SAGE Open Medical Case Reports
Volume 10: 1–5

DOI: 10.1177/2050313X221088146
journals.sagepub.com/home/sco
SAGE

Concurrence of hemophagocytic lymphohistiocytosis and small-cell lung cancer in bone marrow: A case report and literature review

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Abstract

Hemophagocytic lymphohistiocytosis is a rare and almost universally fatal disease in adults. A 60-year-old female patient presented to our hospital with a 3-day history of weakness and anorexia. Physical examination revealed severe pallor without lymphadenopathy or hepatosplenomegaly. The initial blood test showed a hemoglobin level of 2.6 g/dL and a platelet count of 76×10^9/L. Later the patient experienced persistent high fever for 1 week without any obvious infective symptoms. Biochemical examination revealed hyperferritinemia and low natural killer cell viability. The bone marrow morphology showed hemophagocytosis and infiltration with metastatic small-cell lung cancer. The patient was diagnosed as small-cell lung cancer-related hemophagocytic lymphohistiocytosis. Subsequently, she underwent chemotherapy with dexamethasone and etoposide. However, the patient succumbed within 2 weeks of presentation due to rapidly progressive disease. In conclusion, we reported the first hemophagocytic lymphohistiocytosis case with small-cell lung cancer. It is critical to have early identification of hemophagocytic lymphohistiocytosis in patients with small-cell lung cancer.

Keywords

Hemophagocytic lymphohistiocytosis, fever, bone marrow, small-cell lung cancer, case report

Date received: 30 August 2021; accepted: 1 March 2022

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of severe immune activation and pro-inflammatory cytokine hypersecretion, resulting in damage of tissues and organs.[1] HLH may be triggered by several factors such as drugs, autoimmune diseases, and infections as well as cancers in adults. Timely diagnosis may be challenging because of the rarity of HLH. Among them, malignancy-related HLH (M-HLH) is frequently misdiagnosed with a poor outcome. The median overall survival time is typically less than 2 months.[2] Currently, the majority of M-HLH comes from hematological malignancies in adults, while lung cancer-related HLH is rare. Up to now, only four patients with lung cancer were reported in the previous literature. Of the four cases, three cases (two with adenocarcinoma and one with squamous cell carcinoma) developed HLH caused by pembrolizumab treatment and were rescued by glucocorticoids.[3,4] Another one case was an untreated squamous cell lung carcinoma which was improved by HLH-2004 protocol.[5]

In this article, we report a rare case of a 60-year-old female who presented to our hospital with severe anemia, thrombocytopenia, and persistent high fever for 1 week. Subsequently, the patient was diagnosed as small-cell lung cancer (SCLC)-related HLH.

Case report

A 60-year-old female presented to the department of Hematology/Oncology on 5 November 2018 with a history of weakness and anorexia for 3 days. Her medical history included hypertension, hyperlipidemia, and ischemic heart disease for 5 years and type 2 diabetes mellitus for 1 year.

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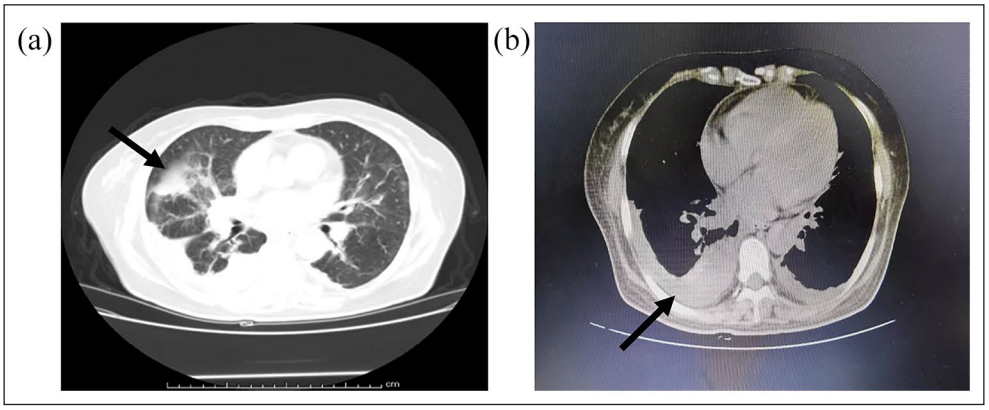

Figure 1. Chest imaging upon admission revealed ground glass opacities with 61% solid components in the right lung ((a) arrow) and bilateral pleural effusion ((b) arrow).

