BRIEF REPORT

Clinicopathological Characteristics of *RET* Rearranged Lung Cancer in European Patients

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ABSTRACT

Introduction: Rearrangements of *RET* are rare oncogenic events in patients with non–small cell lung cancer (NSCLC). While the characterization of Asian patients suggests a predominance of nonsmokers of young age in this genetically defined lung cancer subgroup, little is known about the characteristics of non-Asian patients. We present the results of an analysis of a European cohort of patients with *RET* rearranged NSCLC.

Methods: Nine hundred ninety-seven patients with *KRAS/EGFR/ALK* wildtype lung adenocarcinomas were analyzed using fluorescence in situ hybridization for *RET* fusions. Tumor specimens were molecularly profiled and clinicopathological characteristics of the patients were collected.

Results: Rearrangements of *RET* were identified in 22 patients, with a prevalence of 2.2% in the *KRAS/EGFR/ALK* wildtype subgroup. Co-occurring genetic aberrations were detected in 10 patients, and the majority had mutations in *TP53*. The median age at diagnosis was 62 years (range, 39–80 years; mean ± SD, 61 ± 11.7 years) with a higher proportion of men (59% versus 41%). There was only a slight predominance of nonsmokers (54.5%) compared to current or former smokers (45.5%).

Conclusions: Patients with *RET* rearranged adenocarcinomas represent a rare and heterogeneous NSCLC subgroup. In some contrast to published data, we see a high prevalence of current and former smokers in our white *RET* cohort. The significance of co-occurring aberrations, so far, is unclear.

Keywords: Adenocarcinoma; Clinicopathological characteristics; NSCLC; *RET* rearrangement; Smoking history; TP53

Introduction

Despite advanced treatment options, non–small cell lung cancer (NSCLC) is still the leading cause of cancer-related death in the Western world. In recent years, a growing number of therapeutically amenable genetic alterations have been identified, notably in patients with lung adenocarcinomas (LADs). In particular, chromosomal rearrangements involving the anaplastic lymphoma kinase gene (*ALK*), c-ros oncogene 1 (*ROS1*), the rearranged during transfection gene (*RET*), and most recently the neuregulin 1 gene (*NRG1*) have been described as rare oncogenic events in young adults with either a history of no smoking or light smoking.[1–4]

Fusions of *RET* have long been known to have oncogenic potential in patients with papillary thyroid carcinomas.[5] *RET* rearrangements were identified in 1% of Asian patients with LAD and mostly involve *KIF5B* or *CCDC6*.[1–3] Activation of the fusion protein results in the recruitment of oncogenic signalling cascades, such as the phosphatidylinositol 3-kinase (PI3K)/AKT and RAS/mitogen-activated protein kinase pathways (MAP/K).[6]

Successful targeted treatment of patients with *RET* rearranged adenocarcinoma was published in preclinical studies, case reports, and as preliminary data from a phase II trial with cabozantinib (NCT01639508).[7–9]

Understanding the clinicopathological characteristics of patients with rare genetic driver aberrations is essential to reliably identify patients who might benefit from targeted therapies in a routine diagnostic setting. In this retrospective study, we present the characteristics of a European cohort of 22 patients with *RET* fused LADs.

Methods

Patients and samples

This study was performed within the Network Genomic Medicine (NGM), a collaborative health care provider network for the molecular characterization and personalized treatment of lung cancer (network center: University Hospital Cologne, Germany), in collaboration with the Lucerne Cantonal Hospital (Lucerne, Switzerland), the University Hospital Innsbruck (Innsbruck, Austria), and the University Hospital Basel (Basel, Switzerland). Lung adenocarcinomas and adenosquamous carcinomas with wildtype sequences in *KRAS*, *ALK*, and the sites of common *EGFR* mutations ($EGFR^{del19}$ *and* $EGFR^{L858R}$) were tested for *RET* rearrangements

using fluorescence in situ hybridization (FISH). There was no preselection regarding smoking history, age, stage, or sex of the patients. Screening procedures were conducted in accordance with the local ethical guidelines.

