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Contents

Thrice Monthly Volume 9 Number 30 October 26, 2021

REVIEW

- 8953 Endothelial progenitor cells and coronary artery disease: Current concepts and future research directions
Xiao ST, Kuang CY

MINIREVIEWS

- 8967 Regulation of bone metabolism mediated by β -adrenergic receptor and its clinical application
Zhong XP, Xia WF
- 8974 Tricuspid valve endocarditis: Cardiovascular imaging evaluation and management
Fava AM, Xu B

ORIGINAL ARTICLE

Case Control Study

- 8985 Novel application of multispectral refraction topography in the observation of myopic control effect by orthokeratology lens in adolescents
Ni NJ, Ma FY, Wu XM, Liu X, Zhang HY, Yu YF, Guo MC, Zhu SY

Retrospective Cohort Study

- 8999 Uncertainty in illness and coping styles: Moderating and mediating effects of resilience in stroke patients
Han ZT, Zhang HM, Wang YM, Zhu SS, Wang DY

Retrospective Study

- 9011 Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus
Zhang DY, Huang GR, Ku JW, Zhao XK, Song X, Xu RH, Han WL, Zhou FY, Wang R, Wei MX, Wang LD
- 9023 Preliminary establishment of a spinal stability scoring system for multiple myeloma
Yao XC, Shi XJ, Xu ZY, Tan J, Wei YZ, Qi L, Zhou ZH, Du XR
- 9038 Effect of intrauterine perfusion of granular leukocyte-colony stimulating factor on the outcome of frozen embryo transfer
Zhu YC, Sun YX, Shen XY, Jiang Y, Liu JY
- 9050 "An integrated system, three separated responsibilities", a new fever clinic management model, in prevention and control of novel coronavirus pneumonia
Shen J, He Q, Shen T, Wu ZQ, Tan MM, Chen YL, Weng Q, Nie LM, Zhang HF, Zheng B, Zhang J

Clinical Trials Study

- 9059** Single dose dexamethasone prophylaxis of postembolisation syndrome after chemoembolisation in hepatocellular carcinoma patient: A randomised, double-blind, placebo-controlled study
Sainamthip P, Kongphanich C, Prasongsook N, Chirapongsathorn S

Observational Study

- 9070** Serum calcium, albumin, globulin and matrix metalloproteinase-9 levels in acute cerebral infarction patients
Zhong TT, Wang G, Wang XQ, Kong WD, Li XY, Xue Q, Zou YA

SYSTEMATIC REVIEWS

- 9077** Neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers in the new era of radiotherapy: A review of literature
Delishaj D, Fumagalli IC, Ursino S, Cristaudo A, Colangelo F, Stefanelli A, Alghisi A, De Nobili G, D'Amico R, Cocchi A, Ardizzoia A, Soatti CP

META-ANALYSIS

- 9090** Clinical significance of breast cancer susceptibility gene 1 expression in resected non-small cell lung cancer: A meta-analysis
Gao Y, Luo XD, Yang XL, Tu D

CASE REPORT

- 9101** Particular tumor of the pancreas: A case report
Zhu MH, Nie CF
- 9108** Dynamic changes in the radiologic manifestation of a recurrent checkpoint inhibitor related pneumonitis in a non-small cell lung cancer patient: A case report
Tan PX, Huang W, Liu PP, Pan Y, Cui YH
- 9114** Spontaneous rupture of a mucinous cystic neoplasm of the liver resulting in a huge biloma in a pregnant woman: A case report
Kośnik A, Stadnik A, Szczepankiewicz B, Patkowski W, Wójcicki M
- 9122** Diagnosis and laparoscopic excision of accessory cavitated uterine mass in a young woman: A case report
Hu YL, Wang A, Chen J
- 9129** Unusual cervical foreign body - a neglected thermometer for 5 years: A case report
Yang L, Li W
- 9134** Long-term survival of a patient with pancreatic cancer and lung metastasis: A case report and review of literature
Yang WW, Yang L, Lu HZ, Sun YK
- 9144** Synchronous diagnosis and treatment of acute myeloid leukemia and chronic lymphocytic leukemia: Two case reports
Chen RR, Zhu LX, Wang LL, Li XY, Sun JN, Xie MX, Zhu JJ, Zhou D, Li JH, Huang X, Xie WZ, Ye XJ

