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LETTER TO THE EDITOR

Different co-mutations in triple EGFR mutated adenocarcinomas in a patient

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Dear Editor,

A 78-year-old woman was referred to our hospital for EGFR-TKI therapy. The patient had two nodules in the left lung and one nodule in the right lung. Biopsy specimens were obtained transbronchially from each of the three lesions of adenocarcinoma respectively.

Afatinib therapy was initiated as first-line therapy, and the response was evaluated as partial response (PR). But due to skin toxicity, afatinib therapy was discontinued. Thereafter, gefitinib was prescribed and the response to this drug also achieved PR and the therapy was continued for 55 months without recurrence of these lesions. During the treatment period, her cognitive condition slowly deteriorated, then she received supportive care.

Compound mutations and the content ratio of tumor cells in the tissue sample and the ratio of allele fraction (RAF) were examined using NOIR-SS (DNA Chip Research Inc. Tokyo, Japan) (1,2). RAF is defined as the number of times a mutated base is observed, divided by the total number of times any base is observed at the locus. DNA was extracted from slices of FFPE tissue block of the patient using a Maxwell® RSC DNA FFPE kit (Promega, Madison, USA). 50 ng of DNAs were fragmented by Covaris focused-ultrasonicator (Woburn, MA, USA) and a molecular barcoded next-generation sequencing library was constructed by the NOIR-SS method as described previously (1,2). The constructed library was

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sequenced using the Ion Chef/Ion S5 platform with Ion 540 chip (Thermo Fisher Scientific, Waltham, MA, USA). One of the tumors in the left upper lobe was adenocarcinoma with the main EGFR mutation Exo 21 L858R and the compound mutation G724S (RAF= 0.91), and the other tumor was adenocarcinoma with the main EGFR mutation Exon 19 deletion and the compound mutation G719D (RAF= 0.20). The tumor in the right upper lobe had a main EGFR mutation of Exon 19 deletion and a compound mutation of Exon 21 L858R (RAF= 0.02). Taking these results into consideration, we concluded that the patient had three synchronous adenocarcinomas of the lung. It was interesting to note that adenocarcinoma in lung cancer of the right lung had Ex21 L858R as a compound mutation.

When encountering lung cancers of the same histological type that is pathologically similar, it is difficult to determine whether it is metastasis or synchronous multiple cancers (3-5). Also, at the time of recurrence, it may be difficult to determine whether the same histological type showing the same morphology as the primary lesion is recurrence or metachronous multiple cancer (3-5). There have been several reports of detailed analysis of the EGFR gene using NGS to distinguish between synchronous lesions, recurrence, or metachronous double cancers (3-5). To the best of our knowledge, however, no research has examined RAF using NGS. In such cases, results of the existence of compound mutations and RAF might provide useful information in patients with EGFR mutations as observed in our patient. From this point of view, the results of this case were considered to be very interesting. These genetic investigations may be useful in differentiating future patients who are difficult to correctly diagnose.

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