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Original Article

Genetic mutations in lung enteric adenocarcinoma identified using next-generation sequencing

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Abstract: Primary lung enteric adenocarcinoma is a rare type of invasive lung carcinoma. Its morphological and immunohistochemical characteristics are similar to those of metastatic colorectal carcinoma, but there is no associated primary colorectal carcinoma. The purpose of this study is to identify mutations by assessing the genetic profile of lung enteric adenocarcinoma with next-generation sequencing (NGS). This study included 11 lung enteric adenocarcinoma patients (5 males and 6 females) from three different centers who received treatment between Feb 2013 and Dec 2016. Immunohistochemical analysis failed to reveal any markers that differentiated this carcinoma from primary gastrointestinal adenocarcinoma. NGS analysis identified *ALK/ROS1* primary point mutations in 5 patients (71.42%, 5/7) and *MSH2/MSH6* point mutations in 3 patients (42.86%, 3/7). There was no case with drive genes changed, such as *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, *RET* rearrangement, *MET* amplification or 14 exon skipping mutation. The median overall survival of the 11 lung enteric adenocarcinoma patients was 9.0 months. Further, subgroup analysis showed that the median OS of patients with *ALK/ROS1* primary point mutations was 6.5 months and that of patients with *MSH2/MSH6* primary point mutations was 26.0 months. These two mutations were the most frequent features, but this carcinoma generally showed genetic heterogeneity. Even though we have revealed some hitherto unidentified genetic mutations associated with lung enteric adenocarcinoma, the findings are preliminary and further investigations on more patients will be required to validate our findings.

Keywords: Lung enteric adenocarcinoma, *ALK*, *ROS1*, *MSH2*, *MSH6*, gene mutation

Introduction

According to the 2015 World Health Organization classification of lung tumors, lung enteric adenocarcinoma is a recognized subtype [1]. Lung enteric adenocarcinoma was first reported in 1991 by Tsao and Fraser [2]. It is described as a rare variant that is predominantly composed of cellular structures that resemble those of intestinal adenocarcinoma. There is also a possibility that it is a tumor that metastasizes from primary gastrointestinal adenocarcinoma [1, 3].

Immunohistochemistry is often used to differentiate between gastrointestinal adenocarcinoma and lung enteric adenocarcinoma: the majority of primary lung adenocarcinomas are positive for cytokeratin (CK7), thyroid transcription factor-1 (TTF-1), and napsin A, whereas among intestinal adenocarcinomas, colorectal tumors are positive for caudal type homeobox 2 (CDX-2), mucin 2 (MUC2) and cytokeratin 20 (CK20) and upper gastrointestinal tract tumors are positive for CDX-2 and CK7. The differentiation of this rare histologic type of lung carcinoma from primary gastrointestinal adenocarcinoma is relevant and has important implications. Indeed, a careful analysis of the clinical history of patients should be conducted to exclude metastatic lesions associated with primary gastrointestinal adenocarcinoma.

Table 1. Clinical profile and outcome of 11 patients with lung enteric adenocarcinoma

Case No.	Gender/Age	Smoking status	Stage	Result of targeted NGS	OS (months)
1	F/61	NO	IV	*MSH2* p.L390F *MSH6* p.E1163V *BRCA2* p.C315S	17.0+
2	F/53	NO	IV	Failed	17.0
3	F/48	NO	IV	Failed	9.0
4	M/59	YES	IV	Failed	6.0
5	M/65	YES	IV	*ALK* p.G1326A *BRAF* p.A308T	6.0
6	M/78	YES	IV	*TP53* p.G245C *MSH2* p.Q629R *MSH6* p.E1254D *FBXW7* p.R484Lfs*15 *ROS1* p.S615Y+p.K413Y	6.0
7	F/25	NO	IIIB	*TP53* p.R248Q *NRAS* p.Q61R *ROS1* p.W133R	22.0
8	M/65	YES	IV	*MSH2* p.I766V+A2V *MSH6* p.Y642C *PIK3CA* p.E545A	26.0
9	M/56	YES	IV	*TP53* p.H193R *ALK* p.G1474E	4.0
10	M/64	NO	IV	*TP53* p.V173L *ROS1* p.E268K	7.0
11	M/72	YES	IV	Failed	14.0

