LETTER TO THE EDITOR
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What Happened: Suddenly or Acute Abdomen? Difficult Case of ATRA Related Pneumatosis Cystoides Intestinalis

Aniden Ne Oldu: Akut Abdomen? ATRA İlişkili Pnömotosis Sistoides İntestinalis Gelişen Zor Olgu

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To the Editor;
Acute promyelocytic leukemia (APL) is a hematological malignancy characterized by the accumulation of atypical promyelocytes in bone marrow and peripheral blood. This condition is frequently associated with disseminated intravascular coagulation (DIC)[1], necessitating immediate medical intervention. All-trans-retinoic acid (ATRA) is a key therapeutic agent to manage this condition. However, ATRA treatment may lead to differentiation syndrome, a potentially fatal complication accompanied by peripheral blood leukocytosis, which occurs in approximately 15% of patients [2,3]. Pneumatosis cystoides intestinalis (PCI) is a rare disorder characterized by gas-filled cysts within the intestinal wall. Its multifactorial etiology includes high intraluminal pressure, bacterial gas production, chemotherapy, and connective tissue diseases [4,5]. We present the first reported case in the literature of ATRA-induced PCI, along with its clinical management.
Case Presentation
A 49-year-old male with no known systemic diseases presented to our hospital with fatigue. Laboratory tests revealed a white blood cell count of 1490/mm^3, neutrophil count of 540/mm^3, hemoglobin: 5.8 g/dL, and platelet count of 34,000/mm^3. Renal and liver function test results were within normal limits. Coagulation parameters showed INR: 1.3, fibrinogen: 1.63 g/dL, aPTT: 23.5 seconds, and D-dimer: 32.2 mg/L. Blastic promyelocytes ("faggot cells") were observed in the peripheral blood smears. Based on flow cytometry findings, a diagnosis of APL was established. Treatment with idarubicin and ATRA was initiated immediately, even before the bone marrow biopsy results were obtained. The patient subsequently developed a differentiation syndrome, necessitating intensive care unit admission and temporary discontinuation of ATRA. Arsenic trioxide could not be administered because of the persistent QT prolongation observed on electrocardiography. Remission was not achieved after first induction. Daunorubicin, cytarabine, and ATRA were given second line therapy. On day 9 of the therapy, the patient experienced abdominal pain. A microbiological examination of the stool was performed for the etiology of the patient's abdominal pain, and we did not detect any microorganisms. There was dilatation in the transverse colon on direct abdominal radiography. Ileus was not excluded. Since the SMA, SMV, and main vascular structures were seen to be open on abdominal contrast CT, mesenteric ischemia was excluded. No obstruction or mechanical events were detected by tomography. Abdominal CT revealed diffuse air densities in the transverse colon wall, which were identified as PCI. Since CRP levels continued to increase during the follow-up period, empirical meropenem and teicoplanin were started for bacterial translocation. Antibiotics were stopped on the 7th day since there was no growth in the blood and catheter cultures taken simultaneously from the patient. The patient's acute-phase reactants continued to increase under antibiotic treatment and gradually decreased and normalized after ATRA was stopped. These findings led to the discontinuation of ATRA. A colonoscopy was not performed because of deep neutropenia and high perforation risk. When evaluated for the differential diagnosis of differentiation syndrome, differentiation syndrome was not considered due to the patient's only abdominal complaints, no additional supportive findings such as weight gain or renal failure, and the patient being in hematological remission at the time of the event and its timing. Drug-related PCI was primarily considered in this patient, as radiological evidence is guiding, particularly in the absence of colonoscopic evidence. Abdominal pain resolved within one week of discontinuing ATRA, and subsequent CT showed complete resolution of air densities near the transverse colon (Figure 1).

There are three hypotheses on PCI pathogenesis: (1) mechanical theory, which involves an increase in intraluminal pressure that causes mechanical damage and mucosal rupture of the intestinal wall, leading to the migration of gas from the gastrointestinal cavity to the intestinal wall [6] ; (2) pulmonary theory, which states that chronic lung diseases such as chronic obstructive pulmonary disease, asthma, and interstitial pneumonia lead to alveolar rupture, causing mediastinal emphysema and release of gas along the aorta and mesenteric blood vessels into the intestinal wall [7]; and (3) bacterial theory, which states that aerogenic bacteria penetrate the intestinal mucosal barrier, ferment in the intestinal wall, and gas production. Upon reviewing the literature, we observed four patients with hematological malignancies who experienced complications during the neutropenic period. In three of these cases, the issues were associated with etoposide, while in one case, mitoxantrone was implicated. The complications resolved after discontinuing the related medications and providing supportive therapies. This study also explored the mechanism of gas accumulation due to mucosal damage [8]. In our case, the neutropenic period was the period when his conventional chemotherapy ended, and he was only taking ATRA. The patient, who had a history of dexamethasone exposure with suspicion of differentiation syndrome, was thought to be a risk factor for intestinal mucosal damage, improved after the drug was stopped, later received conventional chemotherapies other than ATRA, and did not have PCI recurrence despite his neutropenic periods, which supports our view that it was related to ATRA. ATRA-associated ulcerations in different organ systems have been reported in many publications before.This case report highlights an unusual and serious adverse event associated with ATRA therapy. ATRA-associated ulcerations in different organ systems have been reported in many publications before [9-13]. With this although murine experiments suggest that retinoic acid derivatives reduce gut inflammation [14], a study on patients with ulcerative colitis found that retinoic acid levels were higher in tissues with high inflammation [15]. In light of all the data, it is obvious that there is a need for more prospective studies on the intestinal effects of retinoic acid derivatives.We hypothesized that ATRA use causes colonic ulcerations, allowing gas to pass through the colon wall and form cysts. Initial antibiotic therapy and bowel rest did not alleviate symptoms. When the literature was reviewed, no such side effects were reported with ATRA or retinoid derivatives. Therefore, it was concluded that this was the first case and the mechanism thought to be the cause was related to mucosal damage in the light of other literature.
Rapid improvement following ATRA discontinuation suggests a drug-related etiology for PCI. Awareness of this rare complication is critical for timely diagnosis and appropriate treatment to minimize patient morbidity.

