

CASE REPORT

Neuroblastoma presenting as haemophagocytic lymphohistiocytosis

Monika Pogorzala

Department of Paediatric Haematology and Oncology, Jurasz University Hospital 1, *Collegium Medicum*, Nicolaus Copernicus University Toruń, Bydgoszcz, Poland

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome of excessive activation of the immune system, which can be primary (genetically determined) or secondary (acquired). Secondary forms are most often triggered by infections, but also by autoimmune processes, neoplastic diseases, drugs, and metabolic diseases. Secondary HLH associated with malignancy occurs more often in adults, mainly in the course of lymphomas and leukaemia. It is rarely induced by solid tumours but can develop during chemotherapy. The presented case of a 1.5-year-old child reflects a very rare situation when symptoms of haemophagocytic syndrome turned out to be the primary manifestation of a non-haematological proliferative disease.

KEY WORDS:

children, haemophagocytic lymphohistiocytosis, neuroblastoma.

INTRODUCTION

Haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), also known as haemophagocytic syndrome (HS), is clinically manifested by a set of symptoms resulting from intense activation of the immune system, presenting as hypersecretion of cytokines, impaired activity of cytotoxic T-lymphocytes, and excessive activation of macrophages [1]. Typical symptoms include fever, hepatosplenomegaly, and symptoms resulting from pancytopenia: pallor, weakness, and haemorrhagic diathesis. Laboratory features of the syndrome include anaemia, thrombocytopenia, neutropenia, hyperferritinaemia, hypertriglyceridaemia, and hypofibrinogenaemia. The syndrome may be primary (genetically driven) or secondary. Both forms are most often triggered by various infectious agents, mostly Epstein-Barr virus (EBV), cytomegalovirus (CMV), or human herpesvirus type 6. Secondary forms of HLH are

also induced by autoimmune diseases and systemic inflammatory diseases (systemic juvenile idiopathic arthritis, systemic lupus erythematosus), malignancies (most often lymphomas and leukaemia, rarely solid tumours), drugs (e.g. phenytoin), in the course of metabolic diseases, immunosuppressive therapy or chemotherapy, and after organ transplants [2, 3]. The objective of the paper is the presentation of a child with the symptoms of HS being the primary manifestation of a solid tumour; a case that in this context has not previously been described in the literature.

CASE REPORT

INITIAL SYMPTOMS AND SIGNS

A 1.5-year-old girl, developing normally, was referred to the oncology and haematology department with suspicion of haematopoietic system malignancy. Patient history

ADDRESS FOR CORRESPONDENCE:

Dr. Monika Pogorzala, Department of Paediatric Haematology and Oncology, Jurasz University Hospital 1, *Collegium Medicum*, Nicolaus Copernicus University Toruń, Bydgoszcz, Poland,
e-mail: m.pogorzala@cm.umk.pl

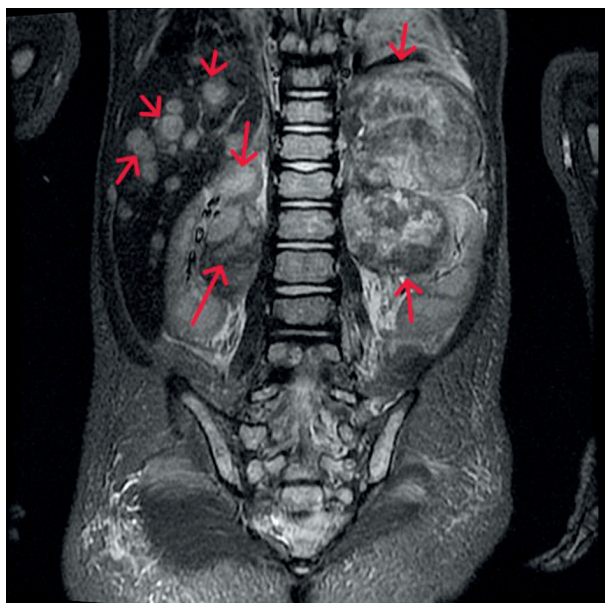


FIGURE 1. Magnetic resonance imaging of the abdominal cavity – pathological masses in the left adrenal gland and para-aortic area, metastatic foci in the liver

