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Pneumatosis Cystoides Intestinalis Complicated during Chemotherapy for Pulmonary Nontuberculous Mycobacterial Disease

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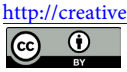


Abstract

Background: Pneumatosis cystoides intestinalis (PCI) is a rare disease characterized by the presence of gas in the intestinal wall. **Aim**: We report two rare cases of PCI that are complicated during the chemotherapy for pulmonary nontuberculous mycobacterial (NTM) disease. **Case Presentation**: In this report, we described two cases (a 72-year-old woman and a 60-year-old woman) of PCI that appeared during the combined chemotherapy consisting of rifampicin, ethambutol and clarithromycin. Because there were few clinical symptoms and increased inflammatory responses, the diagnosis of PCI was delayed. However, there were fortunately no severe complications in both cases. **Conclusion**: Respiratory physicians should be aware of the potential development of PCI in patients during the chemotherapy for pulmonary NTM disease. It is important to detect PCI in the early stage through radiological examinations to avoid severe complications.

Keywords

Pneumatosis Cystoides Intestinalis (PCI), Pulmonary Nontuberculous Mycobacterial (NTM) Disease, Combined Chemotherapy

1. Introduction

Pneumatosis cystoides intestinalis (PCI) is a rare disease characterized by the presence of multiple gas-filled cysts in the submucosa and/or subserosa of the intestinal wall. Since its initial description by Du Vernoy in 1730 [1], it has been reported mainly in the gastroenterological field. PCI is classified into primary

and secondary types and the secondary type is associated with gastrointestinal, traumatic, pulmonary, and collagen vascular diseases. Concerning PCI complicated with respiratory diseases, several PCI cases appeared as complications of chronic obstructive pulmonary disease and lung cancer [2] [3] [4] [5] [6]. However, there has been one case report of PCI associated with the setting of antibiotics use (clindamycin) [7] and few reports except that by Yamasaki *et al.* [8] on PCI during the follow-up of pulmonary nontuberculous mycobacterial (NTM) disease concerning the infectious diseases as far as we investigated in the literature. We report herein two rare cases of PCI that are complicated during combined chemotherapy for pulmonary nontuberculous mycobacterial (NTM) disease.

2. Case Reports

Case 1

A 72-year-old woman visited our hospital with complaints of cough and dyspnea on effort. She had a past history of interstitial pneumonia with rheumatoid arthritis and polymyositis, and immunosuppressive drugs such as corticosteroid and tacrolimus were administered ten years ago. She had no history of smoking or alcohol abuse. She showed a nodular shadow and bronchiectatic lesion in the right upper and middle lobes and left lingula lobe, and a linear-reticular shadow in both lower lungs on chest CT. We suspected pulmonary NTM disease with interstitial pneumonia. Finally, because *Mycobacterium avium* and *Mycobacterium intracellulare* were isolated from the sputum several times, we diagnosed her with pulmonary *Mycobacterium avium* complex (MAC) disease with interstitial pneumonia. We showed the clinical course of case 1 in **Figure 1**. We initiated combined chemotherapy consisting of rifampicin (RFP), ethambutol (EB), clarithromycin (CAM), and streptomycin (SM) for pulmonary MAC disease with a combination of immunosuppressive drugs and continued three antibiotics (RFP, EB, and CAM) two months later. Although the tendency of loose stools and mild nausea appeared after the initiation of combined chemotherapy, the therapy was continued for one year following conservative treatment. Although there were no multiple gas-filled cysts in the intestinal wall on abdominal CT after six months of the initiation of combined chemotherapy, the presence of multiple gas-filled cysts in the intestinal wall was recognized on abdominal CT six months later, we diagnosed her with PCI complicated with pulmonary MAC disease. However, there was no free-air gas in the mediastinum on chest CT (**Figure 2**). On the appearance of PCI, physical examination showed no abnormal findings in the abdomen. The laboratory findings also showed no aggravation compared with the inflammatory data before the onset of pulmonary MAC disease. We stopped the administration of three antibiotics (RFP, EB, and CAM) immediately, but continued immunosuppressive drugs such as corticosteroid and tacrolimus. Subsequently, her mild clinical symptoms disappeared and multiple gas-filled cysts also disappeared after three months on abdominal CT. Thereafter, there are no recurrence of PCI on abdomen CT after six months with no treatment for pulmonary MAC disease.

