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Case Report

Oncology Section

Fatal Haemoptysis Associated with Dramatic Response to Crizotinib in an ALK-Rearranged Lung Adenocarcinoma

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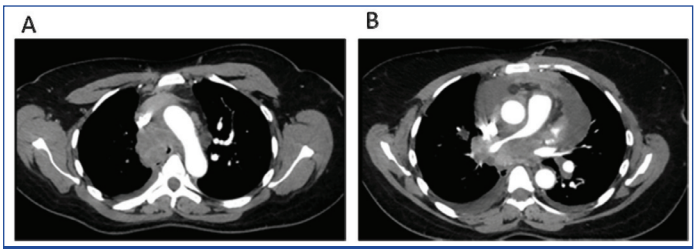
ABSTRACT

The presence of an ALK (Anaplastic Lymphoma Kinase) rearrangement is a rare molecular feature in Non-Small Cell Lung Carcinoma (NSCLC), and concerns mainly non- or light smokers, young patients, with adenocarcinoma histological type. These tumours are particularly sensitive to Alk-targeted therapies, as crizotinib. Crizotinib is usually well-tolerated. We report a case of fatal haemoptysis associated with dramatic response to crizotinib in a patient with an ALK-rearranged lung adenocarcinoma. The patient presented a mediastinal invasion with tracheal involvement and compression of the right pulmonary artery. The initial evolution under crizotinib was good with tumour response. At 6 weeks of crizotinib the patient presented a massive haemoptysis with a tracheobronchial fistula and pneumomediastinum. She died of acute respiratory failure. Our case is the first to report a fatal effect of crizotinib associated with tumour necrosis and good tumour response on a massive mediastinal infiltration. Precautions are recommended with the use of crizotinib in proximal lung tumours with vascular invasion.

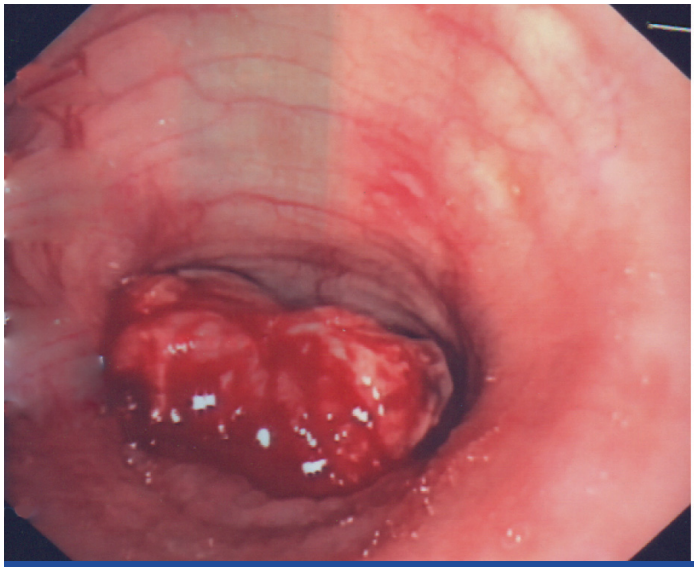
Keywords: ALK rearrangement, Non-Small Cell Lung Carcinoma, Pneumomediastinum

