

A Novel ALK Fusion Gene (NSF-ALK) Identified in a Patient With Recurrent Spindle Cell Sarcoma Respond to Crizotinib: A Case Report

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Case report

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Abstract

Background: Spindle cell sarcoma (SCS) is a rare malignant tumor which relapses quickly and has poor prognosis.

Case presentation: We report a case of SCS deriving from the left side of chest possessed a novel unreported ALK fusion gene named NSF-ALK found by Next Generation Sequencing (NGS) technology. Despite receiving three surgical resections, local recurrence occurred rapidly and distant brain metastasis was eventually observed in this patient. The subsequent administration of crizotinib¹, an oral anaplastic lymphoma kinase inhibitor, resulted in dramatic tumor shrinkage and the patient entered a remission period that has been ongoing for more than 10 months.

Conclusions: In summary, this study is the first to describe a novel NSF-ALK fusion in spindle cell sarcoma which has promising efficacy by crizotinib treatment. More importantly, the case also shows that next generation sequencing provides more information of mutation to guide treatment in clinical decisions by presenting molecular changes.

Introduction

Sarcomas are a rare and heterogeneous group of mesenchymal malignancies arising from either soft tissue or bone. Although they account for less than 1% of adult cancer diagnoses, sarcomas encompass more than 50 pathological subtypes². Spindle cell sarcoma (SCS) is one of subtype of sarcomas and little reported tumor³ which could arise in any part of the body and is connective-tissue tumor that can grow rapidly^{4,6}. The usual treatment for spindle cell sarcoma is surgery to remove the tumor. However, the treatment options should follow the position, size and the grade of the tumor, whether spread to other parts of the body, and so on^{7,8}. In recent years, with the advance of next generation sequencing⁹, novel genetic alterations, including mutations or recurrent gene fusions, have been unraveled, which give the patients who have sarcoma more therapeutic methods¹⁰. The detection of gene fusions involving kinase genes can identify a target for therapy using agents that are approved or available in the setting of clinical trials¹¹. ALK receptor tyrosine kinase (ALK) rearrangement is a common driver mutation for patients with [non-small cell lung cancer](#) (NSCLC)¹², but it is rare reported in sarcoma. Here we report a case of SCS deriving from the left side of chest that possessed a novel unreported ALK fusion gene named NSF-ALK using NGS technology. The subsequent administration of crizotinib¹, an oral anaplastic lymphoma kinase inhibitor, resulted in dramatic tumor shrinkage and the patient entered a remission period that has been ongoing for more than 10 months.

Case Report

A 28-year-old female was admitted to the hospital for cough and shortness of breath with no relevant past medical history. The Computed tomography indicated an occupancy within the left-side of the chest and the patient subsequently underwent first-time radical resection of the tumor. The postoperative

pathological diagnosis was spindle cell sarcoma (Figure 1) and an "ifosfamide + doxorubicin " regimen was applied for 6 cycles. However, tumor recurrence was observed within the left thoracic cavity and left side of the pericardium respectively, thereby prompting a second and third surgical resection. Postoperative pathological diagnosis confirmed our prior result. No treatment was given after the last two surgeries. When conducting a brain MRI due to symptoms of weakness, headache and nausea, we discovered multiple metastatic lesions and identified that the patient encountered additional recurrence. Chest Computed tomography (CT) showed irregular soft tissue shadows on the left side of the pericardium. In this context, we chose "Docetaxel and Anlotinib¹³" to treat for 3 cycles accompanied by 1 cycle of head radiotherapy. Regrettably, there was no obvious therapeutic effect detected by CT. A FFPE sample of the patient's tissue was subjected to an NGS-based pan-cancer 457-gene panel which led to the discovery of an unreported NSF-ALK fusion gene (Figure 2). The results indicated a rearrangement stemming from fusion between intron 20 of an inverted NSF to intron 19 of ALK (Figure 2A). The detected mutation allele frequency was 12.39% (Figure 2B). We established a 105 gene RNA sequencing panel to capture the fusion mRNA and verified this fusion existed. The fusion reads also covered NSF (exon1-20) with ALK (exon20-29) genes (Figure 2A). The fusion protein contained 5'partner gene of SNAP binding, ATPase domain and the C-terminal tyrosine kinase domains of ALK (Figure 2B). According to NGS results, crizotinib was subsequently administered starting September 8, 2019 which resulted in tumor shrinkage (Figure 3)- the remission period has been ongoing for more than 10 months. Thankfully, we gained all written informed consents, including specimen collection, genetic testing, and use of this information for research purposes, which provided by this patient and her families.

Discussion

Sarcomas have long been in dire need of novel therapies, given the aggressive nature and poor prognosis in the metastatic setting¹⁴. Spindle cell sarcoma is a kind of sarcomas which can develop for a variety of reasons, including genetic predisposition. However, owing to the rarity of SCS, there are lack of basic information regarding the tumor incidence, distinctive clinical characteristics, treatment outcome and disease specific prognostic factors. Nowadays, the sophisticated molecular pathologic diagnostic techniques has made which give the SCS patient more therapeutic methods. About 50% of sarcomas have specific pathology-defining molecular alterations including mutations, fusion genes, and gene amplifications¹¹. There are no U.S. Food and Drug Administration (FDA)-approved therapies that are based on treating specific molecular targets. For most patients, current therapies largely focus around cytotoxic chemotherapy agents and tyrosine kinase inhibitors (i.e., pazopanib and olaratumab for soft tissue sarcomas)¹⁵.

