An Extremely Rare Case of Pneumatosis Intestinalis Likely Induced by Afatinib Treatment for EGFR-mutated Stage IV Non-small Cell Lung Cancer

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Pneumatosis intestinalis (PI) is a rare radiological finding given by the presence of gas within the bowel wall, mainly caused by endoscopic procedures, infections and other gastrointestinal diseases. To date, cytotoxic chemotherapeutic agents, immunotherapy drugs and monoclonal antibodies used for molecular targeted therapy in oncological patients have been reported as a possible cause of PI, but their role remains unclear. We hereby report the case of a 61-year-old patient with stage IV lung adenocarcinoma in treatment with afatinib—a tyrosine kinase inhibitor (TKI), since the diagnosis, who presented to the emergency department with abdominal pain secondary to left-colonic PI. A conservative treatment with drug suspension was successfully attempted. To the best of our knowledge, even though many monoclonal antibodies are associated with this condition, this is the first case report of PI likely induced by afatinib. Although PI is extremely rare, clinicians should be aware of the risk of PI in patients undergoing afatinb therapy and the present case represents a significant warning to differentiate the associated conditions of PI and evaluate whether or not emergency surgery is actually necessary. Therefore, abdominal symptoms in patients receiving oncological treatments should not be overlooked, and clinicians should not hesitate to request targeted radiological investigations to facilitate early diagnosis and management of PI. Timely event detection is imperative to optimal management and to prevent further deterioration, recurrent PI, or even perforation, especially in oncological patients.

Keywords: adverse drug events; bowel complication; intestinal pneumatosis; molecular targeted therapy; pneumoperitoneum; case report

Introduction

Pneumatosis intestinalis (PI) is an uncommon radiological finding characterized by the presence of extraluminal gas within the intestinal wall, predominantly in the submucosal or, more frequently, in the subserosal layers [1]. The condition was first documented in 1730 by DuVernoi during a cadaveric dissection and was subsequently identified radiographically in 1946 by Lerner and Gazin, though its clinical significance and etiology remained unclear at the time. Since then, the reported incidence of PI has increased, largely due to advancements in radiological imaging techniques [2].

The prevalence of PI is estimated to be approximately 0.03% in the general population. However, its true incidence may be underestimated due to the frequent occurrence of asymptomatic cases [3]. While PI can be a benign incidental finding, it may also lead to severe complications in certain clinical scenarios.

The pathogenesis of PI is believed to be multifactorial, with several hypotheses proposed to explain its development. The mechanical theory suggests that gas infiltrates the intestinal wall through defects in the luminal surface or via mesenteric blood vessels. The bacterial theory postulates that gas-producing bacteria penetrate the submucosa, leading to intramural gas accumulation. A biochemical theory has also been proposed, wherein excessive hydrogen gas production from bacterial fermentation increases intraluminal pressure, forcing gas into the mucosal layers. Despite certain pharmacological agents have been implicated in PI, the exact mechanisms underlying this association remain incompletely understood [4].

PI is classified into primary (15%) and secondary (85%) forms.

Primary PI, often referred to as pneumatosis cystoides intestinalis, is characterized by cystic gas collections within the submucosal and subserosal layers of the colon. Even though this variant is typically idiopathic, benign, and potentially self-limiting, cystic enlargement may occur over time [5]. As of today, computed tomography (CT) is the most sensitive imaging modality for detecting PI and it is

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particularly useful in identifying advanced disease features, such as hepatic portal and portomesenteric venous gas [4].

Secondary PI is a multifactorial condition with a radiological pattern of linear gas distribution. In adults, it is most commonly associated with underlying gastrointestinal disorders, pulmonary diseases, mechanical ventilation, endoscopic interventions, infections, and immunological conditions [6]. Among the recognized causes of secondary PI, oncologic therapies—including cytotoxic chemotherapeutic agents, immunotherapy, and monoclonal antibodies used in molecular-targeted treatments—are particularly relevant [7]. The high proliferative turnover of the intestinal mucosal epithelium easily exposes to injury from those agents. Chemotherapy-induced mucosal damage disrupts barrier integrity, allowing intraluminal gas to dissect into the bowel wall, reinforcing the mechanical theory of PI pathogenesis [8].

