Clinical Case Report

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Non-Hodgkin lymphoma, diagnostic, and prognostic particularities in children – a series of case reports and a review of the literature (CARE compliant)

Cristina Oana Mărginean[a], Lorena Elena Meliţ, PhD[a,*], Emoke Horvath[b], Horea Gozar[c], Mihaela Ioana Chinceşan[a]

Abstract

Rationale: Non-Hodgkin lymphoma remains an unpredictable condition in pediatric patients.

Patient concerns: *Our first case* describes an 8-year-old boy with a history of iron deficiency anemia, admitted in our clinic for recurrent abdominal pain, weight loss, loss of appetite, diarrheic stools, and fever. *The second case* also describes an 8-year-old boy admitted for abdominal pain and vomiting. *The 3rd case* refers to a 4 years and 10 months old boy admitted in our clinic with abdominal pain and loss of appetite, who was initially admitted in the Pediatrics Surgery Clinic with the suspicion of appendicitis. *Our 4th patient* was a 5-year-old boy admitted in our clinic for abdominal pain and intermittent diarrheic stools.

Diagnoses: In the *first case*, the laboratory tests showed anemia, thrombocytosis, elevated inflammatory biomarkers, a low level of iron, and hypoproteinemia. The abdominal ultrasound and CT exam revealed an abdominal mass, and the histopathological exam established the diagnosis of *diffuse large B-cell lymphoma* of the bowel. In the *second case*, the laboratory tests pointed out anemia, elevated ESR and lactate dehydrogenase level, while both abdominal ultrasound and CT exams showed an abdominal mass. The histopathological exam confirmed the diagnosis of *Burkitt lymphoma*. Regarding our *3rd case*, the laboratory findings revealed leukocytosis, anemia, thrombocytosis, increased inflammatory biomarkers, elevated LDH, and a low level of iron. The abdominal ultrasound and the CT scan revealed an abdominal mass which, according to the histopathological exam, was a Burkitt lymphoma. Due to the cranial CT findings the patient was diagnosed with *IV stage Burkitt lymphoma* with central nervous system metastases. In *our 4th patients* we found leukocytosis, anemia, mildly increased inflammatory biomarkers, a high level of LDH, hypoproteinemia, and a low level of serum Ir. Both ultrasound and abdominal CT exams were negative, but the exploratory laparotomy identified an abdominal mass, and according to the histopathological exam the patient was diagnosed with *Burkitt lymphoma*.

Interventions: All the patients followed chemotherapy (B-NHL BFM 04 protocol) and supportive treatment.

Outcomes: The first patient died approximately 4 months after the completion of chemotherapy due to tumor relapse, the second patient died after the first cure of chemotherapy and the fourth patient died at approximately 2 years after the diagnosis. The third patient is recurrence-free after 2 years.

Lessons: Despite the advances in the management, NHL remains a fatal condition in pediatrics.

Abbreviations: BL = Burkitt lymphoma, CRP = C-reactive protein, CT = computer tomography, DLBCL = diffuse large B-cell lymphoma, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, Ir = iron, LDH = lactate dehydrogenase, PLT = platelets.

Keywords: children, lymphoma, prognosis

1. Introduction

Lymphoma is a malignant condition of the blood with an annual incidence of 15 cases per 1 million children in the USA, representing the 3rd most common cancers in pediatric age.[1] Lymphomas are divided in 2 main categories: Hodgkin (HL) and non-Hodgkin lymphomas (NHL), with specific clinical manifestations and treatment. In children, NHL comprises 4 wide categories: lymphoblastic lymphoma, Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma. Even though most of the children present with the novo NHL, some of these cases may be secondary to other etiologies, such as: inherited or acquired immune deficiencies, viruses, or are included in the spectrum of genetic syndromes.[1] Depending on ethnicity, lymphomas are much more frequent in Black Africans along with leukemias and central nervous system cancers in comparison with other ethnic groups, where leukemias

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[a] Department of Pediatrics I, [b] Department of Pathology, [c] Department of Pediatric Surgery, University of Medicine and Pharmacy, Tirgu Mureş, Romania.

[*] Correspondence: Lorena Elena Meliţ, Department of Pediatrics I, University of Medicine and Pharmacy, 38 Gh. Marinescu St., 540139 Tirgu Mures, Romania (e-mail: lory_chimista89@yahoo.com).

