Case Report

Extramedullary Involvement of the Ascending Colon in Relapsing Acute Lymphocytic Leukemia: A Case Report

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Abstract

Acute lymphoblastic leukemia (ALL) accounts for <1% of adult cancers. Extramedullary relapse of ALL has been primarily reported in pediatric patients or hematopoietic stem cell transplant recipients, and the gastrointestinal (GI) tract is a less frequently reported site of extramedullary relapse. Here, we report a case of a 30-year-old male who was a known case of ALL with multiple relapses and allogenic stem cell transplantations. The patient presented with acute lower GI bleeding and was confirmed to have an extramedullary relapse of ALL in the ascending colon. As the patient already had early relapses after two hematopoietic stem cell transplants in the past, he was managed with palliative chemotherapy, consisting of vincristine, dexamethasone, and rituximab, following which the patient achieved complete remission. This case highlights the importance of recognizing uncommon presentations of ALL such as those involving the GI tract.

Keywords: Acute lymphoblastic leukemia, allogenic stem cell transplantation, gastrointestinal bleeding, lymphoid leukemia, palliative chemotherapy, relapse

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INTRODUCTION

Leukemia is caused by a malignant proliferation of hematopoietic stem cells in the bone marrow and can often be diagnosed as an overlap with lymphoma. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy but accounts for <1% of adult cancers.[1,2] Extramedullary relapse of ALL has been primarily reported in pediatric patients or hematopoietic stem cell transplant recipients.[3] One study identified 264 cases of gastrointestinal (GI) tract leukemic involvement in about 15,0000 autopsies. The stomach, ileum, and proximal colon were noted to be the most commonly involved sites, whereas the duodenum and distal colon were less commonly affected.[4] GI involvement usually occurs when the leukemia is in relapse.[5] GI leukemia is reported to be around 18% to 21% and can present with GI bleeding or obstructive symptoms.[6] ALL relapse commonly present as an isolated bone marrow relapse or combined bone marrow and central nervous system relapse. The GI tract is a less frequently reported site of extramedullary relapse of ALL. In this case report,

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we present a case of colonic relapse of ALL to aid the understanding of this rare presentation and to recognize it in a timely manner.[7]

CASE REPORT

A 30-year-old male presented to the Emergency Room in February 2021 with a 1-day history of passing fresh blood per rectum associated with lower abdominal discomfort. He is a known case of relapsing B-cell ALL (B-ALL) with a negative Philadelphia chromosome diagnosed in August 2017.

After the initial diagnosis, he was started on multiple course chemotherapy and achieved the first remission with 3% blast at day 28, minimal residual disease (MRD) negative. In the period between diagnosis and the first transplant, the patient was followed-up at another hospital. Data from the referring hospital documented that in maintenance cycle 6, he developed one isolated central nervous system (CNS) relapse presenting with a severe headache. Magnetic resonance imaging evaluation of the brain showed abnormal signal changes. Bone marrow aspirate showed hypocellularity with 1% blast by morphology and 0.3% MRD by flow cytometry. Cerebrospinal fluid (CSF) analysis yielded malignant cells. He was started on 5-fluorouracil salvage chemotherapy and intrathecal chemotherapy, following which his CSF analysis became negative. The patient was then referred to our hospital for allogeneic hematopoietic stem cell transplantation (allo-HSCT) from matched sibling, which was done in December 2019 and the patient achieved complete remission. Prior to the first transplant, the patient had received cranial radiotherapy but otherwise had no previous history of radiation.

The first transplant failed, and he developed medullary relapse in June 2020, presenting with abdominal pain, back pain, and a high-grade fever. He was admitted under hematology and evaluated for infectious causes. Evaluations showed splenomegaly on computed tomography (CT) and bone marrow analysis showed >70% blast. He was placed on vincristine, dexamethasone, and inotuzumab.

In October 2020, the patient underwent the second allo-HSCT from a different matched sibling donor. The post-transplantation course was complicated by clinical graft versus host disease (GvHD) of the lower gut based on severe unexplained diarrhea and was resolved with the use of immunosuppressant treatments in the form of steroid and cyclosporine. Bone marrow achieved morphological remission and no MRD was detected by flow cytometry. The patient had the third relapse in 2021 after this.