CASE-REPORT

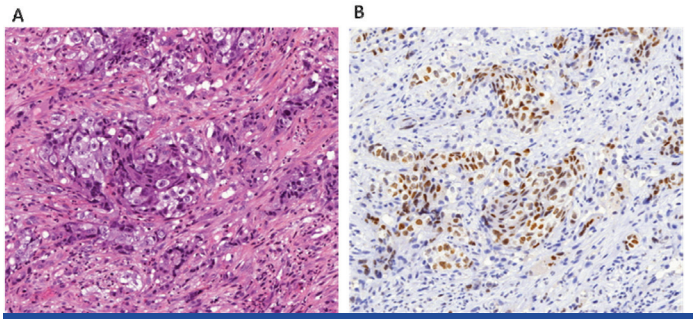
We present the case of a 49-year-old woman with a history of smoking habit (10 packs/year, stopped 18 months previously). Her symptoms were fatigue with a Performance Status (PS) score of 2, and weight loss (10 kg in 3 months). She had persistent mild-abundance haemoptysis. The patient was not under any regular medication. Computed tomography (CT) [Table/Fig-1] and positron emission tomography showed bulky mediastinal infiltration and tracheal invasion of the tumour, large pericardial effusion, proximal invasion of the right bronchus, circumferential right pulmonary arterial compression, and multiple metastatic lesions in the liver, left adrenal gland, and muscles. The patient was hospitalized for a compressive pericardial effusion, treated by pericardial drainage. Bronchial endoscopy showed a 80% stenosis of the trachea caused by the tumour [Table/Fig-2]. Bronchial biopsies provided the diagnosis of thyroid transcription factor 1 (TTF1)-positive lung adenocarcinoma [Table/Fig-3]. Tracheal and bronchial disobliteration was performed by YAG laser, followed by endotracheal prosthesis implantation. Molecular analyses of the tumour showed the presence of an *ALK* translocation in immunohistochemistry [Table/Fig-4], confirmed by fluorescence in situ hybridization. Because of the critical clinical situation, crizotinib (250 mg/d) was prescribed as first-line treatment. After 1 month of treatment, her PS score was 1, and the dyspnea was improved. Six weeks after starting crizotinib, she experienced acute massive haemoptysis. Bronchial endoscopy did not show any migration or bronchial erosion related to the prosthesis [Table/Fig-5]. CT revealed a major mediastinal tumour response [Table/Fig-6] and air in the mediastinum, compatible with a tracheobronchial fistula and pneumomediastinum [Table/Fig-7]. The same day, she had a cataclysmic haemoptysis and died from acute respiratory failure. The final diagnosis was a rupture of the right pulmonary artery caused by tumour necrosis under crizotinib treatment.



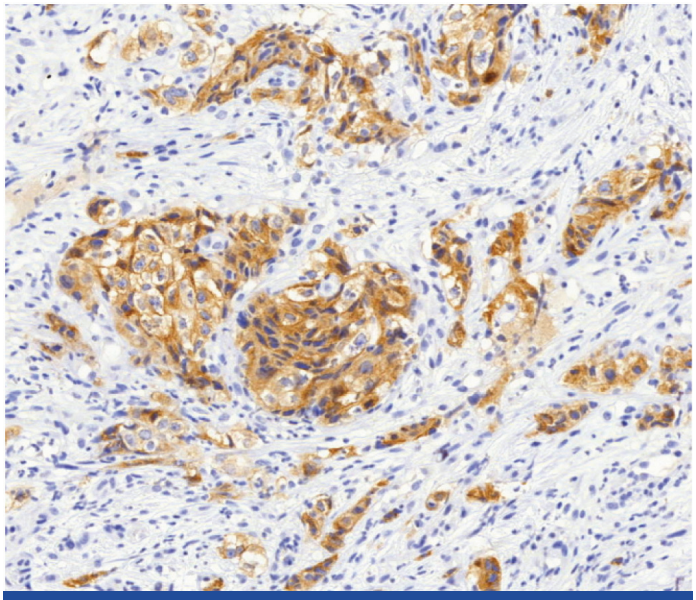
[Table/Fig-1]: a) CT at baseline shows massive mediastinal tumour infiltration with tracheal invasion; and b) infiltration of the right pulmonary artery.



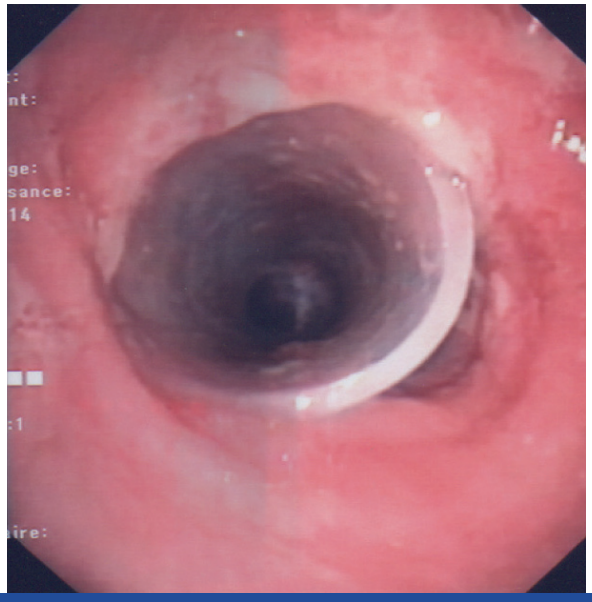
[Table/Fig-2]: Endobronchial aspect at baseline, showing a tracheal obstruction by the tumour.



