Acute appendicitis in acute leukemia and the potential role of decitabine in the critically ill patient

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Abstract

Acute appendicitis in children with acute leukemia is uncommon and often recognized late. Immuno-compromised host state coupled with the importance of avoiding treatment delays makes management additionally challenging. Leukemic infiltration of the appendix though rare must also be considered. Although successful conservative management has been reported, surgical intervention is required in most cases. We present our experience with acute appendicitis in children with acute leukemia and a case of complete remission of acute myeloid leukemia with a short course of decitabine. Decitabine may serve as bridging therapy in critically ill patients who are unable to undergo intensive chemotherapy.

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1. Introduction

Acute appendicitis and typhlitis are the most common causes of gastrointestinal surgical complications in children undergoing chemotherapy for acute leukemia with reported incidences of 0.5–4.4% and 1.7–6.7% respectively [1–4]. Early diagnosis by radiologic imaging is essential as appendicitis usually requires emergent surgical management. Appendicitis with leukemic infiltration as the initial presenting feature may also rarely occur [5,6]. In such situations, the clinician must also balance the risk of further immunosuppression and chemotherapeutic toxicities with the risk of delaying appropriate leukemia therapy.

2. Case series

A retrospective case review of all children ≤ 18 years of age diagnosed with acute leukemia at our institution between January 2002 and December 2011 was performed after obtaining institutional IRB approval. Amongst 154 children eligible, three (1.9%) patients were diagnosed with appendicitis (Table 1). Appendicitis was diagnosed based on clinical, imaging and histologic findings.

2.1. Case 1

A 17-year-old girl with relapsed acute myeloid leukemia (AML) developed nausea, vomiting, mild lower abdominal pain and breakthrough menstrual bleeding three days into hospitalization for induction chemotherapy with cytarabine and mitoxantrone. On day fifteen, her abdominal pain localized to the right lower quadrant (RLQ) followed by fevers three days later. Abdominal CT scan demonstrated a thickened appendix with inflammation in the periappendiceal fat planes.

An emergent open appendectomy was performed. Pathology showed acute appendicitis without perforation or leukemic infiltration. Peri-operatively, absolute neutrophils were too few to count. Blood cultures were negative. She received broad-spectrum antimicrobial therapy and chemotherapy was resumed without delay. Eventually, she underwent a matched unrelated donor bone marrow transplant (BMT) and was in remission at seven-year follow-up.

2.2. Case 2

An 18-year-old girl with relapsed leukemia consistent with acute lymphoblastic leukemia (ALL) was hospitalized for chemotherapy with cytarabine and clofarabine. In addition to intermittent nausea, vomiting, and diarrhea, significant RLQ pain with fever on hospital day nineteen (maximum 39.5 °C) prompted an abdominal CT scan that showed an edematous, thickened appendix.
with surrounding inflammation. She underwent an emergent laparoscopic appendectomy and pathology revealed a non-perforated appendix with inflammatory infiltrate without leukemic involvement. She had too few neutrophils to count. Broad-spectrum antimicrobial coverage was initiated for *Escherichia coli* bacteremia. Chemotherapy was resumed three weeks following surgery. She eventually underwent a matched related donor BMT and was in remission at three-year follow-up.

2.3. Case 3

A 10-year-old girl presented with generalized myalgias, fevers and gingival hypertrophy and was diagnosed with primary AML with maturation (FAB: M2). Cytogenetics revealed no clonal abnormalities and AML panel fluorescent in-situ hybridization studies were normal. During hospitalization for induction chemotherapy, after five days of decitabine (20 mg/m²/day) on study and one dose of systemic cytarabine (100 mg/m²/dose), she developed abdominal pain with high-grade fever (maximum 40.1 °C). Abdominal CT scan demonstrated numerous fluid-filled edematous bowel loops with enhancement, fluid collections, and findings consistent with an inflamed appendix with fecalith. An emergent laparotomy revealed gross soilage of the abdomen due to a perforated necrotic appendix eroding into the distal ileum and colon necessitating a diverting ileostomy and partial right colectomy. At the time of surgery, her absolute neutrophil count (ANC) was 4.08 × 10⁹/L. Histopathology revealed immature myeloid cells, consistent with leukemic involvement of the appendix, in addition to inflammatory infiltrates. Postoperative course was complicated by abdominal abscesses with *E. coli* and vancomycin resistant Enterococcus. Parenteral antimicrobial therapy was continued for approximately 6 weeks during which chemotherapy was held to avoid further immunosuppression. Packed red blood cell and platelet transfusions were required within the first postoperative week following which no transfusion support was needed until resumption of standard chemotherapy about 8 weeks later. During this 8 week period, her ANC fluctuated from 0.64 to 5.33 × 10⁹/L with counts of < 1 × 10⁹/L noted only on 2 occasions at 24 days and 37 days from surgery. She did not experience sustained neutropenia and, hence, no significant issues were noted during this 8 week period.

