Special Issue: Haematology

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(2) 1–6

DOI: 10.1177/0300060519874144
journals.sagepub.com/home/imr
SAGE

Haemophagocytic syndrome triggered by acute lymphoblastic leukaemia with t(9;22)(p24; q11.2)

Huiling Chen[1], Pengyun Zeng[1] and Dekui Zhang[2]

Abstract

Haemophagocytic syndrome (HPS) is a rare and potentially life-threatening condition that requires early diagnosis and prompt combined treatment. This case report describes a male patient with HPS, presenting as acute liver failure, that underwent a thorough evaluation for the cause of his symptoms. A final diagnosis of acute lymphoblastic leukaemia was established more than 2 months after the first presenting symptom appeared. Furthermore, the patient had an unusual chromosomal abnormality with a t(9; 22)(p24; q11.2) translocation, but the reciprocal janus kinase 2-breakpoint cluster region (JAK2-BCR) and BCR-JAK2 fusion transcripts were not be amplified.

Keywords

Haemophagocytic syndrome, acute liver failure, acute lymphoblastic leukaemia, t(9;22)(p24, q11.2)

Date received: 6 December 2018; accepted: 14 August 2019

Introduction

Liver injury is a common manifestation in haemophagocytic syndrome (HPS), however, HPS presenting as acute liver failure (ALF) has rarely been reported in adults.[1,2] Most cases of HPS in adults are secondary to infection, malignancy or rheumatological disorders, with a median survival of less than

[1]Department of Haematology, Lanzhou University Second Hospital, Lanzhou, Gansu Province, China
[2]Department of Gastroenterology, Lanzhou University Second Hospital, Lanzhou, Gansu Province, China

Corresponding author:
Dekui Zhang, Department of Gastroenterology, Lanzhou University Second Hospital, 82 Cuiyingmen Street, Chengguan District, Lanzhou, Gansu Province, 730030, China.
Email: sczdk1972@163.com

2 months after diagnosis,[3] and thus investigation of the underlying disease is necessary. Several malignancies are associated with HPS, the most common being lymphomas, acute leukaemia and multiple myeloma.[4] This current case report describes a unique case of HPS triggered by acute lymphoblastic leukaemia (ALL) with a rare chromosomal translocation.

Case report

In July 2018, a 45-year-old male patient was admitted the Department of Haematology, Lanzhou University Second Hospital, Lanzhou, Gansu Province, China for further evaluation of acute hepatic failure of unknown origin and hepatosplenomegaly. The patient was treated for acute hepatic failure for 1 month in another hospital, until jaundice, joint pain and pancytopenia developed. There was no history of recent acute infection or rash, no history of traveling, pet exposure and past medical history. Furthermore, the family history was negative for blood disorders and cancer, and there was no consanguinity in his family. Physical examination was notable for jaundice and hepatosplenomegaly, no lymphadenopathy, no spider telangiectasia and no palmar erythema were noted. In addition, serology for hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus were negative, and no leukaemia cells were found in the two bone marrow smears prior to referral. The clinical and laboratory tests implemented in the other hospital and in our hospital are shown in Table 1.

To determine whether it was HPS and to find out the cause, further examinations were undertaken. Natural killer cell activity was 11.31% (normal value: $\geq$15.11%) and sCD25 was 7441 pg/ml (normal value: $<$6400 pg/ml), which were accompanied by fever, hepatosplenomegaly, pancytopenia, hypofibrinogenaemia, hypertriglyceridaemia and hyperferritinaemia, which confirmed the diagnosis of HPS. Bone marrow aspirate and biopsy showed no haemophagocytosis, but hypercellularity with 87% lymphoblasts. Immunophenotyping showed the blasts were positive for CD10, CD19, CD20, HLA-DR and TdT, consistent with B-cell ALL. In addition, because of the high level of anti-nuclear antibody (ANA:1:320) detected in another hospital, a labial gland biopsy was performed to determine whether the patient had Sjogren's syndrome. Histopathological examination combined with immunohistochemical staining also confirmed B-cell-derived lymphoma or leukaemia: positive for CD20, CD10, CD79a and the Ki-67 proliferation index was 80%. The findings suggested that HPS was associated with ALL. Cytogenetic analysis showed t(9;22)(p24; q11.2) translocation in nine of 11 metaphases (Figure 1), which has only been reported in a few cases.[5,6] However, neither the janus kinase 2-breakpoint cluster region (JAK2-BCR) fusion transcript nor the BCR-JAK2 fusion transcript was detected.