Although PI is frequently an incidental and benign finding, it can present with abdominal pain, bowel obstruction, gastrointestinal bleeding, nausea, vomiting, weight loss, diarrhea, constipation, flatulence, and anorexia. In severe cases, life-threatening complications may arise approximately in 3% of cases and include bowel obstruction, perforation, volvulus, intussusception, mucosal ulceration with hematochezia, bowel necrosis and pneumoperitoneum [9,10].

From a surgical perspective, it is of the utmost importance recognizing the 70% of cases of linear PI with concomitant portal venous gas and intestinal ischemia which necessitate prompt intervention [2].

Diagnosis of PI requires radiological assessment, often completed with laboratory tests. CT imaging typically reveals cystic or linear intramural gas within the intestinal wall, most commonly affecting the colon and less frequently the rectum and ileum. Laboratory findings may be unremarkable or may show leukocytosis and elevated C-reactive protein (CRP) levels. Serum pH and lactate levels are considered major prognostic markers, historically used as indicators of intestinal ischemia and able to define the need for surgery, especially when associated with pneumoperitoneum. Free intraperitoneal or intraluminal air, resulting from subserosal cyst rupture, may lead to abdominal distension and discomfort. However, emerging evidence suggests that a conservative approach may be appropriate in selected cases [11].

When managed non-surgically, PI treatment typically involves antibiotic therapy and, in some cases, hyperbaric oxygen therapy for 2–3 days. Poor prognostic indicators, such as elevated serum lactate, metabolic acidosis, hyperamylasemia, reduced bicarbonate levels and the presence of portal venous gas, suggest a high likelihood of conservative treatment failure and necessitate urgent surgery [2].

We present the case of a 61-year-old patient with stage IV lung adenocarcinoma who had been receiving afatinib since diagnosis and presented to the emergency department with abdominal pain secondary to left-colonic pneumatosis intestinalis. A conservative management approach was successfully implemented. To the best of our knowledge, although multiple monoclonal antibodies have been associated with PI, this is the first reported case of afatinib-induced PI.

Afatinib is a strong, irreversible, and selective inhibitor of the ErbB family. It covalently binds to all ErbB family members, including EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4. Since the epidermal growth factor receptor (EGFR)-signaling pathway also plays a crucial role in normal physiological processes, its inhibition can lead to various adverse effects, especially in skin and mucosal tissues [12]. Forasmuch as no other potential cause was identified, we believe that afatinib-induced disruption of intestinal membrane integrity may have been responsible for this rare case of secondary PI.

Case Report

A 61-year-old male presented to our emergency department with painless diarrhea with no other symptom related and an anamnesis of approximately six watery stools per day for about 72 hours. He had a six-month history of stage IV lung adenocarcinoma with bone, liver, brain, adrenal, mediastinal lymph node metastasis (T4 N3 M1c according to TNM 8th Edition)and was receiving chemotherapy. The very sensitive EGFR-next generation sequencing (NGS) assay showed an EGFR exon 19 mutation which opened up to the possibility of a tyrosine kinase inhibitor targeted therapy. He had been taking antihypertensive drugs for a long-lasting hypertension diagnosed years earlier and was on 40 mg of afatinib since cancer diagnosis, together with daily 8 mg of dexamethasone and 4 mg of zometa due to the presence of bone metastasis. Vital signs were unremarkable. Body temperature was 37.8 °C. On admission, laboratory tests revealed mild neutrophilic leukocytosis, together with lymphocytopenia and mildly elevated liver transaminase and CRP levels; all remaining values, including lactates, were within the normal range. Abdominal sonography didn't detect any notable pathologic finding, while abdominal radiography revealed the presence of subdiaphragmatic free air and chest-X-ray showed bilateral lung thickening with minimal pleural effusion. High resolution thoracic computerized tomography (CT) showed moderate attenuation of the pulmonary tissue with diffuse and confluent ground glass-like areas, together with thickened interlobular septa resembling crazy-paving pattern of the lower lobes; the well-known right upper parailary discariocinetic lesion, affecting pleural and hilar junction striae, measured approximately 7.5 cm and was associated with diffuse ilo-mediastinal lymphadenopaties. Abdominal CT, performed without contrast due to a mild reduction in GFR later solved, revealed subdiaphragmatic free air predominantly along the colic frame with signs of colic parietal pneumatosis and some hydroaerial levels throughout the

