STRN3-NTRK1: A Novel NTRK1 Oncogenic Fusion in a Patient with Lung Adenocarcinoma

To the Editor:
Neurotrophic receptor tyrosine kinase gene (NTRK) fusions, including those involving the neurotrophic receptor tyrosine kinase 1 gene (NTRK1), neurotrophic receptor tyrosine kinase 2 gene (NTRK2), or neurotrophic receptor tyrosine kinase 3 gene (NTRK3), are oncogenic drivers in a wide variety of malignant tumors.1 Different types of NTRK fusion partner genes have been identified in recent years; they include lamin A/C gene (LMNA)-NTRK1, ETS variant 6 gene (ETV6)-NTRK3, and striatin gene (STRN)-NTRK2. Herein, we report a novel NTRK1 oncogenic fusion in lung adenocarcinoma.

A 56-year-old man was admitted to the hospital for paroxysmal cough accompanied by hoarseness. Positron emission tomography–computed tomography examination revealed small solid nodules in the lingual segment of the upper left lung with high fludeoxyglucose F 18 metabolism. Moreover, multiple lymph nodes and bone metastases were considered as the reasons for the observation of high fludeoxyglucose F 18 metabolism in the lymph nodes of the tracheal gap, aortopulmonary artery window, subcarinal area, and left side of the ilium. No pathological diagnosis was made. However, thoracoscopic wedge-shaped resection of the upper left lung was performed for pathological diagnosis after multidisciplinary consultation, which led to a postoperative diagnosis of stage IV lung adenocarcinoma. Comprehensive genomic profiling was performed, and a novel STRN3–NTRK1 fusion variant was identified (Fig. 1). The STRN3–NTRK1 fusion comprised exons 1 to 3 of STRN3 and exons 9 to 17 of NTRK1, and the complete kinase structure of NTRK1 protein was retained. Further tests, including fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), confirmed the presence of neurotrophic receptor tyrosine kinase 1 (NTRK1) fusion proteins (Fig. 2).

Although the frequency of NTRK gene fusions is less than 5% in lung cancer, an impressive response rate (>75%) has been observed in patients with NTRK fusions.2 Traditionally, FISH and IHC have been used to judge the status of NTRK fusion quickly and at a lower cost, whereas few shortcomings are associated with these two approaches. First, neither FISH nor IHC can identify the specific NTRK fusion types.1 Second, FISH and IHC could not identify the mutations of NTRK kinase.

Figure 1. Next-generation sequencing findings of the primary lung tumor tissue sample. A novel striatin gene (STRN3)-neurotrophic receptor tyrosine kinase 1 gene (NTRK1) fusion variant was identified.
domain mutations that might lead to the primary resistance to tyrosine kinase receptor (TRK) inhibitor. Lastly, significant false-positive data may be obtained by IHC, and multiple FISH probes are required because of existing NTRK1, NTRK2, and NTRK3 genes. Next-generation sequencing can detect all forms of NTRK fusion at once with high sensitivity; thus, DNA- or RNA-based next-generation sequencing detection might be used as an optional and supplementary method in clinical practice. Two tyrosine kinase (TRK) (neurotrophin receptor protein encoded by the NTRK gene) inhibitors, larotrectinib and entrectinib, have been approved for the treatment of NTRK fusion-positive patients, regardless of tumor type. Thus, the patient in this case might benefit from TRK inhibitor treatment, and our case has expanded the NTRK fusion spectrum to provide useful information for the precise administration of TRK inhibitors in future.

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References

Figure 2. Fluorescence in situ hybridization and immunohistochemistry findings of the primary lung tumor tissue sample. (Right) A split signal was observed with a frequency of 50% in the fluorescence in situ hybridization image. (Left) The immunohistochemistry staining indicated strong neurotrophic receptor tyrosine kinase protein expression.