A 15-month-old girl with fever and pancytopaenia

A 15 month-old girl was admitted after a couple of months' history of illness with remittent fever, increasing pallor and a swollen abdomen. On admission she was highly febrile, with palpably enlarged liver and spleen. Blood tests revealed pancytopaenia, a high CRP level and a high serum ferritin level. We describe the diagnostic evaluation, interpretation and treatment.

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The little girl was referred by her primary doctor with remittent fever, poor general condition and anaemia. She had previously been healthy on the whole, but in the last couple of months had had repeated episodes of fever, became gradually more tired and increasingly pale. Treatment for otitis media had been started ten days previously with amoxicillin, which was replaced with clarithromycin after a week because of lack of effect. Blood tests for C-reactive protein (CRP) taken by her primary doctor on the day of admission generated an error message that the CRP level could not be measured because of the low haemoglobin level (Hb), and she was therefore hospitalised for further examination.

On admission she was very pale, in moderately poor general condition, but conscious and with normal respiration and normal capillary filling time. There was no rash, no swollen lymph nodes, good peripheral circulation. She protested at the clinical examination. The mucous membranes of her throat were normal. The left ear drum was normal, the right one was covered with cerumen. Heart and lung were normal to auscultation. Her abdomen was large, but soft and non-tender. The liver was palpable 2–3 cm below the right costal margin, the spleen was palpable 5–6 cm below the left costal margin, as a wedge against the umbilicus.

Blood tests on admission are shown in table 1. The blood smear showed relative lymphocytosis and slightly reduced platelet count, otherwise normal.

The patient was thus in a poor general condition, had fever, splenomegaly and pancytopaenia, and the clinical picture raised suspicion of acute leukaemia. Treatment with cefotaxime was started for neutropaenic fever. We saw no definite immature cells in the peripheral blood smear, but with such a low number of leukocytes this cannot be expected, even in the case of acute leukaemia. She had very high serum ferritin, far higher than is normally seen in an acute phase reaction. The combination of fever, cytopaenia, splenomegaly and ferritin > 500 µg/l could be an indication of haemophagocytic lymphohistiocytosis (HLH). This condition is diagnosed on the basis of a set of clinical and laboratory criteria, five of eight of which must be met (Box 1) (1).

The day after admission, bone marrow aspiration and biopsy were performed under general anaesthesia. Her bone marrow was rich incells, and showed active trilinear haematopoiesis without an abnormal increase of immature cells. Nor was there any immunophenotypic evidence of acute leukaemia. Monocytes/macrophages with inclusions of erythrocytes and nucleated cells were seen in the bone marrow, along with inclusions that we were at first unable to identify (Fig. 1).

Thus she met six of eight diagnostic criteria for haemophagocytic lymphohistiocytosis: fever, pancytopaenia, splenomegaly, hyperferritinaemia, hypertriglyceridaemia and haemophagocytosis in the bone marrow with no sign of malignancy.

Haemophagocytic lymphohistiocytosis is a hyperinflammatory condition characterised by persistent high fever, cytopaenia, hepatosplenomegaly and haemophagocytosis in activated, benign macrophages. The disease may be primary/genetic or secondary to other illnesses, particularly infections, malignant diseases or rheumatic disorders (2, 3). Primary haemophagocytic lymphohistiocytosis is recessively inherited, usually with onset early during the first year of life, and is fatal when left untreated. It is not unusual for the diagnosis only to be made post mortem in cases without a known family history. Secondary haemophagocytic lymphohistiocytosis normally occurs later, and as a rule has a better prognosis than the primary disease, but it is crucial to treat the causal factor. The course of secondary haemophagocytic lymphohistiocytosis can also be very severe, and it may be necessary to start treatment as though it were a primary disease. Since the manifestations of the disease, also in the case of primary haemophagocytic lymphohistiocytosis, can be

Box 1

Diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH) according to the HLH-2004 protocol (1). Either 1 or 2 must be met