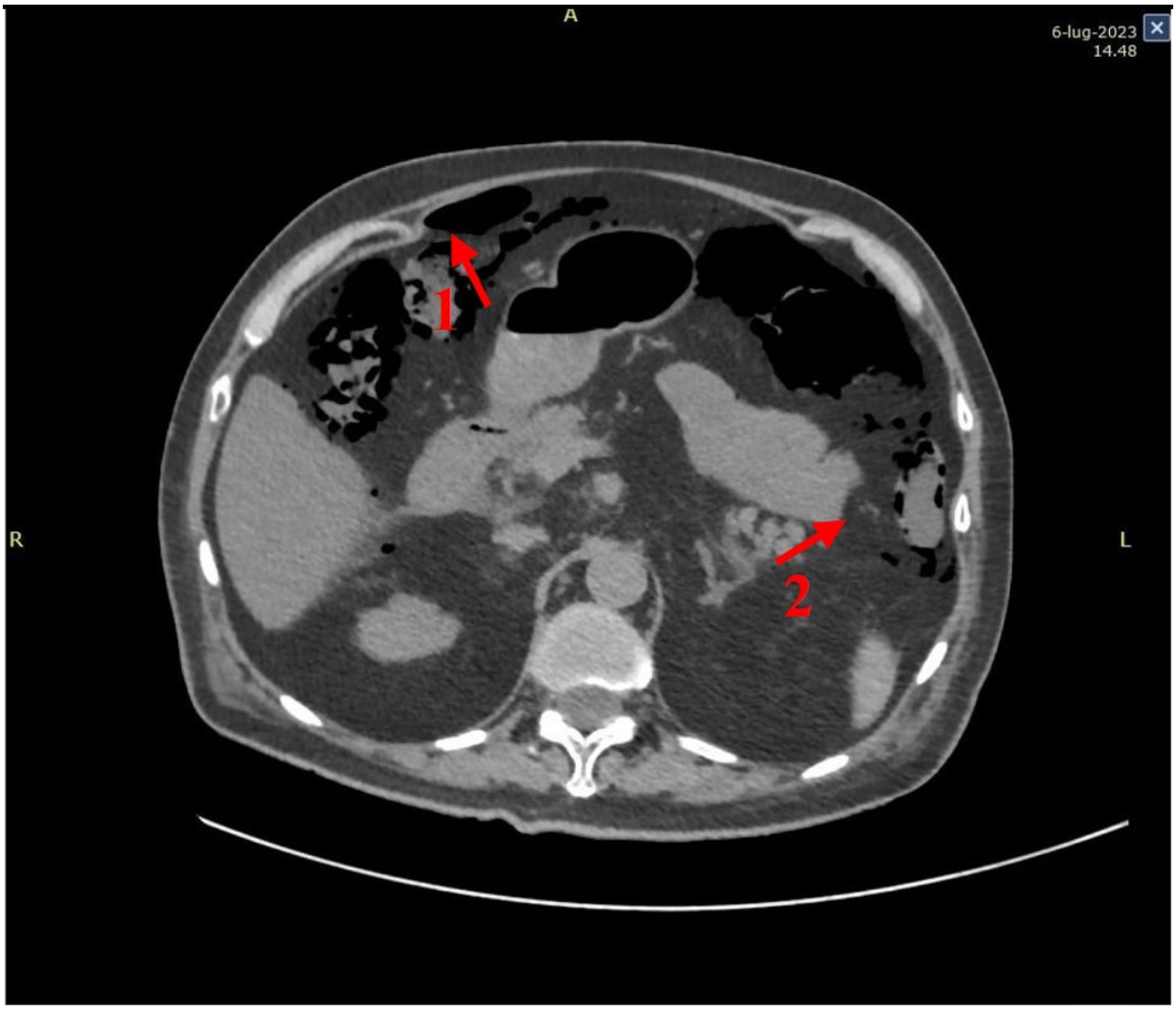

Fig. 1. Abdominal computerized tomography without contrast showed subdiaphragmatic free air predominantly along the colic frame (Arrow n. 1) with signs of colic parietal pneumatosis (Arrow n. 2) and some hydroaerial levels throughout the length of the left colon.

