CASE REPORT

Hodgkin's lymphoma preceded by haemophagocytic lymphohistiocytosis

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SUMMARY

A 71-year-old woman was admitted because of persistent fever for 2 weeks. A diagnosis of haemophagocytic lymphohistiocytosis (HLH) was made on the basis of persistent high fever, pancytopenia, hyperferritinaemia, increased soluble interleukin-2 receptor (sIL-2R) levels and histiocytosis and hemophagocytosis in the bone marrow. CT showed neither infection nor lymphadenopathy. After administration of prednisolone, haematological findings improved and the fever resolved; however, the patient developed persistent fever after 6 months. In addition, levels of lactate dehydrogenase and sIL-2R increased again. CT scans revealed diffuse lymphadenopathy, and Hodgkin's lymphoma was diagnosed by lymph node biopsy. Progression of pancytopenia was observed, and bone marrow examination showed a relapse of HLH. After six courses of chemotherapy were given for Hodgkin's lymphoma, complete remission was achieved with no evidence of pancytopenia. Hodgkin's lymphoma may be the underlying cause in HLH cases of unknown aetiology. Hence, the clinical course should be carefully monitored even in the absence of lymphadenopathy.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is associated with infections, malignancy and autoimmune diseases. Lymphoma-associated HLH accounts for approximately 20% of all HLH cases. Patients with T/natural killer (NK)-cell lymphoma or diffuse large B-cell lymphoma have a high risk of developing HLH; however, the development of Hodgkin's lymphoma has rarely been reported in these patients.^{1 2}

We report a case of Hodgkin's lymphoma that first came to clinical attention with HLH developing 6 months before the appearance of lymphadenopathy.

CASE PRESENTATION

A 71-year-old woman with no significant family medical history, including haemodyscrasia, was admitted in November 2008 because of persistent fever for 2 weeks. On admission, she had a temperature 38.8°C, blood pressure 126/70 mm Hg and a regular pulse rate 94 bpm. Physical examination of the chest and abdomen showed neither abnormal findings such as splenomegaly nor superficial lymphadenopathy. Laboratory test results revealed the following: white blood cell (WBC) count 0.9×10^9 L (neutrophils 0.05×10^9 L); haemoglobin (Hb) 8.4 g/dL; platelets (Plt) 25×10^9 L; inter-

national normalised ratio (INR) 1.39; activated partial thromboplastin time (aPTT) 45.3 s; fibrinogen 207 mg/dL (standard value 150–400 mg/dL); antithrombin (AT) 71.9% (standard value 79–121%); fibrinogen and fibrin degradation products (FDP) 8.1 µg/mL (standard value 0–4 µg/mL); lactic dehydrogenase (LDH) 754 IU/L (standard value 180–370 IU/L); fasting triglyceride 170 mg/dL; C reactive protein (CRP) 21.6 mg/dL; ferritin 4783 ng/mL (standard value 9–220 ng/mL) and soluble interleukin-2 receptor (sIL-2R) 4250 U/mL (standard value 145–519 U/mL). Bone marrow examination revealed the following: nuclear cell count, 1.2×10^4 µL; megakaryocyte count, 0 µL; M/E ratio=4:1. Furthermore, histiocytosis and haemophagocytosis were observed. HLH was diagnosed on the basis of persistent high fever, pancytopenia, hyperferritinaemia, increased sIL-2R levels and histiocytosis and haemophagocytosis in the bone marrow.³

CT did not reveal lymphadenopathy or any source of infection except for borderline splenomegaly (the spleen span was 9.8 cm). Methylprednisolone pulse therapy (1 g/day for 3 days) was given, and prednisolone (20 mg/day) was orally administered as a long-term treatment. After the initiation of steroid treatment, the fever resolved and laboratory findings normalised (WBC count 5.12×10^9 L; Hb 11.3 g/dL; Plt 152×10^9 L; LDH 217 IU/L; CRP 0 mg/dL; ferritin 103 ng/mL and sIL-2R 385 U/mL). Administration of prednisolone was reduced to 2.5 mg/day by March 2009.

However, fever began recurring at night from April 2009. The patient was readmitted on 20 April 2009 for examining the cause of fever in detail. Inguinal lymph nodes on both sides were enlarged to 3 cm, but there was no pain; they were elastic and hard on palpation. Pancytopenia was not observed; however, levels of LDH, ferritin, sIL-2R and CRP increased to 426 IU/L, 4083 ng/mL, 4070 U/mL and 1.3 mg/dL, respectively (table 1).

CT scans revealed a maximum lymph node enlargement of 3.5 cm above the left clavicle, on the right paratracheal area, around the aorta from the level of the coeliac artery bifurcation to the origin of the common iliac artery, at the hilum of the spleen, around the left external iliac artery and in the left and right inguinal areas. In addition, splenomegaly was observed (the spleen span was 15.8 cm); however, neither hepatomegaly nor any source of infection was found (figure 1). ⁶⁷Ga scintigraphy revealed the localised accumulation in the lymphadenopathy and spleen. Positron emission

To cite: Morita Y, Kenzaka T, Yoshimoto H, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010129