included recurrent respiratory and gastrointestinal infections for 1.5 months and – in the last 2 weeks – episodes of fever, increasing weakness, apathy, and pallor. The child stopped walking and refused to drink fluids and eat. An outpatient blood test revealed anaemia (haemoglobin, Hb 6.7 g/dl), thrombocytopaenia (platelets – PLT 75 g/l), and leukocytosis (white blood cells 19.7 g/l). Antigen tests for SARS-Cov2, influenza A/B, and respiratory syncytial virus were negative. On admission, the child's condition was assessed as moderately serious; she was irritable, tearful, and lying down. On physical examination her skin was pale, warm (38.8°C), and had decreased elasticity. Swelling of the feet and lower legs, papular rash on the lower limbs, drying mucous membranes of the oral cavity, bundles of enlarged lymph nodes in the neck and supraclavicular areas, increased heart rate with the presence of a systolic murmur 4/6 Levine, abdomen above the level of the chest, and enlarged liver and spleen reaching, respectively, 5 and 4 cm below the costal arches were present.

LABORATORY TESTS

Severe normocytic anaemia (Hb 5.9 g/dl, mean corpuscular volume 76 fl) and thrombocytopaenia (PLT 48 g/l) were confirmed. The white blood cells count was normal for age (12.7 g/l), the peripheral blood smear showed 5% of immature granulocytes and the presence of 8% of atypical cells. Biochemical parameters showed high lactate dehydrogenase activity (LDH 7029 U/l), increased levels of ferritin (730 µg/l), triglycerides (273 mg/dl), D-dimer (89.684 ng/ml), and hypofibrinogenaemia (64 mg/dl). Inflammation markers were low (C-reactive protein 7.23 mg/l, procalcitonin 0.17 ng/ml). There were no serological markers of infection with EBV, CMV, HBV,

HCV, or HIV. Myelogram did not show the presence of malignant cells, but 12% of phagocytic macrophages were detected.

DIAGNOSIS OF HAEMOPHAGOCYTIC SYNDROME

Based on the clinical symptoms and laboratory test results, HLH was diagnosed, and on the third day of admission combined treatment was implemented: steroid therapy (dexamethasone 10 mg/m²/day) and an antagonist of human interleukin-1 receptors (anakinra, 5 mg/kg/day). No mutation responsible for primary HLH syndrome was detected using the method of next-generation sequencing. Therefore, other causes of HLH were sought. The computed tomography and magnetic resonance imaging (MRI) of the abdomen revealed the presence of pathological masses with foci of calcifications in the projection of the left adrenal gland (75 × 70 × 80 mm) and in the para-aortic area (70 × 45 mm), suggesting a disseminated form of neuroblastoma. Additionally, multiple focal lesions in the liver, pancreas, and intra-abdominal enlarged lymph nodes were found (Figure 1). Computed tomography also showed signs of probable vertebra involvement (TH7 and TH8). No focal changes were detected in brain MRI.

PROGRESSION OF SYMPTOMS

Despite the implemented treatment for HLH, the child's condition deteriorated within the next few days, with bleedings from the injection sites, symptoms typical for disseminated intravascular coagulation (DIC). An increase in blood pressure and abdominal circumference was observed, as well as a further increase in ferritin concentration (1160 µg/l). Due to the high risk of bleeding complications, a tumour biopsy could not be performed. Finally, 4 days after the initiation of HLH treatment, chemotherapy (etoposide and carboplatin) was started based on clinical symptoms typical for neuroblastoma.

