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Case Report

Alectinib-associated pneumoperitoneum in stage IV non-small cell lung cancer - A case report

Renee M. Maina [a], Caroline A. Rader [b], Clarisse S. Muenyi [a], Ramakrishna Battini [c], Nia N. Zalamea [a], Denis A. Foretia [a,*]

[a] Department of Surgery, University of Tennessee Health Science Center, Memphis, TN, USA
[b] College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA
[c] West Cancer Center, Memphis, TN, USA

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ABSTRACT

Introduction and importance: Alectinib, a highly potent, highly selective, brain-penetrant anaplastic lymphoma kinase (ALK) inhibitor is now the first line therapy for patients with metastatic ALK-positive non small cell lung cancer (NSCLC).

Case presentation: We report a rare case of pneumoperitoneum following alectinib initiation for metastatic non small cell lung cancer in a 74-year-old African American female. Patient developed abdominal pain approximately 2 weeks after starting alectinib. She was hemodynamically stable, and imaging revealed pneumoperitoneum. Patient was successfully managed non-operatively.

Clinical discussion: Gastrointestinal perforation presenting as pneumoperitoneum is a very rare complication of alectinib. To our knowledge our patient is only the second case to be reported in the literature since its approval. The complication is likely attributable to the rapid tumor regression in the gastrointestinal tract. Non-operative management should be attempted if possible.

Conclusion: Oncologists should be aware of the risk of gastrointestinal perforation when initiating cytotoxic chemotherapy on patients with metastatic NSCLC. A multidisciplinary approach is critical in appropriately individualizing care in this patient population.

1. Introduction

Pneumoperitoneum, the presence of air in the peritoneal cavity, is most often due to perforated viscus. Other causes include barotrauma, retained post-operative or post-procedural air. In non-cancer patients, emergent operative management is usually warranted.

Cancer patients present a unique challenge and have increased risk of pneumoperitoneum due to local tumor invasion, radiation therapy, and frequent endoscopic procedures [1]. Historically, platinum-based chemotherapy agents were the treatment modality of choice for patients presenting with advanced non-small cell lung cancer (NSCLC) [2,3].

Approximately 5% of NSCLC patients have rearrangements in the oncogenic anaplastic lymphoma kinase (ALK) gene [4]. Alectinib, a highly selective inhibitor of ALK, has recently become the first-line therapy for patients with ALK-positive metastatic NSCLC [5].

It is a highly potent, central nervous system penetrant ALK inhibitor with a relatively low side effect profile. The most common side effects of alectinib therapy are photosensitivity, myalgias, and hepatobiliary disorders; with very few gastrointestinal (GI) complaints reported [6]. In compliance with the 2020 SCARE guidelines, we present a rare case of a 74-year-old female diagnosed with NSCLC who was initiated on alectinib therapy and subsequently developed pneumoperitoneum [7]. Verbal and written consent was obtained for the publication of this case report.

2. Case presentation

The patient is a 74-year-old African American female with recently diagnosed ALK-positive NSCLC metastatic lung cancer who initially presented to our academic medical center with abdominal pain and constipation. Her past medical history included hypertension, gastroesophageal reflux disease (GERD) and hypothyroidism. She had no

Abbreviations: CNS, central nervous system; ALK, anaplastic lymphoma kinase; CT, computed tomography; GI, gastrointestinal; NSCLC, non small cell lung cancer.

* Corresponding author. Department of Surgery University of Tennessee Health Science Center 910 Madison Ave, Ste 323, Memphis, TN, 38163, USA.
E-mail address: dforetia@uthsc.edu (D.A. Foretia).

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previous operations and her home medications included Amlodipine, hydrochlorothiazide, and oral levothyroxine. Physical exam revealed a well-built, hemodynamically stable patient with a body mass index (BMI) of 29.7 kg/m2. Cardiopulmonary exam was unremarkable, but patient was mildly tender to palpation in the lower abdomen without guarding or peritonitis.