1. Molecular diagnosis consistent with haemophagocytic lymphohistiocytosis
2. Diagnostic criteria for haemophagocytic lymphohistiocytosis (at least 5 of 8 must be present):

Original criteria
- Fever
- Splenomegaly
- Cytopaenia of at least 2 cell lines in peripheral blood (Hb < 9 g/100 ml, thrombocytes < 100 · 10 ^{9}/l, neutrophils < 1.0 · 10 9/l)
- Hypertriglyceridaemia and/or hypofibrinogenaemia (fasting triglycerides ≥ 3.0 mmol/l, fibrinogen ≤ 1.5 g/l),
- Haemophagocytosis in bone marrow, spleen or lymph nodes (often not present early in the course of the disease) No signs of malignancy

New criteria
- Low or no NK cell activity
- Ferritin ≥ 500 µg/l
- Soluble CD25 (soluble IL-2-receptor) ≥ 2 400 U/ml

Table 1 Blood test results on admission and developments up to diagnosis and after treatment start

	Reference range	Admission	Day 2	Day 4	Day 6	Day 8	Day 9 Diagnosis and treatment start	Day 12	Day 18–43	Day 50	Day 140
Hb (g/100 ml)	11.0–14.0	5.4	8.3	10.0	8.7	8.2/4.5[1]	8.6	10.9	11.4 [2]	11.2	12.9
Leukocytes (10 ^{9}/l)	6.0–17.0	2.7	3.4	2.5	1.7	2.3	2.8	5.8	7.3 [2]	6.8	11.8
Neutrophils (10 ^{9}/l)	2.0–2.5	0.7	1.2	0.6	0.2	0.3	0.7	0.8	1.1 [2]	1.7	6.1
Thrombocytes (10 ^{9}/l)	150–390	37	48	44	35	36	65	76	196 [2]	220	259
INR (ratio)	0.9–1.2		1.3							1.2	1.1
APTT (sec)	27–40		44							39	
Fibrinogen (g/l)	1.7–4.0		3.7	3.0	2.6	3.3				4.3	3.9
Ferritin (µg/l)	7–140	2 322	3 566	5 334	10 557	7 781	8 622	3 297	1 408[2]	347	137
Triglycerides (mmol/1)	0.45–2.60	3.08	2.17	2.54	5.12	2.63	3.58	5.99	2.71[2]		1.07
Albumin (g/l)	36–48		29	25	25	25	21	28	35 [2]	43	
CRP (mg/l)	0–10	156	151	119	85	92	130	21	4 [2]	15.5	1.7
IgG (g/l)	5.0–11.0			12.4					14.3 [3]		
Direct antiglobulin test (DAT)		Positive							Positive [4]	Negative	

[1] Hb before and after the diagnostic spleen puncture Puncture resulted in haemorrhage despite preparatory treatment with thrombocyte and plasma transfusion
[2] Day 18 after admission
[3] Day 34 after admission
[4] Day 43 after admission

triggered by an infection, at the time of diagnosis it may be impossible to distinguish with certainty a primary from a secondary disease unless there is a positive family history or a known genetic defect can be invoked.

There was no information about haemophagocytic lymphohistiocytosis in the patient's immediate family, nor any cases of unexplained deaths in infants or small children. Since patients with primary haemophagocytic lymphohistiocytosis usually have decreased natural killer (NK) cell activity, we sent blood samples from patient and parents for testing for NK cell activity. All showed normal activity, which makes the diagnosis primary haemophagocytic lymphohistiocytosis unlikely.

Testing for secondary haemophagocytic lymphohistiocytosis yielded negative results for bacterial infections (blood culture, urine, faeces), Epstein-Barr virus (serological and PCR (polymer chain reaction) tests in blood), parvovirus B19 (serological tests), airway viruses and diarrhoea viruses. There was, however, a positive PCR test result for human herpes virus type 6, of uncertain clinical and pathogenetic significance. Also positive were the direct antiglobulin test (DAT, formerly called direct Coombs' test) and the test for autoantibodies against thrombocytes and granulocytes.