length of the left colon, while the well-known metastatic findings were stationary [Fig. 1]. The patient was later hospitalized and, thanks to a stable clinical status and haemodinamics, was managed conservatively. During the hospital stay, giving the suspicion of chemotherapy-related PI, Afatinib was suspended. Two days later, a new abdominal CT with contrast confirmed reduction of wall pneumatosis with pericolonic and subdiaphragmatic few cystic gas collections [Fig. 2]. Given its broad spectrum of activity against many gram-positive and gram-negative aerobic and anaerobic organisms, a carbapenemics-based antibiotic therapy was prescribed and the patient started eating soft foods on postadmission day three. The clinical course was unremarkable, except for a mild respiratory distress for which the patient was transferred to the internal medicine department for continuation of treatment. A new abdominal CT was repeated, showing the complete absence of pneumatosis intestinalis or pneumoperitoneum. During follow-up, a new thoracic CT was performed and tumoral markers were repeated, revealing a severe progression of his lung disease. The patient later died about 2 months after admission due to complications of the neoplastic disease from which he was suffering.

This case has been reported in line with the case report guidelines: Case Report (CARE) Guidelines to ensure the accuracy and completeness of the report (**Supplementary Material**).

Discussion

PI is generally a benign condition that often resolves on its own. However, in some cases, it can result in serious complications, such as bowel obstruction, intestinal perforation, volvulus, or gastrointestinal bleeding, which may necessitate emergency surgery due to the significant risk of mortality [13].