- 9151** Conversion therapy of hepatic artery ligation combined with transcatheter arterial chemoembolization for treating liver cancer: A case report
Feng GY, Cheng Y, Xiong X, Shi ZR
- 9159** Hemophagocytic lymphohistiocytosis secondary to composite lymphoma: Two case reports
Shen J, Wang JS, Xie JL, Nong L, Chen JN, Wang Z
- 9168** Fatal visceral disseminated varicella-zoster virus infection in a renal transplant recipient: A case report
Wang D, Wang JQ, Tao XG
- 9174** Choriocarcinoma misdiagnosed as cerebral hemangioma: A case report
Huang HQ, Gong FM, Yin RT, Lin XJ
- 9182** Rapid progression of colonic mucinous adenocarcinoma with immunosuppressive condition: A case report and review of literature
Koseki Y, Kamimura K, Tanaka Y, Ohkoshi-Yamada M, Zhou Q, Matsumoto Y, Mizusawa T, Sato H, Sakamaki A, Umezu H, Yokoyama J, Terai S
- 9192** Temporary pacemaker protected transjugular intrahepatic portosystemic shunt in a patient with acute variceal bleeding and bradyarrhythmia: A case report
Yao X, Li SH, Fu LR, Tang SH, Qin JP
- 9198** Recurrent pyogenic liver abscess after pancreatoduodenectomy caused by common hepatic artery injury: A case report
Xie F, Wang J, Yang Q
- 9205** Transient ventricular arrhythmia as a rare cause of dizziness during exercise: A case report
Gao LL, Wu CH
- 9211** Successful management of infected right iliac pseudoaneurysm caused by penetration of migrated inferior vena cava filter: A case report
Weng CX, Wang SM, Wang TH, Zhao JC, Yuan D
- 9218** Anterior abdominal abscess - a rare manifestation of severe acute pancreatitis: A case report
Jia YC, Ding YX, Mei WT, Xue ZG, Zheng Z, Qu YX, Li J, Cao F, Li F
- 9228** Monteggia type-I equivalent fracture in a fourteen-month-old child: A case report
Li ML, Zhou WZ, Li LY, Li QW
- 9236** Diagnosis and treatment of primary pulmonary enteric adenocarcinoma: Report of Six cases
Tu LF, Sheng LY, Zhou JY, Wang XF, Wang YH, Shen Q, Shen YH
- 9244** Choroidal metastatic mucinous abscess caused by *Pseudomonas aeruginosa*: A case report
Li Z, Gao W, Tian YM, Xiao Y
- 9255** Diagnosis and treatment of acute graft-versus-host disease after liver transplantation: Report of six cases
Tian M, Lyu Y, Wang B, Liu C, Yu L, Shi JH, Liu XM, Zhang XG, Guo K, Li Y, Hu LS

- 9269** Hepatic portal venous gas without definite clinical manifestations of necrotizing enterocolitis in a 3-day-old full-term neonate: A case report
Yuan K, Chen QQ, Zhu YL, Luo F
- 9276** Emergence of lesions outside of the basal ganglia and irreversible damage to the basal ganglia with severe β -ketothiolase deficiency: A case report
Guo J, Ren D, Guo ZJ, Yu J, Liu F, Zhao RX, Wang Y
- 9285** Skeletal muscle metastasis with bone metaplasia from colon cancer: A case report and review of the literature
Guo Y, Wang S, Zhao ZY, Li JN, Shang A, Li DL, Wang M
- 9295** Biopsy-confirmed fenofibrate-induced severe jaundice: A case report
Lee HY, Lee AR, Yoo JJ, Chin S, Kim SG, Kim YS
- 9302** Missense mutation in *DYNC1H1* gene caused psychomotor developmental delay and muscle weakness: A case report
Ding FJ, Lyu GZ, Zhang VW, Jin H
- 9310** Isolated hepatic tuberculosis associated with portal vein thrombosis and hepatitis B virus coinfection: A case report and review of the literature
Zheng SM, Lin N, Tang SH, Yang JY, Wang HQ, Luo SL, Zhang Y, Mu D

ABOUT COVER

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Hemophagocytic lymphohistiocytosis secondary to composite lymphoma: Two case reports

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Abstract

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening disease caused by inherited pathogenic mutations and acquired dysregulations of the immune system. Composite lymphoma is defined as two or more morphologically and immunophenotypically distinct lymphomas that occur in a single patient. Here, we report two cases of HLH secondary to composite lymphoma with mixed lineage features of T- and B-cell marker expression both in the bone marrow and lymph nodes in adult patients.