Table 2. Expression of immunohistochemical markers in the 11 cases of patients with lung enteric adenocarcinoma

Case No.	CK7	TTF-1	Napsin A	CDX2	CK20	Villin
1	(-)	(-)	ND	(+)	(-)	(+)
2	(-)	(-)	(-)	(+)	(+)	(+)
3	(+)	(-)	ND	ND	(+)	(+)
4	(-)	(+)	(-)	(+)	(+)	ND
5	ND	(-)	(-)	(+)	ND	(+)
6	(-)	(-)	(+)	(+)	(+)	(+)
7	(-)	(-)	ND	(+)	(+)	(+)
8	(+)	(-)	ND	(+)	(-)	(-)
9	(-)	(-)	ND	(+)	(+)	(+)
10	(+)	(+)	ND	(-)	(-)	(-)
11	(-)	(+)	(-)	(+)	(+)	(+)

ND: not done.

Currently, advanced non-small cell lung cancer (NSCLC) is managed using targeted treatment based on genetic mutations that are present in patients. The most common mutation in lung adenocarcinoma is found in the gene that encodes for the epidermal growth factor receptor (*EGFR*), and this mutation is found in 60% of Asian patients [4]. In addition, anaplastic lymphoma kinase (*ALK*) gene rearrangements are found in 2-7% of patients [5]. Wang *et al.* [6] analyzed the *EGFR* gene mutation status in 24 cases of small intestinal adenocarcinoma (SIA) by DNA sequencing, and the results revealed that only two patients had EGFR mutations. Moreover, their results indicated that the *EGFR* mutations in the two cases were minor, and therefore, most patients with SIA may be unsuitable for treatment with the EGFR tyrosine kinase inhibitor (TKI). In addition, another research [7] reported 9 cases of lung enteric adenocarcinoma in which all the tumors expressed wild-type *EGFR* and *KRAS* genes. These findings indicate that the phenotype and gene mutations of lung enteric adenocarcinoma are distinct from those of other pulmonary adenocarcinomas. Therefore, the gene mutations associated with lung enteric adenocarcinoma require deeper investigation.

Next-generation sequencing (NGS) is regarded as a sequencing method that allows for the generation of simultaneous reads of a considerable number of DNA sequences in a parallel way [8, 9]. The National Comprehensive Cancer Network guidelines recommend the use of methodologies that can detect multiple molecular alterations simultaneously, as these may hold great promise for clinical testing in the future. NGS, being one such method, may be able to provide us with a better understanding of lung cancer pathogenesis at the genetic level. Thus, NGS-based detection could be used to discover novel molecular alterations in NSCLC.

We performed this study to analyze the pathogenesis and survival of 11 lung enteric adenocarcinoma cases and investigate gene mutations by NGS. To the best of our knowledge, no previous study has applied NGS in the analysis of lung enteric adenocarcinoma patients.

Patients and methods

Patient eligibility

Eleven lung enteric adenocarcinoma patients, who received treatment at three medical cen-