RET FISH assay

For FISH, 2-μm tissue sections were hybridized with ZytoLight SPEC *RET* Dual Color Break Apart Probes (ZytoVision, Bremerhaven, Germany). The 3′ *RET* probe encompasses the kinase domain (i.e., 3′ probe ZyGreen and 5′ probe ZyOrange labeling). Per case, 100 carcinoma cells were evaluated. *RET* rearrangement criteria for positivity: $\geq$20% (rearrangement fraction; University Hospitals Cologne and Innsbruck) or $\geq$15% (Lucerne Cantonal Hospital and University Hospital Basel) of cells with aberrant patterns of either a break-apart of one or both fusion signals into separated green and red signals or of isolated green signals in addition to fusion signals.

Detection of co-occurring aberrations

Targeted massively parallel sequencing (MPS) was performed at the University Hospital of Cologne on all samples from NGM and the University Hospital of Innsbruck (N = 18) on a MiSeq benchtop sequencer as described previously (Illumina, San Diego, CA).[10] The panel comprises 102 amplicons of 14 proto-oncogenes and tumor suppressor genes, including *EGFR* exons 18 to 21, *KRAS* (exons 2–3), *TP53* (exons 5–8), and *BRAF* (exons 11–15).

Sanger sequencing was performed at the Cantonal Hospital of Lucerne and the University Hospital of Basel for mutations in *KRAS* (exons 2–3), *EGFR* (exons 18–21), *HER2* (exons 21–22), and *BRAF* (exons 11 and 15) on an ABI Prism 3130 Genetic Analyzer (Applied Biosystems, Waltham, MA). FISH was used for identification of rearrangements of *ALK/ROS1* and amplifications of *MET*. Database references included the International Agency for Research on Cancer *TP53* Database (available at http://p53.iarc.fr/TP53GeneVariations.aspx), the Catalogue of Somatic Mutations in Cancer (available at http://cancer.sanger.ac.uk/cosmic), and the p53 Knowledgebase (available at http://p53.bii.a-star.edu.sg/index.php).

Clinical characteristics

The clinical characteristics included age, sex, tumor stage at diagnosis according to the Union for International Cancer Control classification, smoking status, and history of previous cancer therapies. Smoking status was classified according to the 2008 US Centers for Disease Control and Prevention criteria.[11]

Statistics

Qualitative variables were summarized by count and percentage, quantitative variables by mean, standard deviation (SD), median, and range. Distribution of time-to-event, such as overall survival (OS) and follow-up period, were described by the Kaplan–Meier estimator. The overall prevalence of *RET* rearranged adenocarcinomas refers to the prevalence in samples routinely analyzed within NGM (August 2013 to February 2015; N = 2616).

Results

Molecular characteristics

Tissue from 997 patients with *KRAS*-, *EGFR*-, and *ALK*-negative tumors were screened by *RET* FISH (Fig. 1).