A CT scan of the abdomen and pelvis on presentation showed a 7 cm right lung mass and diffuse metastatic disease in the liver, spleen, as well as fecal stasis and she was admitted for supportive management. She also complained of facial droop and an MRI of her brain showed an enhancing extra-axial mass involving the right temporal region consistent with leptomeningeal carcinomatosis.

A multidisciplinary team involving neurology and neurosurgery consulted and ultimately opted for non-operative management, and she was started on dexamethasone for vasogenic edema. Her medical oncology team also saw her while she was inpatient and, given her worsening metastatic disease burden, initiated alectinib 150 milligrams twice daily.

Approximately 2 weeks after initiation of therapy, she began complaining of worsening abdominal pain and distension. A chest x-ray showed new pneumoperitoneum (Fig. 1) and CT scan of her abdomen and pelvis confirmed significant pneumoperitoneum of unclear etiology, as well as colonic distension and a walled-off abscess in the anterior abdomen (Fig. 2). She had had significant treatment response with interval decrease of the right lower lobe mass (from 7 cm × 6.4 cm–4.9 cm × 4.1 cm) as well as decrease in size of the hepatic and splenic metastatic lesions. She also had a near complete resolution of an enhancing 3.4 cm extra-axial mass along the medial right middle cranial fossa.

Given the new findings Interventional radiology was consulted for drainage of the abscess, and General Surgery for management of the pneumoperitoneum. She denied any associated nausea or emesis and was hemodynamically stable without leukocytosis or peritonitis. Given her relatively benign clinical picture and the associated morbidity of a laparotomy in the patient, the surgical team had a frank discussion with the patient and her medical team, and the joint decision was made to proceed with non-operative conservative management. She was placed on bowel rest, started on broad spectrum intravenous antibiotics (Zosyn) and total parenteral nutrition. The supervising surgeon had 10 years post-training experience in acute care management.

Patient was monitored closely with serial abdominal exams and daily laboratory tests. In the ensuing 5 days her abdominal exam remained benign with eventual resolution of tenderness. She then had a small bowel follow through that showed no contrast extravasation along the entire length of the GI tract. At this point, her diet was advanced slowly, and the patient tolerated this well. Follow-up CT scan on day 25 showed interval decrease in the pneumoperitoneum but increase in the abscess (Fig. 3), which was managed through bedside incision and drainage with long-term antibiotics. She was eventually discharged to an inpatient rehabilitation facility on day 38 of her hospitalization and died 7 months later due to cancer-related complications.

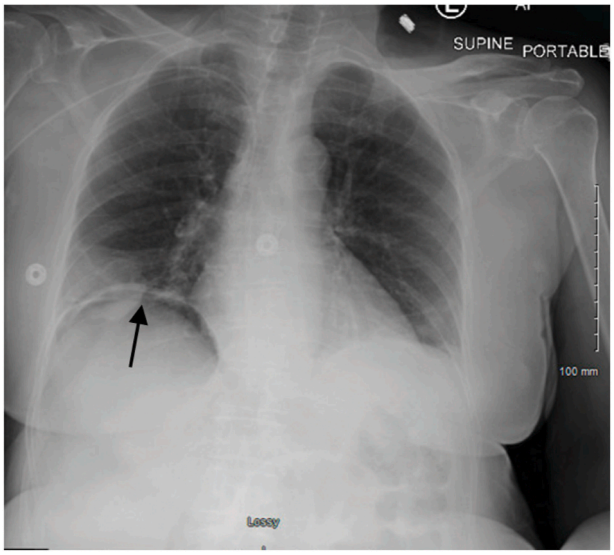

Fig. 1. Chest x-ray showing pneumoperitoneum (black arrow).