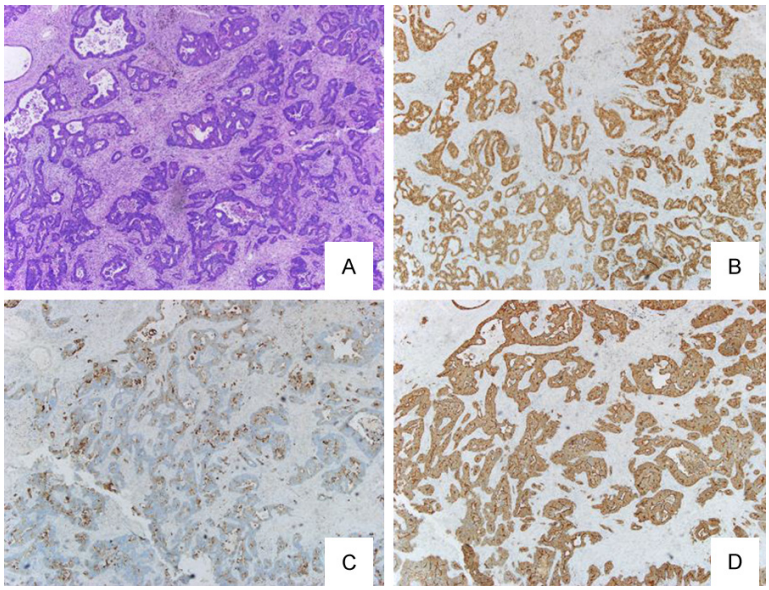

Figure 1. Hematoxylin and eosin staining and immunohistochemical analysis of CDX2, CK20 and villin. A. Histological examination showed a moderately differentiated adenocarcinoma that infiltrated fibrous connective tissue (magnification, × 400); B-D. Immunohistochemical staining for CDX2, CK20 and villin in neoplastic cells, observed using anti-CDX2, anti-CK20, and anti-villin antibodies with slight hematoxylin counterstaining (magnification, × 400). CDX2, caudal-type homeobox transcription factor 2; CK, cytokeratin.

ters (in Beijing, Zhejiang and Fujian) between Feb 2013 and Dec 2016, were included in this study. Histological typing of the tumors was conducted according to the 2015 WHO histological classification scheme. Staging was performed according to the seventh TNM classification. The study protocol was approved by our institutional ethics committee, and all the patients provided their written informed consent for biomarker analysis.

Targeted NGS

Targeted region capture and NGS of the 11 tumor specimens was performed. Genomic DNA sequencing libraries were prepared using the protocols recommended by the Illumina TruSeq DNA Library Preparation Kit. For samples that did not meet the minimum input requirement, additional pre-capture PCR cycles were performed to generate sufficient PCR products for hybridization. The libraries that were generated were hybridized with custom-designed probes (Integrated DNA Technology), including all exons of 170 genes and select introns of *ALK*, *RET* and *ROS1*, for the detection of genomic rearrangements. DNA sequencing was performed on a HiSeq3000 sequencing system (Illumina, San Diego, CA) with 2 × 75-bp paired-end reads. The reads were aligned to the human genome build GRCh37 using a Burrows-Wheeler aligner. Somatic single nucleotide variants and indel calls were generated using MuTect and GATK, respectively. Somatic copy number alterations were identified with CONTRA. Genomic rearrangements were identified by the software developed in house for analyzing chimeric read pairs.

Follow-up examinations

Follow-up examinations were conducted every 3-6 months after treatment, and the last follow-up was on December 31, 2016.

Statistical analysis

Categorical variables were compared using the X^2 test. The Kaplan-Meier method was employed for survival analysis, and the log-rank test was used for comparison between different groups.

Overall survival (OS) was defined as the period from confirmed diagnosis of advanced stage disease to the date of death or the last follow-up. $P < 0.05$ was considered to indicate statistical significance. Analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 11 patients with histologically confirmed lung enteric adenocarcinoma were recruited from three medical centers. The clinical characteristics and immunohistochemical findings of all the patients are shown in **Tables 1** and **2**, respectively. The age of the patients ranged from 25 to 78 years, and 54.55% (6/11) of the patients were older than 60 years. The majority of the patients with lung enteric adenocarcinoma were male (63.64%) and had a his-

tory of smoking (54.55%). The percentage of patients with lung enteric adenocarcinoma stage IIB was 18.18%; stage IIIB, 9.09%; and stage IV, 72.72%. Immunohistochemical analysis for the markers CK7, TTF-1, Napsin A, CDX2, CK20 and Villin showed that they were expressed in 3 out of 10 (30.00%), 3 out of 11 (27.27%), 1 out of 5 (20.00%), 9 out of 10 (90.00%), 3 out of 10 (30.00%) and 8 out of 10 (80.00%) cases, respectively (**Figure 1**).

Molecular analysis

Targeted NGS of 7 cases showed that *ALK/ROS1* primary point mutations were present in 5 cases (71.42%) and *MSH2/MSH6* point mutations were present in 3 cases (42.86%). The mutation was detected at *BRCA2* p.C315S in case 1, *BRAF* p.A308T in case 5, *FBXW7* p.R484Lfs*15 in case 6, *NRAS* p.Q61R in case 7, *PIK3CA* p.E545A in case 8 and *TP53* in case 6 (p.G245C), 7 (p.R248Q), 9 (H193R) and 10 (V173L) (**Figure 2**).