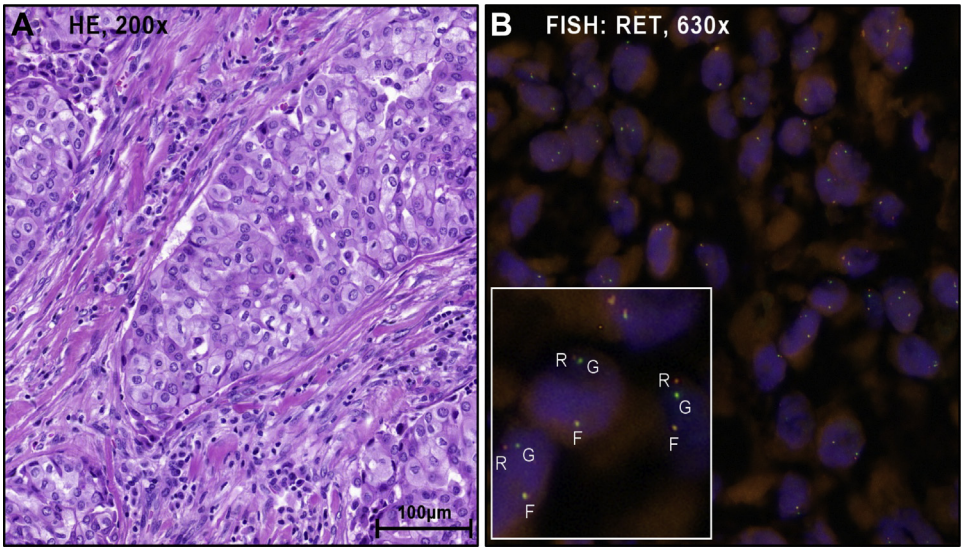

Figure 1. (*A*) Hematoxylin-eosin-stained micrograph of a lung adenocarcinoma with *RET* rearrangement. (*B*) Image of merged signals of a dual color, break apart fluorescent in situ hybridization analysis of a lung adenocarcinoma revealing *RET* rearrangement by separation of green and red signals (ZytoVision, Bremerhaven, Germany).

Table 1. Clinical and molecular characteristics of patients with *RET* rearranged non-small cell lung cancer (N = 22)

Patient ID	Sex	Age at diagnosis (y)	Initial stage (UICC)	Fraction of *RET* rearranged cells (%)	Additional genetic aberrations	Smoking history	Pack years	No. of systemic treatments	Follow-up/ survival (months)
01[a]	F	53	I	34	None	FS	20	0	13
02[a]	M	66	III	87	None	NS	0	2	47
03[a]	F	56	III	100	*CTNNB* p.S33Y	FS	5	2	100
04[a]	M	47	IV	22	*TP53* p.V157F	S	40	2[b]	13
05[a]	F	48	IV	23	*TP53* p.V157F	FS	24	3	17
06[a]	M	80	IV	25	None	NS	0	1	10
07[a]	M	77	IV	27	None	NS	0	2	8[c]
08[a]	M	75	IV	87	None	FS	90	1	18
09[a]	M	49	III	21	*TP53* p.R273H	S	40	1	7[c]
10[a]	F	39	IV	37	*TP53* p.R181H	NS	0	1	2[c]
11[a]	M	76	II	31	*MET* low-level amplification	NS	0	0	5
12[a]	F	51	III	27	*TP53* p.G245C and *EGFR* p.L833F	FS	25	3	17
13[a]	M	57	IV	29	*TP53* p.G244C	NS	0	2[b]	10
14[a]	M	61	III	34	None	S	43	2	8
15	M	62	II	87	None	NS	0	5[b]	62[c]
16	M	63	IV	47	None	FS	5	4[b]	36[c]
17	F	53	II	65	None	NS	0	0	24
18[a]	F	69	II	49	None	NS	0	2[b]	56
19[a]	M	72	IV	77	*TP53* p.S215N	NS	0	5[b]	34[c]
20	M	43	III	40	None	NS	0	2	16
21[a]	F	74	IV	28	None	NS	0	1	3
22[a]	F	67	IV	77	TP53 p.I254fs*10	FS	45	2	8

[a]Massively parallel sequencing performed.
[b]Has received RET targeted therapy.
[c]Died.
F, female; FS, former smoker; M, male; NS, nonsmoker; S, smoker; UICC, Union for International Cancer Control.

Within this subgroup, we identified 22 patients with *RET* rearranged carcinomas (2.2%). The overall prevalence of *RET* rearrangements within the MPS subgroup was 0.7%.

Co-occurring genetic aberrations were detected in 10 of 22 patients (45.5%; Table 1; Supplemental Fig. 1, Supplemental Table 1). Eight patients had mutations in *TP53* (44.4%), of which seven were inactivating *TP53* alterations. Of those, four were transversions (G > T). In addition, we found a low level *MET* amplification and a gain of function mutation in *CTNNB1* (*CTNNB1*^{S33Y}) in one patient each.[12] Another patient's tumor was found to harbor a rare mutation in exon 21 of *EGFR* (*EGFR*^{L833F}).

In our study, the slightly different definition of RET positivity between the Swiss and German centers with selection of either 15% or 20% as a threshold for RET rearrangement had no influence on the overall results, because in all of the Swiss cases >20% of tumor cells had rearrangement signals.

