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CASE REPORT / *OLGU SUNUMU*

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An Exceptional Etiology of a Rare Disease: Pneumatosis Intestinalis in the Intensive Care Unit due to Chronic Graft-Versus-Host Disease

Ender Bir Etiyoloji ile Beraber Nadir Bir Hastalık: Yoğun Bakım Ünitesinde Kronik Graft-Versus-Host Hastalığına Bağlı Pnömatozis İntestinalis

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ABSTRACT Pneumatosis intestinalis (PI) is a rare disease, which presents a wide range of severity. Numerous etiologies, including trauma, inflammation, infections, autoimmunity, drugs, and mechanical procedures, gave rise to this complication. Abdominal computerized tomography is the preferred diagnostic tool with high sensitivity. The diagnosis depends on free air detection in the intramural portion of the gastrointestinal system and main and intrahepatic branches of the portal venous structures. However, the exact mechanism is unknown. The clinical scenario may vary from benign to life-threatening. One of the etiological factors that cause PI is the chronic graft-versus-host disease (cGVHD), which must be considered in patients with solid organ or hematological malignancies. Especially, patients who received long-term immunosuppressive therapies and were diagnosed with cGVHD are prone to developing a PI. Many patients experience unnecessary operational risks if underdiagnosed. A multidisciplinary approach by the primary physician, general surgeon, and radiology specialist is necessary for the proper treatment of these patients. This case report aimed to discuss the clinical presentation of PI in the course of cGVHD in the intensive care unit.
Keywords: Chronic graft versus host disease, pneumatosis intestinalis, intensive care

ÖZ Pnömatozis intestinalis (PI) nadir ve hafiften ağıra değişen geniş bir klinik yelpazede ortaya çıkabilen bir hastalıktır. Travma, enflamasyon, enfeksiyonlar, otoimmünite, ilaçlar ve mekanik işlemleri içeren çok farklı etiyolojiler bu klinik komplikasyona yol açabilir. Abdominal bilgisayarlı tomografi yüksek sensitivite ile tercih edilen tanı aracıdır. Tanı, gastrointestinal kanalın intramural kısımlarında ve portal venin ana gövdesinde ve intrahepatik dallarında serbest hava saptanmasına dayanır. Hastalığın kesin ortaya çıkış mekanizması bilinmemektedir. Klinik bulgular hafiften hayatı tehdit edici durumlara kadar değişiklik gösterebilir. PI'ya neden olabilen ve özellikle solid organ ve hematolojik maligniteli hastalarda akılda tutulması gereken etiyolojik faktörlerden birisi de kronik graft-versus-host hastalığıdır (cGVHD). Uzun süre immünosüpresif ilaç kullanımı öyküsü ve tanı konulmuş cGVHD olan hastalar özellikle bu komplikasyona yatkındır. Doğru tanı konulamaz ise pek çok hasta gereksiz operasyonel risklerle karşı karşıya kalabilir. Bu hastaların uygun tedavileri için hastanın sorumlu hekimi, genel cerrahi uzmanı ve radyoloji uzmanını kapsayan ekibin multidisipliner ortak yaklaşımı gereklidir. Bu olgu sunumunun amacı yoğun bakım ünitesinde cGVHD seyrinde ortaya çıkan PI kliniğini tartışmaktır.
Anahtar Kelimeler: Kronik graft-versus-host hastalığı, pnömatozis intestinalis, yoğun bakım

Introduction

Pneumatosis intestinalis (PI) is a rare disease radiologically characterized by collection of gas in the intestinal wall (1). In some cases, gas can also be seen in intraperitoneal and extra peritoneal spaces and organs (2), and in more severe cases it can be seen in portal venous system which usually accompanies intraabdominal pathologies often associated with surgical conditions (3). Although PI and/or portal venous gas (PVG) can be easily detected by computerized tomography (CT), its clinical significance remains to be a challenge as a wide range of etiologies from benign to catastrophic might be the cause (4,5). PI might have traumatic, inflammatory, mechanical, autoimmune, pulmonary, infectious, drug-related causes. It can also occur as a complication of bacterial or viral infections, interventional procedures such as colonoscopy, chronic obstructive pulmonary disease, gastrointestinal obstructions, immunodeficiency or cancer treatment. One of the most uncommon causes of PI that won't be easily considered in the intensive care unit (ICU) is graft versus host disease (GVHD) (6), unless medical history is well questioned.

