

Pneumatosis cystoides intestinalis mimicking free intraabdominal air following chemotherapy for relapsed acute myeloblastic leukemia in a transplanted neutropenic child: a case report

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ABSTRACT

Background. Pneumatosis cystoides intestinalis (PI) is a rare but important condition in which widespread air sacs are found in the submucosa, and subserosa of the bowel wall. Although it has several etiologies, children receiving chemotherapy are at risk for PI. Preferred imaging tools for the diagnosis are abdominal direct radiography and computed tomography. In patients with PI, rupture of intramural air sacs is the source of benign pneumoperitoneum, causing free air without true intestinal perforation. Intestinal perforation or obstruction are indications for surgical intervention.

Case. Here, we present a 4-year-old patient diagnosed with acute myeloblastic leukemia (AML), who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from a matched sibling donor (MSD) and developed PI after HSCT. The patient was consulted to the pediatric surgery department, and her oral feeding was stopped. Broad spectrum antibiotics (teicoplanin, metronidazol and vancomycin) were initiated. Her fever increased during the 24-hour monitoring, there was no stool passage, CRP (>25 mg/dL, normal value <1 mg/dL) and abdominal distension increased and there was prolonged neutropenia and radiologic investigations could not rule out intestinal perforation, so the patient underwent exploratory laparotomy. No intestinal perforation was found. There was no sign in the intestinal wall and numerous gas-filled cysts of various sizes.

Conclusions. PI is an uncommon complication, and direct radiography/computed tomography scans are very helpful in making the diagnosis in suspicious cases. PI, should be kept in mind, especially in transplanted or relapsed leukemia patients receiving intensive chemotherapy.

Key words: leukemia, pneumatosis intestinalis, surgery, transplant.

Pneumatosis intestinalis (PI) is a rare condition characterized by the presence of gas within the mucosal and submucosal layers of the intestinal wall.¹ Although its etiology is still unknown, many factors including the production of intraluminal bacterial gas are considered to be responsible for the pathogenesis.² It is considered that gastrointestinal tract

permeability increases with the mucosal damage caused by chemotherapy, prolonged neutropenia and interfering infections which leads to the diffusion of gas into the gut wall.³ Several chemotherapeutic agents including cytarabine have been shown to trigger the mechanism.⁴ PI can be asymptomatic, but it may also manifest itself with abdominal pain and distension.⁵ Radiologic diagnosis can be made with direct radiography in two thirds of the cases. However, computed tomography (CT) is necessary to make a diagnosis in one third of the cases.⁶ While a conservative approach

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is possible, emergency surgery may also be necessary. Here, we report a case with acute myeloblastic leukemia (AML) who developed PI following treatment with Flag-Ida because of a relapse following allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Case Report

A four-year-old girl diagnosed with AML underwent matched sibling donor allo-HSCT from her sister due to an early relapse of AML. The patient was routinely monitored from the outpatient clinic under immunosuppressive treatment for graft-versus-host disease (GVHD) prophylaxis without any problems. On the 104th day following the transplant, the patient experienced a second relapse and received a 5-day Flag-Ida chemotherapy regimen consisting of fludarabine (30 mg/m², days 1-5), cytarabine (2 g/m², days 1-5), idarubicin (10 mg/m², days 3-5) and intrathecal therapy (methotrexate 12 mg, dexamethasone 4 mg, cytarabine 30 mg) for the induction of remission. In order to avoid neutropenia, granulocyte colony-stimulating factor was given daily at 5 mcg/kg. The patient had fever and abdominal pain 13 days after the chemotherapy was stopped and routine laboratory tests, abdominal ultrasonography (USG), chest and upright direct abdominal X-rays were performed to investigate the etiology of neutropenic fever. USG was normal except for minimal splenomegaly. Free intraperitoneal air was detected following an upright abdominal X-ray (Fig. 1). Her vital signs were stable except for a fever of 38°C. Physical examination revealed only mild abdominal swelling. There was no abdominal guarding or rebound, and the bowel sounds were unremarkable. There was no sign of peritonitis. Stool passage was normal and there was no history of nausea and vomiting. Laboratory work-up revealed a leucocyte count of 1×10⁹/L, neutrophil rate of 87%, a platelet count of 52×10⁹/L, and a hemoglobin level of 10.2 g/dL. Electrolytes, liver and renal function tests, lipase, amylase, and arterial blood gases were normal. CRP was 23 mg/dL (N <0.1) and



Fig. 1. Image of free air below the diaphragm on the right in the direct X-ray (black arrow).

other laboratory results were likewise within normal limits.

