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SHORT REPORT

Durable response to the ALK inhibitor alectinib in inflammatory myofibroblastic tumor of the head and neck with a novel *SQSTM1–ALK* fusion: a case report

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Summary
An inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm that typically develops in the lungs and seldom in the head and neck region. It is often related to the anaplastic lymphoma kinase (*ALK*) fusion gene. Crizotinib, a first-generation *ALK* inhibitor, has been shown to have a notable response in patients with *ALK*-positive IMT. Here, we report the first case of a 46-year-old man with IMT harboring a novel *SQSTM1–ALK* fusion gene who demonstrated marked response to alectinib. The patient presented a right neck mass (5-cm diameter) that progressively enlarged and expanded to the upper mediastinum. *ALK*-rearranged IMT was diagnosed after complete tumor resection. Spindle cells displayed diffuse cytoplasmic staining for ALK on immunohistochemistry. A fluorescence in situ hybridization analysis revealed the translocation of a part of the *ALK* gene locus at chromosome 2p23. FoundationOne CDx™ assay identified an *SQSTM1-ALK* gene fusion. After a year, right cervical, subclavian, and mediastinal lymph node metastases, considered unresectable, developed. Notably, the patient exhibited a marked response to alectinib treatment and has sustained for 17 months following systemic therapy initiation without significant adverse events. This report highlights the possibility of alectinib being a reasonable option for advanced IMT with the *SQSTM1-ALK* fusion.

Keywords Alectinib · Inflammatory myofibroblastic tumor · Head and neck · ALK gene rearrangement · SQSTM1-ALK gene fusion

Introduction

An inflammatory myofibroblastic tumor (IMT) is a rare neoplasm containing myofibroblastic spindle cells with inflammatory cells and is considered an intermediate malignancy that rarely metastasizes [1]. It usually develops in the lungs, retroperitoneum, or abdominopelvic region [2] of patients aged <40 years [3] and tends to remain dormant in size or shows gradual progression. Despite the successful use of complete surgical resection in affected patients, local recurrence is reported in approximately 25% of cases [2]. Further, although treatments with corticosteroids, radiotherapy, and chemotherapy have been anecdotally reported [4, 5], no standard therapies have been established for patients with recurrent or unresectable IMT to date.

Approximately half of IMT cases are associated with a chromosomal rearrangement at band 2p23, the site of the anaplastic lymphoma kinase (*ALK*) gene in the tyrosine kinase locus [6]. Reportedly, a fusion of *ALK* with several partners can lead to *ALK* overexpression and activation of its kinase domain [7]. The partner genes identified in IMTs include echinoderm microtubule-associated protein-like 4, tropomyosin 3 (*TPM3*), tropomyosin 4 (*TPM4*), ran-binding protein 2 (*RANBP2*), fibronectin 1, and clathrin heavy chain (*CLTC*) [8, 9]. Several clinical trials have demonstrated crizotinib, a first-generation *ALK* inhibitor, to have clinical activities against *ALK*-rearranged pediatric or adult IMTs [10, 11]. Further, alectinib,

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a second-generation *ALK* inhibitor, has been shown to be effective in cases having crizotinib resistance and to markedly inhibit *ALK* tyrosine kinase activity. Upon administration, alectinib binds to and inhibits *ALK* kinase, ALK fusion proteins as well as the gatekeeper mutation ALKL1196M known as one of the mechanisms of acquired resistance to small-molecule kinase inhibitors [12]. The inhibition leads to disruption of ALK-mediated signaling and eventually inhibits tumor cell growth in ALK-overexpressing tumor cells. ALK dysregulation and gene rearrangements are associated with a series of tumors. Although alectinib can be applied to *ALK*-positive IMTs, only anecdotal reports exist regarding patients with pulmonary IMT showing a dramatic response to alectinib [13, 14]. Here, we report the first case of IMT with a novel fusion partner, *SQSTM1*, that developed in the head and neck region and remarkably regressed after treatment with alectinib.

Case report

A 46-year-old man previously visited a hospital owing to a 5-year history of a right subclavian mass. Computed tomography (CT) revealed a right subclavian tumor with central calcification (Fig. 1a). The patient was followed up with annual CT without performing any histological diagnostic procedure. After 4 years, the tumor matured into its maximum size (5-cm diameter) and expanded up to the upper mediastinum without distant metastasis (Fig. 1b). IMT was histologically diagnosed following an open biopsy.

