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SHORT REPORT

Sarcoid-like reaction mimicking disease progression in an ALK-positive lung cancer patient receiving lorlatinib

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Summary
The administration of target inhibitors is paramount to grant the longest survival in patients with ALK-positive non-small cell lung cancer (NSCLC). The eventual resistance to tyrosine kinase inhibitors (TKI) is monitored clinically and radiologically for prompt molecule shift to further generation TKI, if available. However, the early radiological detection of progression pattern (e.g. nodule onset) should be regarded with caution because overlaps exist with non-tumor cell proliferation and/or accumulation. Here we report the case of a stage IV *ALK*-rearranged NSCLC patient exposed to serial crizotinib, brigatinib, ceritinib, and lorlatinib (this latter brought to complete brain and leptomeningeal disease response), in a period of more than five years. During lorlatinib, the appearance of solid pulmonary nodules was obviously interpreted as disease progression. However, surgical biopsies of the pulmonary nodules revealed features of sarcoid-like granulomatous lymphadenitis, namely without tumor cell. This invasive approach, besides documenting for the first time a sarcoid-like reaction to ALK inhibitors, allowed to revert the radiological diagnosis and maintain lorlatinib, for the best patient outcome. The pragmatic relevance of these findings suggests a careful attitude towards the interpretation of radiologic patterns of disease progression in patients under TKI.

Keywords Non-small cell lung cancer · ALK inhibitors · Lorlatinib · Progression-mimicking reaction · Sarcoid-like reaction · Sarcoidosis

Introduction

The availability of several specific inhibitors has drastically changed the outcome of *ALK*-rearranged non-small cell lung cancer (NSCLC) patients [1]. These agents retain a peculiar spectrum of adverse events, notably pulmonary toxicity [2]. Here we report the case of a patient under fourth-line ALK inhibitor lorlatinib [3] who developed solid pulmonary nodules, prospectively interpreted as radiological pattern of disease progression. Surprisingly, at histology the nodules were negative for neoplastic cell but reflected benign sarcoid-like granulomatous lymphadenitis.

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Case presentation

In April 2013, a 44-year old female was diagnosed with stage IV ALK-positive NSCLC (with bilateral lung lesions and supraclavicular lymph nodes). After approximately two years of first-line crizotinib, the patient developed brain metastasis and, therefore, she was switched to brigatinib. Brigatinib administration was set with reduced dose (60 mg daily instead of the registered posology of 180 mg daily after a lead-in of 90 mg with disease control) and allowed disease control for 11 months until appearance of

