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

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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)

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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
2 months after diagnosis, 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. 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 to 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: ≥15.11%) and sCD25 was 7441 pg/ml (normal value: <6400 pg/ml), which were accompanied by fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia, 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. 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
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

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 | In our hospital | After chemotherapy |
|--------------------------|---------------------|-----------------|--------------------|
|                          | 17 July 2018        | 24 August 2018  | 9 October 2018     |
| Presentation             |                     |                 |                   |
| Fever                    | NO                  | YES             | YES               |
| Jaundice                 | YES                 | YES             | NO                |
| Splenomegaly             | YES                 | YES             | YES               |
| Laboratory tests         |                     |                 |                   |
| WBC, ×10^9/l             | 5.31                | 0.35            | 0.6               |
| HGB, g/l                 | 139                 | 101             | 64                |
| PLT, ×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⁺,  | CD10⁺, CD19⁺,     |
|                          |                     | CD20⁺, HLA-DR⁺, TdT⁺ | CD20⁺, HLA-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.
The initial symptom was ALF were eventually diagnosed with HPS. 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. In a study of secondary HPS, 40% of patients were found to have haematological malignancies. 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. Seven genetic subtypes are defined for B lymphoblastic leukaemia according to the World Health Organization classification. 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, one case of acute myeloid leukaemia, one case of myelodysplastic syndrome and in one case of ALL. The BCR-JAK2 fusion transcript was present in some patients and predicted an unfavourable prognosis. 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

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).
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.

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