On physical examination upon this presentation, he was alert, conscious, oriented, and his vital signs were within the normal range. Abdominal examination showed mild lower abdominal tenderness without a rebound tenderness and his bowel sound was normal. There was evidence of fresh blood during direct rectal examination with no identifiable external piles or fissure. His initial laboratory studies showed a new onset of severe leukocytosis (WBC of 140 × 109/L) and thrombocytopenia of 43 × 109/L, compared to results from 2 weeks earlier (WBC of 7.5 × 109/L and platelets of 142 × 109/L). The peripheral blood film showed hyperleukocytosis with 85% being circulating blast cells. Flow cytometry on peripheral blood was consistent with the same original disease B-ALL (87% blast cells), confirming relapse.

The patient was classified as Oakland score 20 (>8 indicating a major lower GI bleed), thereby warranting hospital admission and colonoscopy. He was referred to the gastroenterology department and a colonoscopy after platelets transfusion was planned. Colonoscopy revealed multiple erythematous polypoidal lesions of different sizes ranging from 1 to 4 cm in the ascending colon with signs of recent hemorrhage [Figure 1a and b]. Histological examination showed the replacement of lamina propria and submucosa by discohesive atypical hematolymphoid cells. The cells were of blastoid morphology with scant cytoplasm, condensed chromatin, inconspicuous nucleoli, and frequent mitosis. Immunohistochemical staining of the neoplastic cells showed positivity for CD45, CD20, CD19, and PAX5 in the B cell lineage. In addition, CD99, TDT, CD34, CD43, and CD10 positivity support a precursor lymphoid neoplasm with high proliferative index (KI-67, 90%) [Figures 2 and 3a, b]. His whole-body PET/CT scan showed a nonspecific diffuse splenic and bone marrow increased FDG uptake, most likely due to the known underlying condition, with no suspicious focal FDG-avid

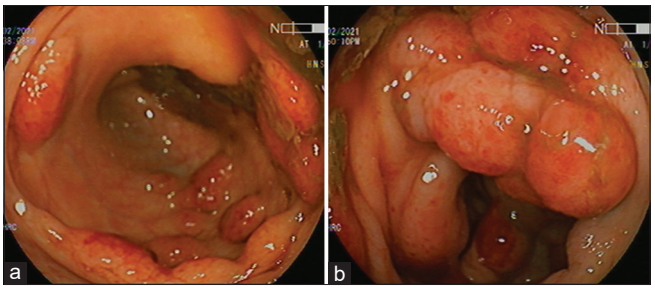

Figure 1: (a) Endoscopic image showing multiple erythematous polypoidal lesions in the ascending colon (b) Signs of recent haemorrhage

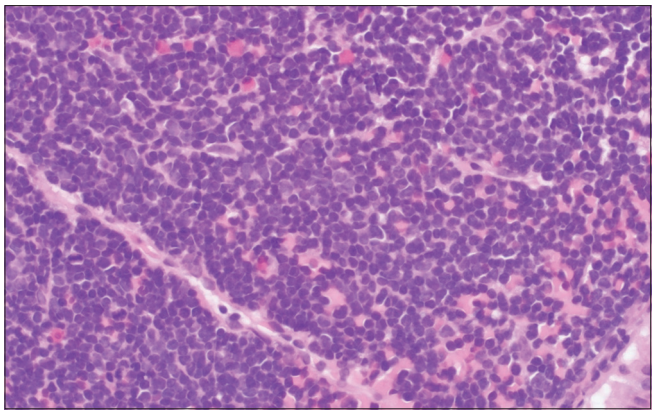

Figure 2: H and E section showing the lamina propria and submucosa are diffusely replaced by sheets of discohesive neoplastic cells. The neoplastic cells are small to intermediate sized monomorphic round lymphoblast with scant cytoplasm, condensed chromatin, inconspicuous nucleoli and frequent mitotic figures

lesions seen in the hollow organs of the abdomen and pelvis. The patient was started on treatment with steroid immediately prior to imaging, which might have masked the PET scan result and been a reason for the tumor not being picked up.

As the patient already had early relapses after two hematopoietic stem cell transplants in the past, it was decided to manage him with palliative chemotherapy, consisting of vincristine, dexamethasone, and rituximab based on the Dana-Farber Cancer Institute protocol. The patient had achieved a complete remission at the time of reporting this case.