DIAGNOSIS OF NEUROBLASTOMA

After the first cycle of chemotherapy, and one week after the first assessment, bone marrow aspiration and trephine biopsy were repeated. Marrow haemophagocytosis increased significantly (up to 44% of cells), but although no neuroblastoma cells were detected by microscopy, *N-myc* gene amplification was detected in bone marrow samples by fluorescence *in situ* hybridisation. Trephine biopsy transpired not to be diagnostic due to massive cytolysis of bone marrow morphological elements. Other biochemical markers of neuroblastoma were also detected: neuron-specific enolase (NSE) activity was beyond the upper limit (> 2000 ng/ml) and increased urinary excretion of dopamine, vanillylmandelic acid, and homovanillic acid were confirmed. At this stage, the girl's condition made

it impossible to transport her to a nuclear medicine centre for diagnostic MIBG scintigraphy. Finally, based on the clinical picture (tumour of the left adrenal gland and retroperitoneal space with metastases to the liver, pancreas, lymph nodes, and probably to the marrow and bones), the diagnosis of disseminated form of neuroblastoma (International Neuroblastoma Staging System 4) complicated by a secondary HS was made.

CHEMOTHERAPY

The child was qualified for oncological treatment according to the current HR-NBL 1.8 SIOPEN program, and induction chemotherapy was continued according to the RAPID-COJEC scheme in parallel with HLH treatment. After the second cycle of chemotherapy (course B) the patient's condition began to improve, haemorrhagic symptoms disappeared, and fibrinogen and D-dimers gradually returned to normal values. Before the start of the third cycle of chemotherapy (course C), anakinra and steroid therapy were discontinued (the child was treated for HLH for a total of 19 days). After 4 cycles of chemotherapy, the myelogram confirmed complete resolution of haemophagocytosis, and no tumour cells were detected in the bone marrow and trephine biopsy. Partial regression of tumour masses were achieved in the left adrenal gland, para-aortic space, and metastatic foci. After completion of RAPID-COJEC chemotherapy, complete remission of metastatic lesions was confirmed and further regression of tumour masses was seen in the left adrenal gland area and para-aortic space with an accompanying decrease in biochemical markers (LDH 259 U/l NSE 18.4 ng/ml, catecholamine excretion and their metabolites within the age norms). Scintigraphy with I^{131} -MIBG showed trace accumulation of radiotracer at the periaortic masses, without pathological uptake in the adrenal tumour or other foci.

FURTHER THERAPY

After having good response to treatment, the child was qualified for surgical treatment. The residual masses of the adrenal gland and periaortic space were radically removed. Histopathological examination showed 100% necrosis within the removed tissues. No viable tissue was found that would have allowed identification of the histological subtype of the tumour. In the next stage of treatment, the child underwent high-dose chemotherapy (Busulfan-Melphalan) followed by autologous haematopoietic cell transplantation.

CENTRAL NERVOUS SYSTEM METASTASES

On the seventh day after transplantation, the girl was diagnosed with veno-occlusive syndrome, and defibrotide therapy was initiated. The following week, the child sud-

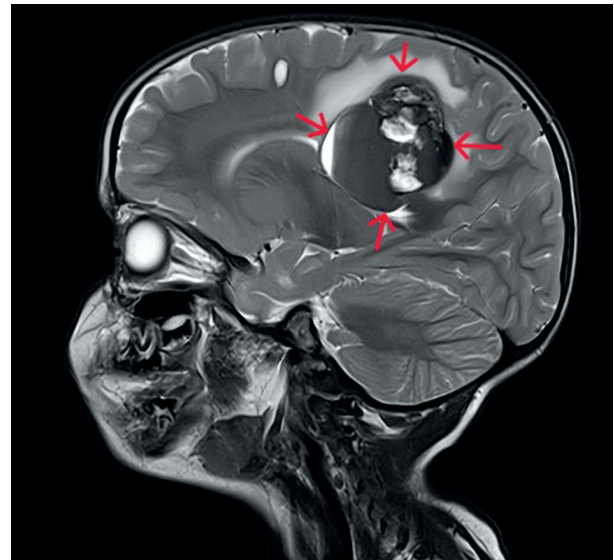


FIGURE 2. Magnetic resonance imaging of the brain: pathological mass ($45 \times 31 \times 39$ mm) in the left frontoparietal area with an oedema zone