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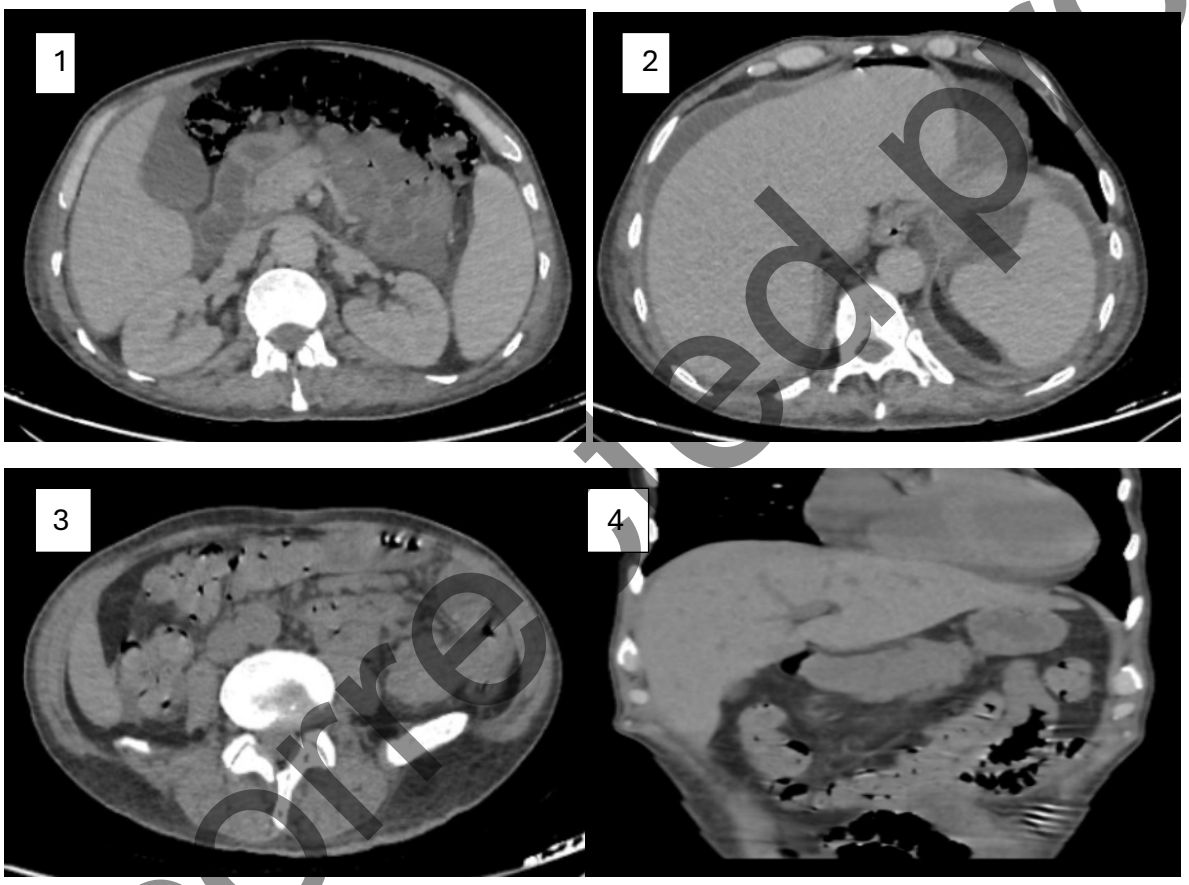

Figure 1: 1)Extensive air densities, consistent with pneumatosis cystoides intestinalis, were noted along the transverse colon up to the level of the splenic flexure, appearing to involve the wall of the transverse colon. 2)Free air was observed anterior and posterior to the transverse colon in the abdominal cavity. 3-4) In the patient's 12/2023 examination, the air densities previously described adjacent to the transverse colon in the 11/2023 evaluation appear to have resolved.