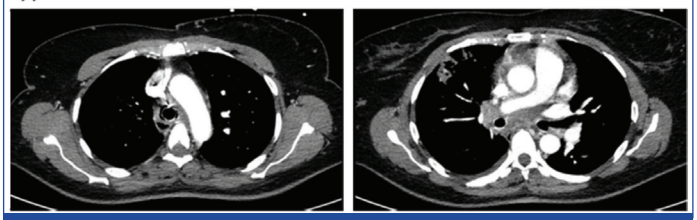
[Table/Fig-3]: Results of the bronchial biopsies. *A*, Haematein-Eosine-Safran (HES) coloration. *B*, thyroid transcription factor 1 (TTF1) positive staining. Magnification x13.



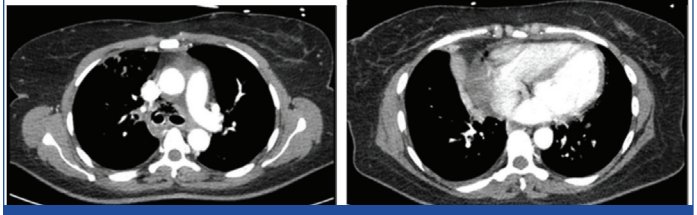
[Table/Fig-4]: ALK immunohistochemistry results, showing strong positive staining in tumour cells. Magnification x13



[Table/Fig-5]: Endobronchial aspect at 6 weeks, showing functional prosthesis without any migration or bronchial erosion.



[Table/Fig-6a&b]: CT after 6 weeks of crizotinib with good tumour response.



[Table/Fig-7a&b]: CT after 6 weeks of crizotinib. Presence of air in the mediastinum compatible with a pneumomediastinum

DISCUSSION

ALK translocation is a rare molecular feature found in 4% of Non-Small-Cell Lung Cancers (NSCLCs). It is often seen in young patients with no/light smoking habit and lung adenocarcinoma [1], as in our patient. Crizotinib is a tyrosine kinase inhibitor (TKI) targeting ALK, MET and ROS1, and is indicated in advanced NSCLC with ALK rearrangement, in first or subsequent lines. Its contra-indications include severe hepatic dysfunction and hypersensitivity to crizotinib. Major tumour responses are seen with crizotinib in NSCLCs with ALK rearrangement, with a response rate of ~60% [1]. Crizotinib has been evaluated in first-line treatment in advanced-stage NSCLCs: the progression-free survival was 10.9 months and the 1-year survival probability was 84% (versus 7.0 months and 79%, respectively, with cisplatin–pemetrexed chemotherapy) [2]. Other TKI targeting ALK are also available, as ceritinib [3] or alectinib [4], but are for now reserved in case of tumour progression after crizotinib treatment. Main toxicities of crizotinib reported in clinical trials with crizotinib are eyesight troubles, fatigue, liver enzyme abnormalities, interstitial lung disease, and QT increases [1,2]. No increase of haemorrhagic events has been reported in these clinical trials, however high selection of included patients could be a potential bias. One case-report described haemoptysis with crizotinib related to diffuse intra-alveolar haemorrhage in third-line treatment in a 63-year old man treated by warfarin potassium [5], but to our knowledge we are the first to report a case of massive haemoptysis due to pulmonary rupture because of a major tumour response. Severe adverse events due to major tumour responses are well known with targeted therapies, especially with antiangiogenic drugs (e.g., bevacizumab [6]). Use of bevacizumab to treat proximal tumours with 180° contact with large vessels or haemoptysis history is associated with a high risk of severe haemoptysis [6]. ALK pathway regulates angiogenesis in NSCLCs [7]. Martinengo et al., [7] have shown in *in vivo* models of ALK-rearranged NSCLC that ALK regulated the production of VEGFA (*Vascular Endothelial Growth Factor A*) and impacted the tumour angiogenesis [5]. But, to date, no precaution is recommended concerning the use of crizotinib for a central tumour in close contact with large vessels. Crizotinib is currently the best treatment option in first line treatment for ALK-rearranged NSCLC, as shown in the phase III trial [2]. Our case, however, suggests caution with close monitoring in case of crizotinib use in bulky central tumours, owing to the risk of fatal haemoptysis.

CONCLUSION

The discovery of oncogenic drivers in advanced NSCLC has opened the way to major tumour responses and prolonged survival with corresponding targeted therapies, as crizotinib in case of ALK rearrangement. However, thoracic oncologists should be prudent in case of proximal bulky tumour infiltration, due to the possibility of tumour necrosis and vascular break associated with the tumour response. Our case describes this lethal effect with crizotinib for the first time, suggesting precaution with the use of this drug in such proximal ALK-translocated tumours.

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