ACTA MEDICA LITUANICA. 2018. Vol. 25. No. 1. P. 23–30


# Primary gastric Burkitt lymphoma-induced anaemia: a case report and a literature review

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**Background.** Primary tumours of the gastrointestinal tract are very uncommon in children. They can present with anaemia caused by gastrointestinal acute or chronic bleeding. One of the most common gastrointestinal tumours is Burkitt lymphoma. This lymphoma is a highly aggressive, rapidly growing B-cell neoplasm, making survival without treatment possible only for a few weeks. For this reason it requires immediate hospitalization and treatment.

**Case report.** We report a case of a gastric Burkitt lymphoma in an adolescent girl who presented with anaemia due to gastrointestinal bleeding. She received out-patient care with iron medications orally due to suspected iron-deficiency anaemia but there was no sufficient effect. The patient was referred to Children's Oncohematology Department with a progression of symptoms (weakness, fatigue, sound in the ears, and nausea) five months after anaemia was diagnosed in the complete blood count. The imaging tests showed a massive solid tumour with bleeding in the stomach. The final diagnosis was a histologically atypical Burkitt lymphoma. Chemotherapy treatment was started according to NHL-BFM 2004 paediatric protocol.

**Conclusions.** Non-Hodgin's lymphoma is the most common malignancy of the gastrointestinal tract in children and about 75% of these tumours are Burkitt lymphomas. They can present with anaemia in the complete blood count due to bleeding. Reticulocyte test and serum ferritin level test help to differentiate pathophysiological origin of anaemia. Combination chemotherapy according to standardized protocols is the best current standard of care and has a very good clinical response without unfavourable risk factors.

**Keywords:** gastrointestinal, Burkitt lymphoma, adolescent, anaemia, bleeding

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## INTRODUCTION

Burkitt lymphoma (BL) is a highly aggressive, rapidly growing B-cell neoplasm that is characterized by dysregulation of the C-MYC oncogene (1). This subtype of non-Hodgkin lymphoma (NHL) generally involves the abdomen as a primary site of presentation (2, 3). Burkitt lymphoma can occur in all parts of the gastrointestinal tract (GI) from the stomach to the rectum, but the most frequent location is small and large intestines (4, 5). Overall, BL is the most common subtype of primary tumours of GI tract. However, the actual incidence in the paediatric population is unknown due to low prevalence (4, 6). Patients with BL often complain of abdominal pain (1). It can also present with anaemia caused by acute or chronic gastrointestinal bleeding (1, 6).

We report an extremely rare case of an adolescent female diagnosed with Burkitt lymphoma located in the stomach. The first symptom of this disease was anaemia in the complete blood count. An informed written consent was obtained from the patient for inclusion in the present study.

## CLINICAL CASE

A 15-year-old female, who presented with a one-week history of weakness and fatigue, was consulted by a family physician. The full blood count showed anaemia with haemoglobin (Hb) 80 g/l (mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were unknown). The physician suspected iron-deficiency anaemia and prescribed iron medication orally. During the one-month treatment period, haemoglobin increased to 90 g/l with regression of symptoms. Five months after anaemia was diagnosed in the full blood count, the patient was admitted to Children's Oncohematology Department. Upon presentation to the department, clinical symptoms were progressing again for four days, with greater weakness, fatigue, sound in the ears, and nausea. She had not had complaints related to gastrointestinal system disorders; the last menstruations were not abundant and regular; her family history was negative for gastrointestinal malignancies. Moreover, the parents pointed out that the girl was on a diet with a limited amount of meat and with plenty of physical activity. On physical examination, the patient presented with pale skin and mucosa, tachycardia (144 beats per minute), and harsh systolic murmur. There was no respiratory distress, lymphadenopathy, abdominal pain and masses, hepatosplenomegaly, and no melena. The laboratory tests showed severe normocytic hypochromic anaemia (Hb 44 g/l, MCV 76.2 fl, MCH 20.6 pg, MCHC 270 g/l), erythrocytopenia ($2.14 \times 10^{12/l}$), low hematocrit level (16.3%), reticulocytosis (5.13%), and an elevated platelet count ($543 \times 10^{9/l}$). The peripheral blood smear revealed no immature cells. Biochemical analysis showed a normal ferritin level (12.38 mkg/l) and normal results of coagulation. Occult blood was positive in the stool. At ultrasound examination, the left subcostal view showed an empty stomach with an unevenly thickened wall (Fig. 1). A closer look revealed a polymorphic tumour with hypoechogenic, nodal architecture (Fig. 2). The tumour emerged from the wall of the antrum and pylorus, and measured $120 \times 102 \times 86$ mm. Gas foci, probably originating from the compressed stomach, were seen inside. The tumour revealed active blood flow (Fig. 3). Lymphadenopathy was observed in the surrounding mesenteric fat. The tumour mass was located adjacent to the pancreas, the spleen, and the left liver lobe. We found neither evidence of invasion of the pancreas nor liver metastasis.