Treatment and survival

Complete resection via lobectomy and postoperative chemotherapy were performed in case 9 and 10. Similar treatment was administered in the remaining cases, except for case 1, in which icotinib (a first-generation EGFR TKI) was administered for more than 1.5 months and nivolumab (immunotherapy drug) was administered for 9.5 months. The median OS of the 11 lung enteric adenocarcinoma patients was 9 months. Further, subgroup analysis showed that the median OS of patients with the *ALK/ROS1* primary point mutation was 6.5 months, and that the median OS of patients with the *MSH2/MSH6* point mutation was 26 months (**Figure 3**).

Discussion

It has recently emerged that lung enteric adenocarcinoma is a rare subtype of lung adenocarcinoma. The focus of research on this tumor is mainly the differential diagnosis of pulmonary metastases from primary colorectal adenocarcinoma, as some of the morphological characteristics of lung enteric adenocarcinoma resemble those of colorectal adenocarcinoma. However, the treatment strategy and prognosis of these two entities are different. An increasing number of gene mutations associated with lung cancer are being discovered, and drugs that target these mutations have also been developed. Research has also shown that the genetic basis of lung enteric adenocarcinoma may differ from that of other lung adenocarcinomas. Therefore, in the present study, we conducted immunohistochemical and NGS analysis of lung enteric adenocarcinoma and examined the prognosis of this cancer.

Lung enteric adenocarcinoma is described as a metastasis of a gastrointestinal tumor in which the enteric component exceeds 50% and there is no evidence of the primary cancer. The immunohistochemical characteristics of primary lung enteric adenocarcinoma and metastatic colorectal cancer are similar. Moreover, lung enteric adenocarcinoma is typically positive for at least one immunohistochemical marker of enteric differentiation. Generally, the majority of primary lung adenocarcinomas are positive for thyroid transcription factor-1 (TTF-1), CK7 and napsin A, but primary intestinal adenocarcinomas are positive for CDX-2 and CK20 (colorectal tumors) or CDX-2 and CK7 (upper gastrointestinal tract tumors) [10, 11]. Nottegar *et al.* [12] analyzed 46 lung enteric adenocarcinoma samples, and the results showed that all the samples were positive for CDX-2, 15 samples (32.6%) were positive for CK20, and 35 samples (76.1%) were positive for villin. Wang *et al.* [13] also explored 9 cases of lung enteric adenocarcinoma in which positive staining for CK7 was observed in 100% of the cases; CK20, 22.2% (2/9); TTF-1, 44.4% (4/9); napsin A, 33.3% (3/9); CDX2, 66.7% (6/9); MUC2, 44.4% (4/9); and villin, 66.7% (6/9). In our study, immunohistochemical analysis showed that CK7 was expressed in 30% of the samples (3/10); TTF-1, in 27.27% (3/11); napsin A, in 20% (1/5); CDX-2, in 90% (9/10); CK20, in 30% (3/10); and villin, in 80% (8/10). Thus, these reports indicate that lung enteric adenocarcinoma has a heterogeneous expression profile and expresses markers of both primary lung adenocarcinoma and intestinal markers. A majority of lung enteric adenocarcinoma cases were positive for CDX-2, which is a transcription factor of the homeobox gene family that is critical for intestinal development [14]. Further, a study compared the expression profiles of lung enteric adenocarcinoma, metastatic colorectal adenocarcinoma, and primary lung adenocarcinoma and reported that CDX-2 was expressed in 71% of enteric lung adenocarcinomas, 100% of metastatic colorectal adenocarcinomas, and

