Letter to the Editor

Chr1 *95026203-ALK*, a novel intergenic fusion identified in a patient with lung adenocarcinoma with nodular ground-glass opacity

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The rearrangement of anaplastic lymphoma kinase (*ALK*) gene accounts for 3–5% in non-small cell lung cancer (NSCLC) (1). Novel variants including intergenic fusion were widely analyzed since they did bring significant clinical benefit for the fusion carriers (2). Therefore, novel variants including intergenic fusions are getting attention to illustrate potential targetable variants. At the meantime, lung cancer with ground-glass opacity (GGO) component predicts better prognosis, while some of them could progress rapidly (3). Therefore, the molecular profile of GGO-featured lung cancer is under widely investigation to improve current understanding on it. Studies has revealed significantly lower frequency of *ALK* fusion in patients presenting GGO, while the occurrence of *ALK* fusion could predict higher tumor burden and more aggressive progression (4). Thus, reporting the potential targetable fusion variant might guide those patients' treatment management. Here we report a novel Chr1 *95026203-ALK* intergenic fusion, identified in a patient with lung adenocarcinoma with nodular GGO.

A 48-year-old male smoker went to our hospital for reexamination in September 2020 after discovering a pulmonary nodule 6 months ago. Chest computed tomography scan revealed an irregular-shaped nodule with GGO in localized apical and posterior segment of superior lobe of left lung and diffuse bilateral pulmonary nodules (*Figure 1A,B,C,D*). Multiple enlarged lymph nodes were observed in mediastinum and left neck. A slight pericardial effusion was also discovered. Pathological examination was conducted with the needle biopsy of the enlarged left cervical lymph node [hematoxylin and eosin (H&E) staining in *Figure 1E*]. The immunohistochemistry (IHC) staining showed TTF-1(+), Napsin A(+), CK7(+), CK5/6(–), P63(+), Ki67(25%+), P40(+), Syn- and PAS(+). The disease was diagnosed as metastatic lung adenocarcinoma (poorly differentiated, T1N3M1b).

To seek for individualized therapy, the formalin-fixed and paraffin-embedded specimens were subjected to DNA-based next-generation sequencing (NGS) analysis [in College of American Pathologists-certified laboratory) with a panel of 9 genes including *EGER*, *ALK*, *ROS1*, *RET*, *MET*, *ERBB2*, *KRAS*, *BRAF*, *NTRK1/2/3*. A novel Chr1 *95026203-ALK* intergenic fusion was detected (*Figure 2A,B*)]. This fusion was generated by

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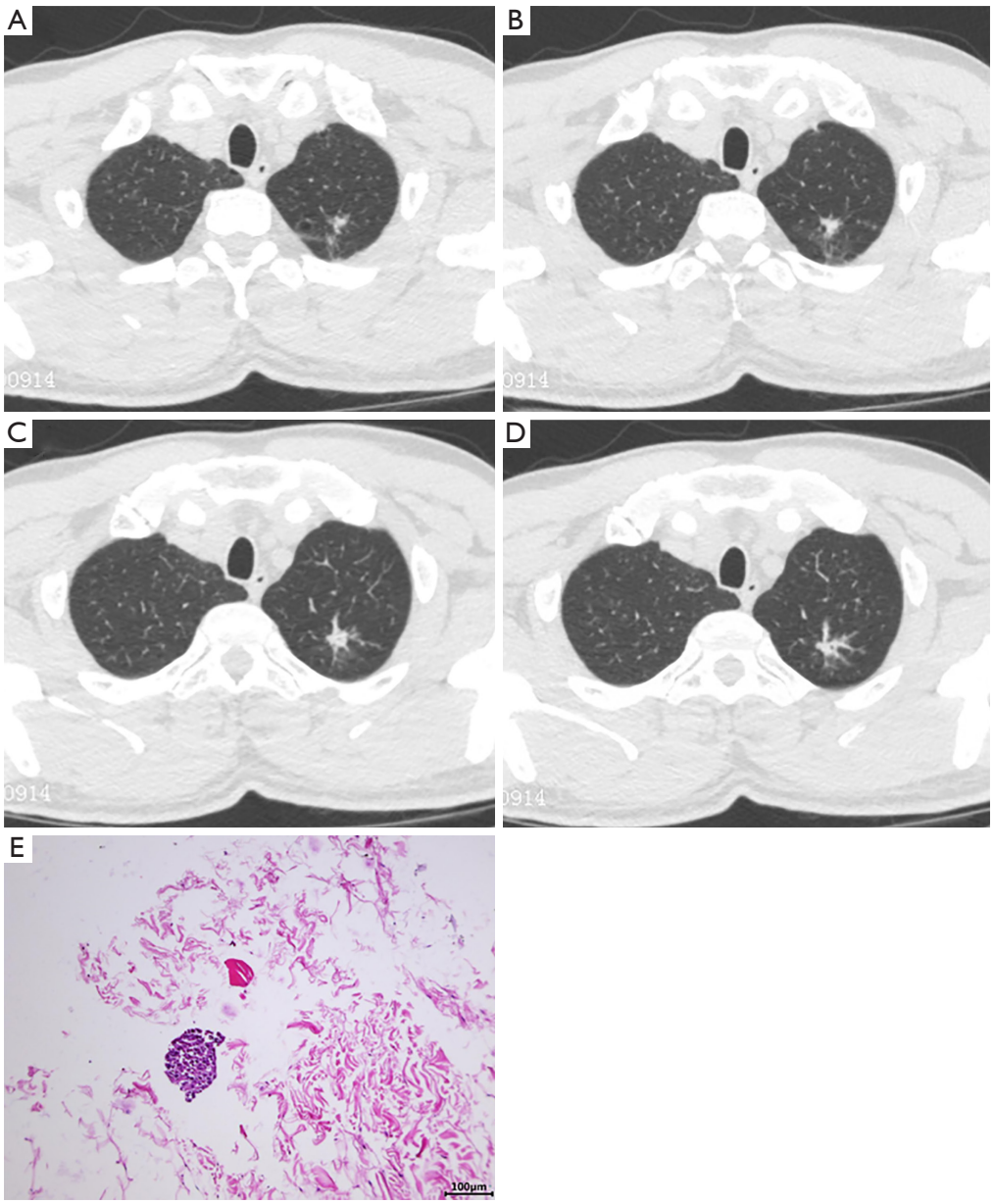

