

## Burkitt's Lymphoma/Leukemia in a 15-Year-Old Male

Tanakorn Songrug, Brent A. Adler, M.D., and Samir B. Kahwash, M.D.

We present the case of a 15-year-old male with sporadic Burkitt's lymphoma/leukemia. The patient presented with right lower quadrant abdominal pain and masses in the terminal ileum and pelvis, and was subsequently demonstrated to have involvement of the bone marrow. We discuss differential diagnoses and approach to diagnose and stage this disease. A review of the clinical, radiologic, and pathologic features of Burkitt's lymphoma/leukemia are also presented.

### Introduction

Burkitt's lymphoma was described in 1958 by Denis Burkitt in Africa [1]. It is a malignancy arising from mature B-cell lymphocytes and one of the most rapidly proliferating neoplasms known with doubling time of only about 25 hours [2]. The World Health Organization Classification of Lymphoid Neoplasms lists three clinical variants: endemic, sporadic, and immunodeficiency-associated [3]. Endemic Burkitt's lymphoma refers to the cases that occur in equatorial Africa, usually

in children 4-7 years old, and often involving the jaws and other facial bones with less involvement of the abdominal organs [2]. Epstein-Barr virus is involved in nearly all endemic cases [4]. Sporadic Burkitt's lymphoma/leukemia often involves the abdomen, especially the ileocecal area. However, the ovaries, kidneys, omentum, Waldeyer's ring, breast and other sites may be involved as well. The sporadic form occurs worldwide with no specific geographic or climate predilection. Within the U.S. and Western Europe, the sporadic form accounts for 1%-2% of all adult Lymphoma and 40% of Lymphoma in children [2]. Immunodeficiency-associated Burkitt's lymphoma primarily occurs in HIV patients, allograft recipients, and individuals with congenital immunodeficiency. By convention, the term Burkitt's Leukemia is used when Burkitt's blasts are present in the bone marrow at 20% or more.

### Case Report

A previously healthy 15-year-old Caucasian male presented with a 5-week history of intermittent right lower quadrant abdominal pain, non-bilious emesis, constipation, and low grade fevers with accompanying

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Abbreviations: CT, computed tomography

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Figure 1. 15-year-old male with Burkitt's lymphoma. Abdominal radiograph shows mucosal thickening in a loop of bowel in the patient's right hemipelvis. There is a soft tissue fullness overlying the right sacroiliac joint that may represent a mass. Moderate amount of stool and gas are presented in the ascending and transverse colon with no evidence of obstruction or calcification.

night sweats and chills. The patient denied chest pain or tightness, palpitation, or dyspnea. Prior to this illness, he had no significant past medical history and took no medication. His only previous surgery or hospitalization was tympanostomy tube placement when he was 6 years old. His symptoms were initially attributed to infectious gastroenteritis. However, his symptoms continued to progress and he had reportedly lost about 15 lb. over the course of this illness. He had one episode of large bloody stool with diarrhea 2 days prior to hospital admission.

On physical exam, the abdomen was soft and distended with a mass in the right lower quadrant that was tender on deep palpation. No hepatosplenomegaly was apparent. There was no palpable cervical, supraclavicular or inguinal lymphadenopathy. There was also no focal neurological deficit. Other physical exam findings were

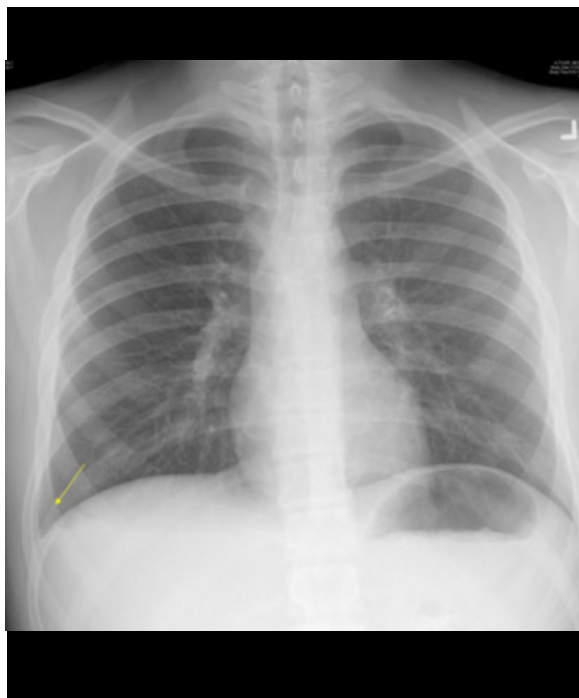


Figure 2. Chest radiograph shows normally inflated lungs without evident hilar adenopathy. There is some blunting of the right costophrenic angle (arrow).

unremarkable.

