Case report: A Novel Intergenic *KIF5B-MET* Fusion Variant in a Patient with Gastric Cancer

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Case Report

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Abstract

Background

MET fusion is a key driver mutation, but it is rare in gastric cancer (GC). Several MET inhibitors have been approved for the treatment of MET-positive patients, but the tumor response is heterogeneous. With the development of next-generation sequencing (NGS), diverse MET fusion partner genes have been identified. We reported a case of a fusion variant involving KIF5B-MET in GC.

Case presentation

After thoracoscopic inferior lobectomy plus lymph node dissection under general anesthesia, a “tumor within a tumor” was found in the lung tumor tissue of a 64-year-old nonsmoker male patient. Combining the medical history and the results of enzyme labeling, the focal area was considered to be GC. To seek potential therapeutic regimens, an intergenic region between KIF5B and MET fusion was identified. This fusion contains a MET kinase domain and coil-coiled domains encoded by KIF5B exons 1-25, which might drive oncogenesis.

Conclusion

Our founding could extend the spectrum and genomic landscape of MET fusions in GC and favor the development of personalized therapy.

Background

Gastric cancer (GC) is one of the most common malignancies.[1] The incidence and mortality of gastric cancer vary by region, but more than 50% of cases occur in East Asia.[2] GC is responsible for 10.6% of new cases and 13.6% of cancer-related deaths in China.[3] Targeted therapies designed to disrupt the activity of specific oncogenic signaling pathways have recently emerged as a promising therapeutic strategy in GC, such as the ToGA trial. Trastuzumab and ramucirumab improved the overall survival (OS) of patients by targeting the *HER-2* and *VEGFR* genes.[4,5]

MET proto-oncogene receptor tyrosine kinase (MET) is a high-affinity proto-oncogene receptor tyrosine kinase that, upon activation, drives oncogenic pathways involved in cell proliferation, survival, and metastasis. As one of the major *MET* variants, *MET* fusion is a key driver mutation. The common fusion proteins are derived from chromosomal translocations, which are usually composed of N-terminal dimerization domains provided by the kinase domains to which fusion partner proteins fuse to tyrosine kinases. These fusion mutations often lead to the activation of the kinase domain and provide ideal targets for the development of anticancer therapies.[6] With the development of next-generation sequencing (NGS), diverse *MET* fusion partner genes, such as *ETV6-MET*,[7] *PTPRZ1-MET*,[8] and *CD74-MET*, have been identified.[9] However, *MET* gene fusion is a relatively rare but promising molecular target for

individualized targeted therapies. Herein, we report a novel intergenic region between kinesin family member 5b (KIF5B) and MET fusion in a patient with GC.

Case Presentation

In April 2019, a 64-year-old nonsmoker male patient came to our hospital for further examination because chest computed tomography (CT) found nodules in the right lower lung two years ago. After admission, chest CT showed irregular patchy shadows in the lower lobe of the right lung, local thickening of the bronchial wall, and narrowing of the lumen, which was slightly denser than that 2 years ago (Fig. 1A). One week later, the patient underwent thoracoscopic inferior lobectomy plus lymph node dissection under general anesthesia. Postoperative pathology revealed that the heterotype glands in the focal area were significantly different from the main tumor body, the cytoplasm was rich in mucus, and most of the tumor cells were located in lymphatics (Fig. 1B). Combining the medical history and the results of enzyme labeling (Ki67 (+), D2-40 (+), MUC5AC (+) and Villin (+)) (Fig. 1C-F), it was considered that the focal area was GC. This lesion collided with the main tumor body, which was described as a "tumor within a tumor". The tumor size was 2.2×1.5×1.0 cm.

To probe the genomic profile of the tumor for targeted therapy, the tissue specimens were subjected to NGS analysis, and an intergenic region between *KIF5B* and *MET* fusion was identified (Fig. 2A). The fusion of *KIF5B-MET* included exons 1-25 of *KIF5B* and exons 15-21 of *MET*, and the complete kinase structure of the MET protein was retained (Fig. 2B). The mutant allele frequency was 15.24%. No other driver gene variants were found.

Discussion And Conclusions

MET fusions are rare in GC, and this is the first documented case of a patient with a *MET* fusion-positive tumor. In this study, we identified a patient with a fusion variant involving *KIF5B-MET* in GC. Our identified *KIF5B-MET* variant was the same as the most recently reported *KIF5B-MET* fusion variant in non-small cell lung cancer (NSCLC).[10] This fusion gene was initially reported in one of 513 lung adenocarcinoma samples.[11] Although several MET inhibitors have been approved for the treatment of *MET*-positive patients, the tumor response is heterogeneous, and the OS ranges from 1 to 36 months.[10,12,13] One explanation is that the response of MET inhibitors to different *MET* fusion types differs. Other possible reasons include the existence of other driver mutations or primary resistance mutations in the kinase structure of the MET protein. Therefore, it seems necessary to comprehensively understand *MET* fusion information, and NGS could serve as a supplementary approach for *MET* status detection because of its high-throughput molecular analysis that can detect gene copy number alterations, deletions, insertions and fusions simultaneously.