3. Discussion

Alectinib is a highly selective ALK inhibitor, with both systemic efficacy and central nervous system (CNS) penetrance. It is the first line treatment for advanced ALK-positive NSCLC in adults with several clinical trials demonstrating less CNS disease progression as well as longer progression-free survival as well as lower rates of adverse events than crizotinib, the first tyrosine kinase inhibitor to be approved for ALK-positive advanced NSCLC [8]. Of these adverse events, hepatobiliary disorders and photosensitivity are the most commonly associated with alectinib [6].

Majority of chemotherapeutic agents have GI side effects, with nausea, diarrhea and constipation being the most commonly reported symptoms. Bowel perforation, although a rare complication, has also been reported in the literature. Antiangiogenic agents such as bevacizumab and aflibercept have been commonly implicated, with several studies reporting bowel perforation secondary to the use of these agents [9–11].

GI perforation is a rare side effect of alectinib therapy, with only one other case of duodenal perforation reported in the literature [12]. In the Phase 2 trial (NP28674) that investigated the safety and efficacy of alectinib in crizotinib-refractory ALK-positive NSCLC patients, one patient died from alectinib induced intestinal perforation [13].

Several risk factors have been linked to bowel perforation secondary to chemotherapy. These include peritoneal carcinomatosis, prior abdominal radiation, a GI primary tumor, and peptic ulcer disease [1, 12]. To our knowledge, our patient did not have any of these risk factors. Our patient's repeat CT scan did not demonstrate any intraabdominal inflammatory changes. It is likely that her non-inflammatory GI perforation was secondary to rapid tumor regression, which was seen in her repeat imaging.

Whereas pneumoperitoneum due to bowel perforation typically warrants surgery, the management of pneumoperitoneum in patients with metastatic, nonobstructive cancer presents a complex decision-making challenge. Factors such as patient presentation, hemodynamic status, frailty, and overall prognosis must be considered. As such a tailored approach that considers both clinical presentation and oncological prognosis should be employed. Prompt surgical evaluation is warranted but the decision-making should be multidisciplinary.

In patients who are hemodynamically stable, like our patient, initial non-operative management is advised. This includes intravenous fluid resuscitation, bowel rest, intravenous broad-spectrum antibiotics, and serial abdominal examination. In a study of patients treated with bevacizumab who developed bowel perforations, the vast majority (79%) did not require operative interventions [1]. Our patient was successfully managed non-operatively.

For hemodynamically unstable patients the decision-making must include a thorough reassessment of goals of care. This includes consideration of the tumor burden, patient's comorbidities, cardiopulmonary operative risks, previous abdominal operations, patient's wishes, overall prognosis, and quality of life as assessed by the medical oncology team. The decision to proceed with operative management in this patient population must therefore be highly individualized.

The main limitation with our case is that we were unable to confirm the specific area of the gastrointestinal tract where the perforation occurred, as operative intervention was not pursued.