Our case first identified a NSF-ALK fusion gene in spindle cell sarcoma and response to ALK inhibitor crizotinib. ALK receptor tyrosine kinase (ALK) fusion is found in many cancers; the highest detection has been in NSCLC. ALK is considered a lung cancer-driven gene, but it was little reported in spindle cell sarcoma. ALK inhibitors are widely used in cancer-targeted therapy now, while the sensitivity to ALK inhibitors of different ALK fusion forms is different. NSF (N-ethylmaleimide sensitive factor) gene is a

novel ALK fusion partner in translocation-associated neoplasia which is an ATPase that plays a crucial role in vesicular transport¹⁶. This is the first study to describe a novel NSF-ALK fusion that may have promising efficacy by crizotinib treatment. In addition, next generation sequencing can provide more molecular change information and also give patients more therapeutic chance. This may be a great progress in spindle cell sarcoma treatment.

The identified NSF-ALK fusion gene is a novel, unreported ALK fusion gene in SCS, which has promising efficacy by crizotinib treatment. Since there is no standard treatment for patients with advanced or recurrent SCS, NGS provides more management strategies for guiding clinical decisions by identifying emergent molecular changes. A further investigation from large clinical trials would still be needed to determine the prevalence of the novel NSF-ALK fusion gene within the patient population as well as the general efficacy of the regimen that was successful in treating our patients. In addition, to constantly exploring the new form of ALK fusion and studying its relevance to drug sensitivity has great clinical significance. If the patient has the resistant to crizotinib, we can try another ALK inhibitor drug like alectinib.

Conclusion

In summary, this study is the first to describe a novel NSF-ALK fusion in spindle cell sarcoma which has promising efficacy by crizotinib treatment. More importantly, the case also shows that next generation sequencing provides more information of mutation to guide treatment in clinical decisions by presenting molecular changes.

Abbreviations

NSF: N-ethylmaleimide sensitive factor; SCS: Spindle cell sarcoma; NGS: Next Generation Sequencing; ALK: ALK receptor tyrosine kinase; NSCLC: [Non-small cell lung cancer](#); CT: Computed tomography;

Declarations

Ethics approval and consent to participate

Current study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. We gained all written informed consents, including specimen collection, genetic testing, and use of this information for research purposes, which provided by this patient and her families.

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Authors' contributions

SJ, LW, QZ, CC contributed equally to the manuscript. WT,HZ, ZL,WM designed the study and provided critical suggestions. All authors read and approved the final manuscript.

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Competing interests

The authors declare no conflict of interest in preparing this article.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions are included within this article.

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Figures

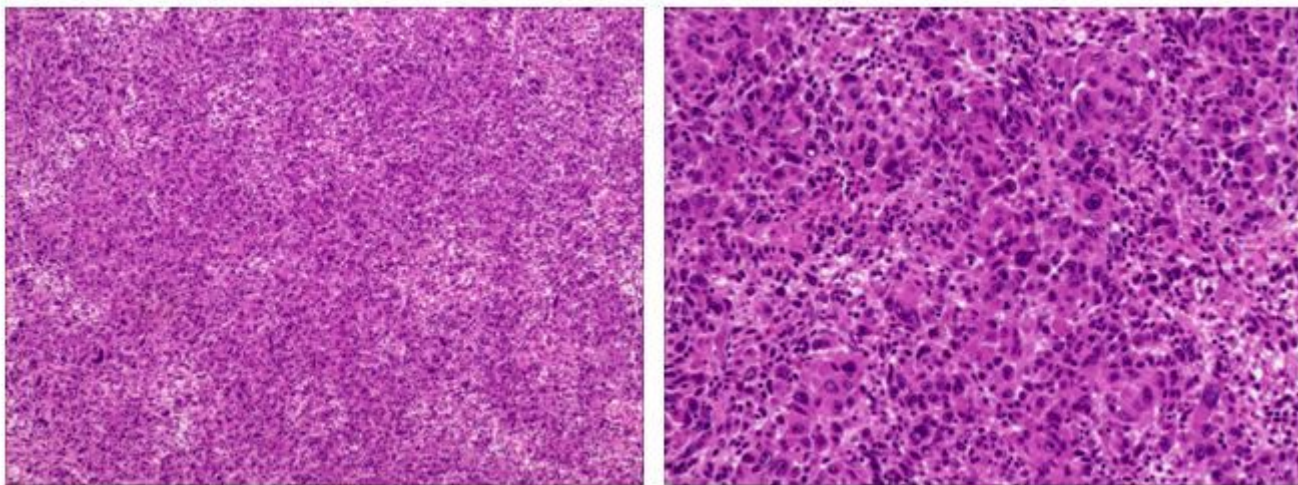


Figure 1

Spindle cell sarcoma shown by pathologic examinations. The left picture is photographed under 40X lens, while the right one is under 100X lens.