It turned out that seven months prior to hospitalisation, the patient had been on holiday on the Mediterranean coast of Spain. She got an insect sting or bite there that was still irritated and itching at the time of hospitalisation (Fig. 2).

A condition that can occur both as a difficult differential diagnosis and a causal factor for haemophagocytic lymphohistiocytosis is visceral leishmaniasis (kala-azar) (2), which causes fever, pancytopaenia and splenomegaly in endemic areas. Visceral leishmaniasis is a lethal infection with the protozoa *Leishmania,* which is transmitted by insect bites, normally sandflies. Leishmaniasis is not endemic in Norway, but is widespread in the Mediterranean area (4). The diagnosis requires detection of the *Leishmania* parasi-

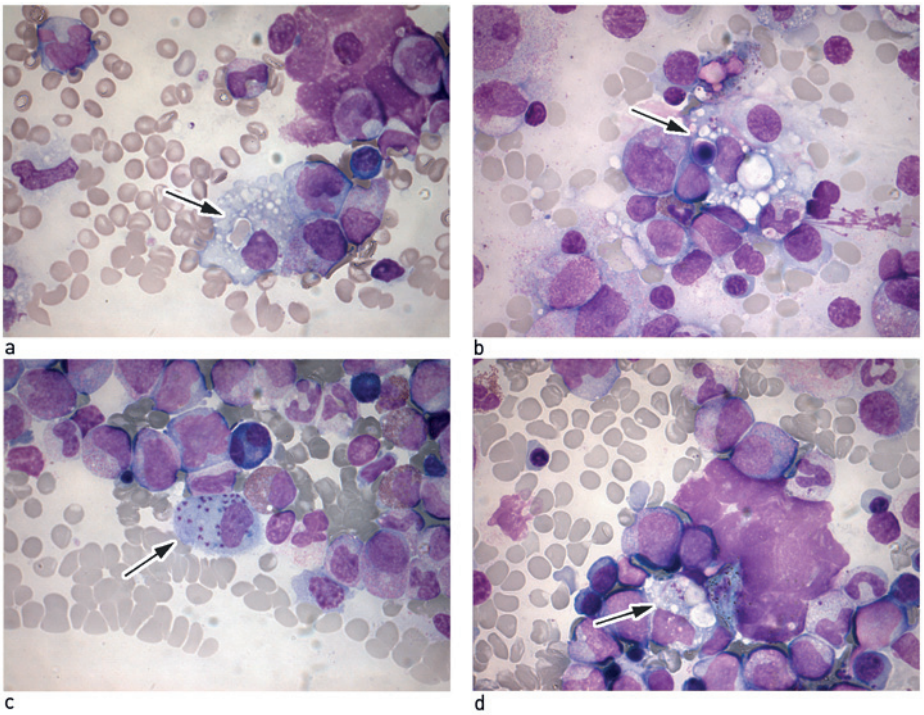

Figure 1 *a) Bone marrow smear with macrophages with inclusions of erythrocytes (arrow). b) Bone marrow smear with macrophages with inclusions of erythrocytes and an erythroblast (arrow). c) Bone marrow smear with macrophages with inclusions of what after a while were identified as* ***Leishmania*** *amastigotes (arrow). d) Bone marrow smear with macrophages with inclusions of erythrocytes and Leishmania amastigotes (arrow). Photo Marit Hellebostad*