The purpose of this case report is to discuss a clinical presentation of PI in the course of chronic GVHD (cGVHD) in the ICU.

Case Report

A 19-year-old male patient was diagnosed with T-cell acute lymphoblastic leukemia in April 2013 at the age of fifteen. He underwent an HLA 7/10 matched haploidentical transplantation from his mother in February 2014. Due to development of stage 2 skin GVHD on day 20 of transplant, 2 mg/kg methylprednisolone was started. He was discharged on the 30th day with complete donor chimerism. However, diarrheae emerged on day 70 posttransplant during steroid taper. Daily 1.5 liters stool with no microbiological cause led to diagnose stage 3 gastrointestinal GVHD. With the history of skin and intestinal GVHD, ongoing skin changes like hypo-hyperpigmentated areas and pruritic erythematous changes and new onset oral GVHD, the patient was diagnosed as moderate cGVHD. Hepatic GVHD developed on day 517 posttransplant. Photopheresis was scheduled. On day 1,144 posttransplant, at age 19, a skin biopsy was performed, which was reported as cGVHD.

While taking mycophenolate mofetil and metylprednisolone for chronic GVHD, he was admitted to the emergency room with high fever, anorexia, nausea, dyspnea, cough, sputum and syncope. The patient who had a cachectic appearance was also suffering from abdominal pain and diarrhea. Although his abdomen was tender to palpation, neither defence nor rebound was detected. Procalcitonin was 30 ng/mL, C-reactive protein: 211 mg/L in the laboratory values. The patient was transferred to a 3rd stage ICU with the diagnosis of septic shock. Piperacillin-tazobactam, levofloxacin, teicoplanin and voriconazole was commenced immediately after his transfer.

Bilateral pneumonic infiltrations were detected in thorax CT. Intramural air was observed in the stomach wall in abdominal CT scan: Milimetric free-air densities were observed within the perigastric fat tissue adjacent to the cardio-esophageal junction and major curvature of the stomach (Figure 1). Intravascular air was seen in the main portal vein lumen and intrahepatic portal veins, which were more prominent in the arteriolar phase images (Figure 2). Local heterogeneity and increased density were observed in peripancreatic and perigastric fat tissue planes and minimal free peritoneal fluid was observed in this region. The radiologic findings was suggesting early phase of perforation.

An emergency operation planned initially was cancelled after considering his medical history together with his current physical examination. Chronic gastrointestinal GVHD was considered as a potential cause of PI and a conservative aproach was preferred in the follow up with the consensus of intensive care, hematology, general surgery and radiology teams. Enteral feeding was stopped and nasogastric decompression was performed.

Levofloxacin-sensitive *Streptococcus pneumoniae* grew in his blood culture. Cytomegalovirus DNA was also

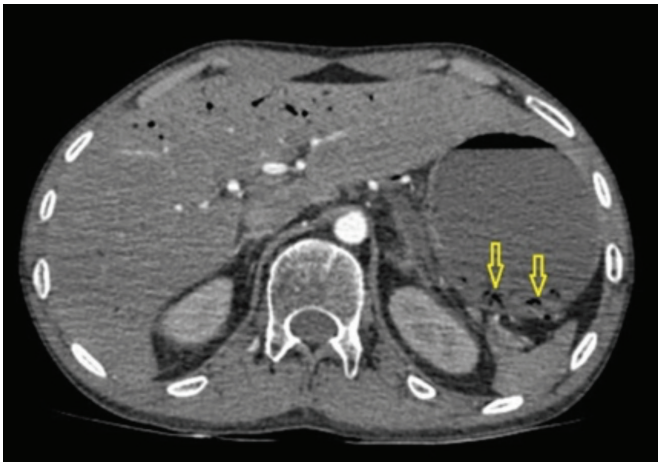

Figure 1. Millimetric air densities in the stomach wall

found positive. There was no growth in the urine and stool cultures. The treatment was supplemented with ganciclovir IV 2x5 mg metylprednisolone was continued. Non-invasive mechanical ventilation (NIMV) support was initiated because of hypoxemia. Despite NIMV support, respiratory distress worsened and the patient was electively intubated. On the 4th day of ICU *Acinetobacter* grew in tracheal secretory culture. Antibiotic therapy was switched to colistin intravenous 2x2.5 mg/kg and colistin inhaler 2x75 mg.