Figure 1 Diagnostic images of tumor lesions and hematoxylin and eosin (H&E) staining. (A,B,C,D) Pulmonary lesions by chest computed tomography scan at diagnose on 14th September, the images of (A,B,C,D) are arranged from top-to-bottom direction. (E) H&E staining of the biopsy specimen (100×). H&E, hematoxylin and eosin.

Chr1 *95026203* (intergenic region between *F3* and *SLC44A3*) and exons 20–29 of *ALK*, with the abundance of 3.86%. No concurrent alterations were detected. This novel fusion retained the whole kinase domain of *ALK* and expression of the *ALK* protein was confirmed by IHC analysis (3+ staining) (*Figure 2C*). The patient adopted chemotherapy (pemetrexed combined with lobaplatin) as first-line treatment eventually due to its lower expense and maintained stable disease after 1 cycle of treatment. According to last follow-up visit on 22 April 2021, no progression was observed after 6 cycle's treatment. The progression-free survival is more than 7 months. *Figure 3* showed the varying trend of carcino-embryonic antigen (CEA).

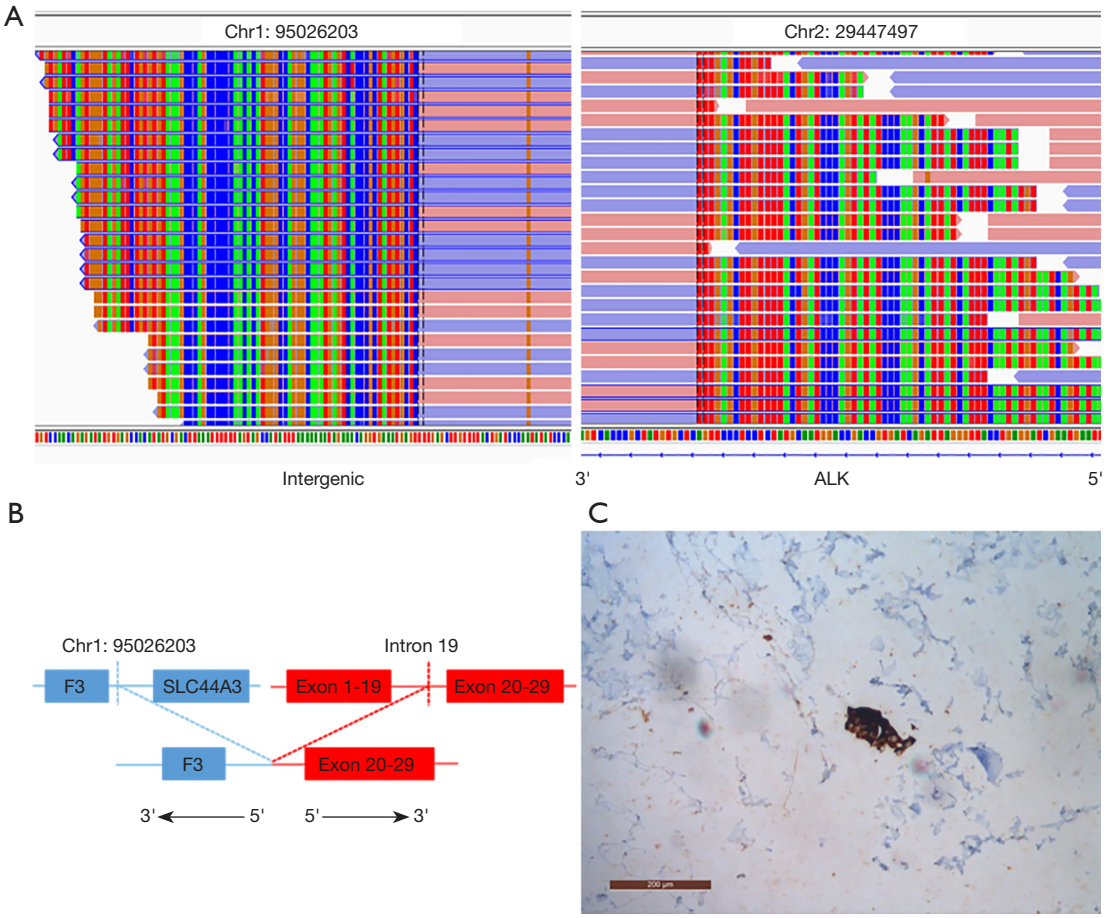

Figure 2 Detection of ALK fusion. (A) The integrative genomics viewer screenshot of Chr1 *95026203-ALK* fusion, detected by DNA-based NGS with specimen of cervical lymph node metastasis. (B) Schematic diagram of the detected fusion, this variant was generated by the fusion of intergenic region between *F3* and *SLC44A3* with exons 20–29 of *ALK*. (C) Positive anaplastic lymphoma kinase expression by IHC (3+, 100×). *ALK*, anaplastic lymphoma kinase; NGS, next-generation sequencing; IHC, immunohistochemistry.

To our knowledge, this is the first report describing the fusion of Chr1 *95026203* with *ALK* in lung adenocarcinoma. Actually, methods for detecting fusions are widely discussed recently. DNA-based NGS was able to identify the specific partner genes and breakpoints, as well as the potential resistant mutations in *ALK* or other concurrent gene alterations. Therefore, it could be a proper primary choice for patients. Generally, fusions compose of intergenic regions are theoretically unlikely to generate functional fusion transcript, while accumulating evidence suggests