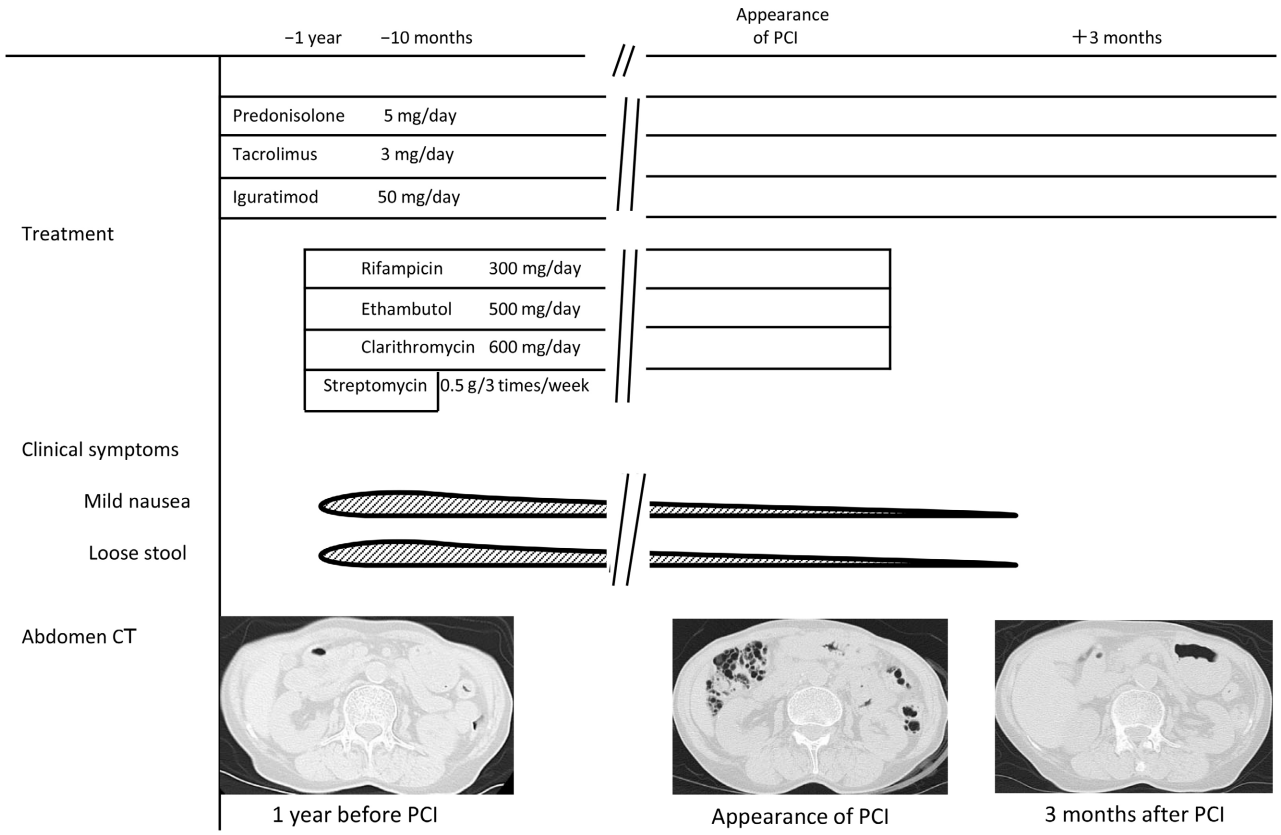


Figure 1. Clinical course (Case 1).

