Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Pneumatosis Cystoides Intestinalis with Fatal Air Embolism after Minor Blunt Abdominal Trauma in a 6-Year-Old Girl Undergoing Hematopoietic Stem Cell Trasplant: Case Report and Review of Literature

Keywords: Pneumatosis cystoides intestinalis; Fatal Air Embolism; Minor blunt abdominal trauma; Hematopoietic stem cell trasplant.

Published: March 01, 2024 **Received: January 05, 2024** **Accepted: February 12, 2024**

Citation: Chinello M., Arnone O.C., Artusa S., Mazzuca G., Bonetti E., Vitale V., Zaccaron A., Raniero D., Cesaro S. Pneumatosis cystoides intestinalis with fatal air embolism after minor blunt abdominal trauma in a 6-year-old girl undergoing hematopoietic stem cell trasplant: case report and review of literature. Mediterr J Hematol Infect Dis 2024, 16(1): e2024028, DOI: http://dx.doi.org/10.4084/MJHID.2024.028

To the editor.

A Caucasian 6-year-old girl was admitted to our Hospital in July 2017 because of T-cell acute lymphoblastic leukemia (T-ALL) with central nervous system (CNS) involvement, diagnosed at 4 years of age. The patient underwent BFM-backbone induction chemotherapy for T-ALL patients, which included dexamethasone, cyclophosphamide, vincristine, daunorubicin, and intrathecal therapy with methotrexate, prednisone, and cytarabine and achieving complete remission in both bone marrow and CNS. The chemotherapy was continued with the consolidation phase, based on high-dose methotrexate, with plans to perform cranial radiotherapy. However, a CNS relapse was detected; therefore, a protocol for HR patients was administered with the indication to proceed with the HCT. The therapy includes three blocks of chemotherapy (HR1, HR2, HR3) and intrathecal therapy with methotrexate, prednisone, and cytarabine. She continued reinduction therapy with protocol III. Moreover, the patient was a candidate for an allogeneic HCT, and a donor search was started. After the reinduction protocol, due to the persistence of CNS involvement, the patient underwent rescue chemotherapy treatment with a FLAG-Myocet regimen followed by HCT. The patient underwent matched unrelated (MUD) HSCT in April 2018. The conditioning regimen consisted of total body irradiation (fractionated TBI, 2 Gy x 2/day for 3 days), Rabbit anti-thymocyte globulin (ATG) 240 mg/m^2/day for 2 days, and cyclophosphamide 60 mg/m^2/day for 2 days. The graft source was bone marrow, and 4.45 total nucleated cells x 10^8/kg and 5.02 CD34+ cells x 10^6/kg were infused. GVHD prophylaxis with cyclosporine and short-term methotrexate was administered. Neutrophil engraftment was observed on day +24, and platelet engraftment on day +29. On day +18, the patient developed a grade II cutaneous GVHD, which was managed with topic and systemic prednisone (1 mg/kg/day). On day +28, she showed signs of grade I intestinal GVHD, which was treated with beclomethasone dipropionate. Coproculture was negative for bacterial, viral and fungal infections. The post-transplant period was complicated by Escherichia Coli sepsis with concomitant posterior reversible encephalopathy syndrome (PRES), requiring hospitalization in the pediatric intensive care unit. Three months after HSCT, an intestinal infection by norovirus was detected, and the patient presented signs of pulmonary and hepatic GVHD. Intestinal GVHD worsened over several months, requiring hospitalizations. Seven months after HCT, she presented persistent diarrhea, vomiting, abdominal pain, and weight loss, and high doses of steroids were administered. Specifically, beclomethasone dipropionate (maximum dosage of 4 mg/Kg/die), prednisone (maximum dosage of 5 mg/Kg/die), and methylprednisolone (bolus of 0.5 mg/Kg of methylprednisolone twice a week) were used. Coproculture was negative for bacterial, viral and fungal infections. Abdominal ultrasound showed an intestinal atony without thickening of the loops. In the following weeks, the immunosuppressive therapy was modulated, introducing mycophenolate mofetil and tacrolimus with a partial clinical response.

Eight months after HCT, while she was playing with other children at home, she was pushed to the ground, hitting the left side of her body. After the fall, the child experienced abdominal pain, and tramadol was administered by her mother. The girl then manifested seizures and trismus. She was promptly taken to the emergency room, where she arrived in cardio-circulatory arrest. Resuscitation maneuvers were performed unsuccessfully. The body autopsy showed

epicardial petechiae, some yellowish myocardial discolorations in the interventricular septum, hypochromic areas in the lungs and kidneys, pulmonary edema, and bowel distension with multiple submucosal bubbles in the colon and cecum. The microscopic examination revealed multiorgan blood stasis, submucosal gas-filled cysts within the colon, and round air bubbles in the renal and pulmonary basal sections. Toxicological analysis was negative.

