact pathological type of lymphoma, we then performed flow cytometry analysis and bone marrow cell cloning. The results of the flow cytometry immunofluorescence analysis showed that the proportion of mature monoclonal B cells in the sample was 14.4%, the immunophenotypes of which were *CD5*⁻, *CD10*⁻, *CD19*⁺, *CD20*⁺, *CD23*⁻, and *FMCT7*, and the expression of the kappa light chain was restricted, suggesting B-LPD involving the marrow (Figure 5). Bone marrow cell cloning revealed no monoclonal rearrangement in the *TCRB*, *TCRG*, or *TCRD* gene, which excluded T-cell lymphoma, and monoclonal rearrangements in the *V* region of the *IGH* gene and *IGK* gene, leading to a definitive diagnosis of B-cell lymphoma. The biopsy of the right axillary mass (FISH test) indicated *Her-2(2+)* metastatic carcinoma originating from the breast. There was no amplification of *her-2*.

Treatment and outcome

First, the patient was diagnosed with pneumonia and treated with moxifloxacin, which lowered the inflammatory indicators. However, the fever was uncontrolled. Meropenem, vancomycin, fluconazole and other antibiotics were successively applied as anti-infection drugs but had little effect according to three different CT scans. Cardiac ultrasonography was then performed to exclude infective endocarditis and showed no abnormalities. The results of the tests for infectious diseases, tuberculosis, and other pulmonary diseases were normal, as were those of the rheumatism series. Combined with her unusual medical history of postoperative breast cancer and lymph node metastasis after breast cancer surgery, noninfectious fever caused by a tumor was considered, and the patient was then transferred to the oncology department. Unfortunately, due to rapid progression of the disease, the patient was believed to have HLH 1 day after being transferred. Three days later, the patient died of HLH.

Discussion And Conclusions

We reported a case of a patient who had breast cancer metastasis as well as B-cell lymphoma, both of which contributed to the development of M-HLH. The diagnosis of M-HLH in this patient was confirmed according to both pathologic findings and the fact that more than 5 of the following 8 diagnostic criteria³ were met: fever (temperature $\geq 38.5^{\circ}\text{C}$); splenomegaly; peripheral cytopenia (affecting ≥ 2 of 3 lineages in the peripheral blood); hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 3 mmol/L, fibrinogen < 1.5 g/L); hemophagocytosis in the bone marrow or lymph nodes without evidence of malignancy; reduced or absent NK cell activity; ferritin ≥ 500 microgram/L; and soluble CD25 (IL-2 receptor) ≥ 2400 U/mL. Infectious factors were excluded based on the negative results of the etiological examination. Likewise, patients with familial HLH often have a clear familial inheritance or an identifiable

genetic mutation, but this information remained unknown for this patient because she had not been tested. However, it is worth noting that the patient's unusual past medical history included 12 cycles of chemotherapy. The abnormal physical examination, as well as her unusual medical history, led us to consider M-HLH.

According to some other research reports, secondary HLH comprises 2 main groups: M-HLH and nonmalignancy-associated HLH. Hematologic malignancies, among which lymphoma, especially of T cell or NK cell origin, are the most reported⁴ and the most common cause of M-HLH².

The majority of published cases and clinical reports of M-HLH have also shown a T cell or NK cell origin. Nonmalignancy-associated secondary HLH is further subclassified as follows: infection-related HLH; autoimmune disease-related HLH, which is most commonly triggered by systemic lupus erythematosus, systemic juvenile idiopathic arthritis, polymyositis, and vasculitis⁵⁻⁷; spontaneous or iatrogenic immune suppression-related HLH; and post hematopoietic or solid organ transplantation HLH.

