

Hemophagocytic lymphohistiocytosis presenting with annular erythema multiforme-like eruptions in a patient with angioimmunoblastic T cell lymphoma: A case report

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Abstract. Angioimmunoblastic T cell lymphoma (AITL)-associated hemophagocytic lymphohistiocytosis (HLH) rarely occurs with annular erythema multiforme-like rashes. The present case report describes a patient who was misdiagnosed with erythema multiforme at an early stage of the disease due to annular erythema multiforme-like eruptions. However, anti-histamine treatment was ineffective. The patient progressed rapidly with high fever, hepatosplenomegaly and pharyngitis. The number of copies of Epstein-Barr virus DNA continuously increased. Accompanied by the swelling of lymph nodes, the blood cell count decreased. Further bone-marrow examination and biopsy of the lymph nodes were conducted. The patient was eventually diagnosed with AITL-associated HLH, and treated with etoposide together with cyclophosphamide, doxorubicin, vincristine and prednisolone. The patient was successfully treated with several courses of chemotherapy. In view of the fact that AITL-associated HLH with annular erythema multiforme-like rashes is relatively rare worldwide and is associated with a high mortality rate, the data on previous cases were reviewed with the hope of providing clinical bases for early diagnosis and treatment of AITL-associated HLH.

Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare, life-threatening

hematological disorder (1). The occurrence rate of HLH in adults is not well known (1). Despite this, epidemiology data collected from tertiary medical centers has indicated that the incidence rate is 1 out of every 2,000 adults (2). However, reported incidence of HLH in children varies among different studies, which may reflect a different prevalence within various ethnic groups (3-5). For example, HLH has been reported to have an incidence of 0.12 per 100,000 children per year in Sweden, with a male to female ratio of 1:1 (4), whereas it was found to be 0.342 per 100,000 in Japan, with a male to female ratio of 0.8:1 (5). HLH is caused by the uncontrolled proliferation and activation of lymphocytes and macrophages (1). It is classified as either familial/primary or acquired/secondary HLH (1). Secondary HLH may be associated with malignancy, viral infection or autoimmune conditions (1). The current therapeutic strategy involves the use of immunosuppressive agents; however, current literature indicates that the mortality rate of patients with secondary HLH is 50-75% (6). Atypical rashes may present in certain patients with HLH; however, to the best of our knowledge annular erythema multiforme-like eruptions have not previously been reported in cases of HLH. Herein, the case of a patient who acquired infectious mononucleosis (IM) and angioimmunoblastic T cell lymphoma (AITL)-associated HLH at the same time as annular erythema multiforme-like eruptions is reported. There are three previously reported cases of AITL-associated HLH (7-9), but these were not accompanied by annular erythema multiforme-like eruptions. This was a rare case, and the patient was initially misdiagnosed with erythema multiforme and drug eruption. The patient was subsequently successfully diagnosed and treated.

Case report

A 53-year-old male patient, who was diagnosed with rectal carcinoma and had undergone chemotherapy following proctectomy for 1 year, suffered from cough and submandibular lymphadenopathy 9 days prior to admitting to the Dermatology Department of Beijing Chao-Yang Hospital (Beijing, China) with swelling and slight pain but no fever. The patient was diagnosed with acute tonsillitis by otolaryngologists and was initially treated with oral cefuroxime axetil tablets (dosage

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not documented). However, treatment was stopped following taking the medicine for 4 days due to the condition not entering remission. Annular erythema and maculopapular rashes or purpura were observed accompanied with pruritus on the patient's legs 7 days prior to admission to the ward (Fig. 1A). Similar lesions appeared on the patient's chest (Fig. 1B) and back (Fig. 1C) at 4 days prior to admission without fever. Complete blood cell count was normal, revealing a white blood cell count of $6.72 \times 10^9/\text{l}$ (normal, $3.5\text{--}9.5 \times 10^9/\text{l}$) (10), monocyte count of $0.48 \times 10^9/\text{l}$ (normal, $0.1\text{--}0.6 \times 10^9/\text{l}$) (10), hemoglobin concentration of 13.7 g/dl (normal, 13.0–17.5 g/dl) (10) and platelet count of $213.0 \times 10^9/\text{l}$ (normal, $125.0\text{--}350.0 \times 10^9/\text{l}$) (10). Initially, the patient was diagnosed with erythema multiforme and drug eruption. In primary care, he was treated with oral prednisolone, antihistamine and steroid ointment.