Initial laboratory investigation revealed a white blood count of  $3.7 \times 10^3/\text{mm}^3$ , hemoglobin of 10.9 g/dL, platelet count of  $159 \times 10^3/\text{mm}^3$ , elevated Lactate dehydrogenase (LDH) and uric acid at 2313 U/L and of 8.9 mg/dL respectively. Other chemistries and liver function tests were within normal limits.

A radiograph of the abdomen demonstrated soft tissue fullness overlying the right sacroiliac joint and mucosal thickening in a loop of bowel in the right pelvis (Fig. 1). There was no evidence of obstruction or calcification. Chest radiograph (Fig. 2) demonstrated blunting of the right costophrenic angle thought to be due to either pleural thickening or pleural fluid. There was no apparent adenopathy. Chest computed tomography (CT) with contrast confirmed small right pleural effusion with small superior/anterior mediastinal adenopathy, a small nodule at the right base of the lung near the diaphragm, and no hilar adenopathy.

Abdominal/Pelvis CT with contrast showed a large

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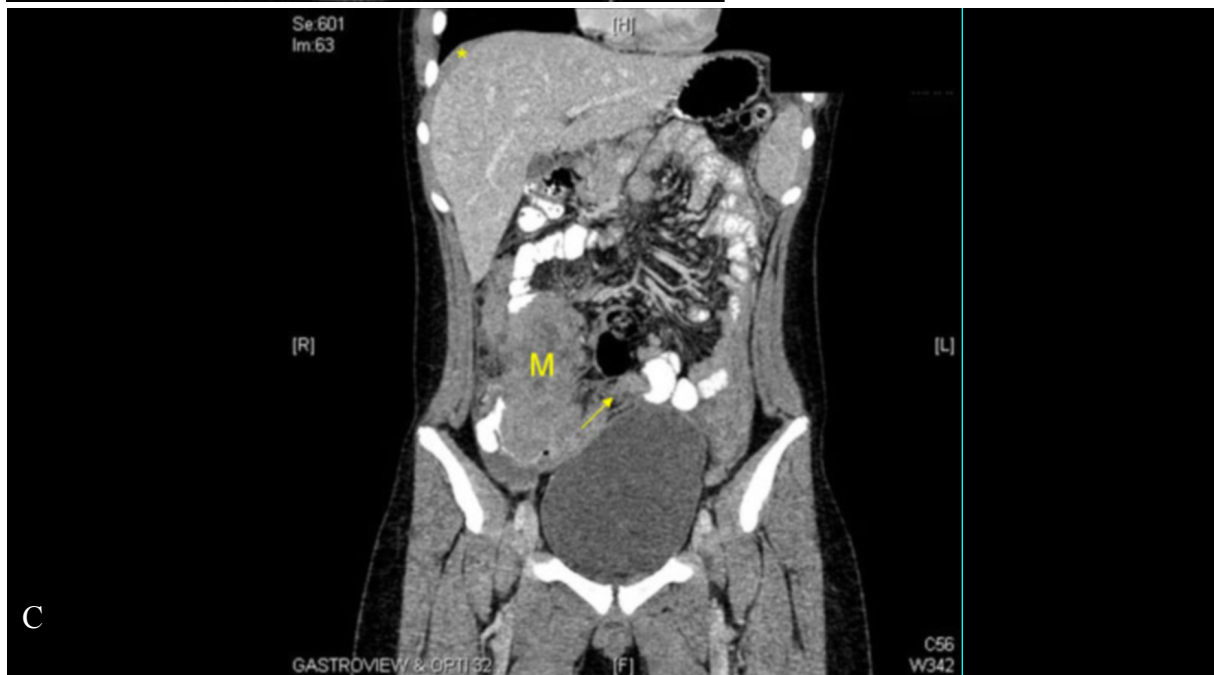
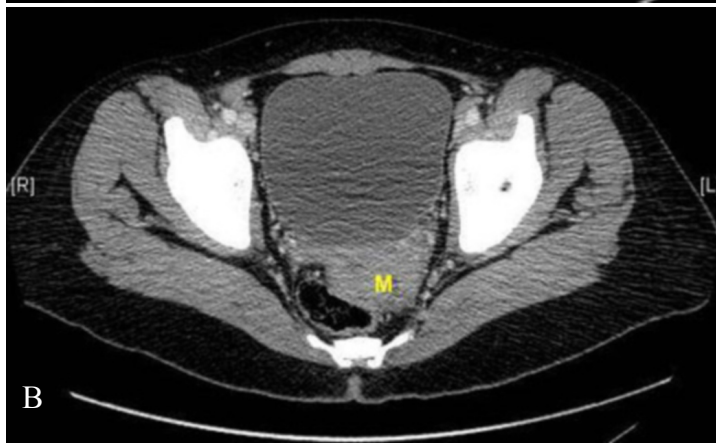