HLH manifestations such as continuous fever, hepatomegaly, splenomegaly, cytopenia, and coagulopathy may suggest malignant diseases, leading to delays in diagnosis as well as treatment; thus, it is a huge challenge for clinical doctors to intervene in the early stage. For tumor patients, it is of great necessity to differentiate HLH from M-HLH to provide timely and effective measurements. Actually, there does exist a close relationship between tumors and HLH. We surprisingly found in some other reports that patients with tumors, especially hematological neoplasms, were susceptible to HLH. Some research has even shown that HLH affects 1% of adults with hematologic tumors, but the incidence can reach up to 20% in some patients with B- and T-cell lymphomas⁸, which helps us better understand the causes of our reported case. Certainly, the patient had recurrence and metastasis of breast cancer, which are also thought to be causes of HLH. According to our research, chemotherapy and radiotherapy have long-term effects, and some patients may develop secondary lymphoma⁹. Chemotherapy agents have a close relationship with bone marrow tumors that may appear decades after primary treatment¹⁰. In fact, after surgery plus chemotherapy, there is an increased risk of developing LPDs, marrow neoplasms (MNs)¹¹, which allows us to understand how B-LPD developed in this patient. Though the most prevalent hematological cancers associated with treatment are acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), treatment-associated lymphomas sometimes occur^{10,12} but are clinically rare^{13,14}. Adjuvant therapies for early-stage breast cancer include anthracyclines (epirubicin and doxorubicin), alkylating agents (cyclophosphamide), antimetabolites (methotrexate and 5-FU), and taxanes (docetaxel and paclitaxel)¹⁵, which have been demonstrated to increase the 10-year hematological cancer risk by 0.5%¹⁶. The patient we described received 12 cycles of chemotherapy, which triggered the development of B-cell lymphoma, and at the same time, she had breast cancer metastasis. Finally, we inferred that both breast cancer and B-cell lymphoma contributed to the development of M-HLH, which has rarely been reported. However, we cannot deny that the existence of genetic factors may have played a role.

The mortality associated with M-HLH has been high (median survival, < 2.0 months)⁴. Survival after a diagnosis of HLH, especially M-HLH, with a mortality rate > 80%, is poor^{17,18}. A previous analysis indicated that < 50% of adults with M-HLH receive HLH-directed therapy because of a lack of awareness and missed diagnoses for adult patients with malignancies.

Patients with lymphoma-associated HLH benefit the most from etoposide-containing regimens and steroids¹⁹. It has also been found that patients with lymphoma-associated hemophagocytic syndrome can achieve complete remission and obtain a good prognosis with allogeneic or autologous hematopoietic stem cell transplantation (HSCT)^{20,21}.

The patient we described died of M-HLH without timely treatment due to nonspecific clinical manifestations and laboratory findings. The etiologies of HLH vary. Early treatments for both the primary disease and HLH are crucial for reducing the mortality rate.

The etiologies of continuous fever vary, making initial diagnoses and therapy strategies difficult. The possibility of HLH should be taken into account early and distinguished from infection and rheumatic diseases. Unusual medical histories, especially a history of cancer, should also be considered. We must be alerted to the possibility of the formation of secondary cancers following therapy for primary cancers, especially hematologic tumors led by solid cancers. HLH should be considered if a patient has both continuous fever and a tumor, especially a hematologic tumor. The mortality of secondary HLH is considerably high once it occurs. However, the incidence of HLH is relatively low, and there is still no consensus on the first-line therapy for HLH in adults due to its complicated etiologies. The initial diagnosis and treatment are crucial for patients. Most importantly, we must all be highly aware of secondary HLH.

Abbreviations

HLH: Hemophagocytic lymphohistiocytosis

HPS: Hemophagocytic syndrome

M-HLH: Malignancy-associated HLH

NK cell: Natural killer cell

CT: Computed tomography

LPDs: lymphoproliferative disorders

MN: Marrow neoplasm

AML Acute myeloid leukemia

MDS Myelodysplastic syndrome

HSCT: Hematopoietic stem cell transplant

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Informed consent statement

Informed consent was obtained from the patient.

Written informed consent

Patient has provided informed consent for publication of the case.

Conflict-of-interest statement

The authors declare that there is no conflict of interest related to this report.

Ethical statement

Written informed consent was obtained from the patient. Ethical approval was obtained from the Ethics Committee of the Jinan Central Hospital affiliated with Shandong University, Jinan 250013, Shandong Province, China

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Contributions

Zhou N and Yin ZX were the patient's respiratory physicians, reviewed the literature and contributed to drafting the manuscript; Chang YL performed the histopathological examination, flow cytometry analysis, and cell cloning for the bone marrow analyses and interpreted the data; Xing CY and Chu YB were responsible for revising the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Figures