An esophagogastroduodenoscopy (EDG), which was performed under general anaesthesia, showed a massive solid tumour in the gastric antrum and pylorus with ulceration and protrusion into the gastric lumen (Fig. 4). Multiple biopsies of the tumour were obtained. Immunohistochemistry revealed that neoplasm cells were positive for CD10, Bcl6, c-MYC (8q24 translocation) and negative for MUM1, TdT and Bcl2, Ki67 proliferative index higher than 95%. The final diagnosis was atypical Burkitt lymphoma. Magnetic resonance imaging (MRI) of the abdomen showed a large mass originating from the gastric wall but not infiltrating the surrounding organs, approximately $13.0 \times 5.0 \times 11.0$ cm, with a pathologic left para-aortic lymph node. The computed tomography (CT) of the chest did not indicate any lymph node involvement or distant metastasis. Bone marrow aspirate and cerebrospinal fluid were negative for lymphoma. Based on the results of

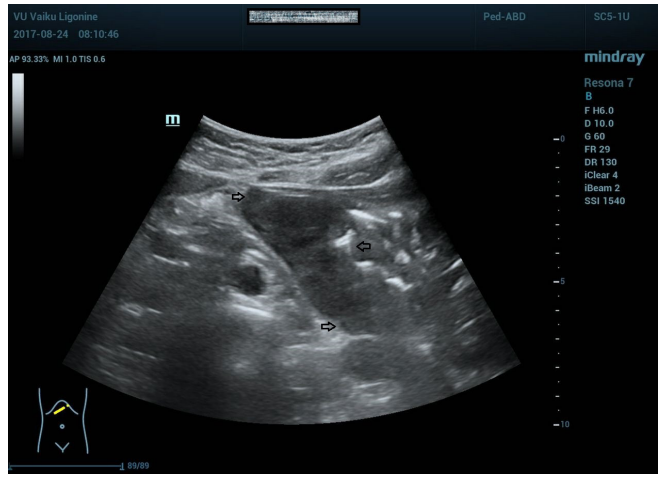


**Fig. 1.** Axial sonogram of the upper abdomen. A mass (arrows) is emerging from the stomach wall. Gas foci can be seen inside the tumour