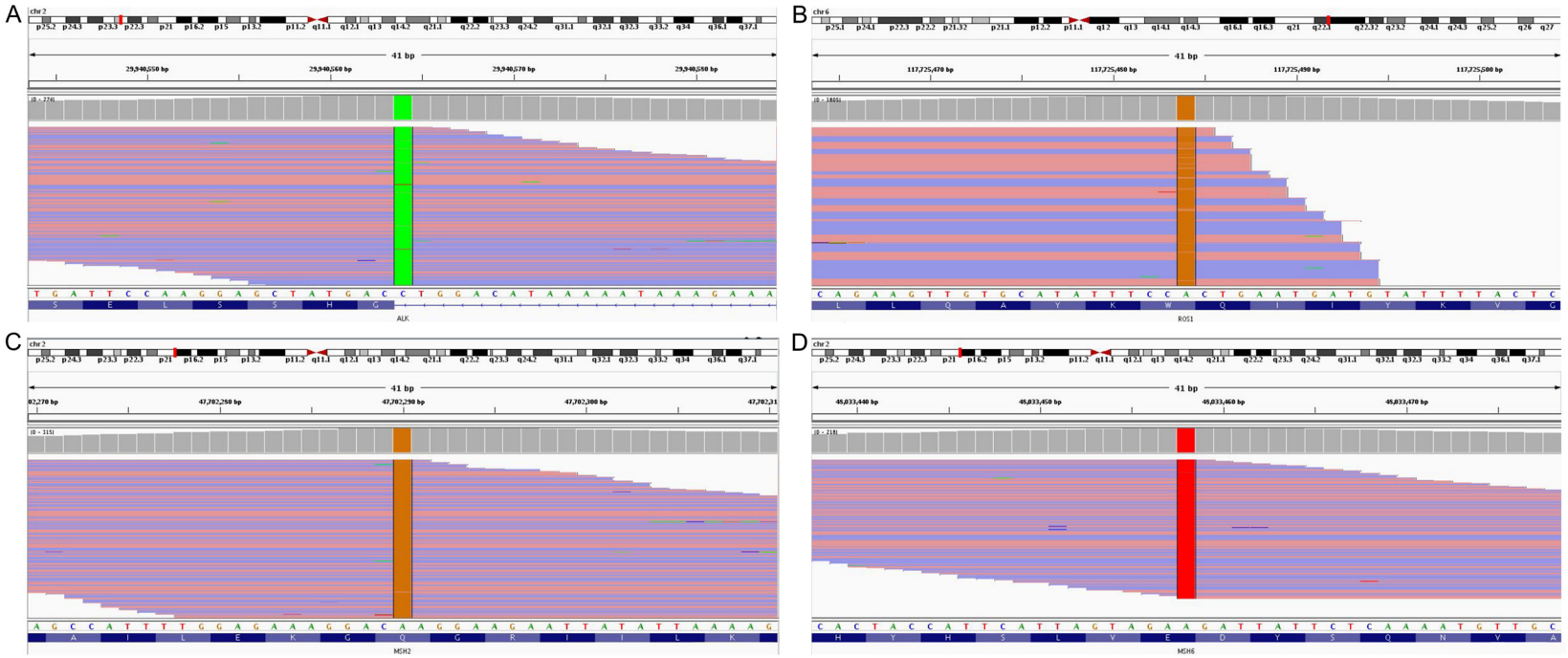

Figure 2. Targeted next-generation sequencing of point mutations. A. *ALK* p.G1474E; B. *ROS1* p.W133R; C. *MSH2* p.Q629R; D. *MSH6* p.E1254D.