The patient was successfully extubated on the 8th day of intubation after he met the weaning criteria. Approximately 20 days after the first CT, control abdominal tomography revealed that the free air densities in the stomach, liver and portal system had resolved (Figure 3).

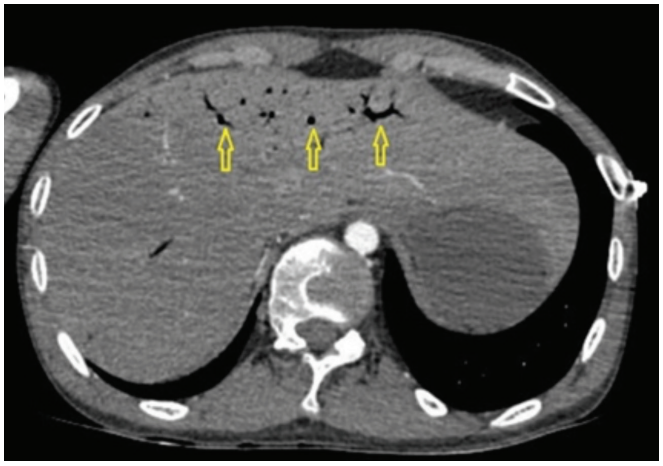

Figure 2. Intravascular air in the main portal vein lumen and intrahepatic portal veins

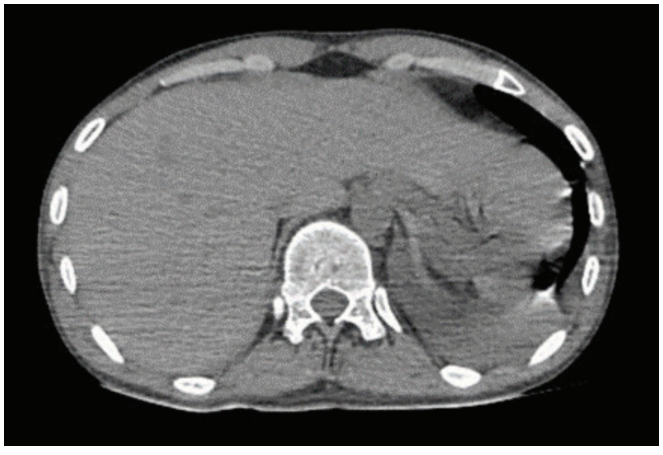

Figure 3. Normal appearance on tomography. Air densities have disappeared

Discussion

PI may be idiopathic (15%) or more frequently secondary (85%) to gastrointestinal or non-gastrointestinal etiologies (7). It can occur in very different clinical situations. It can be asymptomatic in some cases (2), but most patients present with nausea, vomiting, diarrhea and abdominal pain.

Our patient was admitted to the ICU with septic shock. PI was detected in the initial abdominal CT. Some major diseases considered in the differential diagnosis: Intestinal perforation, intraabdominal sepsis, or cGVHD.

Because of the presence of *S. pneumoniae* in blood culture and pneumonic infiltrates in thorax CT, lung was thought to be the primary source of infection. Although there was a possibility of intraabdominal infection, there were no clinical features suggesting an underlying acute abdominal emergency and intraabdominal sepsis. The patient had mild physical examination findings; no signs of peritonitis on abdominal exam (eg, abdominal rigidity, rebound tenderness), no ileus, no metabolic acidosis and low lactate levels in arterial blood gas.