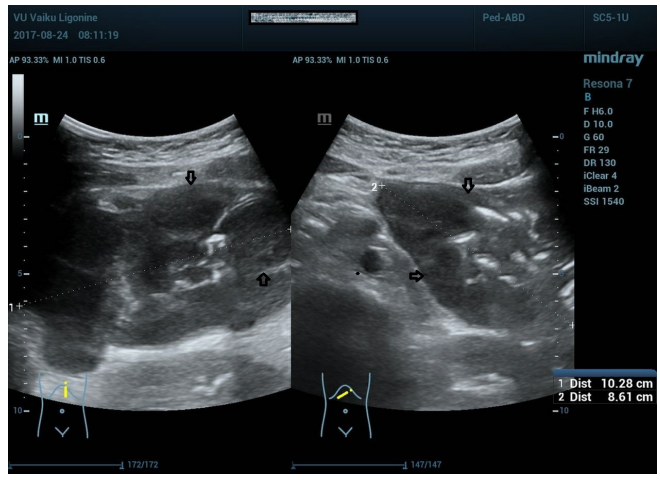


**Fig. 2.** Sagittal (A) and axial (B) sonograms of the upper abdomen. The mass is heterogeneous, nodular elements

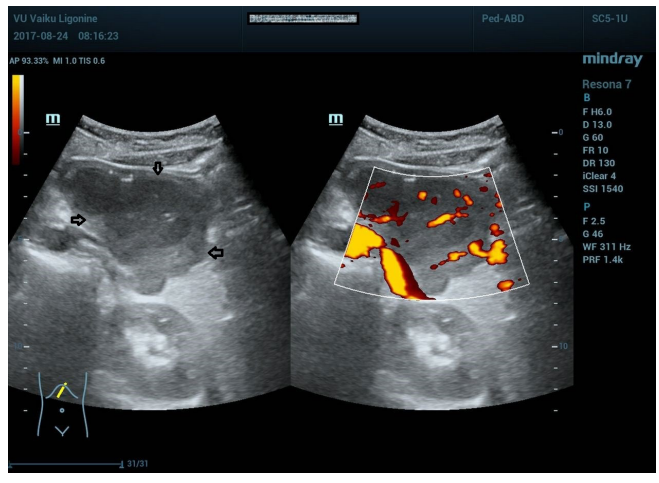


**Fig. 3.** Oblique B-mode (A) and power Doppler (B) views of the mass. Active blood flow

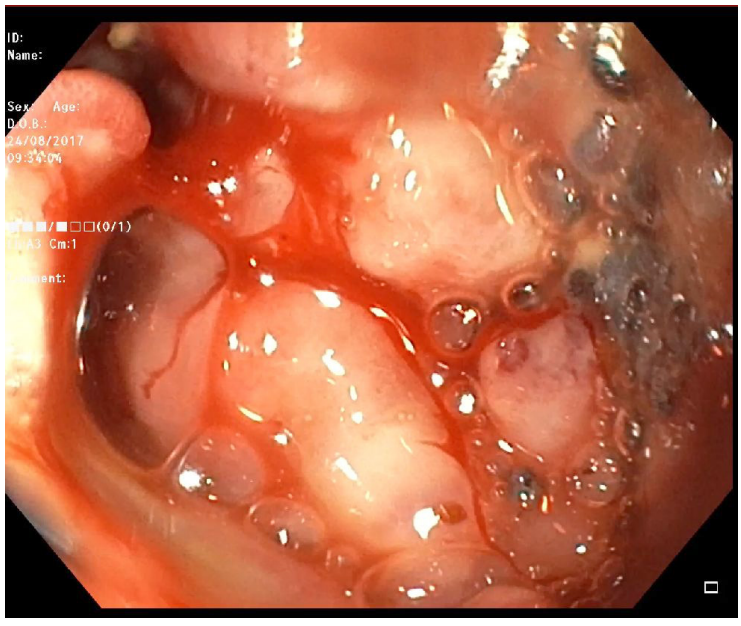


**Fig. 4.** Esophagogastroduodenoscopy revealed a massive solid tumour in gastric antrum and pylorus with ulceration and protrusion into the gastric lumen

the examinations, the patient was graded as a second risk group (R2) since lactate dehydrogenase (LDH) levels were normal 217 U/l. The treatment was started according to the paediatric NHL-BFM 2004 protocol. She went on to receive four chemotherapy blocks. After the second chemotherapy block, a follow-up EGD showed tumour involution and scarification in the gastric wall (Fig. 5).

## DISCUSSION

Non-Hodgin lymphoma is the most common alimentary tract malignancy in children and comprises 74% of all GI cases. The most frequent histological subtype of these tumours is Burkitt lymphoma, which accounts for up to 75% of the lesions (6). In paediatric population, Burkitt lymphoma most

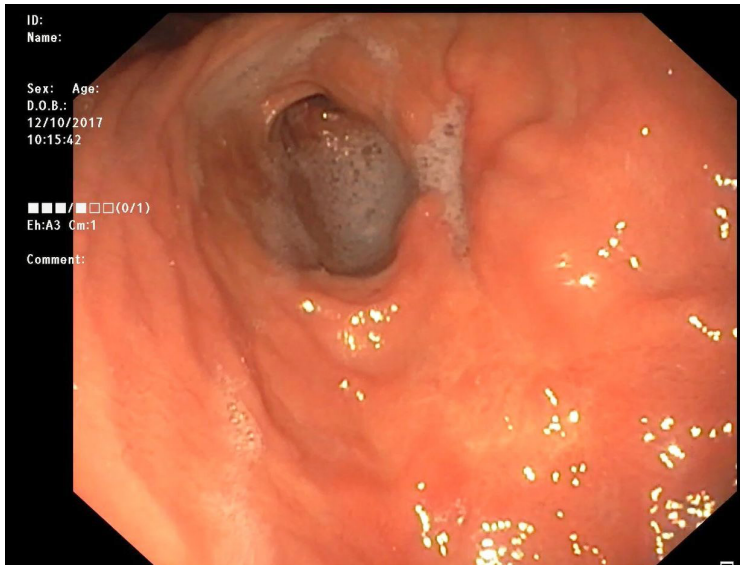


**Fig. 5.** Esophagogastroduodenoscopy showed tumour involution and scarification in the gastric wall after the second chemotherapy block

commonly involves small intestine and the second – large intestine (4). However, this lymphoma rarely develops in the stomach; therefore the majority of the available literature describes single case reports. One large retrospective series on abdominal Burkitt lymphoma in children, published by Alireza Mirshemirani et al. in 2016, identified 17 cases (37%) from 46 patients with BL in small intestine and only two cases (4%) in the stomach (1).