CASE SUMMARY

Two patients were diagnosed with HLH based on the occurrence of fever, pancytopenia, lymphadenopathy, splenomegaly, hemophagocytosis and hyperferritinemia. Immunohistochemical staining of the axillary lymph node and bone marrow in case 1 showed typical features of combined B-cell and T-cell lymphoma. In addition, a lymph node gene study revealed rearrangement of the T-cell receptor chain and the immunoglobulin gene. Morphology and immunohistochemistry studies of a lymph node biopsy in case 2 showed typical features of T cell lymphoma, but immunophenotyping by flow cytometry analysis of bone marrow aspirate showed B cell lymphoma involvement. The patients were treated with high-dose methylprednisolone combined with etoposide to control aggressive HLH progression. The patients also received immunochemotherapy with the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen immediately after diagnosis. Both patients presented with

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highly aggressive lymphoma, and died of severe infection or uncontrolled HLH.

CONCLUSION

We present two rare cases with overwhelming hemophagocytosis along with composite T- and B-cell lymphoma, which posed a diagnostic dilemma. HLH caused by composite lymphoma was characterized by poor clinical outcomes.

Key Words: Hemophagocytosis; Hemophagocytic lymphohistiocytosis; Composite lymphoma; T-cell; B-cell; Case report

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Core Tip: Lymphoma-associated hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening clinical disorder. In particular, composite lymphoma with mixed lineage features of T- and B-cell marker expression is extremely rare. We report two cases of HLH secondary to bi-lineage composite lymphoma with lymphocyte infiltrations both in the bone marrow and lymph nodes in adult patients. Case 1 showed typical features of combined B-cell and T-cell lymphoma in axillary lymph node and bone marrow biopsies. Case 2 showed typical features of T cell lymphoma in lymph node biopsy, and B cell lymphoma in bone marrow biopsy. Both patients highlight the diagnostic dilemma, therapeutic challenges and poor prognosis of HLH secondary to composite lymphoma.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening clinical disorder characterized by uncontrolled hyper-activation of inflammatory responses due to inherited pathogenic mutations and acquired dysregulations of the immune system[1,2]. HLH can be classified into two subtypes: Primary and secondary. Secondary HLH can be triggered by underlying infection, autoimmune disease, or malignancy[3]. Malignancy-associated HLH is more common in adults in certain hematologic malignancies compared to children, and the actual incidence of this disease is unclear[1]. Lymphoma-associated HLH is comparatively common in T-cell or natural killer (NK)-cell lymphoma[4].

The term “composite lymphoma” (CL) was initially introduced as “the occurrence of more than one histological pattern of lymphoma in a single patient”[5]. According to the review by Kim, CL accounts for 1%-4.7% of non-Hodgkin lymphoma (NHL), and can be associated with various combinations of T- and B-cell NHLs and Hodgkin lymphoma (HL)[5]. However, CL presenting with simultaneous occurrence of both B-cell and T-cell lymphomas is extremely rare[6]. Furthermore, only one case report of HLH secondary to CL of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and small B-cell lymphoma/chronic lymphocytic leukemia (SLL/CLL) has been described[7]. It is worth mentioning that the presence of CL in this patient was confirmed at autopsy.

Here, we report two adult cases of HLH secondary to composite T- and B-cell lymphoma in both lymph nodes and bone marrow.

CASE PRESENTATION

Chief complaints

Case 1: A 50-year-old woman presented at our institution with lymphadenopathy in

her bilateral armpits and groins and intermittent fever for 3 mo.

Case 2: A 65-year-old man was admitted to our hospital due to intermittent fever for 4 mo.

History of present illness

Case 1: Approximately 3 mo previously, this patient found an axillary lymph node mass and developed fever, she did not attend a hospital for diagnosis in April 2013. One month before, she was admitted to a local hospital due to fever, axillary and inguinal lymph node enlargement. Fever was not effectively improved with cephalosporin. She lost 10 kg in the previous 3 mo.

Case 2: Approximately 4 mo previously, this patient was admitted to a local hospital due to fever and respiratory infection in February 2013. He was treated with levofloxacin and carbapenem, and the infection was controlled. Three months before admission, the patient was treated at other hospital due to fever, abdominal pain and diarrhea. Positive cytomegalovirus (CMV)-DNA [3.60×10^6 copies/mL (2.50×10^2 copies/mL)] in peripheral blood confirmed CMV infection. After 1-wk of antiviral treatment with ganciclovir, the patient developed pancytopenia and reexamination of CMV-DNA was negative. One month prior to admission, he underwent fine needle aspiration biopsy of his cervical mass. Subsequent histopathological examinations revealed the suspicion of T cell lymphoma. Following his admission to our department in June 2013, the patient had intermittent fever, pancytopenia and splenomegaly. No significant weight loss was reported over the previous few months.