To the best of our knowledge, this is the first report of breakpoints coexisting simultaneously in the intergenic region between the *KIF5B* gene and the *MET* gene, as well as a novel *MET* rearrangement in GC. This fusion contains a *MET* kinase domain and coil-coiled domains encoded by *KIF5B* exons 1-25,

which might drive oncogenesis. Given the recent development of several MET inhibitors and their potential therapeutic efficacy for tumors expressing the *KIF5B-MET* fusion protein, we expect that further investigation of *KIF5B-MET* fusions will enable us to identify GC patients suitable for this targeted therapy.

Abbreviations

GC: Gastric cancer; MET: MET proto-oncogene receptor tyrosine kinase; NGS: next-generation sequencing; KIF5B: kinesin family member 5b; CT: computed tomography.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Jingjiang People's Hospital.

Consent for publication

A written informed consent was obtained from the patient for publication of his clinical details and clinical images in this case report.

Availability of data and materials

There is no supporting data available.

Competing interest

The authors declare no conflicts of interest.

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None.

Authors’ contributions

YL and WZ designed the study, WZ, CQ and HJ drafted the manuscript. SY and CJ conducted the histological evaluation and immunohistochemical evaluation. SY and LW performed the NGS analysis. All authors read and approved the final manuscript.

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None.