Bone marrow biopsy twenty-five days from initiation of induction chemotherapy showed no morphologic features of AML. Despite receiving only a short course of decitabine and one dose of systemic cytarabine, she achieved and maintained complete remission until resumption of standard intensive chemotherapy. She remains in remission 2.5 years following completion of therapy.

3. Discussion

Appendicitis is seen in the general population with a lifetime cumulative incidence rate of 9% [7]. Our calculated incidence rate of appendicitis in the setting of acute leukemia (1.9%) correlates with the reported incidence of 0.5–4.4% [1]. Leukemic involvement of the gastrointestinal tract as well as the treatment thereof can compromise the structural integrity of the intestinal wall [5]. Moreover, atypical presentations of appendicitis are common in immunocompromised patients due to underlying malignancy and ongoing chemotherapy. Early symptoms such as nausea, vomiting, abdominal pain, and diarrhea are non-specific and may be attributed to chemotherapy side effects delaying accurate diagnosis [8]. In addition, typhlitis often mimics the classic presentation of appendicitis, and therefore imaging must be performed to distinguish these entities as their management approaches differ.

Although successful conservative management has been reported [9], the majority require surgical intervention to avoid devastating complications [1,10]. Several groups have demonstrated safety and efficacy of surgical intervention [1,4,10] and operative management may also shorten the length of hospital stay compared to nonoperative management [10]. In our cohort, all three patients were operated upon emergently and all of them including the patient with appendiceal perforation and leukemic infiltration tolerated surgery well.

For the treating clinician, the bigger conundrum is the need to suspend chemotherapeutic treatment during life-threatening infections such as appendicitis, while weighing in a heightened, risk for uncontrolled leukemic cell proliferation. Alternatively, other anti-leukemic agents such as decitabine have been demonstrated to be effective and well-tolerated in adults with myelodysplastic syndrome, high risk AML, as well as those ineligible for standard chemotherapy due to extensive comorbidities such as the elderly [11–13].

Decitabine (5-aza-2’-deoxycytidine) is a cytosine nucleoside analog that after phosphorylation directly incorporates into DNA resulting in inhibition of DNA methyltransferases. The resulting DNA hypomethylation causes reversal of abnormal epigenetic silencing of genes critical to normal cellular differentiation, proliferation, and normal cellular life processes such as apoptosis [14]. It has minimal toxicity and hence is favored in patients who are unable to tolerate standard chemotherapeutic regimens [11].

Our third patient was enrolled in a trial utilizing a short five-day course of decitabine prior to intensive chemotherapy with cytarabine, daunorubicin and etoposide. She achieved and remained in remission with one cycle of decitabine and one dose of cytarabine without significant hematologic toxicities despite considerable delay in resumption of chemotherapy due to overwhelming infection. Low-dose decitabine (20 mg/m²/day for 10 days given every 4 weeks) has demonstrated promising results in children with very high risk relapsed/ refractory AML in whom other treatment options had been exhausted. Three out of eight patients had a complete response, with best responses noted after a median of 2.5 cycles. Despite significant comorbidities, decitabine monotherapy demonstrated minimal toxicity [15]. Recently, sequential treatment with decitabine and cytarabine was found to be more effective than cytarabine alone in xenograft models of childhood AML [16].
Relative to studies with heavily pre-treated patients, our patient was chemotherapy naive and had minimal hematologic or other toxicities secondary to chemotherapy. Given the favorable toxicity profile and efficacy in childhood AML, we suggest that decitabine may serve as a bridging anti-leukemic agent during serious illness and reduce risk of recurrence secondary to prolonged treatment delays. Overall, managing concurrent malignancy and critical illness is a delicate balance, one in which decitabine may play a pivotal role; however further clinical trials are needed.

Conflicts of interests

None.

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