DISCUSSION

ALL is known to have extramedullary involvement of the CNS, pleura, urogenital organs, and skin with the highest incidence in lymphoreticular organs such as the spleen and lymph nodes. Involvement of GI system in ALL is often undermined due to the other more common sites of metastasis and mostly occur in refractory or relapsing disease.[8] Common gastrointestinal complications of leukemia include bowel obstruction, portal hypertension, protein-losing enteropathy, altered immune state, and increased susceptibility to common infections.[9] Leukemic tumors can occur as lesions that grow concentrically as polyps. These cause obstructive symptoms or ulcers that erode through the GI wall, leading to massive hemorrhage, perforation, pneumoperitoneum, or pneumatosis cystoides intestinalis.[5]

One study reported the gross occurrence of GI involvement in refractory cases of leukemia to be around 18%–21%, with about 3% of cases showing extensive and multiple

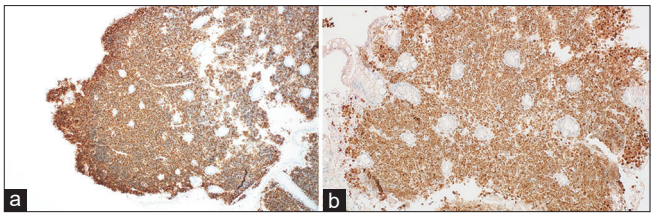

Figure 3: The neoplastic cells are immunohistochemically positive for (a) CD20 staining (b) Terminal deoxynucleotidyl transferase staining

segments of GI tract involvement. Moreover, GI involvement has been identified as one of the main causes of death in leukemia. GI manifestations of leukemia are more common in acute than chronic leukemia, usually occur during a relapse phase, and are present in about 25% of patients at autopsy.[5,6]

Leukemic tumors presenting with relapses in the gastrointestinal organs pose particular challenges. While people with no history of leukemia may present with symptoms and signs suggestive of solid GI cancers or small bowel obstruction are promptly diagnosed and treated, in patients who are known cases of leukemia, symptoms of developing GI tumors may be confused with pharmacological toxicities leading to diagnostic confusion, delays, and tumor spread that eventually leads to death.[6] Once any GI malignancy is suspected, an endoscopy and biopsy are imperative. A PET/CT is not routinely used to assess leukemia, as it does not present with a solid tumor and bone marrow analysis is the gold standard diagnostic test.[10]

The mainstay treatment is chemotherapy consisting of vincristine, steroids, and an anthracycline with some eligible candidates receiving hematopoietic stem cell transplant (HSCT).[11] Allo-HSCT has been recognized as an effective treatment for ALL, and in some cases, has helped in achieving remission. On the contrary, ALL relapse is yet being reported as a prime contributor to death in patients who received HSCT, with an incidence ranging from 30% to 40%. Some risk factors contributing to this decline in survival that are consistent with our patient were hyperleukocytosis at diagnosis, having more than one first complete remission, a short remission timespan (seen as 6 months in our patient), and finally, the occurrence of GvHD (also seen post-transplant in our patient).[12] GvHD has been postulated to cause GI bleeding by resulting in an imbalance in gut microbiota, dysfunctional immune activation in HSCT recipients, and also secondary to infections. However, the incidence of severe gastrointestinal bleeding after HSCT has declined over the years due to prophylactic measures. Nevertheless, despite other causes of GI bleeding in HSCT recipients

owing to esophagitis or hemorrhoids, acute GvHD yet remains one of the most common etiologies.[13]

During a relapse, about 4-6% of patients may present with an acute abdomen warranting immediate surgical intervention, which yields inferior results when compared to elective surgery performed in a state of remission.[2] Colonic resection with stomas, bypass, stenting, and chemotherapy can be offered as palliation.[14] Beyond symptomatic management, palliative approaches encompass social, psychological, and spiritual support. In the future, a prospective trial that identifies the risk factors for patients diagnosed with ALL and stratifies them for risk of GI infiltration would be a valuable tool to determine those more likely to benefit from early endoscopic evaluation. This would also help in avoiding delay in diagnosis and unnecessary procedures in a population already at elevated procedural risk due to immunocompromised state and common presence of cytopenias.[15] We recommend that physicians be vigilant and keep a lower threshold to perform investigations for patients with acute leukemia. As there are no guidelines yet available to screen or treat an asymptomatic course of gastrointestinal metastasis in leukemia, it is pertinent to keep it as a differential diagnosis when there is lower GI bleeding in a leukemic patient, as early diagnosis and treatment can prevent further complications.

CONCLUSION

This case report reports the presentation of acute leukemia with unusual manifestations: our patient presented with an extramedullary relapse of ALL involving the colon following a period of ALL remission. The misinterpretation of common GI symptoms can lead to early death in such patients. Therefore, enhancing clinical suspicion for leukemic tumors will alleviate the total leukemic burden. Due to the lack of extramedullary relapse cases being reported, other dimensions such as prognostic parameters and management are yet being studied and require further exploration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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