Written informed consent was obtained from the patient's parents for the publication of this case report.

Management & Outcome

Abdominal CT was performed, and in addition to intramural gas along the colon, diffuse free intraperitoneal air was detected (Fig. 2). After the patient was consulted to the pediatric surgery department, her oral feeding was stopped. The stomach was decompressed with a nasogastric tube. Intravenous fluid therapy was initiated in accordance with a conservative approach. Broad-spectrum antibiotics (imipenem, amikasin, linezolid) were used in the first week as neutropenic fever treatment in immunosuppressive patients, and then shifted to teicoplanin, metronidazole, levofloxacin, cefepime and finally meropenem and vancomycin. However, her fever increased during the 24-hour monitoring period, there was no stool passage, CRP (>25 mg/dL, normal value <1 mg/dL) and abdominal distension were increased, and there was prolonged neutropenia and radiological investigations could not rule out intestinal perforation, so the patient underwent exploratory laparotomy.

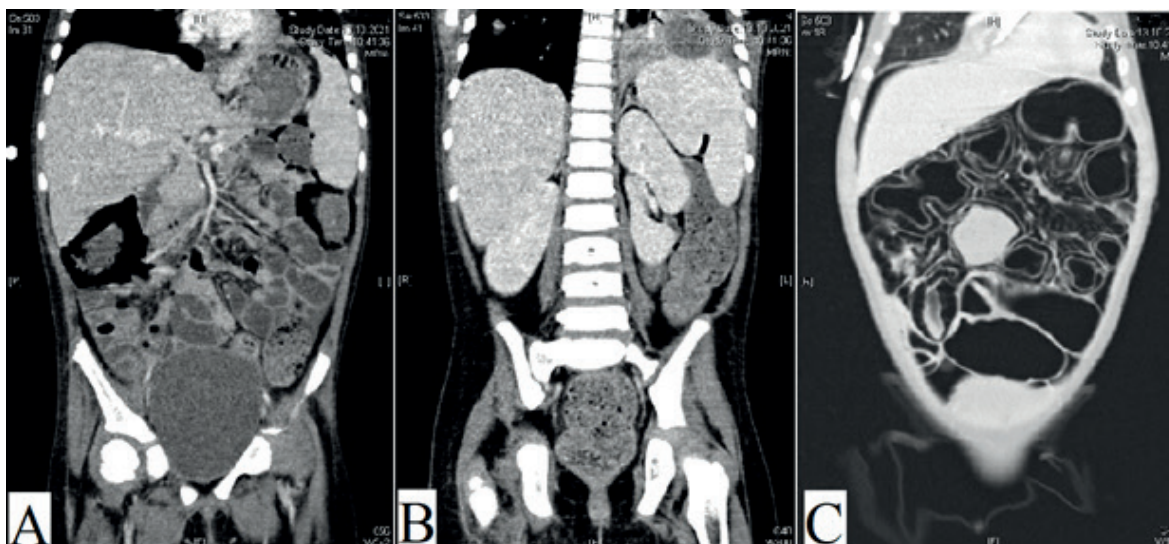


Fig. 2. Pneumoperitoneum can be seen on the abdominal computed tomography (CT) images (A, B). Abdominal CT image shows intramural and extramural gas of the ascending, transverse and descending colon in lung window (C).

No intestinal perforation was found. There was no sign in the intestinal wall, and numerous gas-filled cysts with sizes varying between 0.3 mm and 2 cm were observed on the serosa of ileal loops, leading to the diagnosis of PI (Fig. 3). No positive results were obtained from microbiological analyses (Salmonella, Shigella, Yersinia, or Campylobacter in blood culture and stool). A clostridium difficile toxin test resulted as negative.

Following a 21-day course of treatment, the abdominal distension gradually resolved. Abdominal CT and direct radiography revealed that PI had completely disappeared. In the meantime, neutropenia also resolved. CRP value regressed to 2 mg/dL. However, increases were seen in white blood cell (WBC), lymphocyte and monocyte count in the fourth week of follow-up. Peripheral smears revealed a myeloblast percentage of 25%. These findings led to a bone marrow aspiration, which revealed that the disease was not in remission. Currently, the patient is hospitalized and monitored at the hematologic service of our clinic. Following bone marrow remission, we plan to perform a haploidentical stem cell transplantation.