There was no obvious family history. Physical examination revealed severe pallor without lymphadenopathy or hepatosplenomegaly. The blood test showed a white blood cell count of 4.0×10^9/L (normal range, $4.0–10.0 \times 10^9$/L), a hemoglobin level of 2.6 g/dL (normal range, 11.0–15.0 g/dL), a platelet count of 76×10^9/L (normal range, $100–300 \times 10^9$/L), and a reticulocytes count of 110×10^3/μL (normal range, $20–80 \times 10^3$/μL). The peripheral blood smear showed 4% myelocytes and metamyelocytes. Laboratory examination revealed elevated lactate dehydrogenase 928 U/L (normal range, 120–250 U/L), total bilirubin 37.6 μmol/L (normal range, ⩽20 μmol/L), indirect bilirubin 19.1 μmol/L (normal range, ⩽18 μmol/L), alanine aminotransferase 115.1 U/L (normal range, 9–50 U/L), aspartate aminotransferase 70.7 U/L (normal range, 15–40 U/L), alkaline phosphatase 419.9 U/L (normal range, 45–125 U/L), γ-glutamyl transferase 283.8 U/L (normal range, 10–60 U/L), creatine kinase 2172.1 U/L (normal range, 50–310 U/L), triglyceride 2.52 mmol/L (normal range, ⩽1.7 mmol/L), C-reactive protein 7.73 mg/L (normal range, 0.1–5 mg/L), procalcitonin 0.616 ng/mL (normal range, ⩽0.05 ng/mL). Prothrombin time and activated partial thromboplastin time were within the normal range, while fibrinogen degradation product was elevated (16.96 mg/L, normal range, ⩽5 mg/L). D-Dimer was 2.40 mg/L (normal range, ⩽0.3 mg/L), and fibrinogen was 2.39 g/L (normal range, 2–4 g/L). Human immunodeficiency virus, cytomegalovirus, and Epstein-Barr virus were all negative. Also, the immunologic examinations were normal. Multiple tumor markers were elevated, such as carcinoembryonic antigen 16.34 ng/mL (normal range, ⩽3.4 ng/mL), carbohydrate antigen 125 75.3 U/mL (normal range, ⩽35 U/mL), carbohydrate antigen 199 77.69 U/mL (normal range, ⩽39 U/mL), cytokeratin (CK) fragment antigen 21–1 12.39 ng/mL (normal range, ⩽3.3 ng/mL), neuron-specific enolase 311.2 ng/mL (normal range, ⩽16.3 ng/mL), pro-gastrin-releasing peptide > 5000 ng/L (normal range, ⩽68.3 ng/L), ferritin 1432 ng/mL (normal range, 30–400 ng/mL). Urinalysis showed hematuria and increased urobilinogen. Hemolysis-related tests including Coombs' test, free hemoglobin, and paroxysmal nocturnal hemoglobinuria clones were all at the normal level. Subsequent chest computed tomography (CT) scan showed ground-glass opacities (GGOs) with 61% solid component in the right lung and bilateral pleural effusion (Figure 1(a) and (b)). Ultrasound examination of the abdomen revealed multiple hypoechoic lesions in the liver without hepatosplenomegaly. She was transfused with red blood cells intermittently. Despite broad-spectrum antibiotics treatment, she still experienced persistent fever with a maximal temperature of 40°C for 1 week without obvious infective symptoms. Given the high suspicion of HLH, dexamethasone (10 mg daily) was started on the eighth day (12 November 2018). Further examination revealed low natural killer (NK) cell viability 11.97% (normal range, ⩾15.11%) and normal sCD25 1703 pg/mL (normal range, ⩽6400 pg/mL). Subsequently, flow cytometry analysis of bone marrow aspiration suggested 0.04% karyota of suspected epithelial origin non-hematopoietic cells. Further pathological review showed hemophagocytosis and metastatic carcinoma within the bone marrow (Figure 2). Immunohistochemical staining of bone marrow biopsy confirmed metastatic SCLC (Figure 3). The tumor cells were positive for CK 7 (little +), AE1/AE3 (++), CK8/18 (++), CK5/6 (little +), CD56 (+++), Ki-67(80%), CgA (few +), Syn(+++) and TTF-1 (+++), but negative for CK20, Napsin A, and P63. Therefore, the patient met five of the eight diagnostic criteria of HLH according to the HLH-2004.[6] Then, she was diagnosed as SCLC-related HLH and quickly underwent inductive chemotherapy regimen consisting of dexamethasone and etoposide (100 mg/dL) according to the HLH-1994[7] on the 10th day (14 November 2018). However, the disease progressed rapidly. Finally, she developed a continuous febrile convulsion and died on the 12th day (16 November 2018).