Clinical characteristics

The median age at first diagnosis was 62 years (range, 39–80 years; mean ± SD, 61 ± 11.7 years), the proportion of male sex was 59% (N = 13) and of female sex 41% (N = 9; Table 2). Analysis of smoking status revealed a slightly lower prevalence of history of tobacco use (N = 10; 45.5%) than of never smoking (N = 12; 54.5%). Median quantity of pack-years within the current and ever smoking group was 32.5 (range, 5–90 pack-years; mean ± SD, 33.7 ± 23.38 pack-years). We have observed a higher proportion of inactivating *TP53* mutations in patients with a history of smoking (N = 5; 50%) than in patients with no smoking history (N = 2; 16.7%; Fisher's exact test: $p = 0.172$ [data not shown]). The distribution of stage at the time of initial diagnosis was 23% (n = 5) for stage I and II and 77% (n = 17) for stage III and IV. Of the 11 stage IV patients, only two initially suffered from distant metastases in more than one anatomical region (i.e., the contralateral lung, brain, adrenal glands, liver, or bone). All other patients had single organ/tissue metastases, and only four patients had extrathoracic metastatic lesions (36%; Table 2).

Nineteen patients had received at least one line of systemic antineoplastic treatment (86.4%). The median OS for patients with stage IV disease was 34 months (SD, 18.8 months; mean ± SD, 29.3 ± 4.3 months; Supplemental Fig. 2). The median OS for all stages' patients was not met during the median follow-up period

Table 2. Clinical characteristics of patients with *RET* rearranged non-small cell lung cancer (N = 22)

Characteristics	No.	%
Age at first diagnosis (y)	22	100
Mean ± SD	61 ± 11.7	
Median (range)	62 (39-80)	
Sex		
Female	9	41
Male	13	59
Smoking history		
Never	12	54.6
Former	7	31.8
Current	3	13.6
UICC stage		
I	1	5
II	4	18
III	6	27
IV	11	50
Location of metastases (stage IV)	11	50
Lung	2	18
Pleura	5	45
Bone	2	18
CNS	2	18
Adrenal gland	3	27
Liver	2	18

CNS, central nervous system; SD, standard deviation; UICC, Union for International Cancer Control.

of 17 months (SD, 3.3; mean ± SD, 31.9 ± 7.2 months [data not shown]).

Discussion

To our knowledge, this is the largest study published so far analyzing rearrangements of *RET* in white patients with LADs. Cohorts of similar size have been described in Asian patient populations.[1–3] In line with the prevalence described in these studies, we have detected *RET* rearrangements in 0.7% of patients with adenocarcinomas. Likewise, no significant difference was seen in the age distribution between Asian and white cohorts (median, 62 years and 57.5 years versus 62 years, respectively).[2,3]

In contrast to the findings in Asian patients, the frequency of history of tobacco use was substantially higher in our *RET* cohort (45.5% versus 18.2–31.8%).[1–3] These findings question the practice of preselecting patients for *RET* FISH analysis based on smoking history. Supporting our results, single cases of white patients with *RET* rearrangements and smoking history have been reported.[8]

Of the 11 stage IV patients, only four had extrathoracic organ metastases. This pattern resembles that found in patients with *KRAS*-mutated NSCLC and seems to be different, for instance, from that seen in patients with *ALK*-fused NSCLC.[13]

The median overall survival in the stage IV subgroup was 34 months (SD, 18.8 months; mean ± SD, 29.2 ± 4.3 months; Supplemental Fig. 1). Retrospective analyses of genetically unselected patients found a median OS of approximately 18 months in patients who were inoperable.[14] However, because of the small number of patients in our analysis, the impact of *RET* rearrangements on the prognosis needs to be interpreted with care.

Six of the patients described herein have received RET-targeted therapy (Table 1). For one of these patients, a partial response under treatment with vandetanib has been published.[8] Two of these patients were treated in the Cologne center with cabozantinib without a clinical response. Two additional patients received more than one putative RET inhibitor, but there is only fragmentary information on clinical efficacy. All other patients were treated with chemotherapy only. More patients receiving RET inhibitor therapy are necessary to draw any conclusions on the impact of such a targeted therapy on the survival of these patients.