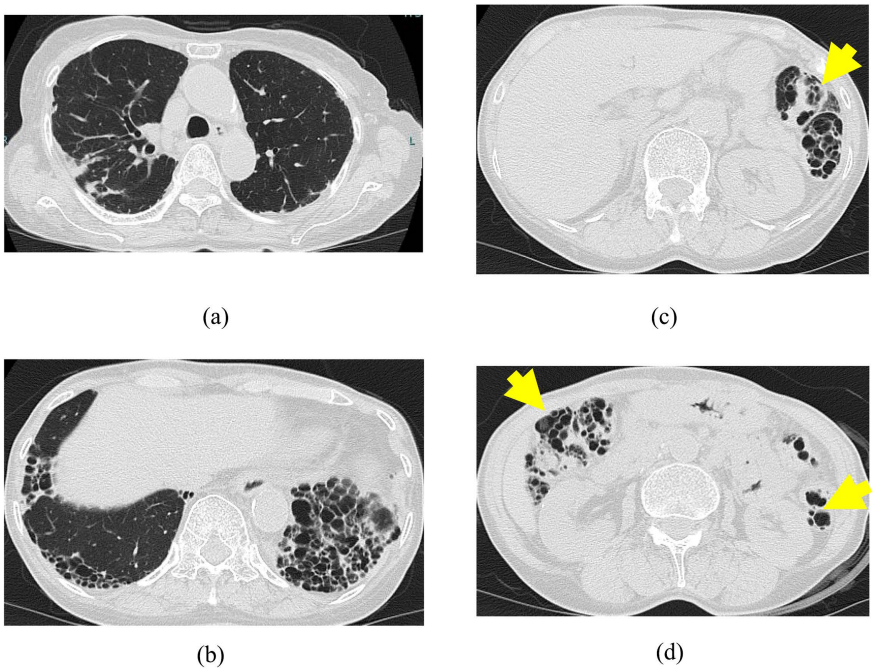


Figure 2. Chest CT ((a) and (b)) showing a nodular shadow with bronchiectatic lesion in the right upper lobe due to pulmonary MAC disease and a linear-reticular shadow in both lower lung fields due to interstitial pneumonia. Abdomen CT ((c) and (d)) showing multiple gas-filled cysts in the intestinal wall (arrows) due to PCI (Case 1).

Case 2

A 60-year-old woman was introduced to our hospital with a complaint of mild diarrhea. She had a past history of IgA nephropathy twenty years ago (no medication), pulmonary MAC disease eight years ago (medication of RFP, EB, CAM, and SM for one year), diabetes mellitus (medication of DPP-4 inhibitor drug), hypertension (calcium inhibitor drug plus ACE inhibitor drug), and dyslipidemia (no medication) four years ago. She had no history of smoking or alcohol abuse. We showed the clinical course of case 2 in **Figure 3**. She had received combined chemotherapy using RFP, EB, and CAM again two years ago because of the aggravation of clinical symptoms (cough and sputum) and worsening of radiological findings. Thereafter, although mild diarrhea appeared, the treatment was continued for two years following conservative treatment. Nodular and bronchiectatic lesions were recognized in the right middle, left lingula, and left lower lung on chest CT, but there was no gas-filled cyst on abdominal CT at the initiation of combined chemotherapy and after six months. Colonoscopy was performed because of a fecal occult blood-positive result in the referral hospital two years later combined with chemotherapy. Multiple large and small polyps were noted over the entire circumference of the whole colon (**Figure 4**). There were multiple gas-filled cysts on abdominal CT, but there was no free-air gas in the mediastinum on chest CT (**Figure 5**). Therefore, we diagnosed her with PCI complicated with pulmonary MAC disease. At the diagnosis of PCI, physical examination showed no abnormal findings in the abdomen. Laboratory findings also showed no aggregation compared with the inflammatory data before the onset of pulmonary MAC disease. We considered that PCI developed as a side effect of the three antibiotics and stopped them immediately. Clinical symptoms such as mild diarrhea disappeared, and multiple gas-filled cysts had disappeared on abdominal CT nine months later. Thereafter, there are no recurrence of PCI on abdomen CT after seven months with no treatment for pulmonary MAC disease.