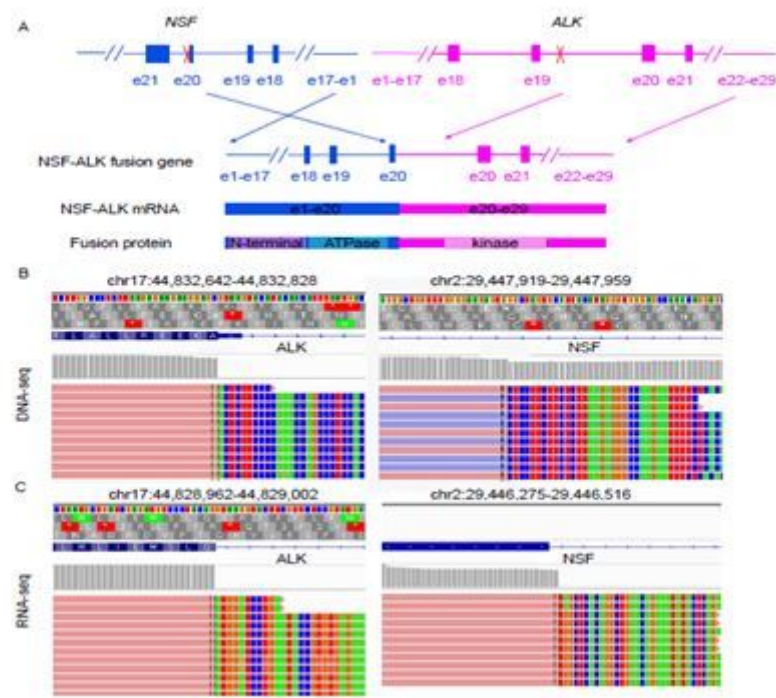


Figure 2

Concomitant NSF-ALK fusion was found in spindle cell sarcoma. (A) Showed the breakpoints detected in the fusion by targeted NGS and the alterations in gene, mRNA and protein caused by this fusion. (B) Demonstrated the DNA sequencing reads indicating fusion region by genomics Viewer (IGV) software. (C) RNA sequencing reads indicating this fusion region demonstrated by IGV.

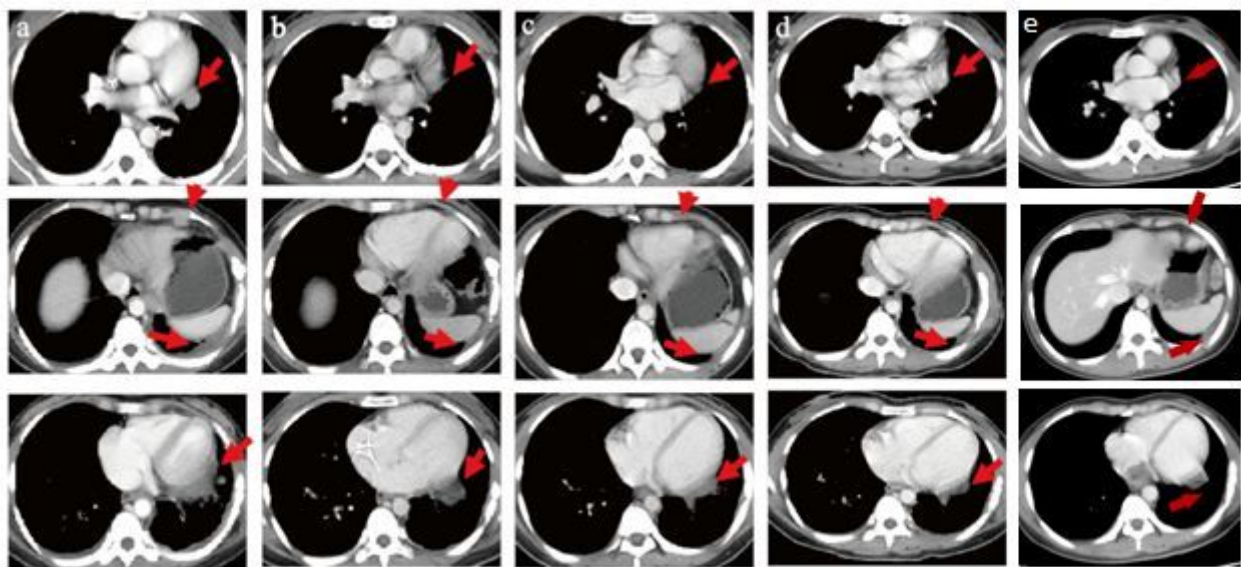


Figure 3

Computed tomography (CT) scan of the patient's chest . (a) before treatment, (b) 2 months after crizotinib treatment, (c) 4 months after crizotinib treatment, and (d) 7 months after crizotinib treatment, (e) 10 months after crizotinb treatment.