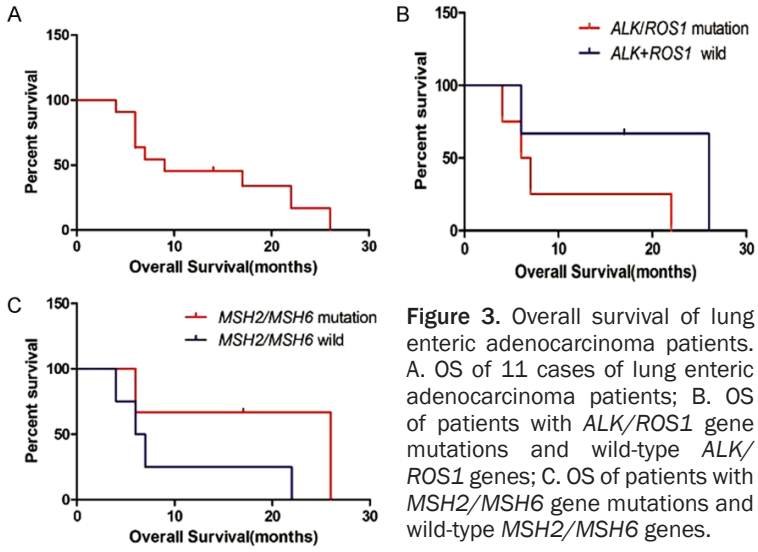

Figure 3. Overall survival of lung enteric adenocarcinoma patients. A. OS of 11 cases of lung enteric adenocarcinoma patients; B. OS of patients with *ALK/ROS1* gene mutations and wild-type *ALK/ROS1* genes; C. OS of patients with *MSH2/MSH6* gene mutations and wild-type *MSH2/MSH6* genes.

3% (1/30) of primary lung adenocarcinomas [15]. Moreover, our research showed that villin was expressed in many cases. Villin is a component of the brush border membrane that is found lining the intestine, so this finding [16]. Therefore, all these findings imply that it is difficult to identify specific immunohistochemical markers for distinguishing lung enteric adenocarcinoma from primary colorectal adenocarcinoma, and that differential diagnosis of these two entities should be based on the clinical manifestations and pathological features of the tumors.

Wang *et al.* [17] evaluated mutations of the *EGFR* and *KRAS* genes in 9 lung enteric adenocarcinoma cases and found that all the samples were positive for wild-type *EGFR* and *KRAS*. In contrast, László *et al.* [18] demonstrated a *KRAS* mutation in one case of lung enteric adenocarcinoma, and Stojsic *et al.* [19] reported two cases of lung enteric adenocarcinoma in which one patient had *KRAS* mutations. Further, Nottegar *et al.* [12] found that lung enteric adenocarcinoma had a high frequency of *KRAS* mutations (60.9%) and a low frequency of *EGFR* gene mutations (2.2%) in a series of 46 lung enteric adenocarcinoma cases. In our study, we utilized NGS to explore gene mutations in 7 cases of lung enteric adenocarcinoma. All 7 patient had wild-type *KRAS*, while one patient had an *NRAS* mutation. *NRAS* is a rare mutation in NSCLC that is found in 1% of patients with this cancer, and *NRAS* mutations might indicate sensitivity to treatment with MEK inhibitors [20]. Our report was the first to report mutations of the *MSH2/MSH6* gene in three patients, who had a median OS of 26.0 months; the survival of these patients was better than that of patients who had wild-type *MSH2/MSH6*. We also found *ALK* gene mutations in 2 patients (28.6%) and *ROS1* mutations in 3 patients (42.9%); the prognosis of patients with the *ALK/ROS1* gene mutation (6.5 months) was worse than that of patients with the corresponding wild-type genes. Nottegar *et al.* [12] found that the incidence of *EML4-ALK* translocation was 13.0% (6/46) in patients with none of the cases reported previously had *BRAF* mutations. However, in our sample, we found one patient with a *BRAF* gene mutation. Moreover, all 7 patients had two or more than two gene mutations, which demonstrates the genetic heterogeneity of lung enteric adenocarcinoma. Since this was a retrospective study, we were not able to deliver personalized treatment to these patients based on our findings. Another limitation was our small sample size. In the future, we hope to focus on the detection of more gene mutations in a larger patient population and the development of personalized alternative treatment approaches for lung enteric adenocarcinoma patients.

We do acknowledge, again, the limitations of our study, which are the small sample size and its retrospective nature.

In conclusion, we have described the immunophenotypic and genetic characteristics of lung enteric adenocarcinoma. *ALK/ROS1 and MSH2/MSH6* mutations were found to be frequent in our study sample, but no significant immunohistochemical markers for differential diagnosis of this carcinoma could be identified. Thus, both the immunohistochemical and genetic profile of patients should be considered for distinguishing this subgroup of lung adenocarcinomas. NGS opens new avenues for understanding the development of this type of tumor and identifying potential target genes for personalized therapy.

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Disclosure of conflict of interest

None.

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