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and central nervous system were the most common types of malignancies.[2] For example, in Africa, the incidence of BL is approximately 50-fold higher than that encountered in the USA,[3] therefore being named endemic BL. Besides, endemic BL, there are also defined another 2 types of BL, sporadic and immunodeficient.

The clinical appearance of HHL in children depends in all cases on sites of involvement and the pathologic subtype. Therefore, lymphoblastic lymphoma presents most commonly as an intrathoracic or mediastinal mass and own a predilection for metastasizing in the bone marrow or central nervous system. Like-wise BL can also spread to those 2 sites, but it usually manifests and an abdominal mass in case of sporadic type, or head and neck in case of endemic type. On the other hand, DLBCL rarely metastasizes to the bone marrow or central nervous system, but it can manifest as both abdominal or mediastinal mass. Last, but not least, anaplastic large cell lymphoma is a particular type, which can present as a primary cutaneous tumor or a systemic disease, and is usually spreads to liver, lungs, spleen, and mediastinum, rarely in bone marrow or central nervous system.[1] Most common manifestations related to the tumor site are: fast lymph node enlargement without associated pain, cough, or dyspnea in case of intrathoracic masses, even superior mediastinal syndrome; ascites and increase of the abdominal perimetrium or bowel obstruction in case of abdominal masses; while in case of Waldeyer ring involvement, nasal congestion, earache, hearing loss, or tonsils enlargement are the most frequent symptoms; and bone pain in case of bone metastases.[1] In particular cases, NHL can also manifest as a life-threatening oncologic condition requiring intensive supportive care, like: superior mediastinal syndrome, acute paraplegias (spinal cord tumors), renal failure, or cardiac impairment due to tumor lysis syndrome, especially in BL, which can lead to hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia.[1] The treatment for children diagnosed with NHL includes multiagent systemic chemotherapy with intrathecal administration, surgical intervention is used mainly for diagnosing the tumors, while radiation therapy is only for central nervous system involvement, superior mediastinal syndrome, or paraplegias.[1]

We present this case series of abdominal lymphomas with the aim of underlining the variability of diagnostic and prognostic particularities encountered in children diagnosed with NHL.

The informed consent was obtained from the patients' mothers (legal guardians) for the publication of these cases.

2. Case series

2.1. Case 1

2.1.1. Presenting concerns. We present the case of an 8-year-old boy, admitted in our clinic with a history of recurrent abdominal pain for approximately 3 months for which he received antiparasytic drugs, weight loss (approximately 3 kg within the last month), loss of appetite, and diarrheic stools for 2 days associated with fever. His personal history revealed the fact that he was diagnosed with iron (Ir) deficiency anemia 3 months before the admission for which he received Ir supplements, but without any improvements.

2.1.2. Clinical findings. The clinical exam revealed the following pathological elements: pallor, poorly represented adipose tissue, small enlarged lymph nodes at the level of the neck and inguinal area, distended abdomen, abdominal tenderness spontaneously and at palpation on the left lateral side, hepatomegaly (at 4 cm under the right costal margin), and splenomegaly (the inferior pole palpable in the inferior left iliac fossa), weight (W): 20 kg, hight (H): 125 cm.

2.1.3. Diagnostic focus and assessment. The complete cellular blood count revealed anemia (hemoglobin [Hb] 8.7 g/dL, hematocrit 30.5%, medium cellular volume 64.5 fL), and thrombocytosis (platelets [PLT] 617,000/μL). We also identified elevated inflammatory biomarkers: C-reactive protein (CRP) 71.15 mg/L and erythrocyte sedimentation rate (ESR): 65 mm/h, a low level of Ir (Ir 2.76 μmol/L), and hypoproteinemia (total proteins 5.97 g/dL). The tests for viral hepatis, toxoplasmosis, rubella, cytomegalovirus, herpes virus, and Epstein Barr virus were within normal ranges. The medullar biopsy was negative. The abdominal ultrasound showed a retroperitoneal mass of approximately 134/61.4 mm that crossed the median line, a hypoechoic mass in the liver, hepatomegaly, splenomegaly, and extrinsic compression of the urinary bladder. We performed an abdominal CT scan which suggested that the aspect of the abdominal mass could plead for an intestinal lymphoma with spleen and renal secondary determinations. Therefore, the patient underwent a surgical intervention consisting in a segmental colectomy and subsequent colostomy in order to establish the diagnosis. The histopathological exam confirmed the diagnosis of DLBCL of the bowel.