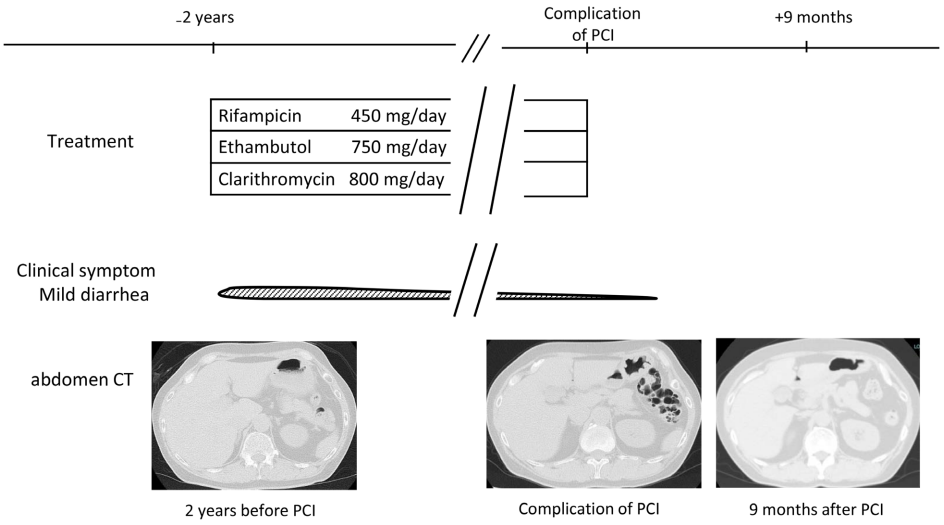


Figure 3. Clinical course (Case 2).

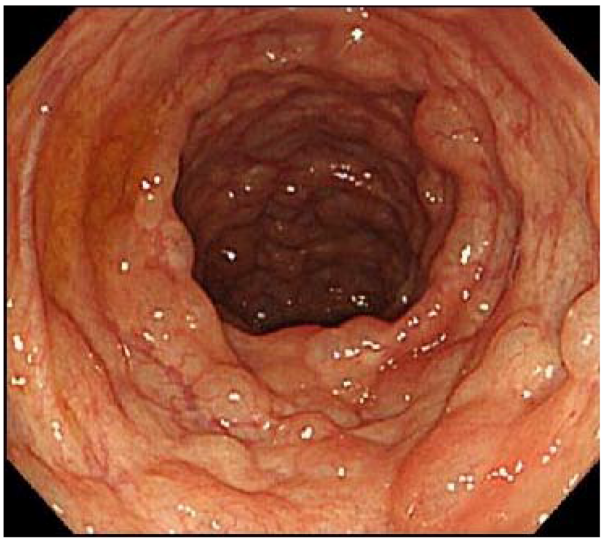
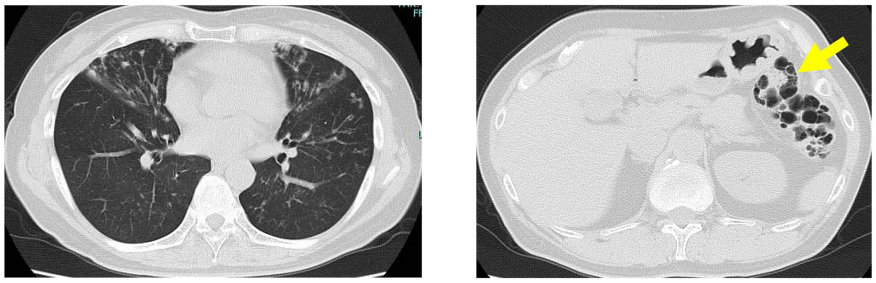


Figure 4. Colonoscopy showing multiple large and small polyps that noted over the entire circumstance of the whole colon.



(a) (b)

Figure 5. Chest CT (a) showing nodular and bronchiectatic lesions in the right middle lobe, left lingula, and left lower lung due to pulmonary MAC disease. Abdomen CT (b) showing multiple gas-filled cysts in the intestinal wall (arrow) due to PCI (Case 2).

3. Discussion

We described two cases of PCI developing during combined chemotherapy for pulmonary MAC disease. PCI can be divided into primary (15%) and secondary (85%) types [9] [10]. The secondary type occurs following underlying diseases such as not only pulmonary disease but also gastrointestinal disease, pulmonary disease, traumatic injury, surgery, and collagen vascular disease. Although we investigated the previous reports about PCI complicated with pulmonary MAC disease, there is only one report [8] and our experienced two cases were thought to be rare.