Fig. 3. Intraoperative image showing gas-filled cysts on the colon serosa of varying sizes (black arrows).

Discussion

PI is a rare clinical condition characterized by multiple gas-filled cysts in the subserosal and submucosal layers of the bowel.⁷ Although the underlying pathology is not clear, many explanations have been proposed. The most emphasized hypothesis is that pressure increases due to the gas released from intestinal bacterial proliferation in a neutropenic patient following cytotoxic chemotherapy, disruption of the mucosal barrier of the

bowel, and subsequent gas accumulation in the submucosal area.⁴ In addition, the myeloablative chemotherapy regimen given for HSCT and immunosuppressive therapy for GVHD prophylaxis, which will contribute to the prolongation of neutropenia, can also be considered risk factors for PI.⁸ A conditioning regimen, which consists of busulfan, cyclophosphamide, and melphalan, was performed on our patient. The disease relapse of our patient in the first 3 months of the post-transplant period while she was taking immunosuppressive agents, including tacrolimus, mycophenolate mofetil, and methylprednisolone, for chronic cutaneous severe GVHD; with all these findings and just 13 days after the administration of chemotherapy were considered important factors for the occurrence of PI. The literature shows that there is an increased incidence of PI in children undergoing allo-HSCT or receiving GVHD prophylaxis.^{9,10} In addition, a recent study conducted by Wallace et al.¹¹ concluded that systemic steroid use was associated with an increased incidence of PI in 990 consecutive pediatric transplant recipients.¹¹ Further, PI may develop as a result of several gastrointestinal system diseases, such as appendicitis, inflammatory bowel diseases, pyloric stenosis, necrotizing enterocolitis, ulcers and following endoscopic procedures.⁷ Usually diseases that involve the colon can affect all regions of the small intestine.¹² There was isolated colon involvement in our case. The cecum, colon ascendens, colon descendens, and, partially, the sigmoid colon were affected. Radiological investigations- abdominal CT (more sensitive) and direct radiography- are quite valuable for diagnosis. In addition to enabling diagnosis in most PI cases, the above-mentioned investigations also provide a differential diagnosis regarding acute abdomen cases requiring emergency surgery. Both investigations show a low-density linear or bubbly pattern of gas in the bowel wall. Although abdominal CT suggested PI in our

case, the general condition of the patient and the severity of the clinical picture necessitated laparotomy.

Although there is no established treatment yet, surgery is not the first choice in asymptomatic cases because spontaneous resolution is observed in 50% of cases. Favorable outcomes have been achieved in these cases with close follow-up and supportive therapy including bowel rest, total parenteral nutrition, and antibiotics.¹³ The clinical status and symptoms of the patient should also be taken into consideration. Deterioration of the general condition of the patient, destabilization of vital signs, suspicion of peritonitis and intestinal perforation probability seem to be the indications for the surgical intervention.¹⁴ Initially, we approached our case conservatively since the course of her disease was stable, abdominal distension was absent and stool passage was normal, but surgical intervention was performed after her fever rose to 39°C, abdominal distension occurred and stool passage stopped. In the case series of Li et al.³ including 514 pediatric patients with AML and acute lymphoblastic leukemia who developed PI, it was concluded that most of the cases could be managed with a conservative approach. In the same study, they found that USG was less sensitive than direct X-ray in making the diagnosis, similar to our case. The presence of febrile neutropenia in the patient and the complex clinical picture caused by the sepsis that occurred following intensive chemotherapy can be considered to have also played a role in the decision to operate in our case.

In conclusion, PI is a rare condition that can be seen in patients who receive chemotherapy for hematological and oncological malignancies. Direct radiography and CT are very helpful in making the diagnosis in suspicious cases. Patients can be managed conservatively with bowel rest and intravenous broad-spectrum antibiotics, and surgical intervention can be needed during follow-up.

Ethical approval

Written informed consent was obtained from the patient's parents for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: UA, BŞK, BA; data collection: UA, ÖÖ, KT, İŞ; analysis and interpretation of results: UA, İŞ, KT; draft manuscript preparation: BA, BŞK, ÖÖ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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