Table 1 Laboratory data at the time of diagnosis of lymphoma

Parameter	Recorded value	Standard value
White blood cell count (/L)	3.71×10^9	$4.00\text{--}7.50 \times 10^9$
Neutrophil (/L)	2.33×10^9	
Lymphocyte (/L)	0.95×10^9	
Monocyte (/L)	0.40×10^9	
Haemoglobin (g/dL)	11.4	11.3–15.2
Haematocrit (%)	33.7	36–45
Platelet (/L)	106×10^9	$130\text{--}350 \times 10^9$
C reactive protein (mg/dL)	1.3	≤ 0.3
Ferritin (ng/mL)	4083	9–220
Soluble interleukin-2 receptor (U/mL)	4070	145–519
Aspartate aminotransferase (IU/L)	35	≤ 35
Alanine aminotransferase (IU/L)	17	≤ 35
Lactate dehydrogenase (IU/L)	426	180–370
Blood nitrogen urea (mg/dL)	15.3	8–20
Creatinine (mg/dL)	0.8	0.4–0.8
Sodium (mEq/L)	135	135–145
Potassium (mEq/L)	4.2	3.5–5.0
Adult T-cell leukaemia virus	(–)	(–)
Hepatitis B surface antigen	(–)	(–)
Hepatitis C virus antibody	(–)	(–)
Rapid plasma reagent	(–)	(–)
<i>Treponema pallidum</i> latex agglutination	(–)	(–)

tomography-CT was not performed. Bone marrow examination showed haemophagocytosis; however, infiltration of abnormal cells was not observed (figure 2).

Lymph node biopsy was performed in the left inguinal area, and mixed cellularity Hodgkin's lymphoma (clinical stage IIIS in Ann Arbor staging classification) was diagnosed. Immunohistochemistry showed atypical cells positive for CD15, CD30 and CD79a. Epstein-Barr virus-encoded small RNA-1 was scarcely positive (figure 3).

After hospital admission, the patient had persistent fever of $>38.5^\circ\text{C}$ and blood cell counts gradually decreased. Methylprednisolone pulse therapy was initiated. However, pancytopenia continued (WBC count $0.57 \times 10^9/\text{L}$; Hb 9 g/dL and Plt $48 \times 10^9/\text{L}$). Coagulation tests revealed the following: INR 1.42; aPTT 37.3 s; fibrinogen 207 mg/dL; AT 71.9% and FDP 8.1 $\mu\text{g/mL}$.

TREATMENT

After Hodgkin's lymphoma was diagnosed, adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy were given for six courses. On initiation of ABVD therapy, pancytopenia gradually improved, and discontinuation of oral prednisolone was tolerated.

OUTCOME AND FOLLOW-UP

Diffuse lymphadenopathy resolved, and complete remission was achieved (figure 4). This remission has been sustained for 39 months at the time of writing this article.

DISCUSSION

Although the development of HLH because of malignant lymphoma is often reported, it is usually associated with T/NK-cell lymphoma and diffuse large B-cell lymphoma.^{1 2} In addition, the association of HLH with Hodgkin's lymphoma has rarely been reported in Japan.^{4–6} In the present case, HLH was diagnosed 6 months before lymphadenopathy became evident. The borderline splenomegaly on the initial CT scan was consistent with the syndrome of HLH and thus not considered ominous. Some similar cases have been reported to date.^{4 7–9} To the best of our knowledge, the oldest patient was 72 years so far with this uncommon presentation.⁴ Splenomegaly was observed in one of these cases; CT scan and other tests did not reveal lymphadenopathy in any of the these cases, and some cases were diagnosed with Hodgkin's lymphoma on the basis of a lymph node specimen that was not enlarged at autopsy. In general, the prognosis of lymphoma-associated HLH is worse than that of other secondary types of HLH.¹⁰ The overall prognosis of Hodgkin's lymphoma is good¹¹; however, in three of these four cases, HLH preceded Hodgkin's lymphoma, resulting in mortality.^{4 7–9} In the present case, enlargement of lymph nodes was not apparent at the first hospital admission, and diffuse lymphadenopathy became evident on the CT scan 3 months later, after the second admission, thereby leading to the diagnosis of Hodgkin's lymphoma. It is important to treat the underlying cause of HLH. Hodgkin's lymphoma may be the cause of HLH even in the absence of an apparent underlying disease,¹² and its course should be carefully observed even when lymphadenopathy is not evident.

Figure 1 CT revealed lymphadenopathy on the right paratracheal area (A), around the aorta from the level of the coeliac artery, at the hilum of spleen (B) and in the left and right inguinal areas (C).

A | B

Figure 2 Bone marrow examination revealed the following: nuclear cell count, $22.7 \times 10^4/\mu\text{L}$; megakaryocyte count (calculated by counting chamber), $120/\mu\text{L}$; M/E ratio=6:1 (A). It also revealed haemophagocytosis; however, infiltration of abnormal cells was not observed (B).

Figure 3 Inguinal lymph node biopsy, H&E stain (A). Immunohistochemistry showed atypical cells positive for CD30 (B). Epstein-Barr virus-encoded small RNA-1 (EBER-1) was scarcely positive (C).

Figure 4 Clinical course and complete blood counts of the patient over the initial admission and subsequent illness and chemotherapy. The green arrows indicate the methylprednisolone pulse therapy and the red arrows indicate the admitted day. Prednisolone was orally administered from December 1 to June 30. ABVD chemotherapy was provided from May 22 to October 27.

Learning points

- ▶ Haemophagocytic lymphohistiocytosis (HLH) is associated with infections, malignancy and autoimmune diseases.
- ▶ Although the development of HLH because of malignant lymphoma is often reported, the association of HLH with Hodgkin's lymphoma has rarely been reported.
- ▶ Hodgkin's lymphoma may be the cause of HLH even in the absence of an apparent underlying disease, and its course should be carefully observed even when lymphadenopathy is not evident.
- ▶ It is important to treat the underlying cause of HLH.

Contributors YM, HY and NO contributed to patient management. YM, HY and NO contributed to drafting of the manuscript. YM and TK contributed to writing and reviewing the report. All authors have read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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