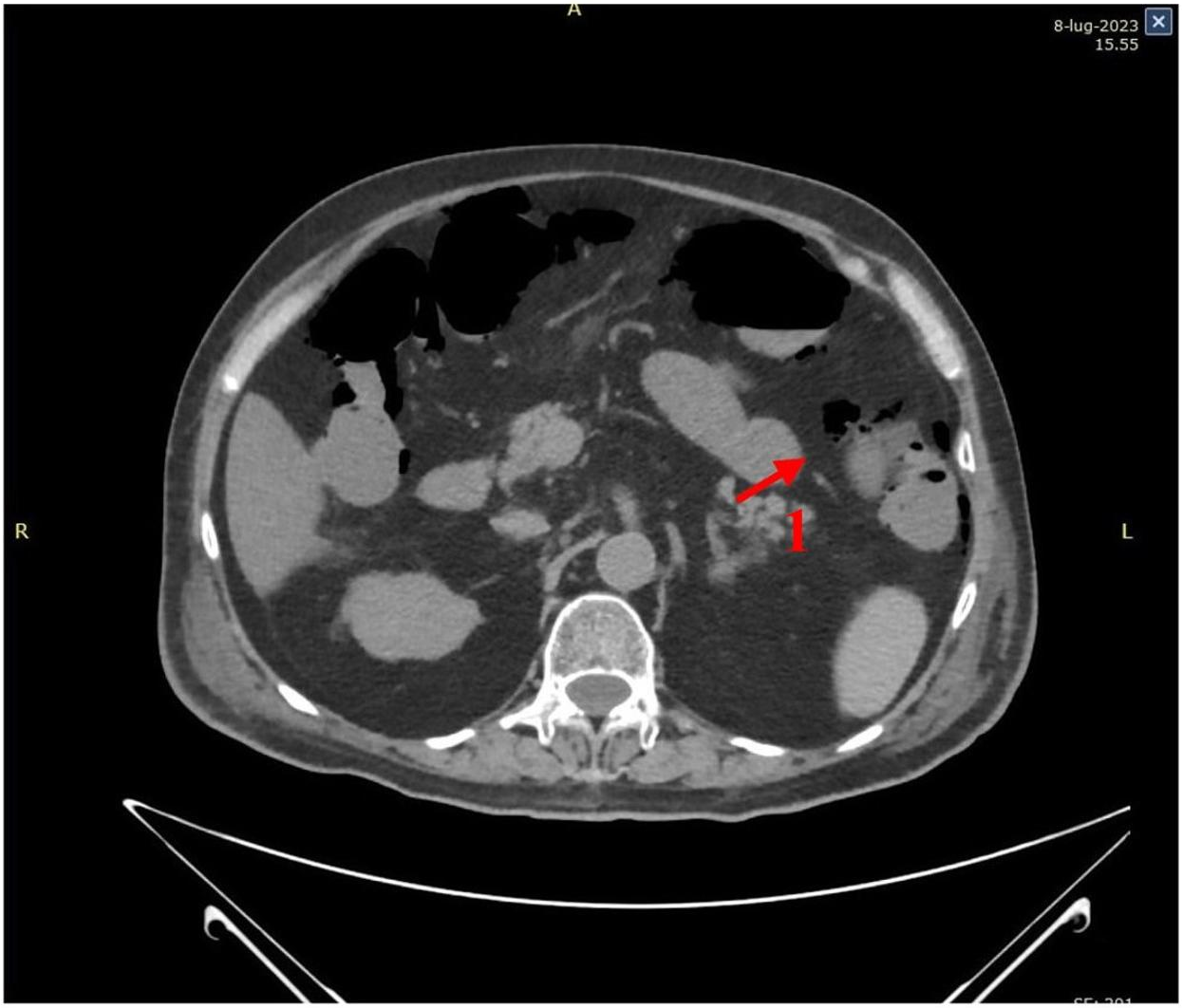

Fig. 2. Two days later, a new abdominal computerized tomography with contrast confirmed reduction of wall pneumatosis (Arrow n.1) with pericolonic and subdiaphragmatic few cystic gas collections.

Chemotherapeutic agents have recently been identified as a recognized cause of PI. A systematic review analyzing 88 patients undergoing cancer treatment found that PI occurs more frequently after targeted therapies, such as monoclonal antibodies and kinase inhibitors (51.1% overall), with a higher prevalence in patients with solid tumors compared to those with hematologic malignancies. Gazzaniga *et al*. [4] reported that PI developed in 36.4% of patients receiving cytotoxic therapy, particularly in those with hematologic cancers. Cases of PI following immunotherapy, either alone or combined with targeted therapies, were rare, accounting for only 2.8%. The remaining 14.8% of cases involved patients undergoing combined regimens of chemotherapy, targeted therapy, and/or radiotherapy [4].

Molecular targeted therapy has revolutionized oncologic treatment thanks to its highly specific mechanism of action, promising long-term effectiveness, and more favorable toxicity profile. It is now commonly employed, either as a standalone treatment or in combination with other therapies, for several widespread malignancies, including melanoma, colorectal cancer, renal cell carcinoma, gastrointestinal stromal tumors and lung cancer [14–18].

As the use of molecular targeted therapy becomes increasingly widespread, unforeseen side effects are emerging. [19]. Assoun *et al*. [20] reported that 42.2% of cancer patients treated with vascular endothelial growth factor (VEGF) inhibitors experienced gastrointestinal complications, primarily digestive perforations, often requiring intensive care due to their potentially life-threatening nature. Bowel toxicity, including PI and bowel perforation, has been linked to molecular targeted therapies such as bevacizumab, a monoclonal antibody targeting VEGF, as well as to the tyrosine kinase inhibitors (TKIs) sunitinib malate and sorafenib, which act on multiple receptors, including VEGF and platelet-derived growth factor [7,21–24]. Those complications have been highlighted in isolated case reports and are also noted in clinical trials assessing new drug regimens [25–27].

Comprehensive studies on PI and bowel perforation remain scarce. The optimal approach to managing these undesirable outcomes—whether through conservative measures or surgery—is not well-defined. Prompt recognition of adverse events associated with molecular targeted therapies is crucial for clinicians to ensure effective management and reduce patient morbidity.

Afatinib, a TKI used to treat non-small cell lung cancer, acts as a covalent, irreversible inhibitor of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor 4 (HER4) [28]. While afatinib has been linked to several adverse effects, including diarrhea, nausea, vomiting, intestinal hemorrhage, colitis, and intestinal perforation [29], to our knowledge, our case is the first documented case of PI linked to afatinib administration in the literature.

Cases of PI have been documented in lung cancer patients undergoing treatment, particularly among those treated with EGFR-TKIs like gefitinib and erlotinib [8,30–37].

The exact pathophysiology of gastrointestinal toxicity induced by EGFR-TKIs, such as afatinib, remains unclear. However, a well-supported hypothesis suggests that epidermal growth factor (EGF) plays a crucial role in maintaining mucosal integrity [38]. Afatinib treatment may lead to a deficiency of EGF in the intestinal mucosa, reducing the efficiency of bowel repair and disrupting mucosal integrity, which can result in symptoms like diarrhea, nausea, and vomiting. These pharmacological effects of EGFR-TKIs may ultimately contribute to the development of PI [32].