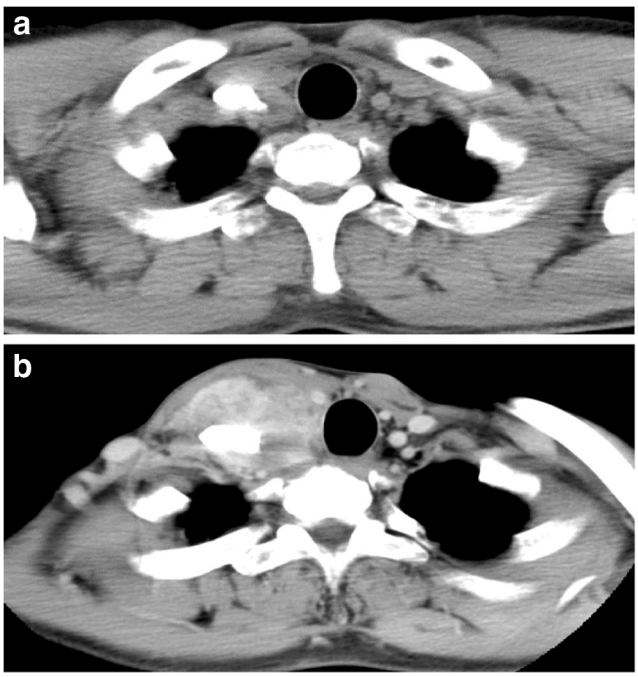

Fig. 1 **a** At diagnosis, computed tomography (CT) shows a well-circumscribed tumor (2.8 × 2.5 cm) in the right subclavian region. **b** A CT before curative surgery shows a tumor with central calcification in the lower right neck region

After definitive diagnosis, he was referred to our hospital where he underwent surgical resection through partial upper sternotomy with a negative margin (Fig. 2a). Pathological examination revealed that the tumor comprised spindle cells with plasma cells and lymphocytes (Fig. 2b). Further, immunohistochemical studies revealed that myofibroblastic spindle cells were considerably positive for ALK (Fig. 2c). Using the dual-color fluorescence in situ hybridization assay, the presence of the *ALK* fusion gene was confirmed (Fig. 2d). FoundationOne CDx™ assay, a next-generation sequencing used for the detection of substitutions, insertions, deletions, copy number alterations in 324 genes, and selective gene rearrangements, reported *TP53* mutation (R158H) and *SQSTM1-ALK* gene fusion. Notably, no additional treatment was performed. After a year, CT revealed local recurrence and multiple lymph node metastases involving the right neck and right upper mediastinum (Fig. 3a and b).

The patient developed a persistent cough and was treated with 600 mg/day alectinib as first-line chemotherapy. Following the treatment, the cough symptoms gradually improved, and drug withdrawal was not required with mild hepatotoxicity. After a 2-month therapy, recurrent tumors markedly decreased in size by 63% in the sum of the unidimensional measurements of target lesions defined as a partial response per the response evaluation criteria solid tumors ver. 1.1 (Fig. 3c). Even after 12 months since the initiation of alectinib treatment, the remarkable response has been maintained (Fig. 3d).

Discussion

To the best of our knowledge, this is the first case report of *SQSTM1-ALK*-positive IMT in the head and neck region successfully being treated with alectinib. An IMT in the head and neck region is extremely rare, and when reported, the nasal cavity, paranasal sinuses, orbit, trachea, and larynx have been the common sites involved. In fact, involvement of the soft neck tissue is considered exceedingly rare and has not been entirely reported [2, 15]. Reportedly, infectious agents, including the Epstein–Barr virus and human herpesvirus 8, and *ALK* rearrangements are responsible for this malignancy [16, 17]. A recent study reported novel actionable genomic alterations, such as *ROS1* and *PDGFRβ* fusions [8]. However, the etiology of IMT remains unclear to date. Moreover, *ALK*-positive IMTs are regarded as entities separate from those related to the Epstein–Barr virus and human herpesvirus 8 [16]. Normally, *ALK* fuses with *TPM3* or *TPM4* in IMTs [9]. Further investigation revealed additional *ALK* fusions, including fusions with *RANBP2-ALK*, *CARS-ALK*, and *SEC31L1-ALK*. The *SQSTM1-ALK* gene fusion detected in our case is often observed in epithelioid cell