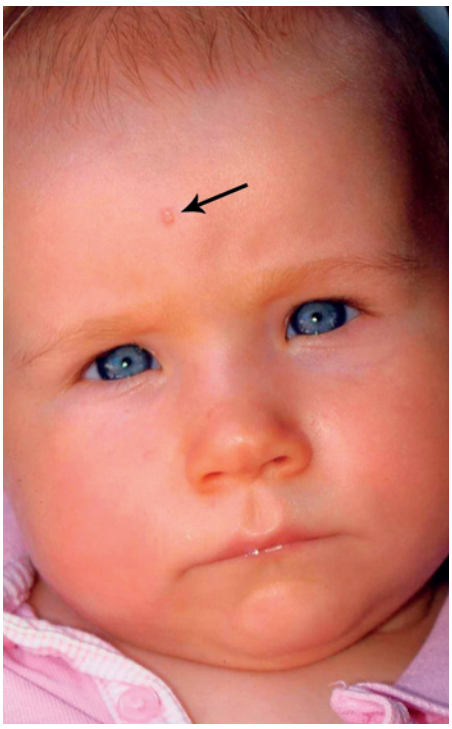

Figure 2 *The bite that is assumed to be the port of entry for the infection. Published with the consent of the patient's parents. Private photo*

te in bone marrow or spleen aspirate, or the detection of specific antibodies.

During the week that had passed in the department, the patient's clinical condition had remained relatively unchanged, except that her abdomen had grown larger because of the increasing spleen size. With haemophagocytic lymphohistiocytosis it may be life-saving to start immunosuppressive treatment before the results of all the diagnostic tests have been received, since the disease may have a very rapid course ending in death. The patient therefore received a 0.8 g/kg dose of immunoglobulin intravenously while we waited the test results, but we chose to wait with treatment according to the HLH protocol, with steroids and etoposide (1), since we believed the situation was under control..

After a week, further bone marrow aspiration and biopsies and spleen aspiration were carried out for cytological and microbiological tests for Leishmania. Spleen aspiration is a risky procedure because of the danger of haemorrhage, and the girl received a transfusion of platelets and plasma before the procedure was carried out. The spleen aspiration nonetheless caused bleeding that made transfusion necessary after the intervention. After the relevant samples for Leishmania diagnosis had been taken, we chose to start treatment with liposomal amphotericin B against leishmaniasis according to the FDA guidelines (5, 6). At the same time, while waiting for the test results, dexamethasone was administered for possible haemophagocytic lymphohistiocytosis.

The bone marrow smears were examined immediately (MH). Normal trilinear haematopoiesis was documented again, and macrophages with haemophagocytosed blood cells and inclusions which with eyes made keen by suspicion we saw to be consistent with Leishmania amastigotes (Fig. 1c-d). The next day Leishmania amastigotes were also found in spleen aspirate (NOH), and later culturing of spleen aspirate on NNN medium resulted in growth of Leishmania promastigotes. Serological tests revealed Leishmania antibodies in the blood, and by means of a PCR examination followed by an RFLP examination (restriction fragment length poymorphism) the parasite was identified as Leishmania infantum (7). A cytological examination confirmed haemophagocytosis in the spleen, and the bone marrow biopsy revealed reactive haematopoiesis with a diffuse increase in histocytic cells with haemophagocytosis and «double dot» elements, consistent with leishmaniasis.

The diagnosis was thus visceral leishmaniasis with secondary haemophagocytic lymphohistiocytosis.

The day after starting amphotericin B and dexamethasone, the patient was afebrile for the first time in several weeks. Whether this was due to the steroids or to amphotericin B, was at that time impossible to tell. The question now was whether there was a need to continue the treatment for haemophagocytic lymphohistiocytosis. After discussion among the specialists, we agreed to terminate dexamethasone after 36 hours and only treat the patient for leishmaniasis. She was treated with liposomal amphotericin B, 3 mg/kg daily for five days, followed by a single dose on day 14 and one on day 21 – a total of 21 mg/kg (5, 6). Once treatment started, she recovered rapidly, her spleen shrank gradually and her blood tests gradually normalised (table 1).

The patient went to outpatient check-ups for four months after completing treatment, and there was telephone contact with her family after a further four and eight months. The girl was well during this period. At the four-month check-up, the mark on her forehead from the insect bite had vanished.