2.1.4. Therapeutic focus and assessment. The patient underwent the B-NHL BFM 04 cytostatic protocol without any incidents during the treatment. We also administered supportive treatment.

2.1.5. Follow-up and outcome. Unfortunately, the patient was admitted at approximately 1 month after the completion of chemotherapy with an early recurrence presenting peritoneal carcinomatosis and multiple hepatic and renal secondary determinations. We initiated the B-NHL BFM 04 protocol, but the parents requested the cessation of the treatment and the patient's discharge due to the unfavorable prognosis. The patient died after approximately 3 months.

2.2. Case 2

2.2.1. Presenting concerns. The 2nd case also describes an 8-year-old boy admitted in our clinic due to the following complains: abdominal pain for approximately 2 weeks associated with 2 episodes of vomiting. His personal and family history did not reveal anything pathological.

2.2.2. Clinical findings. The clinical exam showed: multiple ecchymoses on the legs and surrounding the umbilical area, distended abdomen, a palpable abdominal mass in the right lateral side, hepatomegaly (2 cm under the right costal margin), W: 40 kg, H: 143 cm.

2.2.3. Diagnostic focus and assessment. The laboratory tests showed anemia (Hb 11.5 g/dL), elevated ESR (70 mm/h), and severely increased lactate dehydrogenase level (LDH 1174 U/L). The tests for viral hepatis, toxoplasmosis, rubella, cytomegalovirus, herpes virus, and Epstein Barr virus were within normal ranges. The medullar biopsy was negative. The abdominal ultrasound showed a giant retroperitoneal mass of approximately 149/145 mm with Doppler signal, comprising the bowel loops, and enlarged liver. The abdominal CT scan revealed a giant abdomino-pelvic mass (141/108/95 mm), with central necrosis, in

contact with small bowel loops, ascending colon, right psoas muscle, imprinting the right ureter, the inferior vena, and the right common iliac artery, abdominal enlarged lymph nodes, minimum ascites, and 1st degree right uretero-hydronephrosis due to compression. The patient benefited by partial surgical resection of the tumor, and the histopathological exam established the diagnosis of non-Hodgkin lymphoma, most-likely BL.

2.2.4. Therapeutic focus and assessment. We initiated the B-NHL BFM 04 cytostatic protocol, but on the 1st day after the first cure of chemotherapy (AA-24), the patient developed a severe medullary aplasia for which he received substitutive treatment (erythrocyte and PLT mass, human albumin), growth factor for granulocyte colonies, wide spectrum antibiotics, and supportive treatment.

2.2.5. Follow-up and outcome. The patient's evolution worsened progressively and he was transferred to the intensive care unit, where after a few hours he went into cardiac arrest and died.

2.3. Case 3

2.3.1. Presenting concerns. The 3rd case refers to a 4 year and 10 months old boy admitted in our clinic with abdominal pain for approximately 1 month and loss of appetite. We mention that the patient was initially admitted in the Pediatrics Surgery Clinic with the suspicion of appendicular block for which he received antibiotics treatment without any improvements, and the ultrasound revealed an abdominal mass with Doppler signal in the right iliac fossa. His personal and family history did not reveal anything pathological.

2.3.2. Clinical findings. The clinical exam at the time of admission in our clinic showed pallor, multiple small enlarged lymph nodes on the right side of the neck, and an abdominal mass in the right iliac fossa, W: 15 kg, H: 104 cm.

2.3.3. Diagnostic focus and assessment. The laboratory findings revealed leukocytosis (Leu 14,730/μL), anemia (Hb 11.2 g/dL), thrombocytosis (PLT 623,000/ μL), increased inflammatory biomarkers (CRP 15.62 mg/L, ESR 31 mm/h), elevated LDH (1123 U/L), and a low level of Ir (4.38 μmol/L). The tests for viral hepatis, toxoplasmosis, rubella, cytomegalovirus, herpes virus, and Epstein Barr virus were within normal ranges. The medullar biopsy was negative. The abdominal ultrasound performed in our clinic showed a solid mass in the right iliac fossa of approximately 74/44 mm, hypoechoic, with a hyperechoic center and Doppler signal, irregulated margins, that crossed the median line. The abdominal CT scan confirmed the ultrasound aspect, and therefore the patient underwent a surgical intervention with partial resection of the tumor, and subsequent left colostomy. The histopathological exam established the diagnosis of BL. The cranial CT scan showed secondary determination within the brain, and therefore our final diagnosis was stage IV BL, with central nervous system impairment.