denly presented with gait disturbances and right-sided hemiparesis. Magnetic resonance imaging of the brain was performed showing a pathological mass in the left frontoparietal area with an oedema zone measuring $45 \times 31 \times 39$ mm (Figure 2). The image suggested the presence of an evolving haematoma or bleeding into a central nervous system (CNS) tumour. Magnetic resonance imaging of the spinal canal did not reveal any other foci suspected of spreading the process to the CNS. Biochemical markers of the tumour determined at that time were normal (LDH, NSE, and urinary catecholamine excretion).

FOLLOW-UP

The neurosurgical operation was done, and neuroblastoma cells were identified among the evacuated haemorrhagic masses, which confirmed the metastasis of the tumour to CNS. Molecular analysis showed no presence of mutations in the *ALK* gene, so targeted treatment was not possible. Despite additional cycles of chemotherapy (TOTEM, ICE) and surgical removal of another metastatic lesion, dynamic growth and further metastases in CNS were observed (Figure 3). The child died 8 weeks after the diagnosis of progression.

DISCUSSION

The clinical picture of HLH/MAS is non-specific and may take various forms: from prolonged fever to life-threatening multi-organ failure syndrome accompanied by symptoms of DIC. In secondary forms, the diagnosis may be particularly difficult due to overlapping symptoms of primary disease [3, 4].

In the presented case, the clinical symptoms: recurrent fever, weakness and pallor progressing over a short



FIGURE 3. Magnetic resonance imaging of the brain – progression of central nervous system changes. Tumour regrowth in the bed after the first resection, new foci in the parietal lobe

TABLE 1. Diagnostic criteria for haemophagocytic lymphohistiocytosis by the Histiocyte Society [5]

- I. A molecular diagnosis consistent with HLH
- II. And/or the presence of at least 5 of the following 8 criteria:
 1. Fever $\geq 38.3^{\circ}\text{C}$
 2. Cytopenia affecting at least 2 of 3 lineages in the peripheral blood
 - haemoglobin $< 90\text{ g/l}$ (in newborns: $< 100\text{ g/l}$)
 - platelets $< 100 \times 10^9/\text{l}$
 - neutrophils $< 1.0 \times 10^9/\text{l}$
 3. Splenomegaly
 4. Hypertriglyceridaemia $> 3\text{ mmol/l}$ and/or hypofibrinogenaemia $< 1.5\text{ g/l}$
 5. Increased ferritin $> 500\text{ ug/l}$
 6. Haemophagocytosis in bone marrow or spleen or lymph nodes or cerebrospinal fluid
 7. Low or absent NK-cell activity
 8. Elevated soluble CD25 (IL-2 receptor α) in the blood $\geq 2400\text{ U/ml}$

HLH – haemophagocytic lymphohistiocytosis, NK-cell – natural killer cell

TABLE 2. Overlapping symptoms in the presented case

Symptoms and laboratory test results	Attributed to	
	Neuroblastoma	Haemophagocytic syndrome
An ill appearing child	+	+
Fever	+	+
Hepatomegaly	+	+
Splenomegaly	+/-	+
Lymphadenopathy	+	+/-
Tumour	+	-
Anaemia	+	+
Thrombocytopenia	+	+
Neutropenia	+	+
Increased ferritin	+	+
High LDH activity	+	-
Hypertriglyceridaemia	-	+
Hypofibrinogenaemia	+/-	+
Haemophagocytosis in bone marrow	-	+

period of time, hepatosplenomegaly, and lymphadenopathy combined with bilineage peripheral blood cytopenia, raised the suspicion of a malignant disease of the haematopoietic system. Myelogram assessment excluded leukaemia, while the detection of a population of activated macrophages in the bone marrow directed further diagnostics towards HS.