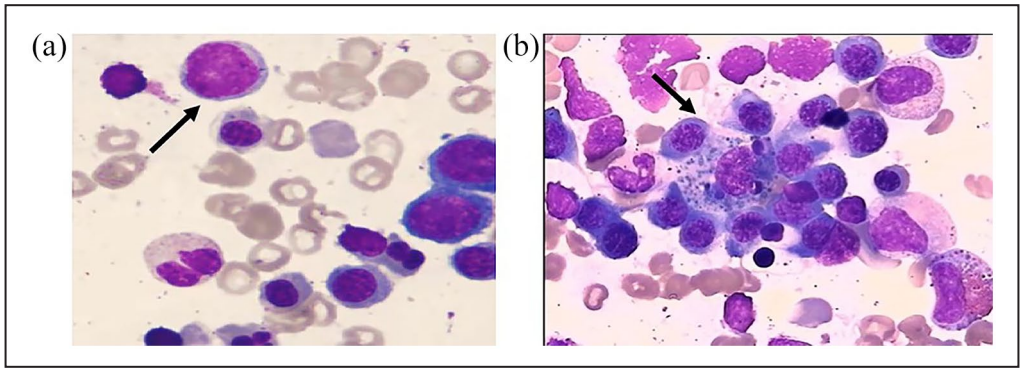

Figure 2. The morphology of bone marrow cells. The pathological result showed metastatic carcinoma of bone marrow ((a) arrow) and hemophagocytosis ((b) arrow).

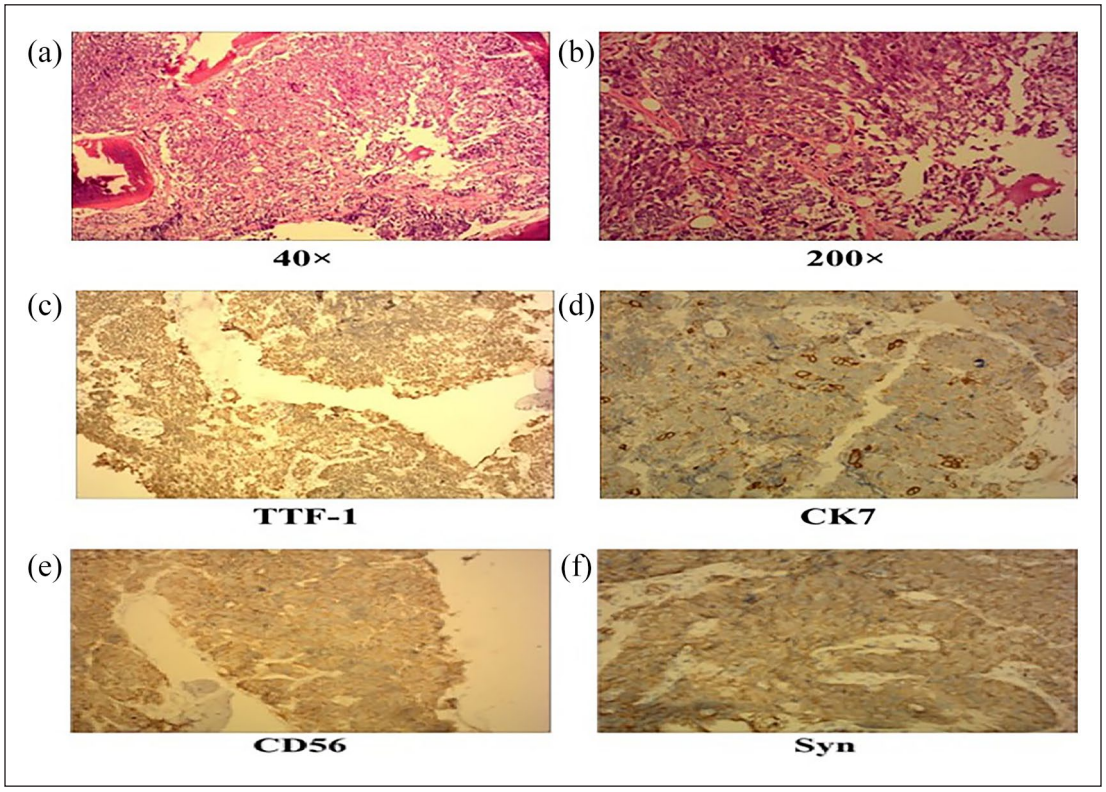

Figure 3. Histopathology of bone marrow biopsy. Histopathology of bone marrow revealed metastatic small-cell lung cancer (a) (H&E, 40×) and (b) (H&E, 200×). Histochemical staining of tumor cells for (c) TTF-1 (+++), (d) CK7 (little +), (e) CD56 (+++), and (f) Syn (+++).