Figure 3. CT with contrast. (A) The bulky heterogenous mass (M) measured 6 cm. in AP dimension and 7 cm in transverse dimension. Contrast material from the lumen of the bowel is seen around it, suggesting that the mass arises from the bowel wall. (B) A smaller mass (M) in the patient's pelvis located left of the rectum and posterior to the bladder. It measures 5.8 cm in transverse dimension, 4.2 cm in AP dimension. (C) Coronal reconstruction of the Abdominal/Pelvis CT. The right lower quadrant mass (M), measured 12 cm in Superior-Inferior (SI) dimension, appears to infiltrate the bladder wall and displaces it from left to right. There is a tubular structure (arrow) that is seen extending from the large mass and draping over the colon. This may represent an infiltrated and enlarged appendix. There is abnormal thickening of the diaphragm adjacent to the liver (\*).

heterogenous mass (Fig. 3A) infiltrating the wall of the terminal ileum, cecum and mesentery with evidence of metastasis to the omentum, the diaphragm and the pelvis. The mass did not cause obstruction and contrast material was clearly seen into the colon. A smaller mass was also identified in the pelvis posterior to the bladder (Fig. 3B). There was no evidence of bowel perforation because no extravasation of contrast material was seen outside the bowel. A small amount of free fluid was noted in the pelvis and abdomen along with small lymph nodes along the diaphragm on the thoracic side.

Percutaneous needle biopsy of the mass of the right lower quadrant was performed under ultrasound guidance. Pathologic examination (Fig. 4B) demonstrated sheets of small to medium size lymphoid cells. The cells displayed scanty cytoplasm with brisk mitotic rate. The lymphoid cells were interposed with cellular debris-laden macrophages creating a starry-sky pattern classically associated with Burkitt's Lymphoma/Leukemia. Immunohistochemical stains (Fig. 5) were positive for CD45 or leukocyte common antigen (LCA). Markers for B-lymphocyte CD20, and CD79a, were also positive, while the Pan T-cell marker CD3 was negative. Our sample was predominantly positive for kappa and negative for lambda light chain, indicating monoclonality which supports a neoplastic proliferation. Further studies revealed involvement within the bone marrow

(Fig. 4A), at 42% of marrow cells, making the diagnosis of Burkitt's Leukemia (rather than Lymphoma) more applicable. Traditionally, this extensive bone marrow involvement means that the diagnosis can be classified as L3 acute lymphoblastic Lymphoma/Leukemia (FAB [French-American-British] L3 ALL). However, according to the World Health Organization (WHO) Classification of Lymphoid Diseases, the Lymphoma and leukemic phases of the disease are classified as a single entity; a mature B-cell neoplasm, with subtype Burkitt's Lymphoma/Burkitt's cell Leukemia [3]. There was no evidence of leukemia in the cerebrospinal fluid.

For staging, a positron emission tomography (PET) study was performed with the injection of F-18 labeled fluorodeoxyglucose (FDG). The results demonstrated extensive FDG accumulation in the area of the dominant mass and increased FDG accumulation along the pericolic gutters. There were multifocal bone uptakes within the vertebral bodies, the long bones of the upper and lower extremities, several ribs, and sternum. This finding suggested diffuse bony metastases. The extensive bone marrow involvement suggested that the patient was in stage IV of the St. Jude/Murphy Staging System for Burkitt's Lymphoma/Leukemia [2].