Discussion

Haemophagocytic lymphohistiocytosis

The characteristic features of the disease are fever, pancytopaenia and hepatosplenomegaly. Neurological symptoms are seen in up to a third of patients. The diagnosis is made if the patient meets a set of clinical and biochemical criteria, as described above, or if a mutation consistent with the diagnosis is found (1).

Pathophysiologically, there is a disproportionate activation of lymphocytes and macrophages with haemophagocytic lymphohistiocytosis. When the immune system is stimulated by an infectious agent/antigen, cytotoxic cells are activated (macrophages, dendritic cells (histiocytes), NK cells and cytotoxic T-lymphocytes (CTL) which exercise a mutually stimulating effect, partly through receptor interaction and partly through secretion of inflammatory cytokines. In persons with an intact immune defence system, this interaction will lead to infected cells being removed and the immune response stopping. In the event of defective function by NK cells and cytotoxic T-lymphocytes (congenital or acquired) this process is disrupted – the infected cells are not removed, and the immune response persists. A persistently high level of inflammatory cytokines gives rise to the clinical picture of haemophagocytic lymphohistiocytosis (2).

As a rule, the onset of symptoms of haemophagocytic lymphohistiocytosis occurs already in the first year of life, and without treatment the illness can rapidly run a fatal course. One should therefore be aware of this diagnosis in patients with septic conditions that do not respond as expected to supposedly appropriate treatment. An important marker is a strongly elevated serum ferritin level, often far higher than is normally seen in acute phase reactions (8). It is not a matter of routine to analyse the ferritin level in cases of acute illness that look like an ordinary infection, but in the event of an aberrant clinical course or failure to respond to treatment, ferritin is a useful and generally available variable for which results can rapidly be obtained. Patients with primary haemophagocytic lymphohistiocytosis need immunosuppressive treatment until haematopoietic stem cell transplantation can be effected. At present this is regarded as the only curative therapy (9). The treatment is described in detail in the HLH-2004 protocol, in which we participate (1). A number of genetic defects have been identified over time that are responsible for familial haemophagocytic lymphohistiocytosis, and it has become clear that some genetic variants have a later onset than previously believed (10). This further complicates the distinction between primary and secondary disease.

Haemophagocytic lymphohistiocytosis can also be seen in connection with some genetic immunodeficiency conditions (X-linked lymphoproliferative syndrome (XLP), Griscelli's syndrome 2 (GS-2), Chédiak-Higashi's syndrome (CHS)) (1, 2).

In secondary haemophagocytic lymphohistiocytosis, the clinical picture and degree of severity show a greater degree of variation, but secondary disease may also have a fulminant course with high mortality. The condition occurs secondarily to infections (virus associated haemophagocytic syndrome, VAHS, or infection-associated haemophagocytic syndrome, IAHS), malignant diseases and rheumatic or autoimmune disorders (represent a slightly different entity,

macrophage activation syndrome, MAS) (2). Most cases occur in somewhat older children or adults. Cases of IAHS may be triggered by a virus (e.g., Epstein Barr virus, particularly prevalent in Japan) (11), bacteria, protozoa or fungi. *Leishmania* infection may be a relatively frequent triggering factor (12).

Leishmaniasis

Visceral leishmaniasis is a tropical disease, and if untreated it is often fatal. There are a number of varieties of *Leishmania* that can cause disease in humans, affecting different organs: skin, mucous membranes and visceral reticuloendothelial organs. Cutaneous leishmaniasis is cosmetically disfiguring, but not fatal, while mucocutaneous leishmaniasis can lead to lethal secondary infections. Visceral leishmaniasis is due either to *Leishmania donovani* (East Africa and India) or *Leishmania infantum* (Europe, North Africa and South America). The transmission of the parasite takes place either zoonotically, i.e., by means of an animal as intermediate host, or anthroponotically, i.e., from human via insect vector to human. Dogs are the main hosts in Europe, but other animals, including rodents, can also be intermediate hosts. After transmission from the insect vector, the parasite is absorbed by macrophages where it is transformed from promastigote to amastigote, reproduces and spreads to the entire reticuloendothelial system. The infection can also be asymptomatic, but in the event of impaired immunity, for example due to concurrent HIV infection, the probability of a severe course increases (13–15).

