LETTER TO THE EDITOR

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What Happened Suddenly - Acute Abdomen? A Difficult Case of ATRA-Related Pneumatosis Cystoides Intestinalis

Aniden Ne Oldu: Akut Abdomen? ATRA İlişkili Pnömatozis 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 [1], necessitating immediate medical intervention. All-trans retinoic acid (ATRA) is a key therapeutic agent for managing 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 together with its clinical management.

A 49-year-old man with no known systemic diseases presented to our hospital with fatigue. Laboratory tests revealed white blood cell count of 1490/mm^3, neutrophil count of 540/mm^3, hemoglobin of 5.8 g/dL, and platelet count of 34,000/mm^3. Renal and liver function test results were within normal limits. Coagulation parameters revealed international normalized ratio of 1.3, fibrinogen of 1.63 g/dL, activated partial thromboplastin time of 23.5 s, and D-dimer of 32.2 mg/L. Blastic promyelocytes were observed in 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 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 as second-line therapy. On day 9 of the therapy, the patient experienced abdominal pain. A microbiological stool examination 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 superior mesenteric artery, superior mesenteric vein, and main vascular structures were seen to be open on abdominal contrast computed tomography (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 the patient's C-reactive protein 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 blood and catheter cultures taken simultaneously. The patient's acute-phase reactants continued to increase under antibiotic treatment but 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. In evaluations for differential diagnosis, differentiation syndrome was not considered due to the patient having only abdominal complaints, the absence of supportive findings such as weight gain or renal failure, and the patient being in hematological remission at the time of the event. Drug-related PCI was primarily considered for this patient based on the radiological evidence, particularly in the absence of colonoscopic evidence. The abdominal pain resolved within 1 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) the 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) the 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) the bacterial theory, which states that aerogenic bacteria penetrate the intestinal mucosal barrier, ferment in the intestinal wall, and cause gas production. Upon reviewing the literature, we identified four previous 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 relevant medication and providing supportive therapies. The mechanism of gas accumulation due to mucosal damage was also explored [8]. In our case, the neutropenic period was the period in which the patient's conventional chemotherapy had ended and he was receiving only ATRA. The patient had a history of dexamethasone exposure with suspicion of differentiation syndrome and was thought to be at risk of intestinal mucosal damage, but he improved after the drug was stopped. He later received conventional chemotherapies other than ATRA and did not have PCI recurrence despite neutropenic periods, which supports our view that the case was related to ATRA. Thus, the present 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 [9,10,11,12,13]. Although murine experiments suggested that retinoic acid derivatives reduced gut inflammation [14], a study of 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 the symptoms. When the literature was reviewed, no such side effects were previously reported with ATRA or retinoid derivatives. Therefore, it was concluded that this was the first case of its kind and the causal mechanism was thought to be related to mucosal damage in light of other similar studies in the 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.

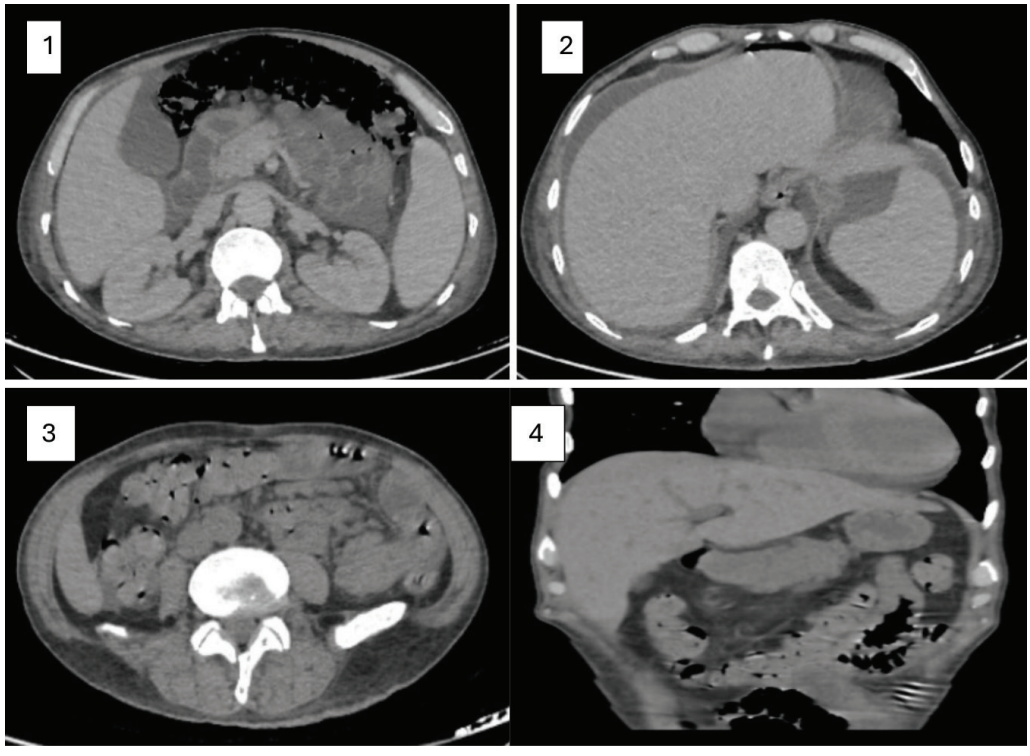

Figure 1. 1) Extensive air densities, consistent with pneumatosis cystoides intestinalis, were noted along the transverse colon up to the level of the splenic flexure, appearing to involve the wall of the transverse color. 2) Free air was observed anterior and posterior to the transverse colon in the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

Keywords: Acute promyelocytic leukemia, Pneumotosis cystoides intestinalis, ATRA, All-trans retinoic acid, ATRA-related toxicity

Anahtar Sözcükler: Akut promiyelositik lösemi, Pnömatozis sistoides intestinalis, ATRA, All-trans retinoik asit, ATRA ilişkili toksisiteler

Ethics

Informed Consent: No photograph revealing the patient's identity is included, and informed consent has been obtained from the patient for clinical sharing purposes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E.E., E.İ.K., F.C.; Concept: M.E.E., G.Ö., S.D.; Design: M.E.E., G.Ö., S.D.; Data collection and Processing: M.E.E., A.C., E.Ö.; Analysis or Interpretation: M.E.E.; Literature Search: M.E.E., A.C.; Writing: M.E.E., A.C.

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