



Case Report

Childhood Biphenotypic Acute Leukemia with Extramedullary Intestinal Infiltrate, Presenting As a Mesenteric Thrombosis-A Case Report

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Abstract

The authors describe an unusual case of a childhood biphenotypic acute leukaemia with an extra medullary intraabdominal infiltrate, presenting as a mesenteric thrombosis and intestinal infarction. The child was first admitted to the Department of Surgery because of unspecific complaints of infrequent abdominal pain, nausea and vomiting without significant haematological deviations. The exploratory laparotomy found enlargement of the liver and spleen, bulky groups of enlarged mesenteric and retroperitoneal lymph nodes and total mesenteric thrombosis with necrotic changes involving the small bowel, leading to the misdiagnosis of Non-Hodgkin lymphoma. The diagnosis of biphenotypic acute leukaemia was confirmed by the immunohistochemistry analysis of the biopsied intraabdominal mass. The bone marrow aspiration biopsy showed blast cell infiltration with monoblasts/monocytes, consistent with the diagnosis of acute monoblastic leukaemia. Despite the aggressive chemotherapy induction, clearance of the blast cells and second-look surgery the outcome was fatal. The case report highlights an unusual and life-threatening surgical complication of a very rare malignancy.

Introduction

Mixed-phenotype acute leukaemia (MPAL), also known as biphenotypic acute leukaemia (BAL) is a category, introduced in the World Health Organization (WHO) classification to describe cases with multilineage expression of surface markers on the blast cells or concomitant presence of two separate cell lineages in one malignant clone [1]. It is a rare entity in childhood, accounting for approximately 2-5% of the cases with acute leukaemia in some reported series [2]. There are no specific clinical presentations or chromosomal aberrations reported for BAL. On the other hand, acute leukaemia can present with a variety of life-threatening features: acute tumour lysis syndrome, cerebral and pulmonary leukostasis, superior mediastinal compression, disseminated

intravascular coagulation or hypercoagulability state and an increased risk of thromboembolic events. The latter complication affects more frequently adults, predominantly involves the venous circulation and rarely the arteries [3]. Mesenteric arterial thrombosis is unusual as an initial manifestation of acute leukemia. We present a very rare case of a childhood BAL with an extramedullary intraabdominal infiltrate, presenting as a mesenteric thrombosis and intestinal infarction.

Case Report

An 11-year-old female was admitted to the Department of Surgery with complaints of infrequent abdominal pain, nausea and vomiting for the last two weeks. She was treated conservatively

without any improvement. The physical examination was only remarkable for marked abdominal distension, tenderness on palpation, positive Blumberg's and Mendel's signs and ineffective attempts for defecation. The laboratory results on admission showed haemoglobin – 102 g/l, red blood cells – $3.83 \times 10^{12}/l$, platelets – $236 \times 10^9/l$, leukocytes – $8.47 \times 10^9/l$, differential blood count: neutrophils – 66%, monocytes – 22%, lymphocytes – 12% and lactate dehydrogenase – 601 UI/l. The abdominal contrast enhanced computed tomography (CT) scan revealed severe dilation and increased fluid content of the duodenum and the intestinal loops, diffuse changes in the intestinal wall and pneumatosis in some of the loops (indirect sign of bowel infarction), lack of contrast in the spleen artery, enlarged abdominal lymph nodes and ascites (Figure 1 and 2). Exploratory laparotomy was performed, and enlargement of the liver and spleen, bulky groups of enlarged mesenteric and retroperitoneal lymph nodes (Figure 3) and total mesenteric thrombosis with necrotic changes involving the small bowel were detected (Figure 4), as well as haemorrhagic effusion in the peritoneal cavity. A lymph node biopsy was taken and a peritoneal drainage was placed, as a bowel resection was not feasible because of the extent of the intestinal involvement. The child was transferred to the Pediatric ICU with the suspicion of a Non-Hodgkin lymphoma. The histological result, which was received later, confirmed the macroscopically suspected diagnosis.

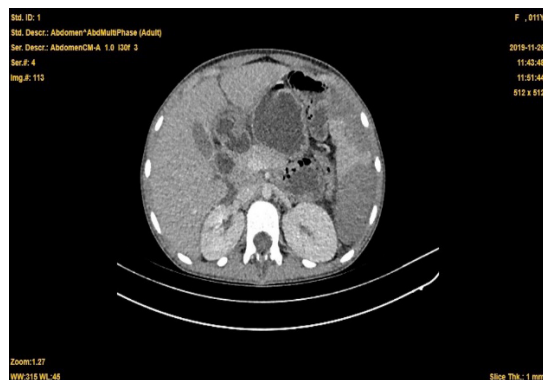


Figure 1: Pre-surgical abdominal CT, showing severe dilation and increased fluid content of the intestinal loops, diffuse changes in the intestinal wall and pneumatosis in some of the loops; spleen infarction.