The incubation period is normally 2–6 months, but may be several years (13). The disease often follows an insidious course, with gradual onset of lethargy, fever, weight loss and hepatosplenomegaly. Anaemia develops as a result of bone marrow failure, haemolysis and hypersplenism. Later, liver failure takes place, with jaundice and ascites. Liver failure and thrombocytopaenia may also cause bleeding diathesis. The name kala-azar (black fever) refers to a darkening of the skin which is one of the clinical symptoms on the Indian sub-continent.

Visceral leishmaniasis causes some 50 000 deaths annually, worldwide (16). The disease is most prevalent in Latin America, Africa and southern parts of Asia, but the occurrence is also increasing in southern Europe. The increase is associated with increased travel activity, more people with an impaired immune system and a growing catchment area for host animals and vectors. There is an abundance of sandflies today in the deciduous forests of northern Spain and central France, although no correlation has been found with climate changes (4). In northern Europe, the disease is most relevant for people who have been to Mediterranean or more remote regions in the course of the past year, and have symptoms.

There are few described cases of haemophagocytic lymphohistiocytosis secondary to visceral leishmaniasis. Since the two conditions have overlapping clinical features, it is easy to overlook visceral leishmaniasis as the causal factor, particularly in our part of the world, where this disease virtually does not occur. Both haemophagocytic lymphohistiocytosis and visceral leishmaniasis may be difficult to detect in bone marrow smears in an early phase of the disease. Visceral leishmaniasis must be considered and excluded in patients with haemophagocytic lymphohistiocytosis before immuneosuppressive treatment is started. In the event of clinical suspicion of visceral leishmaniasis, bone marrow examinations must be repeated, and spleen and bone marrow aspirate cultured. Serological tests may be diagnostic even when bone marrow findings are negative (12, 17). Our patient had a positive direct antiglobulin test and autoantibodies against thrombocytes and granulocytes. This confused us, but has been described previously in connection with leishmania-associated haemophagocytic lymphohistiocytosis. It is assumed that the finding is due to polyclonal activation of B-lymphocytes due to a concurrent high IgG level (12). In our patient a direct antiglobulin test was negative six weeks after start of treatment, while the antibodies against granulocytes and thrombocytes were not checked later. Liposomal amphotericin B is the first choice of treatment for visceral leishmaniasis. Our patient was also given dexamethasone for a day and a half, but no other treatment for haemophagocytic lymphohistiocytosis. After a year of observation, she is still free of symptoms.

This case report describes a prolonged and atypical febrile illness. The GP treated the patient for recurrent airway infections, and at first we suspected acute leukaemia. The diagnosis haemophagocytic lymphohistiocytosis is well known in large paediatric departments, and was made early. Haemophagocytic lymphohistiocytosis secondary to visceral leishmaniasis is very rare in Norway, however.

The girl's mother mentioned the insect bite already on admission, but no weight was attached to it in the first assessment. Later she again commented on the bite, which helped to put us on the track of the correct diagnosis. The case report underscores the importance of a thorough anamnesis, which must be seen in context with the clinical symptoms and the clinical findings. A complete travel history is necessary in connection with febrile diseases after time spent in tropical and subtropical areas, including the Mediterranean area (Box 2).

The patient's parents have consented to the publication of the article.

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Box 2

Things to remember about your trip

- Local conditions (standard of living, drinking water, day trips)
- Other fellow travellers who are/were sick
- Close contact with insects or other animals (bites, stings, bathing)
- Geographical conditions (detailed description of travel itinerary)
- Vaccination status (basic vaccinations, relevant vaccinations, malaria prophylaxis)
- Epidemics and known outbreaks of tropical diseases in the area
- Infections during travel
- Illness after return home

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