Comparing paediatric and adults studies, Burkitt lymphoma is a very rare variant of gastric lymphomas in adults as well. The most common types of gastric lymphomas in adult population are diffuse large B-cell lymphoma (DLBCL) and marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) (7, 8). In one large study, 61 primary lymphomas of the GI tract were diagnosed in Clinical County Emergency Hospital of Romania from 2010 to 2016. Thirty-four of these cases were in the stomach. According to the histological type, 25 of the 34 gastric lymphomas (73.53%) were diagnosed as DLBCL, six as MALT lymphomas (17.65%), two as B-cell lymphomas-not otherwise specified (5.88%), and only in one case (2.94%) Burkitt lymphoma was identified (9). For adults, MALT lymphoma is associated with *Helicobacter pylori* infection in the stomach (10).

MALT lymphoma in children population is extremely rare: only a few cases are found in the literature. Also, the relationship between NHL and *H. pylori* in paediatric population is controversial. One single study revealed that two cases of gastric BL were related with *H. pylori* infection (11). Results of another study suggested that *H. pylori* may not be the responsible agent for NHL in the abdomen in childhood (12).

The peak age for Burkitt lymphoma in children is 5–15 years, with more cases in boys than in girls (3.9:1.1) (13). BL is characterized by dysregulation of the c-MYC oncogene (13). Deregulation of c-MYC prevents B-cell differentiation and has oncogenic activity (6). Cytogenetic evidence of c-MYC rearrangement is the gold standard for the diagnosis of BL (14). Three major clinical types of Burkitt lymphoma exist: (1) the endemic form, which is a common childhood malignancy strongly associated with the Epstein-Barr virus (EBV), (2) the non-endemic (sporadic) form which is rare, and (3) immunodeficiency-related BL, mostly seen in AIDS patients. The sporadic form typically presents itself as extranodal disease. The clinical manifestation is related to the location of the primary tumour. According to various studies, the most common presentation of primary abdominal Burkitt lymphoma is reported to be abdominal pain (85%), followed by abdominal swelling, vomiting, constipation, diarrhoea, melena, and rectal bleeding (1, 5). Symptoms can present themselves urgently with an acute exacerbation caused by intussusception, appendicitis, perforation, or bowel obstruction (6). About 14% of Burkitt lymphoma tumours can arise in the bone marrow. This variety is called Burkitt cell leukemia (3). CNS involvement is diagnosed in 8.8% of patients with Burkitt lymphoma/leukemia (13).

The stage of the disease in children in NHL is usually determined according to the St. Jude staging system modified by Murphy. In this staging classification, primary localized gastrointestinal tumour is identified as stage II. The German Berlin-Frankfurt-Munster (BFM) protocol distinguishes four therapy risk groups (R1-R4) based on the stage of the disease, resectability, the amount of LDH and CNS, or bone marrow involvement (2, 13). The diagnosis of Burkitt lymphoma and its stage are confirmed by histological and imaging findings (15). However, these diagnostic methods come with a number of distinct challenges in paediatric population. Esophagogastroduodenoscopy in children almost always needs to be performed under anaesthesia. In our case report, esophagogastroduodenoscopy under general anesthesia was done on the second day after abdominal ultrasound findings.

The main treatment is combination chemotherapy according to the B-NHL BFM 2004 protocol (13). Considerable progress has been achieved, with survival rates exceeding 80%, largely because of a better understanding of the biology of the different subtypes and national and international collaborations (16). Burkitt lymphoma usually has good clinical response to chemotherapy treatment. In several clinical reports, the 5-year event-free survival (EFS) is about 82–88% in adolescent and children respectively. The 3-year EFS is more than 95% for R1 and R2 group patients, 93% for R3 and R4 group patients, and 70% in patients with CNS disease at presentation according to paediatric NHL-BFM-95 protocol (13, 17). Between

July 1989 and March 2007, relapses were studied in the LMB89, 96 and 2001 studies of the French Society of Paediatric Oncology (Société Française des Cancers de l'Enfant). Of 1322 patients, 67 (5%) relapsed: 57 had Burkitt lymphoma and ten had large-cell histology. Relapse was associated with the increase of lactate dehydrogenase (LDH) level to double the normal level, and CNS and/or bone marrow involvement (18).