History of past illness

Case 1: The patient had the history of colon cancer and received six cycles of chemotherapy with tegafur and oxaliplatin 5 years ago.

Case 2: The patient's history of past illness was remarkable for pruritus and increased eosinophilia for 5 years.

Personal and family history

Both patients had no previous or family history of similar illnesses.

Physical examination

Case 1: After admission, the patient's temperature was 39.0°C, heart rate was 120 bpm, respiratory rate was 20 breaths/min, and blood pressure was 110/70 mmHg. Physical examination revealed enlargement of multiple superficial lymph nodes and splenomegaly. Based on an abdominal ultrasound image, the long diameter of the spleen was 21.8 cm.

Case 2: The patient's temperature was 36.0°C, heart rate was 72 bpm, respiratory rate was 18 breaths/min, and blood pressure was 110/75 mmHg. Physical examination revealed splenomegaly and superficial lymphadenopathy was not palpable.

Laboratory examinations

Case 1: Complete blood count revealed pancytopenia (white blood cells 1.4×10^9 /L; hemoglobin 5.8 g/dL; and platelets 18×10^9 /L), elevated levels of liver enzymes indicating possible liver injury, and an increased lactate dehydrogenase (LDH) level [522 IU/L (120-250 IU/L)] indicating the tumor load. Prothrombin time (PT) was 17.7 s (11-15 s), activated partial thromboplastin time (APTT) was normal and fibrinogen (FBG) level was 1.29 g/L (2-4 g/L). Increased ferritin level was 4760 ng/mL (11-306 ng/mL), and increased IL-2 receptor (SCD25) level was more than 44000 pg/mL (< 6500 pg/mL). A bone marrow biopsy revealed the occurrence of hemophagocytosis and lymphomatous infiltration (Figure 1A and B), along with atypical small or medium size neoplastic cell diffuse involvement with focal large irregular lymphocyte infiltration (Figure 1C). Immunohistochemical (IHC) analysis of bone marrow samples exhibited positive staining for large neoplastic cell markers CD20, PAX5, CD30, and granzyme B, and small neoplastic cells expressing CD2, CD3, and CD7 markers, and non-immunoreactivity for CD56, CD10 and CD21 expression (Figure 1D and E). *In situ* hybridization for Epstein-Barr virus (EBV) encoded nuclear RNA (EBER) in bone marrow biopsy was positive. The diagnosis was considered to be diffuse large B cell lymphoma (DLBCL) involving bone marrow, EBV infection, and suspected T-cell lymphoma involvement. Cytogenetic study of the bone marrow showed a normal karyotype.