that intergenic fusion might also generate functional fusion protein after transcription (chromothripsis and alternative splicing as potential mechanism) (2). Therefore, further RNA-level or protein-level validation was often recommended to capture the possible actionable fusions and guide target therapy (2). In this case, *ALK* kept the whole kinase domain according to results of DNA-based NGS and *ALK* fusion protein was demonstrated positive by IHC. This indicated fusion of Chr1 *95026203-ALK* might generate functional fusion protein and the patient might benefit from *ALK* inhibitors when considering the following treatment.

Another key point is that this novel fusion was identified in a patient with GGO. To figure out the molecular profile of GGO-featured lung cancer, studies on driver gene like *EGFR* and *ALK* are increasing (5). Frequency of *ALK* fusion (2.9% in lesion with pure GGO) was found significantly lower in GGO-featured lung cancer (6), leaving less

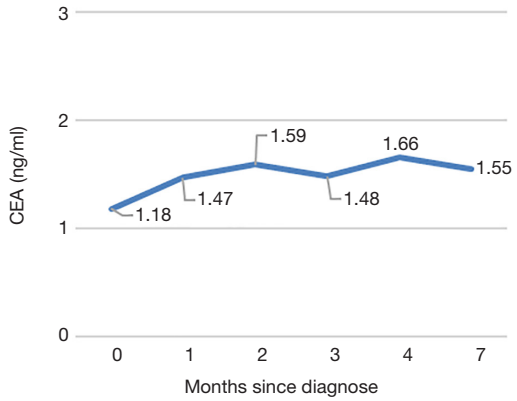

Figure 3 The level of CEA from diagnose in September 2020 to the last follow-up visit in April 2021. CEA, carcino-embryonic antigen.

opportunity of *ALK* inhibitors for those patients. While fusion of *ALK* is found associated with advanced stage and larger tumor size, suggesting its association with aggressive progression of lung adenocarcinoma. Therefore, it is important to identify potential targetable *ALK* fusion variant and accordingly decide individualized management strategy. In this case, this novel fusion of Chr1 *95026203-ALK* was detected, although with lymph node metastasis, it is probably shared by the nodule with GGO, since a 98% concordance of *ALK* fusion between primary and lymph node metastasis was revealed (7). This might enrich the evidence of *ALK* fusion in GGO-featured lung cancer and implied potential tumor progression trend and target therapy for this subgroup. Future studies on the molecular difference of tumor cells between GGO and solid lesions, as well as its impact on patients' tumor progression are also needed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013).

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