2.3.4. Therapeutic focus and assessment. The patient underwent a complete cytostatic treatment according to the protocol B-NHL BFM 04, also receiving supportive treatment.

2.3.5. Follow-up and outcome. The patient's evolution was favorable, without any side-effects of the cytostatic regimen. The assessment after the chemotherapy proved the remission, without any signs of recurrence at 2 years after the diagnosis.

2.4. Case 4

2.4.1. Presenting concerns. The 4th case describes a 5-year-old boy admitted in our clinic due to abdominal pain and intermittent diarrheic stools for approximately 6 months. The patient was initially misdiagnosed in the regional hospital with severe malnutrition, edema due to hypoproteinemia, where he also benefited by an abdominal CT scan which did not reveal any pathological elements. His personal history revealed an obstetrical brachial plexus paresis and epilepsy at the age of 3 years for which he received antiepileptic treatment.

2.4.2. Clinical findings. The clinical exam at the moment of admission in our clinic revealed pallor, edema of the inferior limbs, multiple dental caries, poorly represented adipose tissues and muscular mass, hypotonia of the right superior limb, distended abdomen, abdominal tenderness, and diarrheic stools, W: 14 kg.

2.4.3. Diagnostic focus and assessment. The laboratory tests showed leukocytosis (Leu 15,500/μL), anemia (Hb 7.76 g/dL, medium cellular volume 64.6 fL), mildly increased inflammatory biomarkers (ESR 25 mm/h, CRP 15.1 mg/L) and LDH level (300 U/L), hypoproteinemia (total proteins 5.76 g/dL), and a low level of serum Ir (3.23 μmol/L). The tests for viral hepatis, toxoplasmosis, rubella, cytomegalovirus, herpes virus, and Epstein Barr virus were within normal ranges. The medullar biopsy was negative. The abdominal ultrasound was hindered by the patient's severe bloating, but it revealed ascites. Therefore, we decided to repeat the abdominal CT scan that revealed severe stasis at the gastro-duodenal level, a fistula between the proximal jejunal loops and the descending colon, ischemia of the bowel loops, mesenteric enlarged lymph nodes, and minimal adjacent fluid collections. Based on all these findings, the patient underwent an exploratory laparotomy that revealed a tumor mass involving the left colic angle, the terminal part of the duodenum, and the angle between the duodenum and the jejunum, with covered perforations at the level of the duodenum, jejunum, and colon. A partial surgical resection was performed, and the histopathological exam established the diagnosis of BL.

2.4.4. Therapeutic focus and assessment. The patient's evolution after the surgical intervention was initially burdened by multiple complications, and therefore, he underwent multiple re-interventions. After approximately 2 weeks, we were not only initiated the cytostatic B-NHL BFM 04 protocol, but also supportive treatment with favorable evolution.

2.4.5. Follow-up and outcome. The patient completed the chemotherapy without any major incidents. His evolution was favorable within the next 2 years after the diagnosis, but unfortunately, he eventually developed a relapse consisting in a retroperitoneal tumor mass and cerebral metastasis. Therefore, his parents refused treatment and he died.

3. Discussions

The incidence of lymphomas varies worldwide, 60% being classified as NHL, accounting for 8% of all pediatric malignant conditions.[4–6] In approximately 70% of patients diagnosed with NHL, the onset of the disease involves extranodal involvement, such as bone marrow and central nervous system impairment, being labeled as stage III or IV tumors.[1] Only one of our patients presented with advanced disease, diagnosed with stage IV BL due to the central nervous system metastasis. Despite this fact, he was the only one who survived. Sporadic BL is the most common