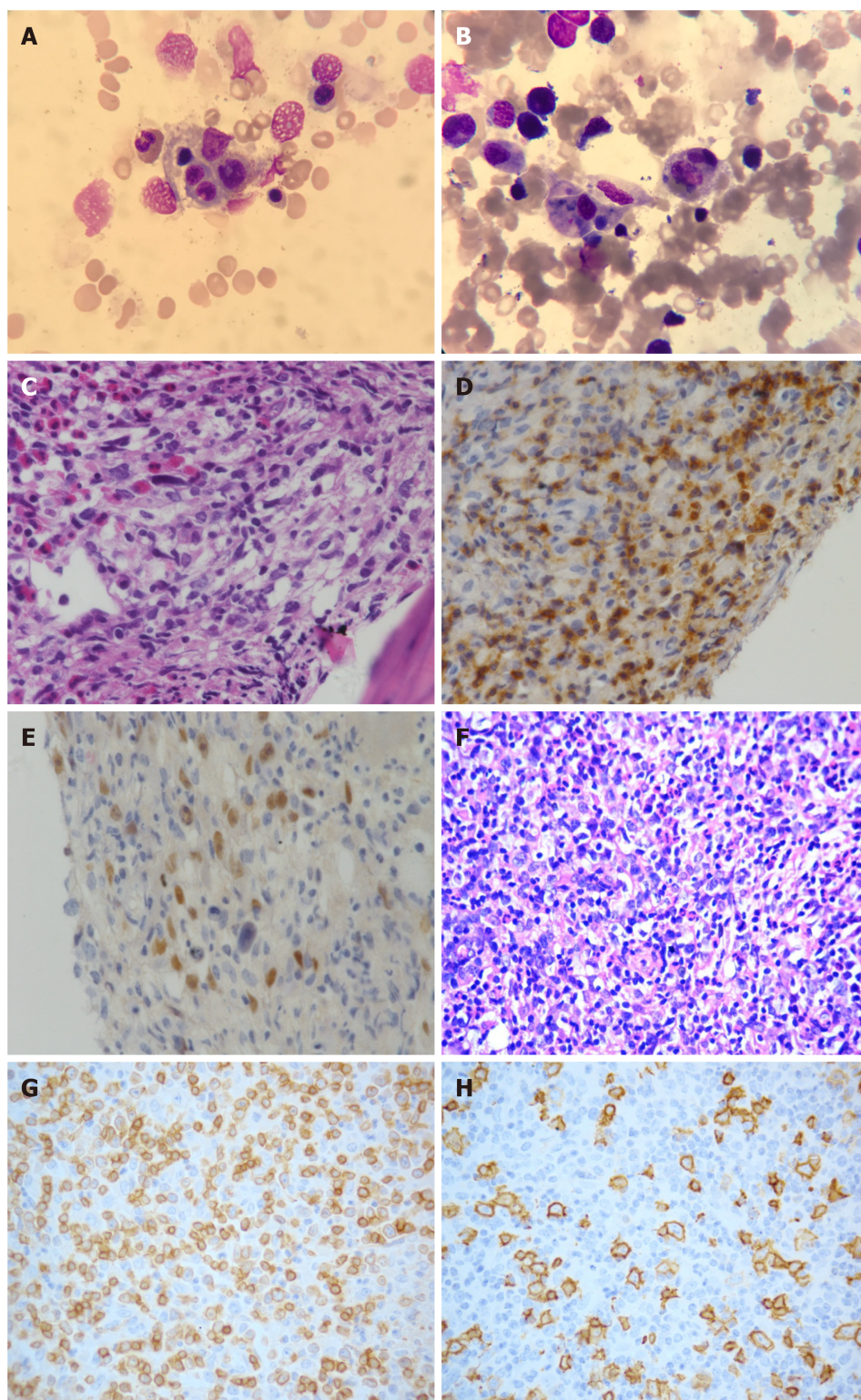


Figure 1 Morphology of bone marrow aspirate smear and biopsy in Case 1. A and B: Hemophagocytosis (A) and tumor cells (B) (Wright's stain, $\times 1000$); C: Diffuse small to medium-sized lymphocytes admixed scattered large atypical cells (hematoxylin-eosin stain, $\times 400$); D and E: The tumor cells were positive for CD3 (D) and PAX-5 (E) (immunohistochemistry, IHC $\times 400$); F: Lymph node biopsy sections showed a marked nodular aggregate of medium-sized lymphocytes with scattered large lymphocytes (hematoxylin-eosin stain, $\times 400$); G and H: The tumor cells in lymph nodes were positive for CD3 (G) and CD20 (H) (IHC $\times 400$).

Histopathological examination of the left axillary lymph node biopsy sample revealed invasion of atypical lymphocytes, indicating the occurrence of lymphoma (Figure 1F). IHC staining of tumor cells showed positive expression of CD2, CD3, CD5, CD7, CD20, CXCL-13, and BCL6 markers, and negative results for CD10 and CD21 markers (Figure 1G and H). Furthermore, Ki-67 showed a proliferation index of over 50%. We then performed a T-cell receptor (TCR) gene rearrangement study of the lymph node, using a previously published protocol[8] to assess the clinical outcome

and survival probability of the patient. Both clonal immunoglobulin heavy chain (IgH) gene and TCR γ chain rearrangements were detected in the same specimen by polymerase chain reaction (PCR) (Figure 2).

Case 2: Laboratory investigations of his blood sample revealed pancytopenia (white blood cells $2.0 \times 10^9/L$; hemoglobin 9.6 g/dL; and platelets $37 \times 10^9/L$). Further investigations of liver functions showed an increased level of LDH [389 IU/L (120-250 IU/L)], decreased albumin level [23.9 g/L (40-55 g/L)], an increased ferritin level [980 ng/mL (11-306 ng/mL)], and decreased FBG level [1.49 g/L (2-4 g/L)], suggesting liver dysfunction. Further, investigation revealed a high level of soluble CD25 [> 44000 pg/mL (< 6500 pg/mL)], and reduced NK cell activity [13.85% (31%-41%)].