Consequently, the rashes did not disappear and fever developed on the third day with temperature fluctuating between 36.3 and 39.0°C in the ward. Physical examination detected superficial lymphadenopathy (size, <1x1 cm). Diffuse membranous tonsillitis appeared and spots of small hemorrhage also appeared on the hard and soft palates and the connection between the hard and soft palates (Fig. 1D). Blood cell count revealed that monocyte content increased when compared with levels at admission, with a white blood cell count of $8.35 \times 10^9/\text{l}$, monocyte count of $1.02 \times 10^9/\text{l}$, hemoglobin concentration of 13.0 g/dl and platelet count of $211.0 \times 10^9/\text{l}$. Notably, a population of medium-sized morphologically atypical lymphocytes in the blood accounted for 9% of all lymphocytes. The concentrations of liver enzymes were slightly increased compared with normal ranges; the concentration of alanine aminotransferase was 52 U/l (normal, 9–50 U/l) (11) and of aspartate aminotransferase was 30 U/l (normal, 15–40 U/l) (11). The level of triglyceride was normal. Antinuclear antibodies, anti-double-stranded DNA antibodies and rheumatoid factor were negative. The level of C-reactive protein was elevated (3.96 mg/dl; normal, 0–0.8 mg/dl) (12), and the erythrocyte sedimentation rate was increased (43 mm/h; normal, 2–15 mm/h) (12). Epstein-Barr virus (EBV) DNA was detected in peripheral blood at a high copy number ($8.42 \times 10^4/\text{l}$ copies IU/ml; normal, $<5.0 \times 10^2/\text{l}$ copies IU/ml) by quantitative polymerase chain reaction (measured in hospital's molecular genetics department) (13). A serological examination (measured in hospital's molecular genetics department) (14) indicated that EBV immunoglobulin (Ig)G was positive and EBV IgM was negative. Other serologic profiles, including of EBV viral capsid antigen and nuclear antigen, were not examined in hospital. The patient refused skin biopsy, and abdominal ultrasound indicated splenomegaly. As a result, the patient was diagnosed with IM and was treated with ganciclovir and prednisone.

After 8 days, the rashes on the patients' limbs and torso diminished slightly following treatment. However, body temperature increased repeatedly (maximum, 39.5°C for >7 days) and sweating was experienced during the night. Furthermore, the size of supraclavicular lymph nodes increased (>1x1 cm). Computed tomography scans confirmed hepatosplenomegaly and lymphadenopathy of multiple nodes in the abdominal, pelvic cavity, retroperitoneal and the inguinal regions. In addition, blood cell count as aforementioned, revealed that hemoglobin concentration and platelet count in the patient continued to decline progressively, with a hemoglobin concentration of

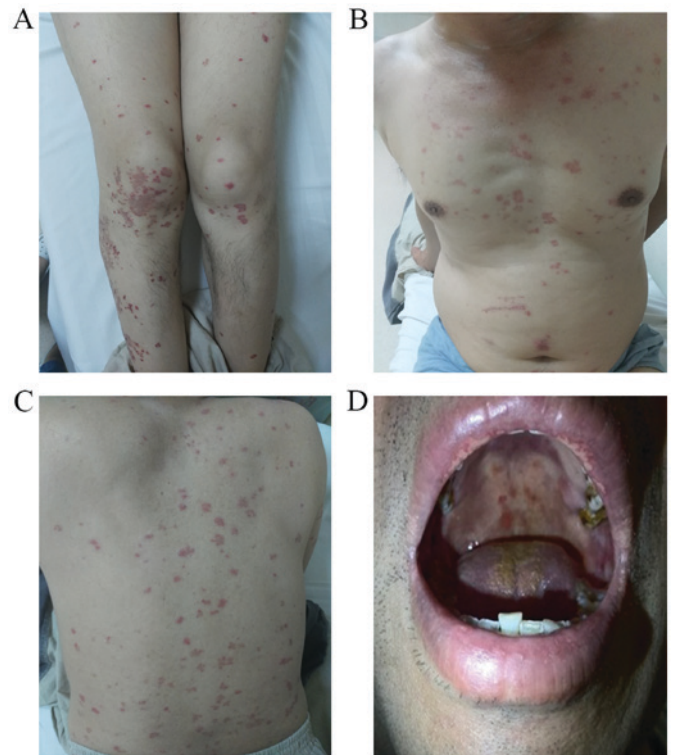


Figure 1. Clinical characteristics of the patient. Lesions were observed on the (A) legs, (B) chest and (C) back presented as red maculopapular or purpuric rash, or ecchymosis. (D) Bleeding spots also appeared on the upper jaw.