A previous report documented the occurrence of pneumatosis after more than four months of treatment with molecular targeted therapy [23]. Nevertheless, a different scientific publication determined that the average time before the onset of PI or bowel perforation during molecular targeted therapy was three months. Additionally, 25% of patients experienced symptoms as soon as one month after beginning treatment [39]. The effectiveness of molecular targeted therapy in tumor reduction was noticed just within one to two months of starting treatment [40,41]. Consequently, it is expected that the related toxicity could also appear in the early stages of treatment.

Little is known about the reversibility of impaired digestive integrity following the withdrawal of treatment. However, rebound tumor growth and revascularization were observed in both mice and humans after discontinuation of anti-VEGF therapy [42,43]. A recent systematic review of 88 patients undergoing anticancer treatment found that most of them (86.4%) showed resolution of the CT findings, while only one (4.5%) experienced worsening. The condition deteriorated in both patients who persisted with molecular targeted therapy and it reappeared in three out of four patients who resumed treatment after an initial resolution. Interestingly, no recurrence was observed once molecular targeted therapy was suspended [4]. Those reports prove that ongoing or resumed treatment with molecular targeted therapy may lead to the worsening or recurrence of pneumatosis or to bowel perforation.

An important clinical consideration is the reintroduction of therapy after PI.

In a study of 88 patients receiving anticancer treatment, therapy was restarted in 18 patients after PI resolution. Relapse of PI occurred in 6 of them (33.3%), though no fatal outcome was reported. Given the treatment context and the potential clinical benefits of resuming the therapy, Gazzaniga *et al*. [4] recommend a careful assessment before restarting treatment, with close monitoring of early symptoms and stringent radiological follow-up. In our experience, afatinib was reintroduced after hospital discharge, and no recurrence of PI was observed during the remaining follow-up period.

Steroids have been proved to be significantly linked to the development of PI [44,45]. The true incidence of benign PI as an adverse drug reaction secondary to corticosteroids is unknown [46,47]. Steroids decrease lymphocyte levels in the gastrointestinal wall, especially in Peyer's patches, compromising the bowel's protective barrier and lead to increased intestinal wall fragility [48]. The thinning of the mucosa results in greater mucosal permeability, allowing gas to dissect into the non-inflamed bowel wall [49,50]. Furthermore, defects in the lymphoid tissue of the bowel wall may facilitate the entry of bacterial gas [51]. In our experience, dexamethasone suspension effectively resolved PI, as reported by Choi *et al*. [52] and Goh and Shelat [53], so that we tend to hypothesize that in our patient the combined effects of steroids and afatinib may have worked synergistically to cause PI.

PI appears as a linear or bubbly pattern of air along the intestinal wall [6]. However, the presence of PI on an abdominal CT scan confirms bowel ischemia in only 60% of cases [54].

Additional findings, such as bowel wall thickening, absent or intense mucosal enhancement, dilated bowel, arterial or venous occlusion, ascites, and gas in the hepatic portal or portomesenteric veins can increase the likelihood of a serious underlying condition [55]. One key advantage of CT imaging is its ability to detect gas in the portal vein, which is crucial for guiding therapeutic decisions [56]. Despite previous debates regarding the clinical significance of portomesenteric pneumatosis, numerous studies highlight its association with patient outcome [57–59].

Wiesner *et al*. [60] analyzed 23 patients with PI and found that 16 of them had portomesenteric venous gas, with an overall mortality rate of 44%. However, in patients who exhibited both portomesenteric venous gas and PI on CT scans, the mortality rate rose to 72%.

Similarly, the Lassandro group [61] identified a correlation between portomesenteric pneumatosis and transmural ischemia, noting that 91.5% of patients with portomesenteric pneumatosis on CT had also confirmed bowel ischemia or infarction during surgery. The presence of portomesenteric

gas is likely associated with a higher mortality rate because it typically indicates mesenteric infarction or ischemia. According to Knechtle *et al*. [6], portomesenteric pneumatosis is linked to a 37% mortality rate. Furthermore, Lassandro *et al*. [62] found that gas in the portal vein was present in about 25.5% of PI patients, who experienced a higher incidence of intestinal obstruction with a mortality rate of 50%. In our case, the CT scan revealed colic parietal pneumatosis without intra-hepatic portal vein gas, suggesting that non-operative management was appropriate.