A bone marrow aspirate smear showed 2% of scattered hemophagocytosis (Figure 3A) and medium-sized atypical cells comprising 45% of the total cell population (Figure 3B). These atypical cells showed positive expression of CD19, CD20, CD79b and lambda light chain markers but were negative for CD5, CD23, CD10, CD103, and CD25 markers as measured by flow cytometry. Cytogenetic analysis of bone marrow revealed an abnormal karyotype of 47, XY, + 5 [22]. Furthermore, the bone marrow biopsy revealed diffuse infiltration of medium-sized atypical lymphocytes (Figure 3C) with positive staining for PAX5 (Figure 3D), BCL6, CD20, lambda light chain, and negative for EBER. Similarly, Ki-67 scoring was more than 50%, indicating high cell proliferation. Based on the above-mentioned bone marrow histopathological features, a diagnosis of DLBCL was made. However, the immunophenotype of the left inguinal lymph node biopsy was not consistent with the diagnosis of DLBCL. The atypical lymphocytes were positive for CD3 expression and negative for CD 20, CD79a, CD30, and CD56 markers. Granzyme B and TIA-1 (T-cell intracellular antigen) staining was positive, and *in situ* hybridization for EBER was negative (Figure 3E-H). Pathological diagnosis of the lymph node was PTCL-NOS.

Imaging examinations

Case 1: Enhanced computed tomography (CT) imaging revealed multiple cervical, axillary, mediastinal, retroperitoneal, pelvic and inguinal lymphadenopathy as well as splenomegaly. There were many low-density lesions in the spleen and spleen infarction.

Case 2: Positron emission tomography-CT scanning revealed that the spleen was enlarged and ^{18}F -fluorodeoxyglucose uptake was normal. Hypermetabolic lesions were also detected in the bone marrow, bilateral inguinal and bilateral lung hilar lymphadenopathy (Figure 4).

FINAL DIAGNOSIS

Case 1

The patient was diagnosed with secondary HLH, PTCL-NOS with DLBCL stage IV with B symptoms.

Case 2

The patient was diagnosed with HLH. HLH was secondary to stage IV composite PTCL-NOS and DLBCL lymphoma with B symptoms.

TREATMENT

Case 1

The patient was treated with a high dose of methylprednisolone (3 mg/kg) for 3 d and etoposide (100 mg/m²) one dose to control HLH. Three days later, the patient received combination chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Case 2

To control HLH, high dose methylprednisolone (5 mg/kg for 3 d, tapering over 2 wk), and etoposide (100 mg/m²) weekly for 2 wk were administered. The patient had recurrent fever and diarrhea, and he received a cycle of chemotherapy with R-CHOP.

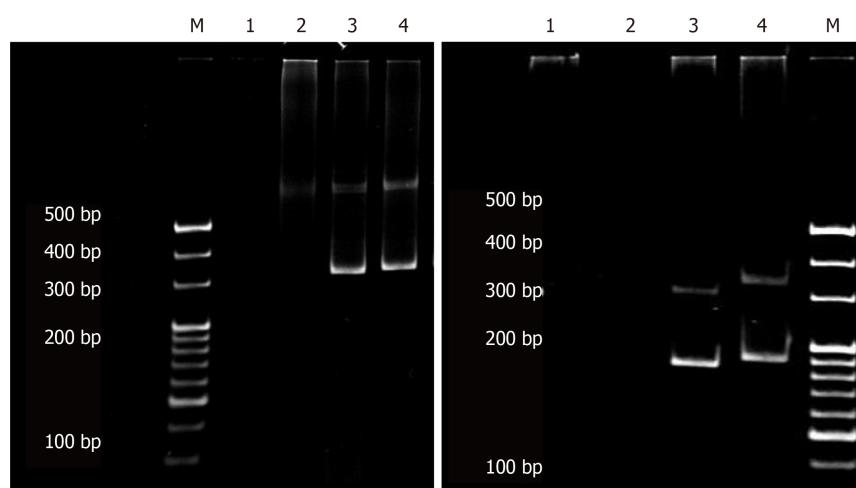


Figure 2 Monoclonal patterns of T-cell receptor and immunoglobulin H rearrangements detection in Case 1. DNA was extracted from the patient's lymph node samples and amplified by polymerase chain reaction with primers for the framework 2 portion of the immunoglobulin VH region (left) and the T-cell receptor (TCR) γ chain (right). M: Marker; 1: Water; 2: Negative control; 3: Positive control; 4: Sample.