With pathologic confirmation, the patient underwent cytoreductive phase therapy (COP) with cyclophosphamide, vincristine, and prednisone with

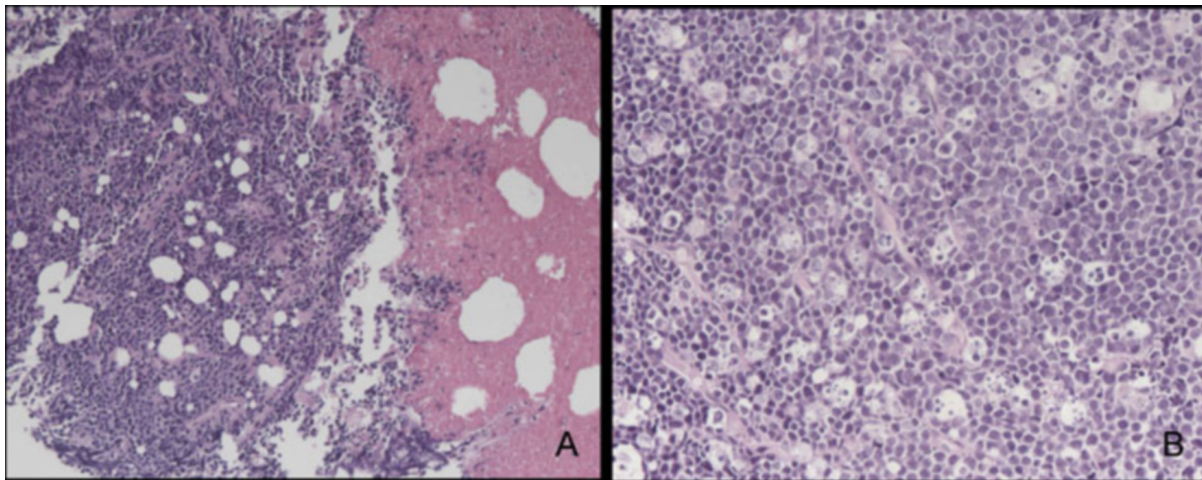


Figure 4. Hematoxylin and eosin (H&E) stained microscopic images from bone marrow aspiration clot (A) and from mass in the right lower quadrant (B) demonstrating sheets of medium size lymphoid cells with high mitotic activity interspersed with macrophage forming "starry-sky" pattern.



intrathecal methotrexate and hydrocortisone. Induction therapy was then employed with COPADM1 regiment consisting of cyclophosphamide, vincristine, prednisone, doxorubicin and high-dose methotrexate. The patient tolerated the chemotherapy well and showed clinical and radiological improvement.

Abdominal/Pelvis CT with contrast [Fig. 6] two months after initiation of chemotherapy revealed that the original mass which involved the terminal ileum and cecum is now seen as two discrete masses. The superior mass involved the mesentery located just superior to the terminal ileum [Fig. 6A] while the other is at the terminal ileum itself [Fig. 6B]. Surrounding them are a number of lymph nodes that may have been involved in the previous consolidated mass. The two masses combined displayed significant reduction in size when compare to the previous study. The superior mass also displayed interval central necrosis suggesting response to therapy. The mass in the pelvis [Fig.6C] was also significantly decreased in size. In addition, there was a significant decrease in the amount of thickening seen along the peritoneal cavity, particularly the diaphragm, and a decrease in the infiltration of the omentum when

compared to the previous study.

## Discussion

Lymphoma is the most common malignancy of the small bowel and often presents as bowel wall thickening or dilatation of the bowel lumen [5]. Many types of Lymphoma can involve the small bowel, but most cases are due to non-Hodgkin's lymphoma. The terminal ileum, with the greatest concentration of lymphoid tissue, is the most common site of small bowel B-cell lymphoma. In our case, Burkitt's lymphoma was thought to be the most likely diagnosis due to the location and size of the dominant mass at presentation, the age of onset of this patient as well as the clinical presentations. Other etiologies such as adenocarcinoma, desmoid tumor, and sarcomas were also considered, although they were thought to be significantly less likely. The soft tissue sarcomas and neuroblastoma are primarily retroperitoneal tumors and ascites is not commonly associated with either diagnosis [6]. Obstruction is uncommon in small bowel lymphoma because the mass is usually soft and pliable but it is more common in adenocarcinoma.