Historically, PI was considered a sign of intestinal ischemia, often warranting surgical intervention, particularly when it was accompanied by pneumoperitoneum. Exploratory laparotomies were routinely performed on patients with both PI and pneumoperitoneum, as CT scans suggested potential bowel necrosis and perforation. However, the presence of pneumoperitoneum on CT could also be due to the rupture of subserosal cysts associated with PI [63–65]. In the study by Shinagare, only 38.9% (7/18) of patients with perforation developed pneumoperitoneum [39]. As a result, there is a lack of large-scale studies reporting the incidence of pneumoperitoneum in patients with PI.

Recent evidence suggests that a conservative approach may be appropriate for certain cases of PI [6,66]. Badgwell *et al*. [67] demonstrated that selected cases of intestinal perforation associated with molecular targeted therapy can be managed conservatively, using treatments such as oxygen therapy, antibiotics, and parenteral nutrition. The role of antibiotics is to inhibit the growth of harmful intestinal bacteria, thus preventing the production of hydrogen.

However, any decision to pursue conservative management should be made carefully, taking into account the clinical context. Surgical intervention should be considered in symptomatic patients showing clinical signs, such as abdominal pain, intestinal obstruction, bleeding, peritoneal irritation, acidosis, portal gas, or pneumoperitoneum, due to the risk of ongoing ischemic colitis, necrosis, or intestinal obstruction [68,69]. A careful integration of laboratory results, abdominal CT scan findings, and clinical presentations will enable clinicians to differentiate between benign and life-threatening PI, guiding the decision on whether urgent surgical intervention is necessary. Surgical decisions should be based on the presence of associated risk factors, physical examination signs suggesting peritonitis, and analytical markers of poor prognosis (such as pH $<$7.3, bicarbonate $<$20 mL/L, lactate $>$2 mmol/L, or serum amylase $>$200 U/L), or the presence of portal venous gas [70]. Pneumoperitoneum alone is not a reliable predictor of severity nor an indication for emergency surgery [71]. Clinical signs like abdominal rebound tenderness, sepsis, and failure to respond to conservative treatment are clear indications for surgical intervention.

As highlighted in this case report, ambiguous radiological findings can be challenging to interpret. The coexistence of PI and intra-peritoneal free air on a CT scan can easily be mistaken for bowel ischemia and perforation peritonitis [72]. In our experience, the incidental discovery of pneumoperitoneum, in the absence of significant symptoms, with normal physical, paraclinical examinations, no signs of peritonitis, allowed for non-surgical management. The main limitation of this study is the concurrent use of other medications by the patient in addition to afatinib. It is well known that there is a correlation between the development of PI and corticosteroid therapy. This complicates the interpretation of the causal relationship between targeted therapy and the onset of PI. Therefore, it is not possible to definitively conclude that afatinib was the primary cause of PI.

Conclusions

PI is an uncommon, yet clinically relevant condition, described in cancer patients undergoing anticancer pharmacological treatments that, even when asymptomatic, can lead to life-threatening complications. Although it is important to consider other causes and risk factors for pneumatosis and perforation, clinicians should be aware that PI and intestinal perforation can occur as an effect of drug toxicity. Abdominal symptoms in patients receiving oncological treatments should not be overlooked, and clinicians should not hesitate to request targeted radiological investigations to facilitate early diagnosis and management of PI. Timely event detection is imperative to optimal management. Most patients experiencing intestinal complications related to molecular targeted therapy can be managed conservatively through the suspension of the drug, which can help prevent further deterioration, recurrent PI, or even perforation. Close and careful monitoring of patients with PI is essential to promptly identify emergent signs of severe complications, particularly in oncological patients. In conclusion, we believe gastrointestinal perforation should be included in the differential diagnoses, when patients, treated with TKIs as well as with afatinib, complain of even a mild abdominal pain.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

LA and AC conceptualized the research study while RC, SV, DB contributed to methodology design. GS and APD collected data. LA, SU, LB and VS analyzed data and wrote the manuscript. All authors contributed to editorial important changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out according to the Declaration of Helsinki. The patient signed an informed consent regarding publishing his data. Ethical approval was not required for this study.

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Conflict of Interest

Roberto Cirocchi is serving as one of the Editorial Board and Guest Editor members of this journal. We declare that Roberto Cirocchi had no involvement in the peer review of this article and has no access to information regarding its peer review. Other authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3879.

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