OUTCOME AND FOLLOW-UP

Case 1

After the first cycle of R-CHOP the patient presented with continued progression of lymphoma and eventually died of lymphoma 1 mo after diagnosis.

Case 2

After the first cycle of R-CHOP the patient died due to severe pneumonia as he was diagnosed with HLH for 2 mo.

DISCUSSION

To the best of our knowledge, this is the first report of the diagnostic dilemma in detecting underlying lymphoma in patients, which could complicate therapeutic decisions. HLH with CL is characterized by poor clinical outcomes. In the present study, we report an uncommon and difficult-to-diagnosis clinical scenario of CL of PTCL-NOS combined with DLBCL. Both patients presented with HLH, which is an aggressive and potentially fatal immune disease. CLs with variable combinations have been reported, however, HLH with CL is rare with only one case reported so far[7,9-11].

Clinically, HLH is characterized by excessive immune activation and cytokine release (cytokine storm) stimulating bone marrow macrophages to engulf hematopoietic cells, a pathological condition known as hemophagocytosis[12]. When HLH develops in the secondary setting of malignancy, it is usually found to be associated with NK/T-cell lymphoma, which is a relatively severe trigger of HLH. Currently, HLH-94 or HLH-04 guidelines suggest standard therapeutic strategies for treating HLH[13]. If HLH is secondary to CL with PTCL-NOS combined with DLBCL that would be difficult to control. In these two patients, we controlled HLH with high doses of methylprednisolone in combination with etoposide. When CL diagnosis was confirmed we treated the patients with R-CHOP, but the treatment response was poor. HLH with composite T- and B-cell lymphoma is aggressive, and the management is challenging. This makes treatment decisions more complicated, as the general therapeutic strategy is against both disease components. Traditional first-line treatment was not effective in these high-risk patients. Important advances have been made in lymphoma and the Bispecific antibodies (BsAbs) (Anti-CD19 -CD3) and immune checkpoint inhibitors should be considered as future treatments[14].

There are three possible reasons to explain the poor outcome of these two patients. First, both patients had intermittent fever for 3 mo before they were admitted to our hospital. It took time to clarify the diagnosis leading to exacerbation of HLH. Second, HLH in adults is life-threatening, and CL with bone marrow involvement may also be associated with a poor prognosis. Third, HLH in both patients highlighted the