Intraabdominal sepsis related PI is a very rare condition in ICU. PI more often occurs after a major abdominal surgery or endoscopic procedure or during intraabdominal catastrophes (eg, intestinal obstruction, ischemia, infarction, perforation, necrotizing enterocolitis, typhlitis). In one of the two reported cases of intraabdominal sepsis, it was seen that PI was accompanied by paralytic ileus (8). In the other case the diagnosis of septic shock was due to ischemic bowel (9).

GVHD is a very common complication of allogeneic stem cell or bone marrow transplantation and emerges when immunocompetent donor cells recognize recipient cells as foreign. The chronic form of the disease usually occurs a few months after transplantation and is associated with the release of autoreactive T-cells and the induction of antibody production by autoreactive B-cells. Clinical manifestations of chronic GVHD include skin involvement; oral mucosa; gastrointestinal tract; and high serum bilirubin. Reported incidence rates of chronic GVHD range from 6 to 80 percent, depending upon the presence of risk factors and the diagnostic criteria used (10). The skin, liver, gastrointestinal tract, musculoskeletal system and lungs are the principal target organs (11). Among patients with small bowel and colonic involvement, common symptoms and signs include anorexia, nausea, vomiting, chronic diarrhea, malabsorption and weight loss. A scoring system for cGVHD was created by the National Institutes of Health in 2005 and revised in 2014

(10,12). The overall severity is scored as mild, moderate, or severe.

Considering the multi organ involvement and a major disability, our patient appeared to have severe cGVHD. cGVHD in the gastrointestinal tract leads to mucosal atrophy, bacterial and fungal superinfections, fibrosis and malabsorption syndromes with ulcer formation. Intestinal mucosal injury, concomitant infections, infiltration of inflammatory cells and defect in the connective tissue related with steroid therapy, are the predisposing factors to PI (6).

Although PI appears to be based on many factors, its exact cause is unknown. Several theories have been proposed in the literature. Mechanical theory: Gas dissects into the wall of the bowel from the luminal surface or through the serosal surface by tracking along mesenteric blood vessels (13,14). Bacterial theory: PI results from gas-forming bacteria gaining access to the submucosa. Biochemical theory: Luminal bacteria produce excessive amounts of hydrogen gas through fermentation of food. In addition cancer treatment or steroid administration in immunosuppressed patients can lead to impaired lymphatic drainage. It can also cause mucosal injury and aspiration of air through the intestinal lumen. It was obvious that our patient had long-term steroid use and accompanying immunosuppression.

Emergent exploratory laparotomy indications for PI are reported to be 1. Signs of peritonitis (eg, abdominal rigidity, rebound tenderness), 2. Metabolic acidosis (arterial pH<7.3, HCO_3<20 mmol/L), 3. Lactate >2.0 mmol/L, 4. PVG (7,15). None of them were present in our patient except PVG. Our decison was conservative treatment. Combination of antibiotics and an elemental diet referaining from enteral feeding was our protocol.

cGVHD, should be considered as an etiological factor in the differential daignosis of PI with ischemic mucosal lesions and possible gastrointestinal perforation and treatment plan should be made with caution. The presence of free air and fluid in the peritoneal cavity is not always an evidence of perforation, and can be seen as a complication of PI. For this reason, close colloboration with radiology, surgery and intensive care doctors might be life saving.

Regardless of the underlying pathologic factor, PI has a wide ethiological spectrum from life-threatening to benign. For this reason management can range from emergency surgery to observation. Clinicians need to interpret the radiographic findings in accordance with the clinical scenario so that they can make a correct diagnosis and apply appropriate treatment. In patients with gastrointestinal GVHD, PI or pneumoperitoneum is not always related with a perforation and conservative approach should always be the primary approach unless perforation is proved, to mimimize unnecessary surgical interventions. Early recognition of the clinical picture is perhaps the most important factor in deciding whether to distinguish critically dangerous and life-threatening causes from non-urgent causes effectively.

Ethics

Informed Consent: An informed consent form was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.Ç., Design: T.Ç., M.K., Data Collection and Process: T.Ç., H.Ö., B.T.E., V.U., Analysis or Interpretation: T.Ç., H.Ö., M.K., V.U., Y.S., B.C., Literature Search: T.Ç., H.Ö., B.T.E., Writing: T.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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