The patient was treated according to the Oncology Protocol of China (2016) for adults, which included induction chemotherapy with 10 mg dexamethasone intravenous (i.v.) (days 1–28), 1200 mg cyclophosphamide i.v. (day 1 and day 15), 15 mg idarubicin i.v. (days 1–3), 2 mg vincristine i.v. (day 1, day 8, day 15, day 22) and 2500 IU PEG-asparaginase intramuscular (day 3); and intrathecal 15 mg methotrexate, 35 mg cytarabine and 5 mg dexamethasone (day 1, day 15). A bone marrow aspirate on day 15 of induction showed remission of ALL with 2% blasts as well as a low level of minimal residual disease by flow cytometry (0.18%). Clinical and laboratory signs of HPS transiently improved. The laboratory tests after chemotherapy are also shown in Table 1. Unfortunately, pancytopenia developed on

Table 1. Clinical and biochemical characteristics of a 45-year-old male patient that was admitted for further evaluation of acute hepatic failure of unknown origin and hepatosplenomegaly with data collected at three time-points.

Clinical characteristics	In another hospital 17 July 2018	In our hospital 24 August 2018	After chemotherapy 9 October 2018
Presentation			
Fever	NO	YES	YES
Jaundice	YES	YES	NO
Splenomegaly	YES	YES	YES
Laboratory tests			
WBC, $\times 10^9$/l	5.31	0.35	0.6
HGB, g/l	139	101	64
PLT, $\times 10^9$/l	23	10	28
ALT, U/l	1024	506	59
AST, U/l	823	518	46
TBIL, μmol/l	430.5	230	21.7
DBIL, μmol/l	348	148.6	18.7
ALB, g/l	34.6	33.0	33.7
LDH, U/l	910	564	289
CREA, μmol/l	118	111	206.4
BUN, μmol/l	12.3	11.87	23.96
TG, mmol/l	3.02	1.85	1.32
PT, s	13.5	11.7	11.5
APTT, s	41.0	35.5	28.2
INR	0.99	0.78	1.02
FIB, g/l	1.5	1.2	1.35
Ferritin, μg/l	28.86	1689	524
Bone marrow examination			
Primary cells, %	0%	87%	2%
Cytochemical staining	NA	POX^-, PAS^+	POX^-, PAS^+
Immunophenotype	NA	$CD10^+$, $CD19^+$, $CD20^+$, $HLA\text{-}DR^+$, TdT^+	$CD10^+$, $CD19^+$, $CD20^+$, $HLA\text{-}DR^+$, TdT^+
Karyotype analysis	NA	t(9;22)(p24; q11.2)	t(9;22)(p24; q11.2)
Fusion gene	NA	Negative	NA

WBC, white blood cell; HGB, haemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBI, indirect bilirubin; ALB, albumin; LDH, lactate dehydrogenase; CREA, creatinine; BUN, blood urea nitrogen; TG, triglyceride; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen; POX, peroxidase; PAS, periodic acid-schiff stain; NA, not available.

day 22 after initial diagnosis and the patient died on day 35 because of severe sepsis due to multiple bacterial infections, including pseudomonas aeruginosa, staphylococcus aureus and candida albicans.

This report was approved by the Ethics Committee of Lanzhou University Second Hospital (no. 2019A-223).