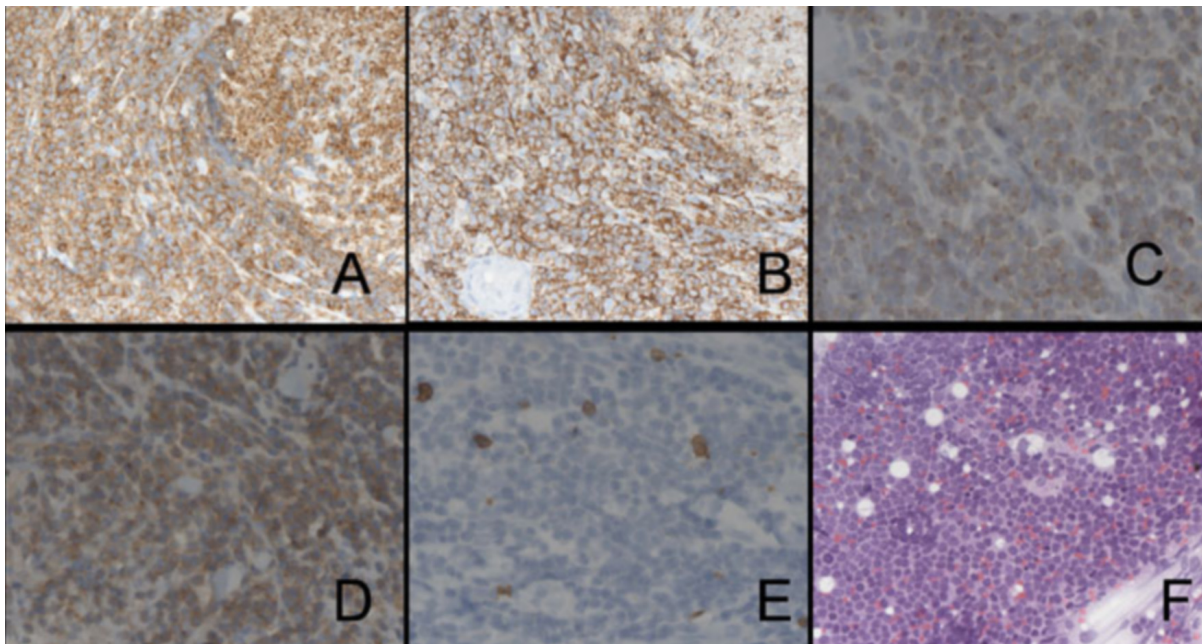


Figure 5. Immunohistochemical stains showing positive leukocyte common antigen (A), CD20 (B), CD79a (C), Kappa light chains (D), negative Lambda light chains (E) and Diff-Quick stained Touch prints cytology (F).

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Figure 6. Two months after initiation of chemotherapy. (A) The superior mass (M) measured 50 mm in transverse dimensions, 39 mm in anterior-posterior dimension. Compared to the previous study, the mass showed interval decrease in size and increase in the amount of central low attenuation consistent with increased tissue necrosis. (B) The inferior mass (M) associated with the terminal ileum now measured approximately 29 mm in transverse dimension, 23 mm in anterior-posterior dimension. The lumen of the terminal ileum is discernible in this study. Some discrete lymph nodes are seen around the mass (arrows). (C) The previously seen pelvic mass shows significant reduction in size. In this study, only minimal amount of enhancing soft tissue (M) measuring approximately 10 mm in thickness is appreciated.

Desmoid tumor arises from fibroblastic proliferation originating from fascia and muscle aponeurosis that primarily involves the anterior abdominal wall [7]. Classically, the disease is more common in females, in patients with history of trauma (often surgical) to the site of the tumor [8], and in patients with familial polyposis of the colon [9]. Our case shares none of these characteristics. In addition, mucinous carcinoma of the appendix could also create the peritoneal metastasis observed in the abdominal CT. However, primary appendiceal malignancy is rare and makes up of only about 0.5% of all intestinal tumors [10]. In addition, the majority of the appendiceal malignancies are carcinoid tumors that do not present as a bulky mass.