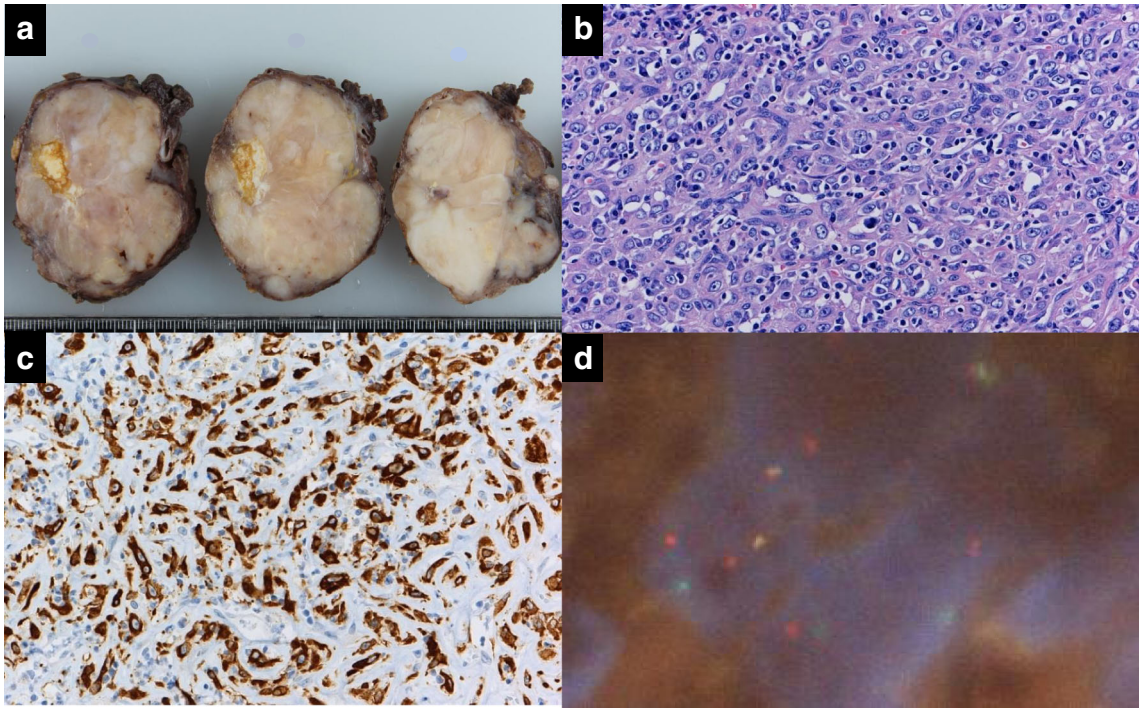

Fig. 2 **a**–**d** Histological images of the tumor. Macroscopic images of the tumor resected at the first surgery (**a**), the tumor comprises spindle cell neoplasm with inflammatory infiltrates (**b**), strong cytoplasmic staining for ALK is detected by immunohistochemical assay (**c**), and the *ALK* fusion gene is confirmed with the dual-color fluorescence in situ hybridization assay (**d**)

histiocytoma [18] but has not been reported in IMTs. The *SQSTM1* gene maps on the 5q35 locus and encodes a multifunctional ubiquitin-binding protein, sequestosome-1, which is involved in several cell signaling pathways and autophagy, and the oncogenic potential of the *SQSTM1-ALK* fusion has been reported in large B cell lymphoma [19, 20].

The discovery of *ALK* fusions in patients with non-small cell lung cancer facilitated the clinical development of *ALK*