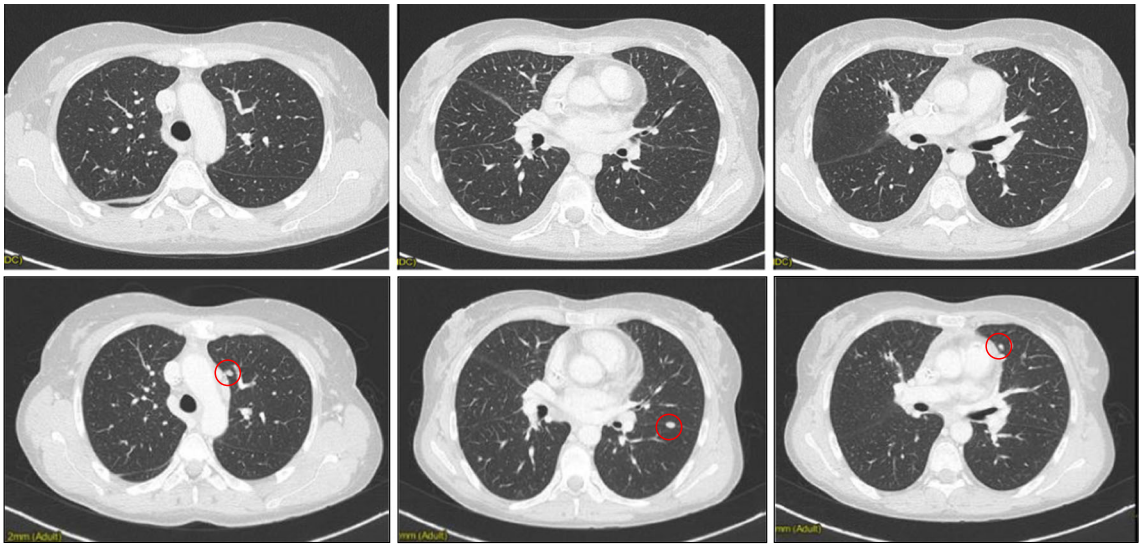

Fig. 1 Appearance of lung nodules between the first (upper line) and second (lower line) CT scans since lorlatinib introduction. The radiologic features of the lesions, identified by red circles and subsequently resected, were unequivocally consistent with disease progression

brain progression, which prompted switch to ceritinib. Noteworthy, the patient developed different types of lung injury both during brigatinib and ceritinib, as previously described [2]. Brigatinib administration was indeed followed by the early onset of pulmonary symptoms [4] and the appearance of a large lung consolidation [2], despite reduced dosage. Ceritinib administration was complicated by acute fibrinous pneumonia. Both events were successfully managed with temporary drug withdrawal and steroid administration [2]. After 19 months of ceritinib (October 2017), further brain disease progression with meningeal involvement led to switch to lorlatinib, a third-generation ALK inhibitor. Three months later (January 2018), complete intracranial response was reported by MRI, with no evidence of extra-cranial disease at CT scan. Lorlatinib treatment was overall well tolerated, only grade 2 hypercholesterolemia was reported and treated with statin [3]. Complete brain response was maintained for further three months (April 2018), whilst radiological pattern of disease progression was depicted in the left lung: onset of solid nodules with random distribution (Fig. 1). PET-CT was not performed because the radiological pattern was securely interpreted as progression; moreover the relatively small nodules size (diameter range 4–10 mm) would have limited the accuracy of metabolic interpretation. In the face of isolated pulmonary disease progression without other clinical indicators of disease, surgical biopsy of the nodules was proposed to perform molecular analyses for disease control by first- or second-generation ALK inhibitor, as recently suggested for post-lorlatinib resistance [5, 6].

Video-assisted thoracoscopy (VATS) documented innumerable sub-centimetric subpleural nodes, in absence of pulmonary nodules or macroscopic elements of malignancy. In particular, slightly enlarged and soft lymph nodes were found where the CT scan indicated the onset of solid pulmonary nodules. Three of these lymph nodes were resected (Fig. 1) and one was submitted for frozen sections that documented an inflammatory lesion (Fig. 2). The permanent sections showed a granulomatous lymphadenitis (Fig. 3) with histological features

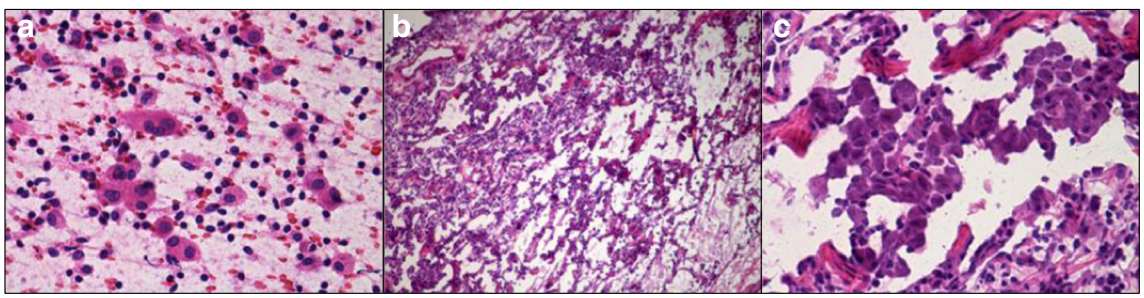

Fig. 2 Pathologic findings at frozen sections. **a** (10X): Cell smears showing numerous epithelioid macrophages admixed with small lymphocytes. Macrophages have oval and reniform nuclei with fine chromatin and small nucleoli, large eosinophilic cytoplasms and indistinct cell borders. **b** (4X) and **c** (10X): Frozen section showing a subpleural lymphoid aggregate and alveolar aggregates of macrophages