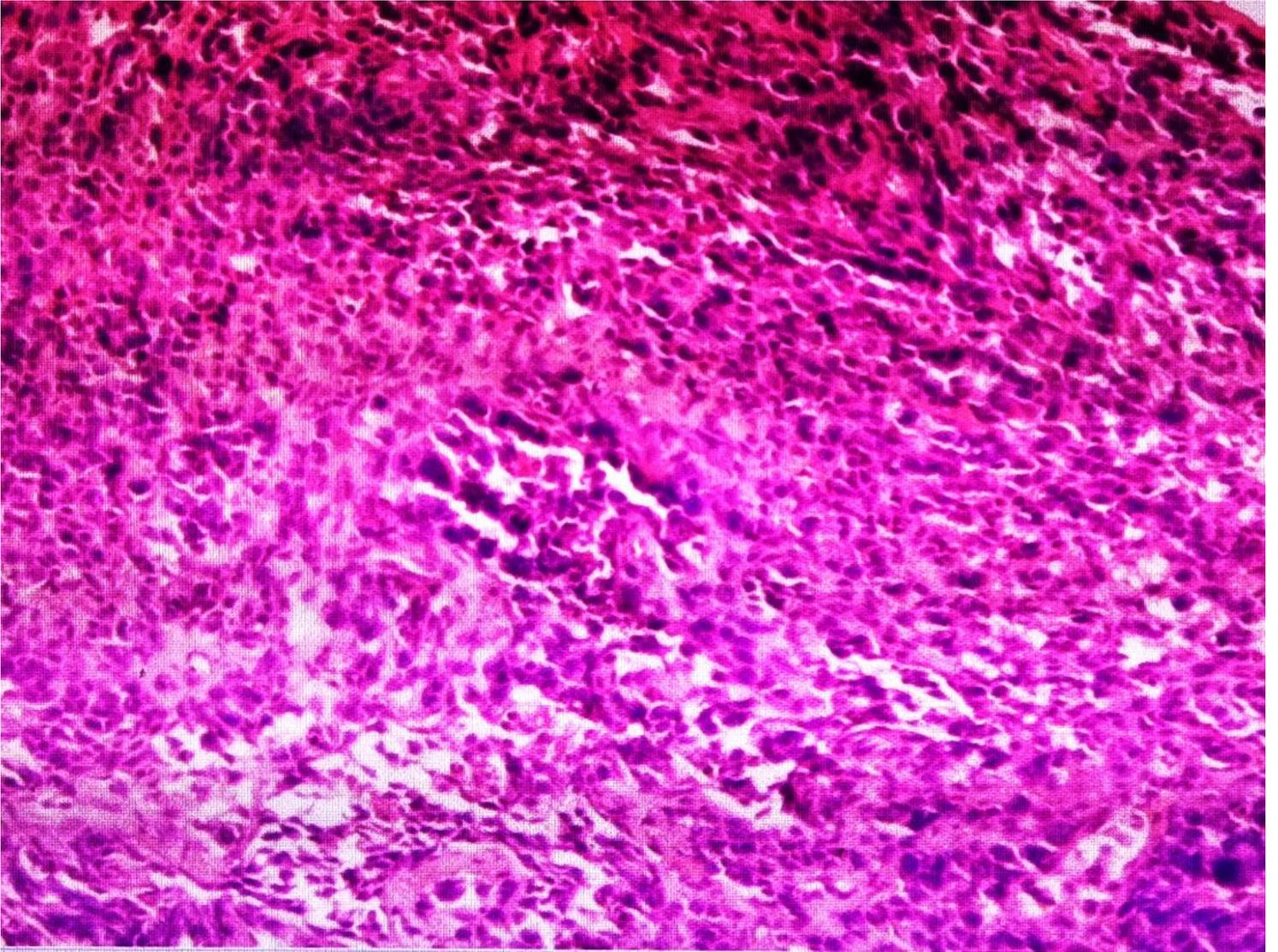


Figure 1

Biopsy of the right axillary mass. Biopsy of the right axillary mass showed metastatic carcinoma.