subtype in the USA and Western Europe, where the incidence is of approximately 2.2 cases per 1 million.[7] The most common onset age reported in the literature for BL is between 5 and 9 years of age.[8–10] Most frequently, BL affects males,[8,9] but it can also appear in females.[10] Similarly, our 3 cases diagnosed with BL were males, 2 with the age between 5 and 9 years, and 1 close to the age of 5 years, that is, 4 years and 10 months. The onset age for BL differs depending on the subtypes, therefore usually endemic BL appears at younger ages, 5 to 6 years of age in comparison to sporadic BL, 8 to 9 years of age.[11,12] Also, according to the study performed by Stefan and Lutchman,[13] white population tends to follow the sporadic pattern of BL. Even though our patients belong to the Caucasian population and therefore presented with sporadic BL, only 1 of 3 diagnosed with this type of malignancy had the age of 8 years, the other 2 tended to follow the endemic pattern of BL due to the younger age of onset, approximately 5 years.

It is well-known that the gastrointestinal tract is one of the most common sites for NHL, and that up to 90% of the primary gastrointestinal lymphomas are of B-cell origin.[14,15] B-cell NHL comprises BL and DLCBL. These types of malignancies affecting the gastrointestinal tract can manifest with different symptoms, such as abdominal pain, anorexia, weight loss, diarrhea, and ileus.[16] All of our 4 cases presented abdominal pain, 2 also presented diarrhea, anorexia was encountered in 2 of the 4 cases described above, while weight loss was found in only 1 case. In rare cases, DLBCL can also lead to bowel intussusception.[14,17] In addition to intussusception, presenting symptoms of both BL and DLBCL can also mimic appendicitis. Similarly, one of our patients with BL was initially admitted in the Pediatrics Surgery Clinic with the diagnosis of appendicitis. It is well-documented that sporadic or nonendemic BL has, in most of the cases (91%), an abdominal presentation affecting the distal ileum, the stomach, the cecum and/or mesentery, the kidneys, testis/ovary (6%), but it can also involve the breast, bone marrow (20%), and/or central nervous system (14%).[18] Similarly, all 4 cases described above were diagnosed with abdominal NHL. Among them, 2 out of 4 involved the colon, 1 affected the cecum, and 1 also extended to the small bowel. The literature also reported that BL can rarely involve the pancreas.[19,20] In addition, bone marrow involvement is encountered in under 10% of the cases at onset, but is more frequent in case of recurrence or with treatment resistance.[21] Of our 3 cases diagnosed with BL none presented bone marrow involvement, either the one with IV-stage BL, but in exchange that patient presented central nervous system metastasis. The diagnosis of NHL is suspected based on ultrasound or CT scans, but it is only confirmed by the histopathological exam. Nevertheless, a careful ultrasound exam performed by an experimented individual will guide the diagnosis very well.[22] CT scan is a useful diagnostic tool in case of patients with abdominal masses that can guide properly the surgical intervention, but it also establishes the exact stage of the tumor or the mediastinal adenopathies, and pleural, pericardial, renal, muscle, and peritoneal metastases.[23] Even though CT scans are very important for the diagnosis of abdominal tumors, in one of our cases this exam was not relevant, and therefore, we were forced to perform an exploratory laparotomy in order to identify the exact cause of the patient's symptoms.

The prognosis of children diagnosed with NHL is reported as very good, even in those with advanced disease. Due to the advances in the management of these cases, the prognosis children diagnosed with this type of tumor improved very much in the last decades. According to the studies performed on children below the age of 15 years, the survival rate at the ages of 5 and 10 years increased from 76.6% and 73%, respectively, between 1990 and 1994 to 87.7% and 86.9%, respectively, between 2000 and 2004. Even better, the survival rate at the age of 10 years in case of children diagnosed between 2005 and 2009 improved to 90.6%.[24] Despite all these data, only one of our patients diagnosed with NHL survived 2 years after the diagnosis. Many studies tried to identify the factors that influence the prognosis, and some of them underlined that high levels of LDH may be a negative prognostic factor for these patients.[25] Contrariwise, in our series of cases, only one patient of all 3 who died, presented a severely increased level of LDH.

4. Conclusions

NHL is one of the most aggressive tumors of childhood. Its clinical manifestations depend mostly on the tumor site. The prognosis of these tumors is not mandatory influenced by the tumor stage because the survival rate can be high even in cases of advanced stages at onset. Despite all these facts, NHL remains a fatal condition in children.

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