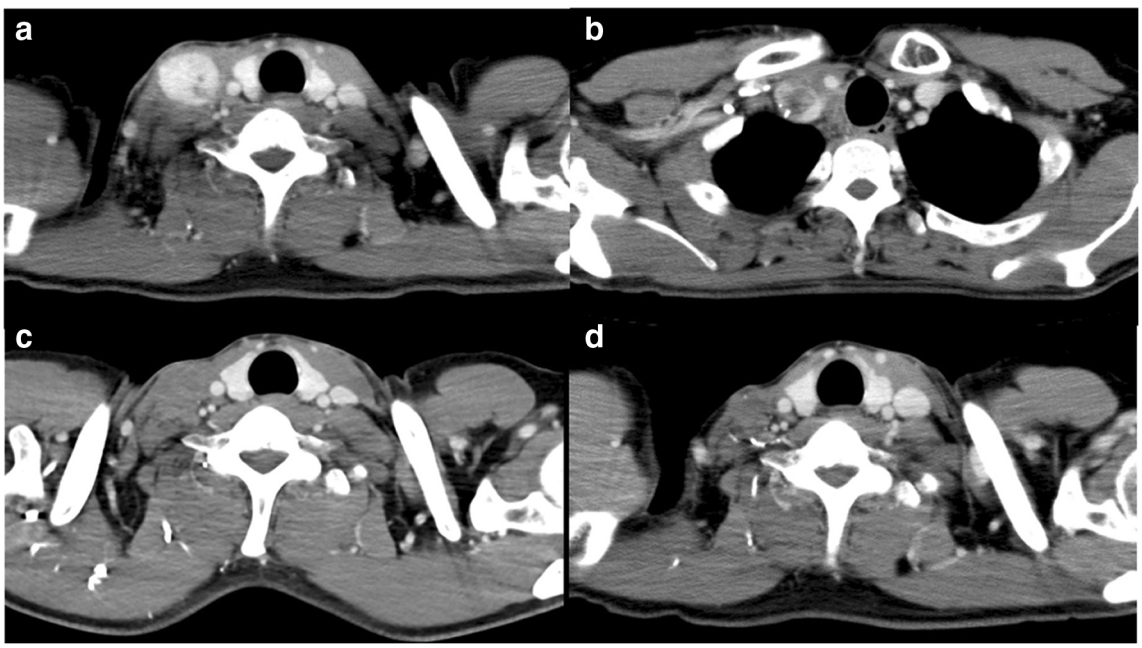

Fig. 3 **a** and **b** Computed tomography (CT) before the initiation of the alectinib administration reveals local recurrence and multiple lymph node metastases involving the right neck and right upper mediastinum. CT shows a dramatic response with alectinib treatment after 2 months (**c**) and 12 months (**d**)

inhibitors, including crizotinib and alectinib. In a phase III trial comparing crizotinib and chemotherapy in treatment-naïve *ALK*-positive IMT patients, crizotinib improved progression-free survival, response rate, and quality of life [21]. In the pooled analysis of two phase 2 trials of alectinib for patients with a crizotinib-resistant, *ALK*-positive metastatic disease, the objective response of approximately 50% patients was obtained with an acceptable safety profile [22]. Further, two phase 3 trials (J-ALEX and ALEX) comparing alectinib and crizotinib in *ALK* inhibitor-naïve patients reported superior efficacy and more favorable toxicity of alectinib than of crizotinib [23, 24]. Reproducibly, grade 3 or higher adverse events were less prevalent with alectinib than with crizotinib in both trials. Moreover, the median progression-free survival with alectinib was not attained, and it markedly improved with alectinib compared with crizotinib in the J-ALEX trial [hazard ratio (HR), 0.34; 99.7% confidence interval (CI): 0.17–0.70] [23] and ALEX trial (HR, 0.47; 95% CI: 0.34–0.65) [24]. Taken together, these findings theoretically recommend the adoption of *ALK* inhibitors for *ALK*-rearranged malignancies, except for non-small cell lung cancer, as in our case.

The first case of IMT showing a marked and sustained response to crizotinib was reported in a patient with *ALK* rearrangements, but not in a patient without such rearrangements [10], highlighting the dependence of this response on signal transduction mediated by activated *ALK* in IMT and non-small cell lung cancer. In the Children's oncology group trial of crizotinib for *ALK*-positive IMT ($n = 14$), the overall response rate was 86% and median duration of therapy was 1.6 years [11]. To the best of our knowledge, to date, alectinib has been reported in only two cases of *ALK*-positive pulmonary IMT [13, 14]. Yuan et al. [10] reported a patient with pulmonary IMT, which metastasized to the brain, who experienced disease stabilization for 8 months with alectinib, despite post-treatment disease progression with crizotinib and ceritinib. Saiki et al. [14] reported about a 26-year-old man with *ALK*-positive pulmonary IMT harboring a subcutaneous tumor on the left forearm. The patient's disease rapidly progressed with the development of respiratory failure and deterioration of performance status. Nevertheless, Saiki et al.'s [14] patient responded to alectinib as the first-line treatment and displayed rapid improvement in symptoms and performance status. Based on the anticipated response and favorable safety profile of alectinib compared with those of crizotinib, our patient was successfully treated with alectinib and accordingly exhibited a rapid, dramatic response and improvement in symptoms. Overall, this case report suggests that the identification of *ALK* rearrangement in cases of malignant IMTs offers a rationale to adopt selectively targeted therapies for this rare form of tumor.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest to disclose.

Ethical approval This study does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient for the publication of this case report.

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