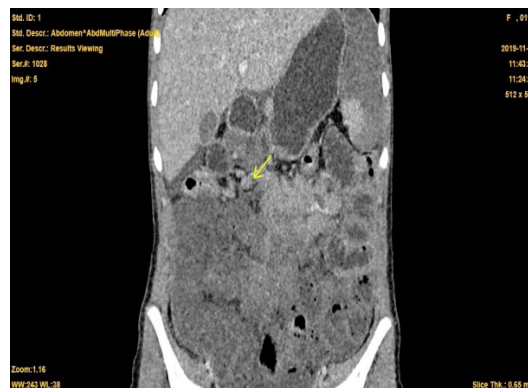


Figure 2: Abdominal CT before the first surgery (longitudinal plane), showing severe dilation and pneumatosis in some of the loops and extramedullary leukemic infiltrates (arrow).

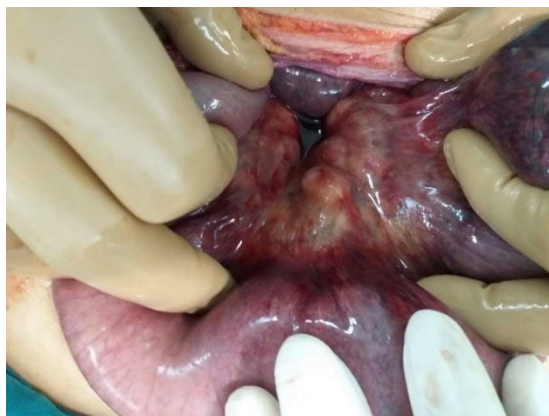


Figure 3: Macroscopic intraoperative findings of extramedullary leukemic infiltrates and hemorrhagic effusion.



Figure 4: Macroscopic intraoperative findings of intestinal infarction and necrotic changes.

Upon the admission to the Pediatric ICU the patient was in a severely impaired general condition, but alert and orientated, with moderate diffuse abdominal pain on palpation and abdominal distension, decreased peristalsis and unconvincing signs of peritoneal irritation. There was no peripheral lymph nodes' enlargement or hepatosplenomegaly on palpation. The breathing sounds were clear bilaterally without tachypnea or dyspnoea. The arterial blood pressure was 100/60 mm Hg and the heart rate – 88 beats/minute. The complete blood count showed anaemia: haemoglobin – 75 g/l, leucocytosis – $46 \times 10^9/l$ and mild thrombocytopenia: $138 \times 10^9/l$ and the following differential blood count: neutrophils – 66%, monocytes – 23% and lymphocytes – 11%. The chemistry results were within reference range except for mildly elevated lactate dehydrogenase – 601 UI/l and C-reactive protein – 19 mg/l. The coagulation tests showed prolonged prothrombin time: 21.5", elevated D-dimers: 35.7 mcg/ml and normal activated partial thromboplastin time – 26.3". The blood gas analysis showed normal pH, mild hypoxia and hypercapnia. As a part of the oncological work-up, we performed bone marrow aspiration biopsy. Morphologically the bone marrow was hypercellular, infiltrated by large-sized blast cells (50% of the cellular content) with abundant basophilic vacuolated cytoplasm, containing granules and irregularly shaped "monstrous" nucleus, consistent with acute monoblastic leukaemia (AMoL, M5 FAB subtype). The flow cytometry of the bone marrow showed 25% monoblastic population positive for myeloperoxidase, CD13, CD33, CD64, CD14 (\pm), CD11b, CD36 (\pm), CD15 (\pm), CD16 (\pm) and negative for CD300e, HLA DR, CD34, CD117 and 30% monocytic population positive for CD64, CD14, CD36 and CD300e. The second review of the immunohistochemistry of the biopsied intraabdominal infiltrate detected biphenotypic malignant clone, compatible with T-cell lineage (positivity for CD3, CD5, CD7 and CD2) and myeloid lineage (positivity for CD11c, CD33, CD68, and lysozyme). The molecular genetic tests from the bone marrow sample were negative for AML1-ETO, CBF β -MYH11, M-BCR-ABL, m-BCR-ABL, FLT3-ITD and FLT3-TKD.