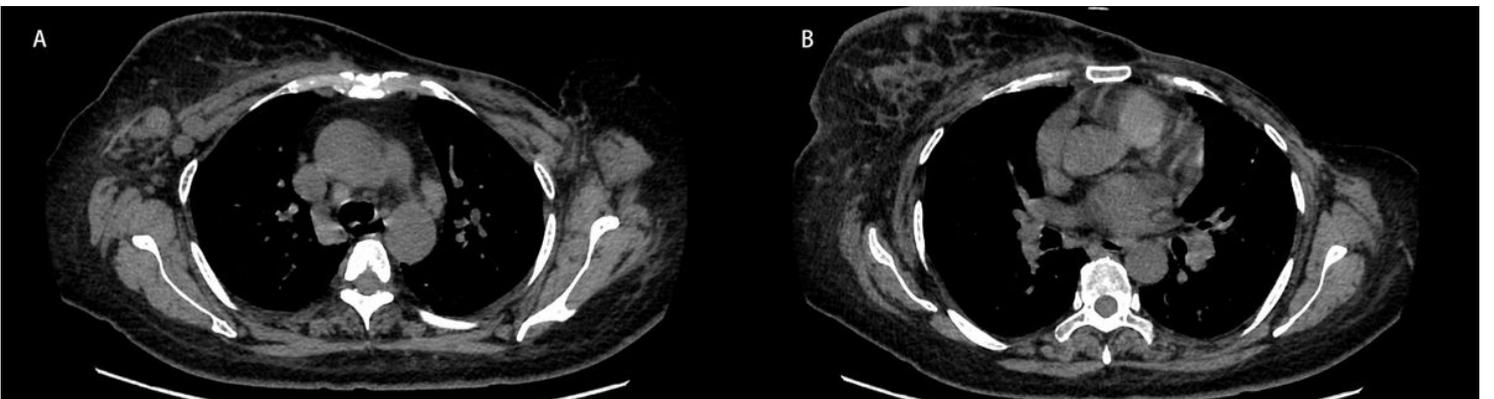


Figure 2

Chest CT scan at first admission. There were nodules in the lung and enlargement of the right axillary and mediastinal lymph nodes.

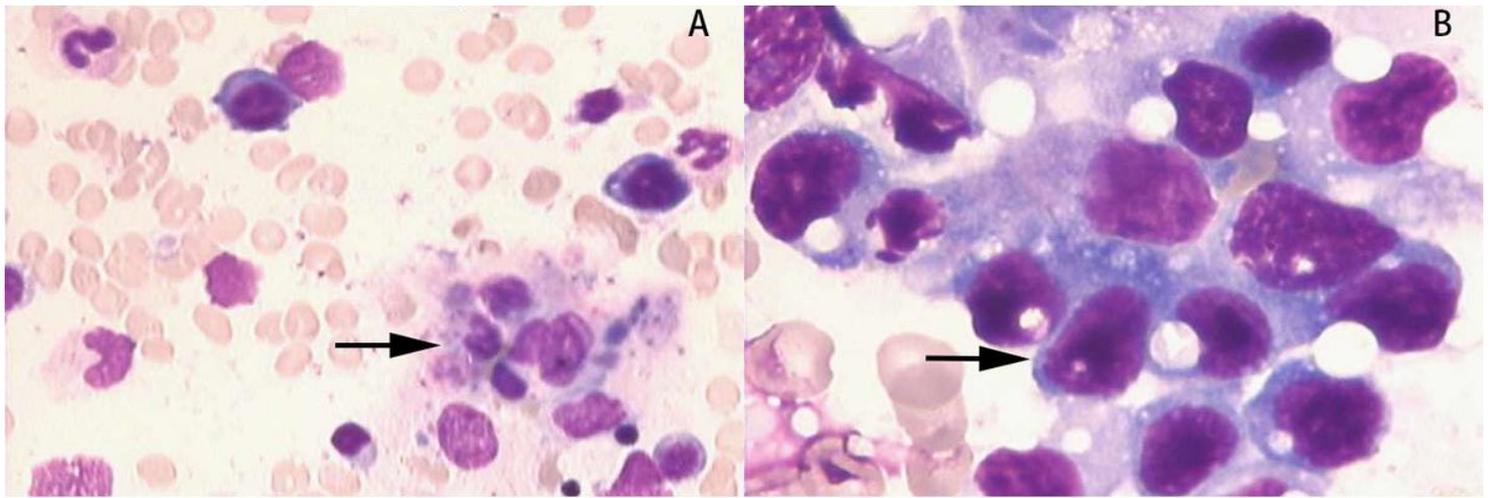


Figure 3

Bone marrow smear. A: Bone marrow sample with visible blood cells that could be phagocytosed (black arrow). B: Unidentified cells were observed (black arrow). The cells were of an uneven size, and their nuclei were large and eccentric. They were distributed in clusters. The possibility of bone marrow metastasis of lymphoma was high.