Discussion. Pneumatosis cystoides intestinalis (PCI) is a relatively rare clinical condition in which gas accumulates in the gastrointestinal tract lining, forming cysts, specifically in the submucosal and subserosal bowel wall.[1] PCI can be asymptomatic or present with very mild and unspecific symptoms, including abdominal pain, diarrhea, flatulence, nausea, obstruction, and hematochezia. The severity of clinical presentation and outcome depends on the triggering pathologies, which could be numerous: mechanical and traumatic factors, autoimmune and inflammatory disease, infections, cardio-respiratory conditions, surgeries, and use of drugs.[2,3] PCI in the non-neonatal period can be generally considered a benign condition with spontaneous resolution in about 80% of cases.[2] In certain specific cases, it can become a serious and life-threatening condition. GVHD, bowel ischemia, presence of portal venous gas, and acidosis are correlated with poor prognosis.[2] The estimated incidence of PCI in the pediatric oncology population is 1%.[4] The use of chemotherapeutic agents (i.e., cyclophosphamide, cytarabine, vincristine, doxorubicin, daunorubicin, etoposide, docetaxel, irinotecan, and cisplatin), immunosuppressive drugs (i.e., corticosteroids), infectious colitis, septic shock, and GVHD emerge as important causes of PCI in the pediatric population in the non-neonatal period.[3,5] Several pathophysiological mechanisms leading to PCI have been described. According to the immunosuppression theory, chemotherapeutic use and steroid administration determine a rapid constriction of lymphatic nodules and, as a consequence, mucosal damage and aspiration of air from the bowel lumen.[1,5] Furthermore, a gastrointestinal form of chronic GVHD (cGVHD) leads to intestinal mucosal damage with the development of atrophic mucositis, which leads to ulcers, infections, and fibrosis. This condition, along with the concomitant use of steroid therapy, predisposes to PCI. The development of asymptomatic PCI is a benign condition following HCT.[4] The risk of PCI is increased in patients with gastrointestinal GVHD, in patients receiving steroid therapy, and in those relying on supplemental nasogastric tube feeds for at least one-half of their total daily nutrition.[6] Cases of PCI in patients with cGVHD described in the literature occurred 2–8 months after bone marrow transplantation and were usually mild.[1,5,7] In our case, the development of PCI cannot be dated exactly. During the hospitalization, one month prior to the event, the patient presented with persistent diarrhea, abdominal pain, weight loss, and vomits, and such symptoms could be consistent with PCI.

The increase in steroid therapy can certainly play a decisive role. Autopsy and histological examination showed a thickened and emphysematous colic wall, as well as the presence of multiple gas cysts, confirming PCI (**Figure 1** e **2**). In addition, the microscopic examination also showed multiple optically empty circular areas within the vascular sections of the lung and kidney, consistent with gaseous bubbles. This evidence leads to the assumption that the contents of the intestinal intraparietal cysts embolized, then collected in the intestinal venous drainage system pertaining to the portal system, passed through the hepatic filter, and from there reached the heart (which had an obliterated foramen ovale), and finally the pulmonary circulation. The diffuse pulmonary embolism found on histological examination leads to the conclusion that a cardio-respiratory failure was the pathophysiological process that led to the death of the patient.

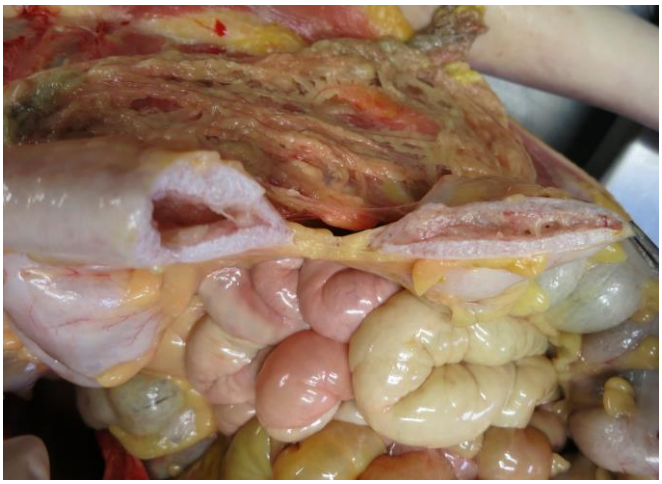

Figure 1. Macroscopic appearance of the bowel during autopsy. Macroscopic appearance of open bowel during autopsy, with evidence of wall thickening and emphysema.