11.6 g/dl and a minimum platelet count of $37.0 \times 10^9/\text{l}$ with 10% atypical lymphocytes. Serum ferritin and lactate dehydrogenase levels were 785.80 ng/ml and 370 U/l, respectively. The level of EBV DNA increased to $6.0 \times 10^5/\text{l}$ copies IU/ml. The coagulation profile revealed prothrombin time of 3.4 sec (normal, 9.6–13.0 sec), activated partial thromboplastin time of 41.2 sec (normal, 21.0–34.0 sec) and fibrinogen of 240.8 mg/dl (normal, 170.0–400.0 mg/dl). A serological examination indicated the presence of polyclonal gammopathy with a value of 2,280 mg/dl for IgG (normal, 715–1,560 mg/dl), 677 mg/dl for IgM (normal, 82–453 mg/dl) and 1,550 mg/dl for IgA (normal, 46–304 mg/dl). The bone marrow examination indicated hemophagocytosis and abnormal lymphocytes. The level of soluble cluster of differentiation (CD)25 was increased ($>44,000$ pg/ml; normal $<6,400$ pg/ml; test result from Beijing Friendship Hospital, Beijing, China) (15), and natural killer (NK) cell activity was normal (25.38%; normal $\geq 15.11\%$; test result from Beijing Friendship Hospital, Beijing, China) (16). Therefore, there was a clear indication of HLH. The patient was subsequently treated with ganciclovir, dexamethasone and etoposide. At 1 day following chemotherapy, the platelet count increased to $63 \times 10^9/\text{l}$ and the patient exhibited a normal temperature.

Simultaneously, biopsies of the left cervical lymph node indicated the disappearance of normal structure, infiltration of eosinophil cells and small to medium-sized lymphoid cells in the extra membrane and vascular proliferation (Fig. 2A and B). The immunohistochemical staining of lymphoid infiltrates indicated diffuse positive staining for CD2, CD3, CD5, CD7 and CD10 as well as weak positive staining for CD20, paired-box domain 5 and telomerase B (17). The staining for CD21 suggested damage of follicular dendritic cells and a