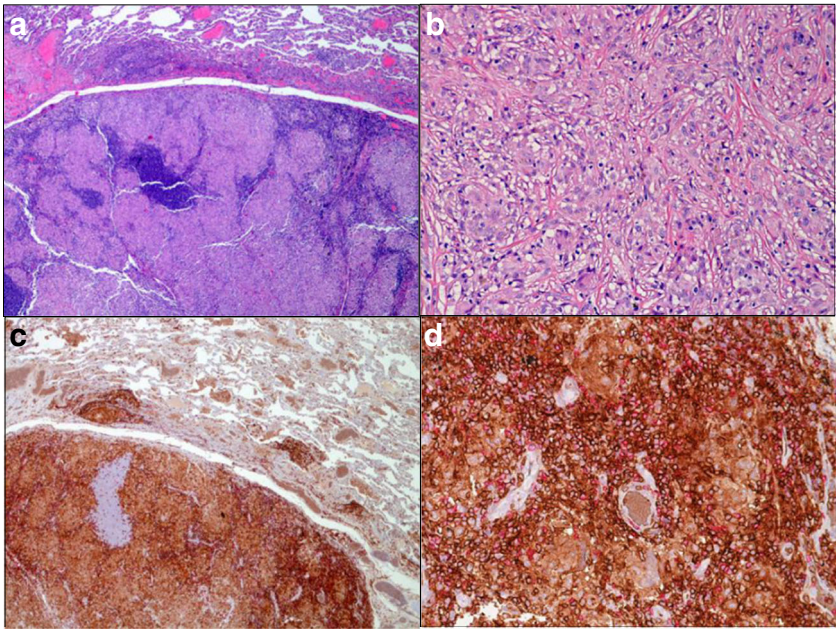

Fig. 3 Histology of formalin-fixed paraffin-embedded tissue. **a** (20X) and **b** (40X): Hematoxylin and eosin stains showing sarcoid-like granulomatous lymphadenitis with non-confluent, 'bare', epithelioid granulomas with multinucleated giant cells, with fibrosis and devoid of necrosis. **c** (4X) and **d** (40X): Immunostains with anti-CD4 (brown) and -CD8 (red) showing a CD4-positive predominant immune infiltrate

suggestive for sarcoidosis (Fig. 3) and no evidence of malignant cells. The postoperative course was uneventful and the patient was discharged four days after VATS, maintaining lorlatinib. At the last follow-up of July 2018, complete brain response and lack of evolution of the pulmonary nodules, still present in the left, lung were confirmed.

Discussion

Sarcoid-like reaction has been recently reported under immune-checkpoint and BRAF inhibitors [7, 8], yet this is the first report of such pattern in a patient undergoing ALK inhibitor. An increasing number of patients undergo sequential ALK inhibitors with remarkable improvement in survival despite central nervous system involvement [3, 9, 10]. Lorlatinib is frequently used after several lines of previous generation TKI, representing the ultimate targeted agent in this setting to date. Therefore, our report suggests a cautious attitude in the management of patients under ALK inhibitors and with radiological pattern of disease progression, namely nodule onset (Fig. 1). Sarcoid-like granulomatous lymphadenits should be considered in the differential diagnosis of pulmonary nodules occurring under treatment, to avoid misinterpretation for disease progression. If the radiological diagnosis had been accepted in our patient, this would have caused the harmful withdrawal of lorlatinib. In the present case, the history of pulmonary complication during multiple lines (brigatinib and ceritinib) [2] could suggest that our patient harbors idiosyncrasy to ALK inhibitors. Therefore, we suggest that radiological patterns should be interpreted carefully during the administration ALK inhibitors, notably with clinical overview of the subjective history to a specific class of drugs. This approach might grant the optimal management in cases with atypical radiological presentation.

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Compliance with ethical standards

Conflict of interest Marcello Tiseo declares he has attended advisory boards and has received speakers' fee from Pfizer, Novartis, Ariad and Takeda. Other authors have no conflicts of interest to disclose.

Ethical conduct This report is in line with the ethical conduct of research involving human participants and patients whose histories are reported have provided informed consent.

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