Discussion

Haemophagocytic syndrome, or haemophagocytic lymphohistiocytosis, can be caused by primary or acquired disorders of uncontrolled immune response, but secondary HPS is more common in adults.[7] Liver injury has been found in most cases of HPS, however, only a few patients whose

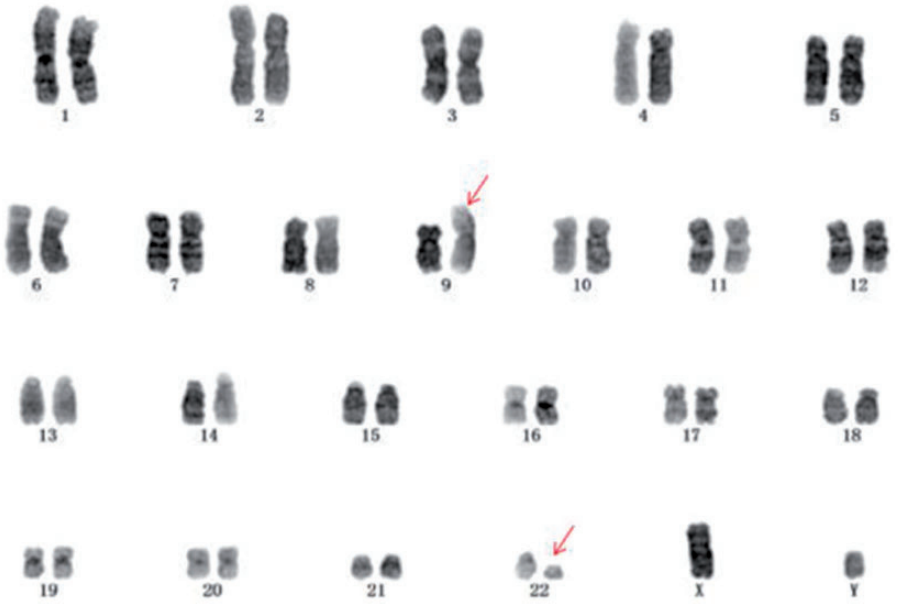

Figure 1. G-banding karyotyping of bone marrow cells from a 45-year-old male patient that was admitted for further evaluation of acute hepatic failure of unknown origin and hepatosplenomegaly showing a t(9;22) (p24; q11.2) translocation (arrows).

initial symptom was ALF were eventually diagnosed with HPS.[2] The patient described in this current case report was diagnosed and treated for ALF of an unknown cause in another hospital until severe cytopenia and progressive hepatosplenomegaly developed. HPS should be suspected in patients presenting with fever, jaundice, and hepatomegaly or splenomegaly.

Once a diagnosis of HPS is established, it is necessary to identify the underlying pathology as soon as possible.[8] In a study of secondary HPS, 40% of patients were found to have haematological malignancies.[9] Although both the first and second bone marrow examinations were negative, a third examination was undertaken to confirm the final diagnosis of this current patient. We recommend multiple bone marrow examinations for HPS patients if necessary.

To date, several numerical and structural chromosomal abnormalities have been characterized in ALL.[10] Seven genetic subtypes are defined for B lymphoblastic leukaemia according to the World Health Organization classification.[11] We characterized a rare chromosomal translocation t (9;22) (p24; q11.2). According to the literature, t(9;22)(p24; q11.2) has been observed in only three cases of chronic myeloid leukaemia,[12–14] one case of acute myeloid leukaemia,[15] one case of myelodysplastic syndrome[16] and in one case of ALL.[17] The BCR-JAK2 fusion transcript was present in some patients and predicted an unfavourable prognosis.[18] It may be worthwhile trying to use JAK2-selective inhibitors for those with the t(9;22)(p24; q11.2) translocation. The Ph-like ALL gene signature, PDGFRB, CRLF2, ABL1, ABL2 and CSF1R were all negative using fluorescence

in situ hybridization in this current case and none of the 40 common leukaemia fusion genes was detected.