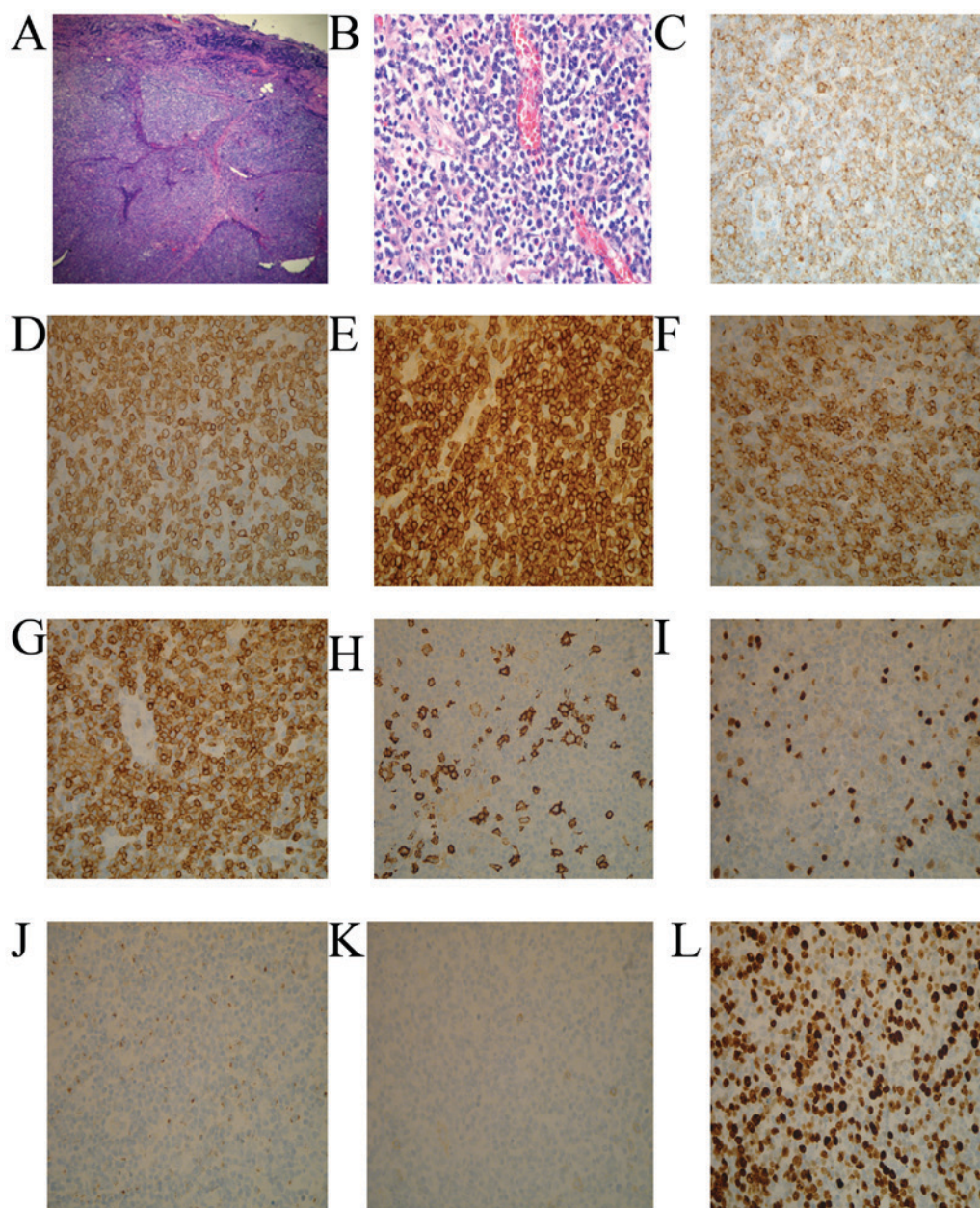


Figure 2. Histological and immunohistochemical staining findings of the patient. A biopsy sample taken from the left cervical lymph node revealed that normal structure had disappeared, and small to medium-sized atypical lymphoid cells had infiltrated the lymph node region. (A) H&E staining; original magnification, x10. (B) H&E staining; original magnification, x40. (C-G) On immunohistochemical staining, the lymphoid cells were diffusely positive for CD2, CD3, CD5, CD7 and CD10 (H&E staining; original magnification, x40). (H) CD20, (I) paired-box domain 5 and (J) telomerase B staining were weak positive (H&E staining; original magnification, x40). (K) CD21 staining suggested follicular dendritic cells net damage (H&E staining; original magnification, x40). (L) Proliferative index with Ki-67 stain was high (H&E staining; original magnification, x40). H&E, hematoxylin and eosin; CD, cluster of differentiation.

high expression of Ki-67 (Fig. 2C-L) (17). EBV-encoded RNA *in-situ* hybridization (EBER) revealed that the tumor cells were positive for EBV (18). Therefore, there was a clear indication of AITL. Consequently, the patient was treated with etoposide together with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP regimen). The patient was successfully treated with several courses of chemotherapy, and clinical manifestations improved. The rashes faded away completely. The patient was followed up once every 2 weeks for 3 months and he was deemed to be in good condition.