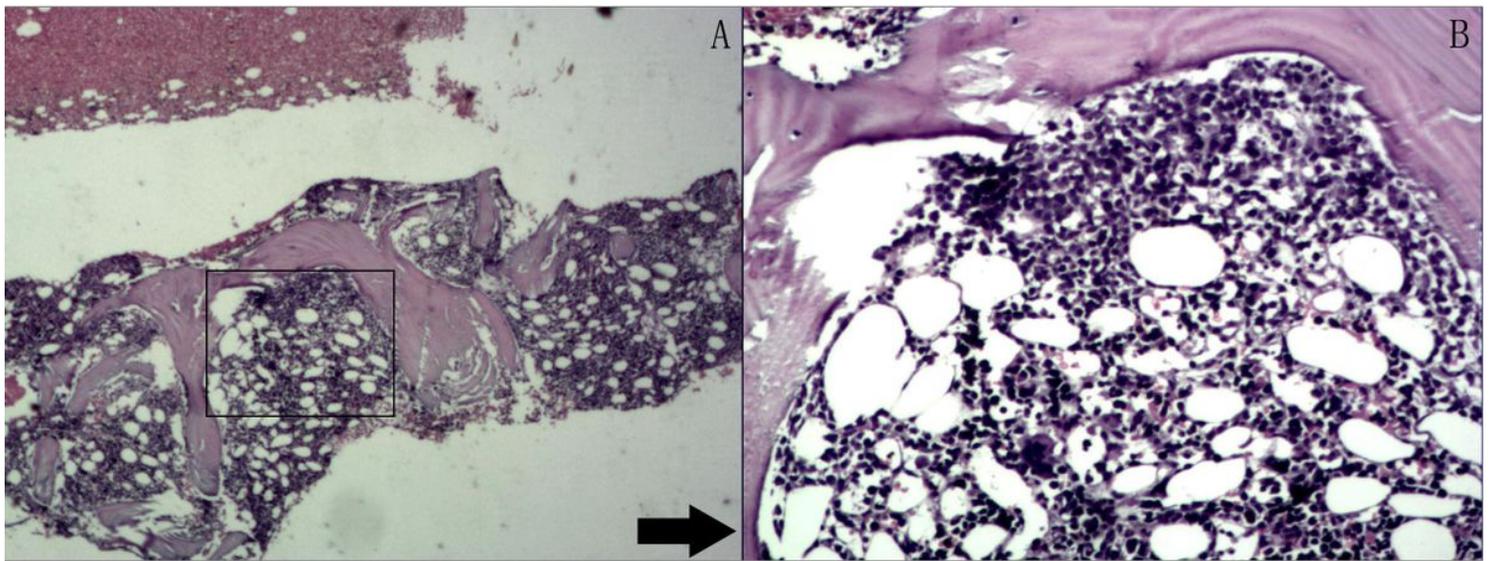


Figure 4

Bone marrow pathology. A: An image from bone marrow pathology. B: Inset from picture A (black frame). Bone marrow hyperplasia was active, and there were lymphoid cells with multiple foci and small flaky distribution. The cells were medium to large, chromatin was delicate, and nucleoli could be seen. The ratio of granulocytes to erythrocytes was generally normal. There were many cells in the infantile stage of granulation, mainly in the middle and young stages. The red blood cells were mainly middle and late juvenile red blood cells. Megakaryocytes were numerous, mainly lobulated nuclei. Reticular fiber staining (-). IHC: CD20(+) CK(-) CD34(-) CD117(+) CD68(-) CD61(+) and CD3(+). B-cell lymphoma was considered.