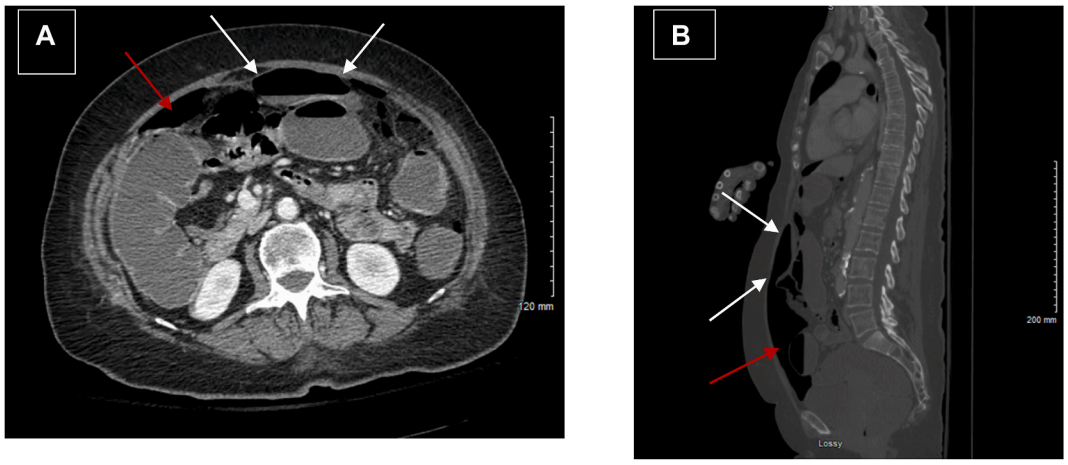

Fig. 2. CT A/P confirming pneumoperitoneum and developing 'abdominal abscess 2 weeks after initiation of alectinib. A) Axial view, (B) Sagittal view. White arrows = developing abdominal wall abscess, Red arrows = free intraabdominal air. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

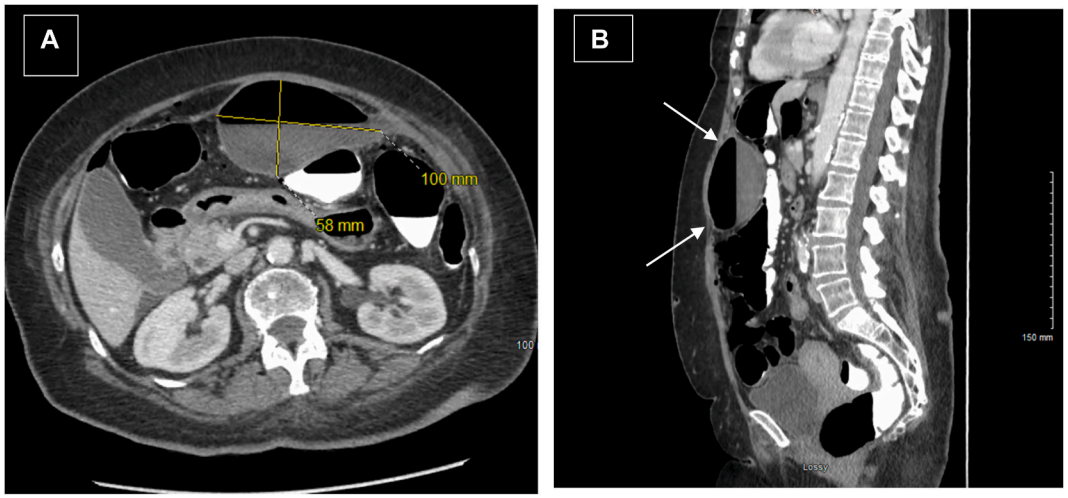

Fig. 3. Repeat CT A/P with interval decrease in pneumoperitoneum but increase in size of the anterior abdominal wall abscess (white arrows). A) Axial view, (B) Sagittal view.

4. Conclusion

Chemotherapy-associated bowel perforation is a rare complication that has been reported with a handful of chemotherapeutic agents, and care should be individualized to each patient. The risks and benefits of operative intervention should be carefully weighed, and early goals of care should be elicited from this patient population.

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Authors contribution

Renee Maina: formal analysis, data curation, writing – original draft.

Caroline Rader: formal analysis, data curation, writing – original draft.

Clarisse Muenyi: writing – review and editing.

Ramakrishna Battini: writing – review and editing.

Nia Zalamea: writing – review and editing.

Denis Foretia: conceptualization, data curation, formal analysis, supervision, project administration, writing – original draft, and writing – review and editing. All authors approved the final manuscript.

Please state any conflicts of interest

NONE.

Registration of research studies

1. Name of the registry: None
2. Unique Identifying number or registration ID: none

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): N/A

Guarantor

Denis A.Foretia, MD MPH MBA FACS.
Department of Surgery, University of Tennessee Health Science Center, 910 Madison Ave,Memphis, Tennessee, 38163. dforetia@uthsc.edu.

Consent

Written informed consent has been obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104601.

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