Test results, including EBV DNA qPCR, lymph node biopsies and EBER, were collected from professional clinical laboratory technicians and professional pathologists from

Beijing Chao-Yang Hospital (Beijing, China). To perform qPCR patient DNA was extracted. Blood was collected into EDTA-coated tubes and isolated manually using the QIAamp Blood Mini kit (Qiagen Inc., Valencia, CA). Quantitative PCR was then performed using a TaqMan PCR Core Reagent kit (PerkinElmer, Inc., Waltham, MA, USA). In this system, a dual-labeled fluorogenic hybridization probe was included. DNA samples were quantified for EBV DNA using a real-time qPCR system targeting the *Bam*HI-W fragment region of the EBV genome (19). The *Bam*HI-W system utilized the following primers: W-44 forward, 5'-CCCAACACTCCACCACACC-3' and reverse, W-119 5'-TCTTAGGAGCTGTCCGAGGG-3'. GAPDH was used

Table I. List of reported patients with angioimmunoblastic T cell lymphoma associated with Hemophagocytic lymphohistiocytosis, clinical manifestation, treatment, and outcomes.

Age, years/sex	Clinical manifestation	Therapy	Outcome	Reference
58/F	Fever, pharyngeal pain, lymphadenopathy, splenomegaly	CHOP, fludarabine, cyclosporine A, allogeneic peripheral blood stem cell transplantation	Successfully treated	7
57/M	Fever, neutropenia, thrombocytopenia, lymphadenopathy	Cyclophosphamide, prednisolone, etoposide, cicloporin	Succumbed to multiorgan failure	8
62/F	Fever, lymphadenopathy, hepatosplenomegaly, loss of weight	CHOP, mesna, ifosfamide, mitoxantrone, etoposide; allogeneic hematopoietic stem cell transplantation	Successfully treated	9

F, female; M, male; CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisolone.

as the internal reference gene (forward, 5'-GTCTTCACC ACCATGGAGAAGGCT-3' and reverse, 5'-CATGCCAGT GAGCTTCCCCTTCA-3'). The dual-labeled fluorescent probe W-67T [5'-(fluorescent reporter) CACACACTACAC ACACCCACCCGTCTC (TAMRA fluorescent dye)-3'; PerkinElmer, Inc.] (19). Primer/probe combinations were designed using Primer Express software (PerkinElmer, Inc.). Fluorescent probes were custom-synthesized by PerkinElmer, Inc. PCR primers were synthesized by Thermo Fisher Scientific, Inc. (Waltham, MA, USA). The thermocycling conditions were as follows: Initial denaturation for 10 min at 95°C; 40 cycles at 95°C for 15 sec, 56°C for 1 min and 72°C for 45 sec. Sequence data for the EBV genome were obtained from the GenBank Sequence Database (<https://www.ncbi.nlm.nih.gov/nucleotide/V01555>) (13). PCR assays were performed in triplicate. The following quantitative PCR detector systems were used: STF-Rotor-gene Q (Qiagen, Inc.), 7700 Sequence Detector (Apple, Inc., Cupertino, CA), and the sequence detection system software (version 1.7) was developed by PerkinElmer, Inc (13). Pathological biopsies were fixed at room temperature for 6 h using 10% formalin, dehydrated, embedded in paraffin, sectioned (thickness, 3–5 µm), de-waxed and stained with hematoxylin at room temperature for 5–15 min and eosin at room temperature for 2–3 min as previously described (17). Reagents were from OriGene Technologies, Inc. (Rockville, MD, USA). Like immunohistochemical staining, the protocols were as follows: De-waxing, antigen repair using Histostain™-SP kits (OriGene Technologies, Inc.) and antibody incubation. The antibodies utilized included: with CD2 (cat. no. UMAB86), CD3 (cat. no. UM570048), CD5 (cat. no. UM570009), CD7 (cat. no. TA506337), CD10 (cat. no. TA590055), CD20 (cat. no. UM800065), CD21 (cat. no. TA327627) and Ki-67 (TA801577) all diluted at 1:100. paired-box domain 5 (cat. no. TA801884) and telomerase B (cat. no. TA301588) were diluted at 1:50 (all antibodies were obtained from OriGene Technologies, Inc.) and hematoxylin staining as previously described (17). EBV-encoded RNA *in-situ* hybridization involved sample de-waxing, proteinase K digestion (25 µg/ml, 37°C for 10 min; Merck KGaA, Darmstadt, Germany). Oligonucleotide probes (5'-CTCCTC CCTAGCAAAACCCCTCAGGACGGCG-3' from OriGene

Technologies, Inc. were labeled using a Labeling kit (Boehringer Mannheim, S.A., Barcelona, Spain). Labeled probes were diluted to a concentration of 0.1 µg/ml in hybridisation medium (50% formamide, 5% dextran sulphate, 2x sodium citrate, sodium chloride (SSC); all provided by the EBER hybridization kit, OriGene Technologies, Inc.). Diluted probes were spotted onto tissue sections and a coverslip was placed on top. Diaminobenzidine tetrahydrochloride (as obtained from the EBER hybridization kit) was used as the chromogen (18). Hybridisation signals were detected using a three layer ABC-peroxidase technique (Vector Laboratories, Ltd., Peterborough, UK) (20).