Burkitt's lymphoma/leukemia is a rare form of cancer in the United States. The incidence is reported as about 0.3 - 0.5 per 100,000-years [11]. Interestingly, the incidence is steadily increasing as demonstrated in a study of its incidence from 1945 to 1995 in central Ohio [12] and recently the overall incidence in the US is increasing at about 8% per year from 1991 to 2001 [13]. Patients with sporadic Burkitt's lymphoma/leukemia often present with abdominal pain, nausea, vomiting, gastrointestinal bleeding, and other syndromes mimicking acute appendicitis or intussusception [2]. Patients may quickly manifest significant metabolic derangement and renal function impairment due to the rapid growth of the tumor. At diagnosis, patients often have bulky mass and elevated uric acid as well as lactate dehydrogenase. In adults, bone marrow involvement is found in 30-38% and 13%-17% are found to have central nervous system involvement [2].

CT remains the most useful imaging modality in diagnosing and assessing the disease stage in gastrointestinal lymphomas. Small bowel B-cell Lymphoma in general may appear as a bulky mass in the intestinal wall with extension into the small bowel mesentery and regional lymph nodes (as in our case) or as aneurysmal dilation of the lumen due to replacement of the muscularis propria and destruction of the autonomic nerve plexus by lymphoma [5]. Abdominal and pelvic masses are the most common finding in sporadic Burkitt's lymphoma [6,14]. In one study, the combination of intraperitoneal mass, with or without ascites, intraperitoneal adenopathy but sparing of retroperitoneal nodes is a very strong indication of Burkitt's Lymphoma [6].

Morphologically, neoplastic cells of classic Burkitt's

lymphoma/leukemia are uniform and medium sized with round nuclei, moderate size cytoplasm, and high mitotic rate. Characteristically, the starry-sky pattern is described due to numerous admixed tingible body macrophages with abundant phagocytosed apoptotic debris within their cytoplasm [2]. Endemic and sporadic Burkitt's lymphoma/leukemias typically have this classic morphology. Immunodeficiency associated Burkitt's lymphoma/leukemia often has plasmacytoid differentiation [4]. All variant of Burkitt's lymphoma/leukemia express monotypic surface IgM, pan-B-Cell antigens, including CD19, CD20, CD22, and CD79a, and coexpress CD10, Bcl-6, CD43, and p53, but not CD5, CD23, Bcl-2, CD138 or TdT [2].

A hallmark of Burkitt's lymphoma/leukemia is the translocation of c-myc gene, a transcription factor that influences transcription of proteins involved in cell cycle regulation, apoptosis, cell growth, cell adhesion, and differentiation [2]. Eighty percent of cases of Burkitt's lymphoma/leukemia are found to have translocation between chromosome 8 and 14, t(8;14), resulting in juxtaposition of the c-myc gene with IgH gene. The remaining 20 percent have either t(2;8) or t(8;22) which places the c-myc gene close to either the kappa or the lambda light chain gene [2]. This rearrangement results in cells being in a perpetual proliferative state [4].

Due to the high growth rate of Burkitt's lymphoma/leukemia, standard treatment employs short-duration, intensive, combination chemotherapy. There are several regimens, but common agents include cyclophosphamide, vincristine, methotrexate, doxorubicin, and cytarabine. Central nervous system prophylaxis with intrathecal chemotherapy is required for treatment in most adults and not uncommon in disseminated pediatric cases. Burkitt's lymphoma/leukemia is quite chemosensitive even in patients with central nervous system or bone marrow involvement [2]. With intensive chemotherapy, children with localized disease have over 90% 5-year survival rate [15] while children with widespread disease (including leukemic presentation) may achieve over 90% complete response rate [16]. In adult, complete response rates of 65%-100% and overall survival rates of 50%-70% have been reported [4].

In terms of imaging follow up, patients with bulky abdominal masses who failed to have complete radiographic resolution may require repeated biopsy or imaging with positron emission tomography or gallium

scintigraphy to ascertain the response to therapy [2]. One study reported that the presence of residual mass in children with complete clinical remission does not alter the long-term prognosis and therefore expectant watching may be appropriate in children who achieve complete clinical remission with residual mass [17].

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