The etiology of PCI is not clear, and one mechanism cannot explain all cases. However, there are four major theories: 1) The mechanical theory: increased intraluminal pressure forces gas within the bowel lumen to breach the mucosal or serosal layers, and the gas migrates from the gastrointestinal lumen into the submucosal or subserosal layer of the intestinal wall. Vomiting or intestinal obstruction increases intraluminal pressure and causes mechanical injury to the

intestinal wall [11]. 2) The pulmonary theory: chronic pulmonary disease, such as chronic obstructive pulmonary disease and interstitial pneumonia, causes alveolar rupture, and air leakage from the alveolar rupture travels to the retroperitoneum through the mediastinum and retroperitoneum and is located within the bowel mesentery [12]. 3) The bacterial theory: gas is produced by gas-forming bacteria such as *Clostridium species* and *Escherichia coli* that enter the mucosal barrier through mucosal rents or increased mucosal permeability and produce gas within the intestinal wall [13]. 4) The chemical theory: Increased production of hydrogen gas during carbohydrate metabolism raises the intraluminal pressure, which forces the gas into the weakened intestinal wall. Corticosteroids and immunosuppressants have also been considered to exacerbate PCI [14] [15]. Ammons *et al.* reported that renal transplant patients treated with prednisolone and cyclosporin developed PCI. Some immunosuppressive drugs were suggested to shrink Payer's patches, with a resultant loss of structural integrity in the intestinal wall [16]. Several recent reports have suggested that PCI may be associated with molecular targeted therapy agents such as vascular endothelial growth factor (VEGF) inhibitors, tyrosine kinase inhibitors (THI), mammalian target of rapamycin inhibitors, and immune modulators [17]. Molecular targeted therapy has been hypothesized that the decreased blood supply caused by angiogenesis inhibition may reduce the capillary density of intestinal villi, possibly causing abdominal hypoxia and allowing air to infiltrate the intestinal wall [17] [18].

In this report, because case 1 received immunosuppressive treatment for the underlying disease for ten years, we initially considered that immunosuppressive treatment may be the cause of PCI. However, PCI appeared at the completion of combined chemotherapy for one year for pulmonary MAC disease regardless of no complication of PCI on abdominal CT before six months, and it disappeared on abdomen CT three months after stopping the three antibiotics in spite of the continuation of immunosuppressive treatment (**Figure 1**). Case 2 also complicated PCI after finishing chemotherapy for two years for pulmonary MAC disease regardless of no complication of PCI on abdominal CT before one year, and PCI disappeared on abdomen CT nine months after stopping the three antibiotics (**Figure 3**). Therefore, we speculate that combined chemotherapy for pulmonary MAC disease may influence the appearance of PCI in both cases. Concerning the etiology of PCI, although the bacterial theory or chemical theory due to the three antibiotics (CAM, RFP, and EB) among the four theories may be suspected in both cases, the correct underlying mechanism is not well-understood. In the previous report of PCI related to antibiotics (clindamycin), Syed *et al.* also described that the timeline fits the patient symptoms, and owing to the absence of any other explanation, and concurred that this may be the cause [7].

Concerning the clinical characteristics, PCI lesions are mainly located in the colon (47%), small intestine (27%), and large and small intestine (7%), respectively [19]. The clinical symptoms of PCI are nonspecific such as abdominal pain, diarrhea, nausea, and vomiting, gastrointestinal disorders appeared in our two cases. However, because both cases showed mild clinical symptoms before

the appearance of PCI, we think that combined chemotherapy for pulmonary MAC disease causes these clinical symptoms.

The appropriate therapy for PCI is related to the etiology of PCI. The majority of patients without pronounced clinical symptoms were cured with no treatment. If the clinical symptoms are pronounced, conservative treatment is performed, such as intestinal rest, parenteral nutrition, and infusion management. On the other hand, the surgical treatment is indicated for patients involving elevated WBC or CRP levels as well as sepsis, bowel perforation or free air-gas near the portal vein [10] [20]. Fortunately, there were no severe complications in our two cases. To avoid the serious complication of PCI, if PCI is suspected, CT examination should be performed when conditions permit as soon as possible. Several researchers reported that abdominal CT characteristics of PCI are multiple submucosal or subserosal cystic transmission areas that resemble a bunch of grapes [21]. CT images taken at different levels enable the estimation of lesion location and extent through three-dimensional scanning.

4. Conclusion

Respiratory physicians should be aware of the potential development of PCI in patients during combined chemotherapy for pulmonary MAC disease. Although chemotherapeutic agent has been reported to be associated with PCI, the pathogenesis is unknown and clinical symptoms and treatments have changed corresponding to the severity of PCI. Therefore, it is important to detect PCI in the early stage through radiological examinations to avoid surgical treatment.

Conflicts of Interest

The authors state that they have no conflict of interest (COI).

Informed Consent

We obtained that both patients had given their consent for the case reports to be published.

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