It should be noted that the mild abdominal trauma that the patient suffered from could represent a contributing factor towards the initiation of the overall process. Portosystemic air emboli are a rare but mortal complication of PCI described only in a few pediatric cases.[8] PCI can be detected through an X-ray of the digestive tract; however, computed tomography (CT) and endoscopy are the methods of choice for the diagnosis.[5,7] There is no standardized treatment for PCI; it is usually managed conservatively, while complications can require surgery.[1] To our knowledge, this is the first case of death from portosystemic embolism in a child with intestinal GVHD and PCI.

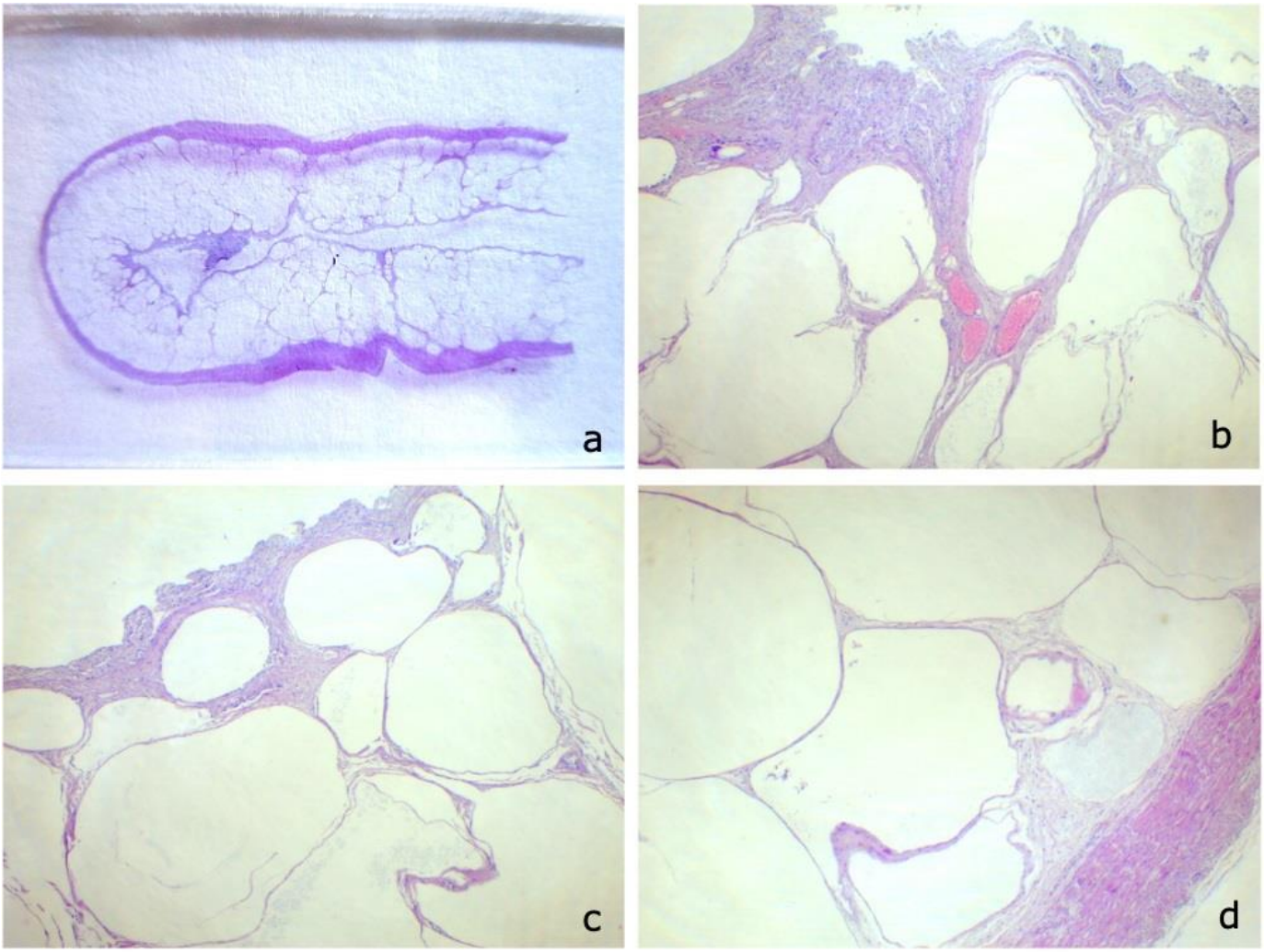

Figure 2. Histological preparations with traditional haematoxylin-eosin staining. (**a**) Full view of the thickness of the intestinal wall (x10 magnification). (**b, c**) Air bubbles below the mucosa (x40 magnification). (**d**) Air bubbles above the muscular layer (x40 magnification).

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Competing interests: The authors declare no conflict of Interest.

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