Discussion

HLH is an excessive inflammatory reaction disease caused by uncontrolled proliferation of activated lymphocytes and histiocytes which secrete a large number of inflammatory cytokines, involving multiple tissues, organs, and systems. HLH can be divided into primary HLH (pHLH) and secondary HLH (sHLH). pHLH mainly includes familial HLH and immunodeficiency syndrome with HLH-related gene deficiency. Secondary HLH is associated with various underlying diseases, such as infections, tumors, rheumatologic, and some metabolic diseases. Malignant tumors, especially NK/T cell lymphoma, are the main causes of sHLH. M-HLH can occur in all age groups and is more common in adults. A large sample study showed that M-HLH accounted for 48% of adult HLH, of which 93.7% was caused by hematological malignancies.[8] Lymphoma was the most common type, followed by leukemia and Castleman's disease. M-HLH also occurred in a small number of patients with solid tumors, including embryonic cell tumors, thymoma,

and gastric cancer.[9] To our knowledge, this is the first HLH case reported with SCLC. In this study, although the lung pathology was not performed due to the rapidly progressive disease, the diagnosis of SCLC was suggested based on the biopsy pathology of bone marrow. Considering that lung malignancy which presents as GGOs was usually seen with bronchoalveolar carcinoma/adenocarcinoma rather than SCLC and the lack of lung pathology, extrapulmonary small-cell neoplasm with bone marrow involvement might be also a possibility.[10]

HLH is a rare and almost universally fatal disease in adults. Due to lack of recognition, under-diagnosis, or delayed diagnosis, M-HLH had a poor outcome in adults and the majority of patients died from infection as well as multi-organ failure within 2–4 weeks.[11] Therefore, it is very important to make a clear diagnosis and give early treatment to control the disease timely.

At present, HLH-2004 is the standard international criteria, which requires to meet five of eight criteria to make a diagnosis of sHLH.[6] Because of atypical early symptoms and rapid progress, HLH is easily misdiagnosed. Therefore, early identification of HLH and assessment of the underlying causes are critical to formulate optimal treatment strategies.

HLH-1994 regimen is widely used in the world. Hematopoietic stem cell transplantation plays a key role in improving the long-term survival rate of pHLH.[12] For M-HLH, combined chemotherapy should be given to the corresponding tumors and timely and effective supportive treatment is essential.[13] With the development of HLH research, some biological targeted agents such as alemtuzumab, interferon-γ, tumor necrosis factor-α, interleukin (IL)-6, IL-1β, and ruxolitinib have been assessed.[14] In this study, we are fully aware of the diagnosis of HLH. The patient was hospitalized with persistent high fever and cytopenia. Further examination revealed elevated ferritin and lung tumor markers. Combined with chest CT scan, the diagnosis of M-HLH was strongly suspected. Given the highly lethal disease of HLH, we treated the patient with dexamethasone quickly. At the same time, we performed the examination of NK cell activity, sCD25 as well as bone marrow biopsy to confirm HLH. As soon as the patient was confirmed with SCLC-related HLH, HLH-1994 regimen was used timely. Unfortunately, our patient succumbed within 2 weeks of presentation due to rapidly progressive disease. Therefore, our experience suggests SCLC-related HLH has a rapid progression and high mortality. It is critical to have early identification of HLH in patients with SCLC.

Conclusion

SCLC-related HLH is a very rare disease in adults. It progresses rapidly, resulting in high mortality. It is critical to have early identification of HLH in patients with SCLC. Given the extremely low incidence and limited knowledge, further studies are needed to enlarge the number of cases to investigate the clinical outcomes.

Acknowledgements

The authors would like to thank Dr Tamasin Evans (Western General Hospital, The University of Edinburgh, United Kingdom) for critical review of the manuscript.

Author contributions

Wenyan Xu analyzed data and wrote the paper. Zhenxing Guo analyzed data and reviewed the paper.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case was obtained from the First Hospital of Tsinghua University of Ethics Committee (approval number 2021-19).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the legal guardians of the patient for their anonymized information to be published in this article.

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