The deviations detected in laboratory tests were typical for HS. Together with clinical symptoms, they met the HLH-2004 diagnostic criteria (Table 1). The H-score assessment (available online), including 12 clinical and laboratory features, also confirmed this diagnosis:

the H-score was 171 points, providing estimated probability 54–70% of HS [6, 7].

While our patient met the HLH 2004 criteria, it is still possible that some of the HLH findings, such as hepatosplenomegaly, lymphadenopathy, cytopenia, and hyperferritinaemia, were caused by the malignancy itself (Table 2). In HS, rapid diagnosis and immediate treatment are key factors to suppressing the activated immune system and then, if possible, quickly removing the trigger.

Current guidelines for HLH/MAS developed in 2022 by the European Alliance of Associations for Rheumatology/American College of Rheumatology recommend starting

immunomodulatory treatment as early as possible, immediately after diagnosis, without waiting for further diagnostic steps to determine the basis of the HS [8]. In syndromes with initially sparse symptomatology, this can protect the patient from multi-organ failure and catastrophic consequences [9]. This was done in our patient, implementing empirical therapy with glucocorticosteroids and anakinra, human interleukin-1 receptor antagonist (recommendation 2B) [8, 10]. Unfortunately, there are no clear guidelines regarding the treatment of secondary HLH/MAS [11, 12]. The key issue is to identify and treat the triggering factor. Since the child had signs of disseminated cancer that were clinically consistent with neuroblastoma, it was decided to introduce chemotherapy typical for neuroblastoma as soon as possible, in parallel with the HLH/MAS treatment.

The induction therapy regimen for neuroblastoma includes etoposide, a very important drug in the treatment of HLH. Etoposide was implemented into the HLH-94 protocol, and since then, significant improvement in treatment results has been documented, especially in severe forms of HLH with organ failure, as well as in malignancy-triggered HLH [13, 14]. Although our patient's general condition did not allow for full oncological diagnosis, and no final histopathological confirmation of the diagnosis was obtained, a good response to treatment — both in terms of HLH and neuroblastoma confirmed by the negativity of all malignancy markers and complete necrosis of the residual tumour masses — confirmed the correctness of the decisions made. In the context of a good response to induction chemotherapy and just 3 weeks after high-dose chemotherapy, the early and fulminant course of disease relapse — with absolutely lack of response to the applied second-line treatment — was surprising.

There are quite a lot of descriptions in the literature of paediatric cases of malignancy-related HLH, usually concerning lymphomas or leukaemia [15–20]. Two multicentre publications mention neuroblastoma among the causes of HLH: 2 cases in Turkey and one in China (but here during chemotherapy) [21, 22]. And only 3 independent reports presented children with neuroblastoma, but the HLH described therein was not the first manifestation of the malignancy; 2 cases describe HLH during chemotherapy of neuroblastoma [23, 24] (chemotherapy induced HLH) and the third one during relapse [25], which confirms the extreme rarity of the presented case.

CONCLUSIONS

Immunological mask of paediatric malignancy might cause many diagnostic and therapeutic problems, and it might contribute to complications and an unfavourable course of disease. Increased clinical awareness of malignancy-triggered HLH should facilitate diagnosis and therefore the optimal selection of therapeutic interventions. Further research is needed to understand the clinical