On the basis of the morphological and flow cytometry findings from the extramedullary abdominal infiltrate we made the diagnosis of BAL with prevailing monoblastic/monocytic malignant clone, which was the only present in the bone marrow of the patient. Chemotherapy was started according to AML BFM 2012 protocol with AIE induction (Cytarabine at a dose of 100 mg/m²/day as continuous infusion on days 1 and 2; Cytarabine at a dose of 100 mg/m² as a 30-minute infusion every 12 hours on days 3 to 8; Idarubicin 12 mg/m² on days 3, 4, and 5; Etoposide 150 mg/m² on days 6, 7, and 8) with omission of the lumbar puncture and intrathecal injection of Cytarabine to avoid the abdominal discomfort resulting from the recent surgery and the placed drainage. Dexamethasone was also added to the induction therapy because of the presence of a T-cell malignant clone in the abdominal

leukemic infiltrate. The supportive therapy consisted of parenteral nutrition, antibiotics and antifungal drugs, anticoagulation with enoxaparin and continuous infusion of morphine. After the end of the chemotherapy block granulocyte colony-stimulating factor was also added. During the next weeks the marked abdominal distension, diffuse tenderness on palpation and decreased to absent peristalsis persisted and the patient was not passing stools except for several episodes of hematochezia. The daily discharge of biliary to feculent materials from the nasogastric tube reached 2500 to 3000 ml and the hemorrhagic secretion from the peritoneal drainage also persisted. Despite the conducted chemotherapy and the clearance of the blast cells from the peripheral blood, on the 20th post therapeutic day intestinal perforation occurred, which required relaparotomy. Intraoperatively diffuse necrotic changes on the thinned intestinal wall were detected and bowel resection with ileostomy was not feasible. Three days after the second surgery a fatal outcome due to multiple organ failure followed.

Discussion

Herein we report a very rare case of childhood BAL with extramedullary abdominal infiltrate, causing total mesenteric thrombosis and widespread intestinal infarction, thus turning out to be the life-limiting prognostic factor of the malignancy. The diagnosis is based on the WHO flow cytometry criteria, which are met by the immunohistochemistry findings in the biopsy specimen from the intraabdominal lesion [4]. In this case we have detected two separate populations of blast cells, thus meeting the criteria of T/myeloid MPAL. T/myeloid MPAL accounts for less than 1% of all acute leukemia cases and is probably more frequent in children than B/myeloid MPAL [1]. Generally, the frequency of BAL remains largely unknown, as well as the best standard of treatment. Myeloid-directed and lymphoid-directed therapies are explored without proven advantage on the treatment response [4,5]. Because of the monoblastic/monocytic lineage specificity of the malignant clone in the bone marrow we started AML-directed therapy combined with Dexamethasone and this resulted in peripheral blast clearance. The clinical presentation of the reported case is more consistent with a myeloid sarcoma concomitant with a bone marrow involvement from AMoL, but the surprising bilinear characteristic (T-cell and monoblastic) of the extramedullary abdominal infiltrate also poses therapeutic challenges. The myeloid sarcoma is defined as an extramedullary mass, which consists of myeloid blast cells and could occur concurrently with acute myeloid leukemia in the bone marrow or as an isolated lesion. The frequency in children is higher than in adults and the most frequently involved sites are the skin and the bones, especially the orbit [6,7]. The gastrointestinal tract is a rare localization of a myeloid sarcoma with few case reports in the literature [8-14]. The largest reported series describes 11 cases, of which only one is with full-thickness intestinal infiltrate, proven by a biopsy [15]. The

authors find a strong association with CBFb-MYH11 positivity of the blast cells in this case series, confirmed also by other case reports [16]. Besides, mesenteric thrombosis especially with this severity is exceedingly rare in children and there are only few published case reports and small series [18,19]. Most commonly it is associated with hereditary thrombophilia, nephrotic syndrome or polyarteritis nodosa [20,21]. In a case series of 24 children with venous thromboembolism at uncommon sites, only 2 cases of mesenteric thrombosis were observed [22]. To our knowledge, this is the first reported case of total mesenteric artery occlusion associated with childhood leukemia. In conclusion, the surgeons should be aware of this rare and potentially fatal complication of childhood leukemia, which could occur without any alarming hematological signs, pointing out towards a malignancy. Although the most common cause for an intestinal obstruction by a tumor is Non-Hodgkin lymphoma, other causes should also be considered.

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