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Figures

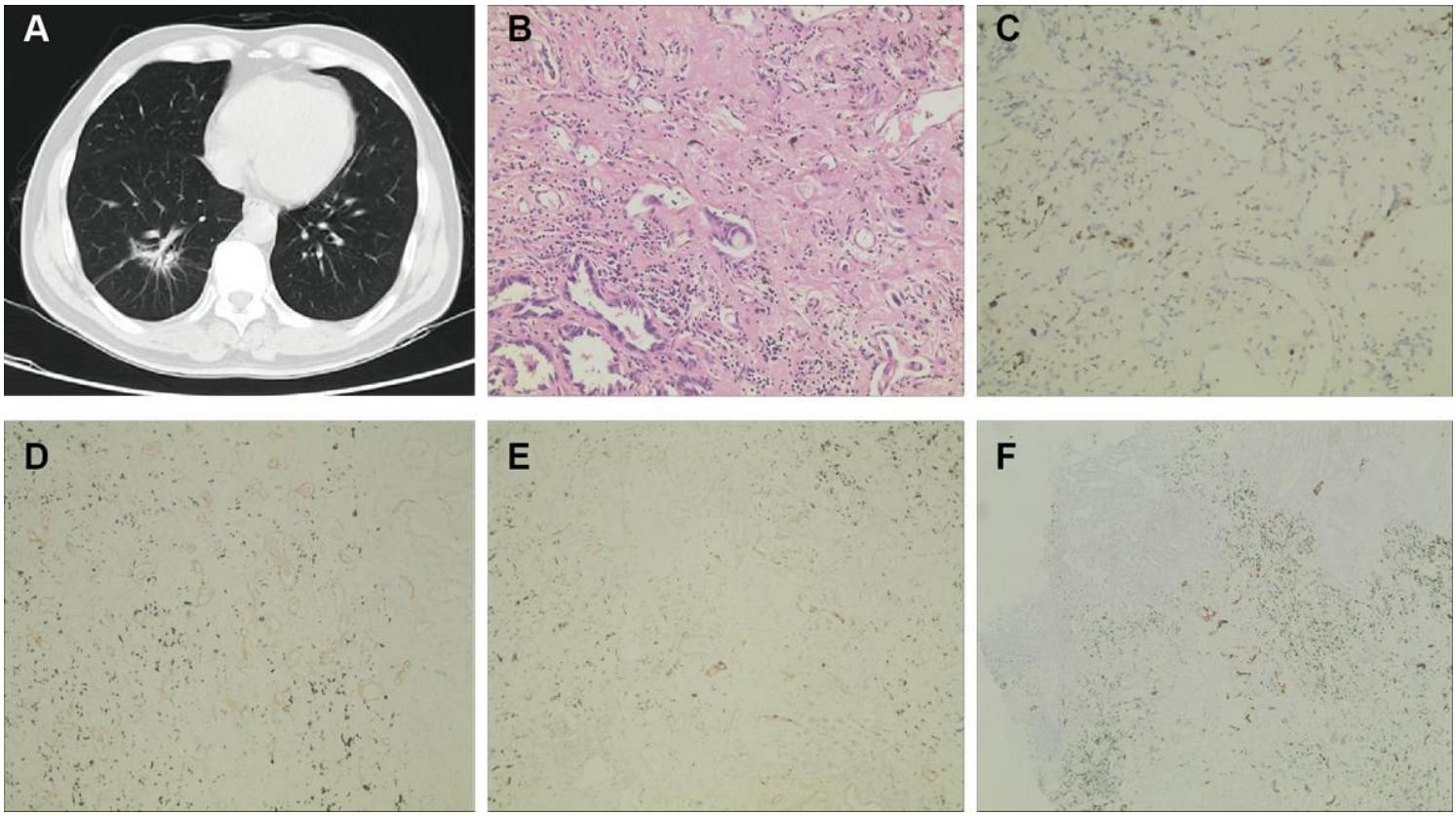

Figure 1

Patient disease diagnosis. A. CT diagnosis of lung tissue. B. Typical images of postoperative pathology. C-F. Immunohistochemistry staining images of Ki67 (+), D2-40 (+), MUC5AC (+) and Villin (+).

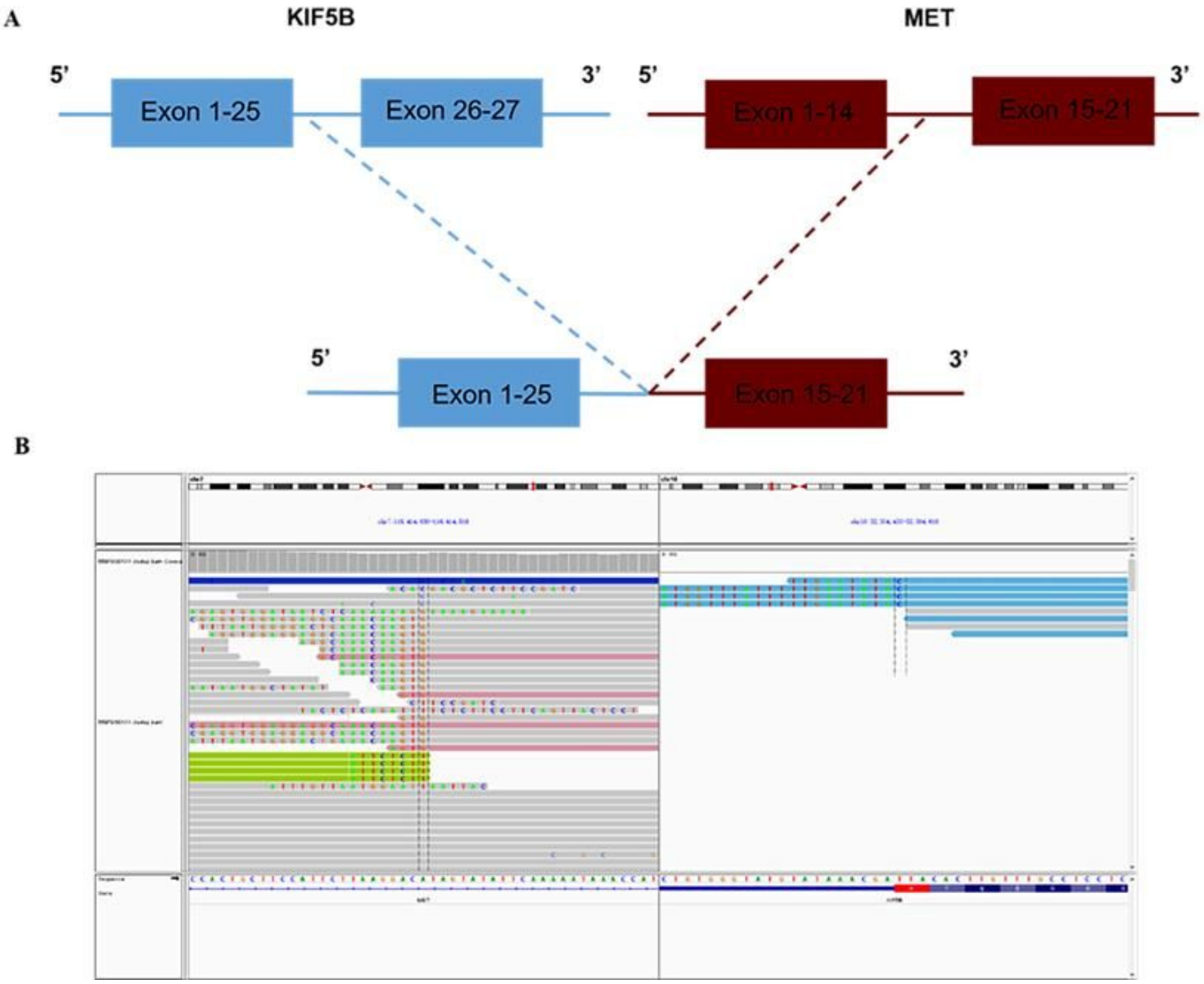

Figure 2

NGS findings for tumor tissue samples. A. A novel intergenic region between KIF5B exons 1-25 and the MET exon 15-21 fusion variant was identified. B. NGS results showing the breakpoint of the KIF5B-MET fusion.

Supplementary Files

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- CAREchecklist.pdf