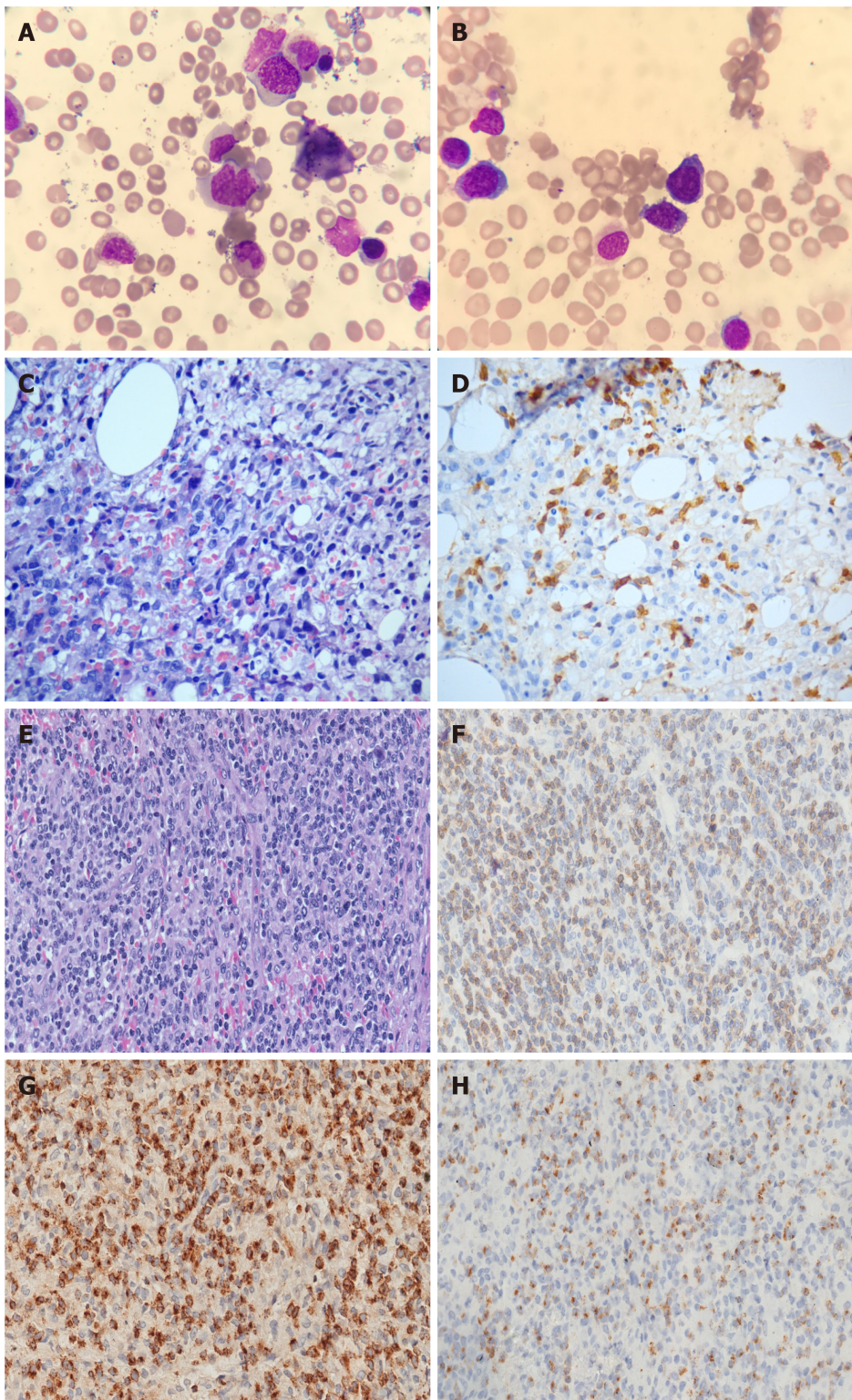


Figure 3 Morphology of bone marrow aspirate smear and biopsy in Case 2. A and B: Hemophagocytosis (A) and tumor cells (B) (Wright's stain, $\times 1000$); C: Diffuse medium-sized atypical lymphocytes infiltrated with the effacement of normal architecture (hematoxylin-eosin stain, $\times 400$); D: The tumor cells were positive for PAX-5 (immunohistochemistry, IHC $\times 400$); E: Lymph node biopsy sections showed that nodular tissue architecture was effaced by small- to intermediate-sized lymphocytes (hematoxylin-eosin stain, $\times 400$); F-H: The tumor cells in lymph nodes were positive for CD3 (F), TIA-1 (G) and granzyme B (H) (IHC $\times 400$).

importance of immune dysregulation which was triggered by viral infection. EBER was positive in the case 1 and CMV-DNA was positive in case 2, which was associated with an immunosuppressive microenvironment.

In these patients, it was difficult for the hematopathologist to make the diagnosis when combinations of variable numbers of histocytes, B cells and T cells were present in the same tissue. The diagnosis of CL is quite challenging and is often neglected without comprehensive clonal tests. The incidence of CL has reportedly increased with



Figure 4 Positron emission tomography-computed tomography scanning in Case 2. The maximum intensity projection of ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography revealed that the spleen was enlarged and ^{18}F -fluorodeoxyglucose uptake was normal. Hypermetabolic lesions were detected in bone marrow, bilateral inguinal and bilateral lung hilar lymphadenopathy.

the development of molecular genetics-based screening methods. The clinicopathological characteristics of CL have been well reviewed[5]. CLs include combinations of HL and NHL or two distinct types of NHL; however, composite B-cell and T-cell lymphoma have rarely been reported. The exact etiology and mechanisms of CL are unknown. There are several mechanisms to explain the simultaneous occurrence of the two different clones. The involvement of both genetic predisposition and environmental risk factors could be the major explanation for the development of CL in two unrelated precursors (B-cell and T-cell lymphoma). Bi-directional differentiation of pluripotent cells may be a possible reason for the two lineages. An EBV-driven PTCL with uncontrolled expansion of B-cell clones has been reported[15].

CONCLUSION

In conclusion, these two case reports presented unique findings in that rare HLH secondary to bi-lineage CL with lymphocyte infiltrations in both the bone marrow and lymph nodes were observed. EBV or CMV infection also reflected immune dysfunction. We hypothesize that the presence of immune dysregulation was associated with CL in these two cases.

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