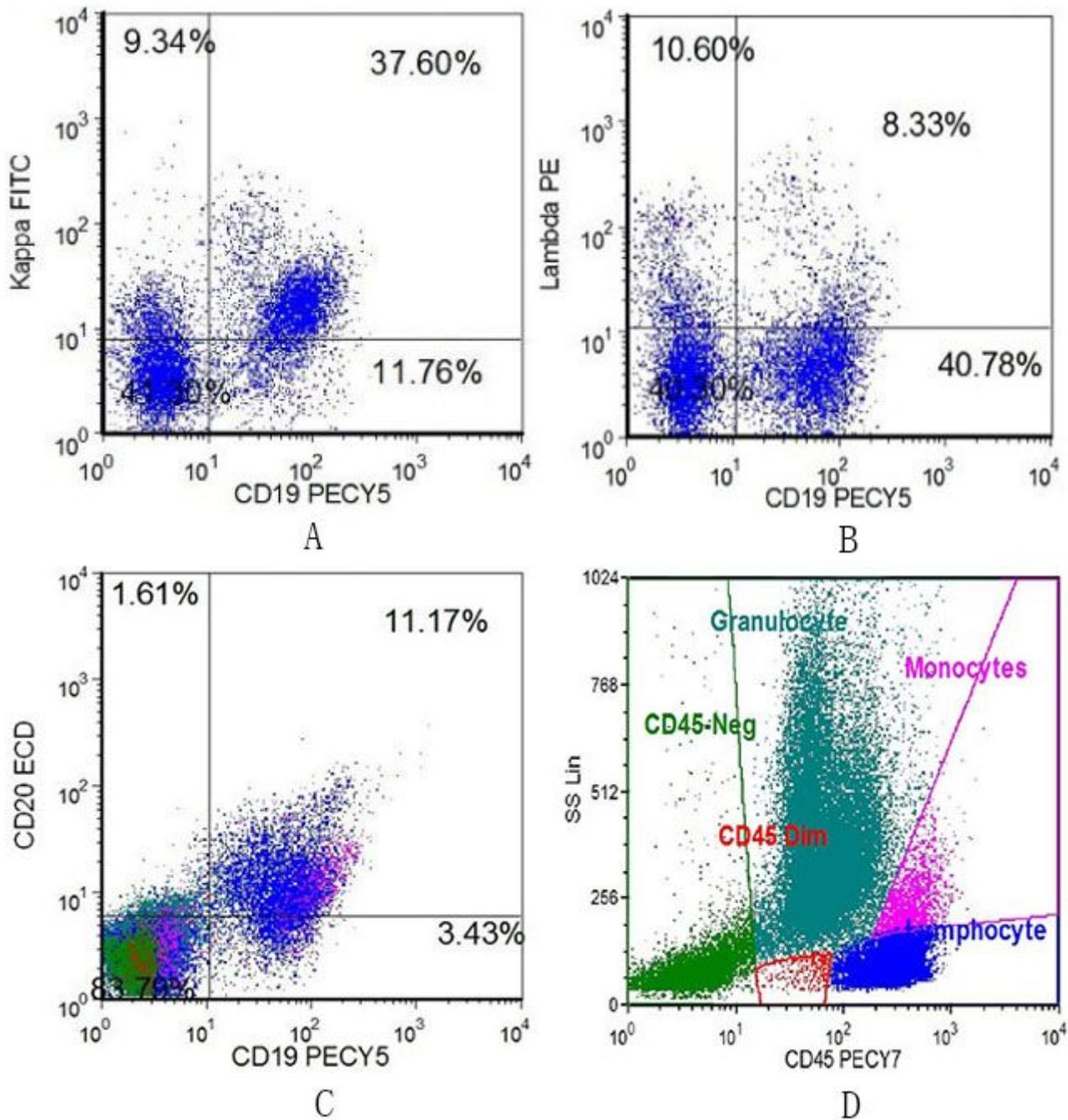


Figure 5

Flow cytometry immunofluorescence analysis. A: The distribution and number of cells. B: The expression of CD19+ and CD20+ C, D: Restricted expression of the kappa light chain. Lymphoid (22.5%): some monoclonal lymphocyte B cells were seen; Grans (60.5%): normal relative proportion; Monos (3.7%): normal; CD45-Dim (0.7%): normal; CD45-Neg (12.6%): mainly red nuclei and cell debris. The results of flow cytometry immunofluorescence analysis indicated no increase in CD34+ cells, the lymphocyte proportion was relatively elevated, the proportion of mature monoclonal B cells in the sample was 14.4%, the immunophenotypes of which were CD5-, CD10-, CD19+, CD20+, CD23-, and FMC7-, and the expression of the kappa light chain was restricted, suggesting B-LPD involving the marrow.

Supplementary Files

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