In summary, the present case had adult ALL with a special onset and a rare translocation event. More cases are needed to confirm whether this chromosomal abnormality is associated with ALF and HPS. Furthermore, awareness of this particular ALL needs to be improved.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Huiling Chen https://orcid.org/0000-0001-8288-6631

References

1. Lin S, Li Y, Long J, et al. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults: a case report and review of the literature. *Medicine (Baltimore)* 2016; 95: e5431.
2. Goldberg E and Chopra S. Acute liver failure in adults: etiology, clinical manifestations, and diagnosis. UpToDate®, https://www.uptodate.com/contents/acute-liver-failure-in-adults-etiology-clinical-manifestations-and-diagnosis, 2018.
3. Otrock ZK and Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol* 2015; 90: 220–224.
4. Li F, Yang Y, Jin F, et al. Clinical characteristics and prognostic factors of adult hemophagocytic syndrome patients: a retrospective study of increasing awareness of a disease from a single-center in China. *Orphanet J Rare Dis* 2015; 10: 20.
5. Gindina T. t (9;22) (p24; q11.2) BCR/JAK2. *Atlas Genet Cytogenet Oncol Haematol* 2019; 23: 46–48.
6. Duployez N, Nibourel O, Ducourneau B et al. Acquisition of genomic events leading to lymphoblastic transformation in a rare case of myeloproliferative neoplasm with BCR-JAK2 fusion transcript. *Eur J Haematol* 2016; 97: 399–402.
7. Arca M, Fardet L, Galicier L, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol* 2015; 168: 63–68.
8. Malinowska I, Machaczka M, Popko K, et al. Hemophagocytic syndrome in children and adults. *Arch Immunol Ther Exp (Warsz)* 2014; 62: 385–394.
9. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014; 66: 2613–2620.
10. Shago M. Recurrent cytogenetic abnormalities in acute lymphoblastic leukemia. *Methods Mol Biol* 2017; 1541: 257–278.
11. Chiaretti S, Gianfelici V, O'Brien SM, et al. Advances in the genetics and therapy of acute lymphoblastic leukemia. *Am Soc Clin Oncol Educ Book* 2016; 35: e314–e322.
12. Griesinger F, Hennig H, Hillmer F, et al. A BCR-JAK2 fusion gene as the result of a t(9;22)(p24;q11.2) translocation in a patient with a clinically typical chronic myeloid leukemia. *Genes Chromosomes Cancer* 2005; 44: 329–333.
13. Lane SW, Fairbairn DJ, McCarthy C, et al. Leukaemia cutis in atypical chronic myeloid leukaemia with a t(9;22)(p24;q11.2) leading to BCR-JAK2 fusion. *Br J Haematol* 2008; 142: 503.
14. Bellesso M, Santucci R, Dias DF, et al. Atypical chronic myeloid leukemia with t(9;22)(p24,11.2), a BCR-JAK2 fusion gene. *Rev Bras Hematol Hemoter* 2013; 35: 218–219.
15. Cirmena G, Aliano S, Fugazza G, et al. A BCR-JAK2 fusion gene as the result of a t(9;22)(p24;q11) in a patient with acute

myeloid leukemia. *Cancer Genet Cytogenet* 2008; 183: 105–108.
16. Kantarcioglu B, Kaygusuz-Atagunduz I, Uzay A, et al. Myelodysplastic syndrome with t(9;22)(p24;q11.2), a BCR-JAK2 fusion: case report and review of the literature. *Int J Hematol* 2015; 102: 383–387.
17. Tirado CA, Chen W, Huang LJ, et al. Novel JAK2 rearrangement resulting from a t(9;22)(p24;q11.2) in B-acute lymphoblastic leukemia. *Leuk Res* 2010; 34: 1674–1676.
18. Cuesta-Domínguez Á, Ortega M, Ormazábal C, et al. Transforming and tumorigenic activity of JAK2 by fusion to BCR: molecular mechanisms of action of a novel BCR-JAK2 tyrosine-kinase. *PLoS One* 2012; 7: e32451.