We found a high frequency of co-occurring genetic aberrations in our *RET* cohort (N = 10; 45.5%). Missense and nonsense mutations in *TP53* leading to inactivation of the protein were by far the most frequent events in the samples analyzed by MPS (N = 18; Table 2). Interestingly, within the group of patients with smoking history, mutations in *TP53* were more frequent than in patients with no history of smoking. However, because of the small patient numbers, this effect was statistically nonsignificant. Recently, a transcriptome meta-analysis of 753 NSCLC specimens revealed a greater average number of fusions in tumors with missense or nonsense mutations in *TP53* as compared to tumors with wildtype *TP53*.[15] These findings suggest an essential role of *TP53* alterations in *RET*-driven carcinogenesis of lung cancer. In addition, we detected a low-level amplification of *MET* in one patient. Whether low-level amplifications of *MET* are targetable oncogenic aberrations, however, is questionable. The same counts for the rare missense mutation of exon 21 of the *EGFR* gene ($EGFR^{L833F}$) detected in a 51-year-old woman with a history of smoking. For the gain of function mutation in the beta-catenin gene ($CTNNB1^{S33Y}$), a transforming potential has been discussed in T-cell malignancies.[12] In this context, it also has to be noted that according to the diagnostic algorithm that we used to select patients for *RET* FISH analyses, *RET* rearrangement status of patients with activating *KRAS* or common *EGFR* mutation is unknown. Overall, our observations do not argue for a mutually exclusive occurrence of *RET* rearrangements and suggest routine testing for other mutations besides *RET* in these patients.

In summary, our data also show that white patients with *RET* rearranged NSCLC represent a heterogeneous subgroup with regard to smoking history and co-occurring mutations. Screening for *RET* rearrangements should not exclude patients with a history of tobacco use.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.09.016.

References

1. Wang R, Hu H, Pan Y, et al. *RET* fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. *J Clin Oncol*. 2012;30:4352–4359.
2. Takeuchi K, Soda M, Togashi Y, et al. *RET*, *ROS1* and *ALK* fusions in lung cancer. *Nat Med*. 2012;18:378–381.
3. Tsuta K, Kohno T, Yoshida A, et al. *RET*-rearranged non-small cell lung carcinoma: a clinicopathological and molecular analysis. *Br J Cancer*. 2014;110:1571–1578.
4. Fernandez-Cuesta L, Plenker D, Osada H, et al. CD74-NRG1 fusions in lung adenocarcinoma. *Cancer Discov*. 2014;4:415–422.
5. Grieco M, Santoro M, Berlingieri MT, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. *Cell*. 1990;60:557–563.
6. Plaza-Menacho I, Mologni L, McDonald NQ. Mechanisms of *RET* signalling in cancer: current and future implications for targeted therapy. *Cell Signal*. 2014;26:1743–1752.
7. Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov*. 2013;3:630–635.
8. Gautschi O, Zander T, Keller FA. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. *J Thorac Oncol*. 2013;8:e44–e45.
9. Kodama T, Toshiyuki T, Satoh Y, et al. Alectinib shows potent antitumor activity against *RET*-rearranged non-small cell lung cancer. *Mol Cancer Ther*. 2014;13:5036–5941.
10. König K, Pfeifer M, Fassunke J, et al. Implementation of amplicon parallel sequencing leads to improvement of diagnosis and therapy of lung cancer patients. *J Thorac Oncol*. 2015;10:1049–1057.
11. Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2008. *Morb Mortal Wkly Rep*. 2009;58:1232–1235.
12. Groen RW, Oud ME, Schilder-Tol EJ, et al. Illegitimate WNT pathway activation by beta-catenin mutation or autokrine stimulation in T-cell malignancies. *Cancer Res*. 2008;68:6969–6977.
13. Doebele RC, Lu X, Sumey C, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer*. 2012;118:4502–4511.
14. Clinical Lung Cancer Genome Project (CLCGP), Network Genomic Medicine (NGM). A genomics-based classificaton of human lung tumors. *Sci Transl Med*. 2013;5:209ra153.
15. Dhanasekaran SM, Balbin O, Chen G, et al. Transcriptome meta-analysis of lung cancer reveals recurrent aberrations in NRG1 and Hippo pathway genes. *Nat Commun*. 2014;5:5893.