In the literature, the second most common gastrointestinal tumour of childhood is carcinoma (4). However, in most cases of gastric Burkitt lymphoma need to be differentiated with gastrointestinal stromal tumour (GIST). GIST is found in the stomach in about 60% of cases. The macroscopic view is similar to the one that was found in our patient during endoscopic investigation: solid, white or rosy, commonly ulceral, hemorrhagic surface with cystic degeneration and necrosis (19, 20). There is female predominance and the median age of diagnosis is 14 years. Kaemmer and colleagues documented 59 patients from 106 published articles and 86% of them presented with anaemia (acute and/or chronic), melena, hematemesis, pallor, fatigue, or syncope (20). GIST is diagnosed on the basis of the morphology and immunohistochemical findings (21). The 3-year EFS of GIST is lower compared to Burkitt lymphoma (22).

Differential diagnosis of anaemia helps to identify the origin of anaemia. Iron deficiency anaemia is a type of microcytic hypochromic anaemia with decreased or normal levels of reticulocytes and decreased serum ferritin level (23, 24). After acute bleeding the most typical view is reticulocytosis and normocytic hypochromic anaemia (23, 24). In addition, the reticulocyte count can increase in post hemolytic anaemia and in response to therapies such as iron supplementation (25). Comparing acute and chronic post hemorrhagic anaemia, chronic anaemia attributes of iron deficiency view in laboratory tests (24). Our patient's laboratory tests showed severe normocytic hypochromic anaemia with reticulocytosis and a normal serum ferritin level. These results helped in rejecting iron deficiency anaemia and rapidly finding the source of bleeding.

## CONCLUSIONS

Primary gastrointestinal tumours in children are rare. Non-Hodgin lymphoma remains the most common malignancy of the gastrointestinal tract in children. In most cases the histologic subtype of these tumours is Burkitt lymphoma. It can present with anaemia caused by gastrointestinal acute or chronic bleeding. Complete blood count with reticulocyte test and ferritin level helps to differentiate pathophysiology of anaemia. Burkitt lymphoma is a highly aggressive, rapidly growing neoplasm. However, if treatment is started in time and there is no unfavorable risk factors, the good clinical response with 3-years EFS is more than 95%. Combination chemotherapy according to standardized protocols is the best current standard of care.

Received 22 January 2018
Accepted 15 February 2018

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## PIRMINĖS SKRANDŽIO BERKITO (BURKITT) LIMFOMOS SUKELTA ANEMIJA: KLINIKINIO ATVEJO PRISTATYMAS IR LITERATŪROS APŽVALGA

*Santrauka*

**Įvadas.** Pirminiai piktybiniai virškinamojo trakto navikai yra labai retas vaikų susirgimas. Piktybinis procesas gali pasireikšti anemija, kurią sukelia lėtinis ar ūminis kraujavimas iš virškinamojo trakto. Vienas iš dažniausių virškinamojo trakto navikų yra Berkito limfoma. Ši limfoma labai agresyvi, greitai auga B-ląstelių neoplazma, negydant išgyvenamumo trukmė tik kelios savaitės, todėl reikalinga greita hospitalizacija ir gydymas.

**Klininkinis avejis.** Pristatome klinikinį paauglės atvejį, kuri atvyko dėl anemijos, sukeltos kraujavimo iš virškinamojo trakto. Įtariant geležies stokos mažakraujystę, pacientė ambulatoriškai gydyta peroraliniais geležies preparatais, tačiau pakankamo efekto negauta. Po penkių mėnesių, kai bendrame kraujo tyrime buvo nustatyta anemija, mergina pateko į vaikų onkohematologijos skyrių dėl progresuojančių klinikinių simptomų (silpnumo, nuovargio, ūžesio ausyse ir pykinimo). Vaizdiniuose tyrimuose skrandyje buvo matomas didelis kraujuojantis solidinis navikas. Histologiškai patvirtinta atipinė Berkito limfoma. Pradėtas chemoterapinis gydymas, remiantis Europoje standartizuotu vaikų B-NHL BFM 2004 protokolu.

**Išvados.** Ne-Hodžkino limfoma yra dažniausiai nustatomas piktybinis virškinamojo trakto navikas vaikams, 75 % atvejų histologiškai patvirtinama Berkito limfoma. Ši limfoma dėl kraujavimo gali sukelti anemiją. Patofiziologinę anemijos kilmę padeda diferencijuoti bendras kraujo tyrimas su retikuliocitų skaičiumi ir serumo feritino kiekio nustatymas. Geriausias gydymo standartas yra polichemoterapija, taikoma pagal Europoje standartizuotą vaikų B-NHL BFM 2004 protokolą. Nesant prognostiškai nepalankių veiksnių pasiekiamas labai geras atsakas.

**Raktažodžiai:** virškinimo traktas, Berkito limfoma, paauglys, anemija, kraujavimas