Discussion

HLH is a rare and life-threatening disease, which is characterized by cytokine storms (1). This hyper-inflammatory reaction can cause damage to multiple organ systems (1). The causes of mortality in HLH include multiple organ dysfunction syndrome, massive hemorrhaging and infectious disease (21).

HLH can be divided into primary (genetic) and secondary (acquired) HLH. Gene mutations in perforin 1, Unc-13 Homolog D, syntaxin 11 and syntaxin binding protein 2 can result in damaged cytotoxic function of NK and cytotoxic T cells (1). Primary HLH often occurs in children (22). However, it has been demonstrated to also occur in adolescents and adults (22). Infection is a common cause of secondary HLH, particularly EBV infections (1). Of note, hormones and antiviral treatments are often effective against acute EBV infections (1). Secondary HLH, which is triggered by tumors, typically occurs in adults (~45% of cases) (23). AITL, a type of T-cell non-Hodgkin's lymphoma, is frequently accompanied by progressive systemic symptoms, including high fever, cytopenia, body weight loss and night sweats (24,25). AITL, unlike other T cell lymphomas, can be associated with a profound immune deficiency that is caused by chemotherapy or immunotherapy, which leads to the activation of EBV (26). In particular, EBV infections have been reported predominantly in patients with AITL (27). Zhou *et al* (28) previously reported that EBV infections, as a consequence of AITL, may be reactivated in the presence of immunodeficiency rather than contributing to the pathogenesis

of the disease itself (28). AITL-associated HLH has a poor prognosis due to continuous disease aggravation, which leads to an increased risk for opportunistic infections compared with EBV-associated HLH (29). The present case demonstrated that AITL was the cause for triggering HLH. Due to immune deficiency that was induced by rectal carcinoma chemotherapy, the EBV infection in the patient was activated. There are three previously reported cases of AITL-associated HLH (Table I) (7-9).

Skin manifestations occur in 24-40% cases of genetic HLH and 6-65% of cases in acquired HLH (28). Reported cutaneous findings have included erythematous rashes, macules, edema, panniculitis, morbilliform erythema, petechiae and purpura (30,31). The lesions in HLH are not characteristic; the most common cutaneous manifestations are panniculitis and purpura (32,33). Cutaneous manifestations that are associated with HLH are classified into three types. The manifestation may be specific to the underlying malignancy (cutaneous lymphoma or systemic disease), reflect the biological consequences of HLH (thrombopenic purpura or conjunctival jaundice) or can be a generalized, transient, nonpruritic, maculopapular rash (34). However, a case with AITL-associated HLH and annular erythema multiforme-like eruptions has not been previously reported, to the best of our knowledge.

The occurrence of AITL-associated HLH with annular erythema multiforme-like eruptions in a patient is highly rare worldwide, which led to the misdiagnosis of erythema multiforme. From this patient and the other 3 reported patients with AITL-associated HLH, it was observed that AITL-associated HLH occurred in people with an age of >50 years. CHOP and etoposide combined with allogeneic hematopoietic stem cell transplantation may be effective in the early stages of the disease.

In conclusion, this present case of AITL-associated HLH with annular erythema multiforme-like rashes provides novel understanding for clinical diagnosis of the disease. Without rapid diagnosis and early treatment, AITL-associated HLH may lead to short survival times.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LZ, CT and YH designed the present study and drafted the manuscript. YT, SP and LZ collected the clinical and imaging data. TW analyzed and interpreted the patient data regarding the hematological disease. CT and LZ were major contributors

in writing and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patient provided informed written consent for their participation.

Patient consent for publication

The patient provided informed written consent.

Competing interests

The authors declare that they have no competing interests.

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