and biological bases of this complex, often life-threatening condition.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. The author thanks prof. Jan Styczynski for his help in preparing the manuscript.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lympho-histiocytosis: An update on pathogenesis, diagnosis, and therapy. *Best Pract Res Clin Rheumatol* 2020; 34: 101515.
2. Benevenuto C, Mussinatto I, Orsi C, et al. Secondary hemophagocytic lymphohistiocytosis in children. *Exp Ther Med* 2023; 26: 423.
3. Strenger V, Merth G, Lackner H, et al. Malignancy and chemotherapy induced hemophagocytic lymphohistiocytosis in children and adolescent – a single center experience of 20 years. *Ann Hematol* 2018; 97: 989-998.
4. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). *Pediatr Blood Cancer* 2019; 66: e27929.
5. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007; 48: 124-131.
6. Available from: <https://www.mdcalc.com/calc/10089/hscore-reactive-hemophagocytic-syndrome#next-steps>.
7. Debaugnies F, Mahadeb B, Ferster A, et al. Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. *Am J Clin Pathol* 2016; 145: 862-870.
8. Shakoory B, Geerlinks A, Wilejto M, et al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/ MAS). *Ann Rheum Dis* 2023; 82: 1271-1285.
9. Bami S, Vegrecha A, Soberman D, et al. The use of anakinra in the treatment of secondary hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2020; 67: e28581.
10. Eloiseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol* 2020; 72: 326-334.
11. Gurunathan A, Boucher AA, Mark M, et al. Limitations of HLH-2004 criteria in distinguishing malignancy-associated hemophagocytic lympho-histiocytosis. *Pediatr Blood Cancer* 2018; 65: e27400.
12. Lehmborg K, Nichols KE, Henter JI, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematologica* 2015; 100: 997-1004.
13. Bergsten E, Horne A, Arico M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood* 2017; 130: 2728-2738.
14. Henter JI, von Bahr Greenwood T. Etoposide therapy of cytokine storm syndromes. *Adv Exp Med Biol* 2024; 1448: 525-551.
15. Gopalakrishnan M, Ramanathan A, Jayaraman D, et al. Malignancy-associated secondary hemophagocytic lymphohistiocytosis

- mimicking an infection: a case report and review of the literature. *Cureus* 2024; 16: e56738.
16. O'Brien MM, Lee-Kim Y, George TI, et al. Precursor B-cell acute lymphoblastic leukemia presenting with hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2008; 50: 381-383.
 17. Cader FZ, Colmenero I, Mussai F. Hemophagocytic lymphohistiocytosis associated with 2 cases of pediatric lymphocyte-depleted classic Hodgkin lymphoma. *J Pediatr Hematol Oncol* 2019; 41: e341-e345.
 18. Huang Z, Jia Y, Zuo Y, et al. Malignancy-associated hemophagocytic lymphohistiocytosis in children: A 10-year experience of a single pediatric hematology center. *Hematology* 2020; 25: 389-399.
 19. Ćwiklińska M, Czogała M, Balwierz W, et al. Zespół hemofagocytarny u dzieci w różnych jednostkach chorobowych. *Przeg Lek* 2010; 67: 430-435.
 20. Murphy EP, Mo J, Yoon JM. Secondary hemophagocytic lymphohistiocytosis in a patient with favorable histology Wilms tumor. *J Pediatr Hematol Oncol* 2015; 37: e494-e496.
 21. Celkan T, Berrak S, Kazanci E, et al. Malignancy-associated hemophagocytic lymphohistiocytosis in pediatric cases: a multicenter study from Turkey. *Turk J Pediatr* 2009; 51: 207-213.
 22. Zhang WY, Zhang Y, Dong NN, et al. Clinical features and prognosis of malignancy-associated hemophagocytic lymphohistiocytosis in children: a clinical analysis of 24 cases. *Zhongguo Dang Dai Er Ke Za Zhi* 2018; 20: 295-297.
 23. Nascimento FA, Nery J, Trennepohl J, et al. Hemophagocytic lymphohistiocytosis after initiation of chemotherapy for bilateral adrenal neuroblastoma. *J Pediatr Hematol Oncol* 2016; 38: e13-e15.
 24. Kounami S, Nakayama K, Yoshiyama M, et al. Early-onset hemophagocytic lymphohistiocytosis after the start of chemotherapy for advanced neuroblastoma. *Pediatr Hematol Oncol* 2012; 29: 99-103.
 25. Nozawa A, Ozeki M, Yasue S, et al. Proinflammatory cytokine secretion in a patient with recurrent neuroblastoma related to the onset of malignancy-associated hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol* 2020; 42: e199-e201.