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Are there imaging characteristics associated with lung adenocarcinomas harboring ALK rearrangements?

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Abstract

Introduction—5% of lung adenocarcinomas harbor rearrangements of the anaplastic lymphoma kinase (ALK) gene. This study compared computed tomography (CT) imaging features in patients with ALK rearrangements and those with EGFR mutations.

Material/methods—30 patients with ALK rearrangements were studied. 97 patients with epidermal growth factor receptor (EGFR) mutations were used as controls. Features assessed included size and location of thoracic lymphadenopathy, and the size, contour, consistency and location of the primary tumor.

Results—127 lung adenocarcinomas were examined. 30 (24%) tumors harbored ALK rearrangements, 97 (76%) tumors harbored EGFR mutations. ALK tumors had larger thoracic lymphadenopathy than the control group ($p = 0.005$). Both readers identified 17 (57%) patients in the ALK group with lymph nodes >1.5 cm. Reader 1 identified 19 (20%) patients in the EGFR group with lymph nodes >1.5 cm, and reader 2 identified 18 (19%) (kappa 0.969). Patients with ALK rearrangements were more likely to have multi-focal lymphadenopathy. Reader 1 identified 22 (73%) ALK patients versus 35 (36%) EGFR patients with multifocal thoracic nodal enlargement, while reader 2 identified 20 (67%) ALK patients versus 30 (31%) EGFR patients (kappa 0.953). 92% of ALK positive lesions were solid.

Conclusion—ALK positive lung adenocarcinomas are more likely than EGFR mutant lung adenocarcinomas to be associated with larger volume, multifocal thoracic lymphadenopathy. While routine testing for ALK should be standard, the presence of such characteristics in a solid tumor should further prompt testing for ALK rearrangement.

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Keywords

Lung adenocarcinoma; Computed tomography; Anaplastic lymphoma kinase; Radiology; Radiogenomics; Mutation

1. Introduction

Lung cancer accounts for 13% of new cancer diagnoses world-wide and is the leading cause of cancer related deaths [1]. In the past decade several subtypes of lung carcinoma, harboring specific mutations, have been identified [most notably epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS) and anaplastic lymphoma kinase (ALK) mutations]. Conventional chemotherapy for lung cancer has relied on the use of non-targeted cytotoxic agents, however the identification of genetically distinct lung tumor subtypes has allowed the development of therapies specifically targeting the mutated pathway [2].

In 2007 a clinically distinct subgroup of patients with lung adenocarcinoma were identified, whose tumors were found to harbor ALK gene rearrangements [3]. These patients account for between 2 and 7% of all patients with non-small cell lung cancer [2,4,5]. They tend to be younger than patients with non-ALK rearranged tumors, and either light or never-smokers [6]. Among light or never smokers with lung cancer, the prevalence of ALK rearrangements ranges from 8 to 22% [6,7]. Crizotinib, approved by the FDA in August 2011 for the treatment of lung cancer, is a selective inhibitor of ALK tyrosine kinase and is a targeted therapy for tumors with ALK-rearrangements [2]. It has been shown to be superior to conventional chemotherapeutic agents in the treatment of ALK-positive non-small cell lung carcinoma, highlighting the importance of identifying this genetically unique subset of patients [2,8,9].

Radiological evaluation has been used successfully to assess certain genetic subtypes of lung cancer [10,11] however to our knowledge there has been no comprehensive description of the imaging features of tumors with ALK rearrangements. Given the strong association between ALK rearrangements and non-Hodgkins lymphoma, and based on clinical experience in our institution, we postulated that ALK positive lung carcinomas may present with larger volume lymphadenopathy on computed tomography (CT) than non-ALK tumors. The aim of this study was to provide a comprehensive description of the CT appearance of lung carcinomas with ALK rearrangements in an attempt to identify any particular imaging features associated with this subset of tumors.

2. Materials and methods

2.1. Patient cohort

Our institutional review board granted approval and waived the informed consent requirement for this retrospective study. Patients were identified from a prospectively maintained database of patients presenting to the thoracic oncology clinic at our institution between November 1st 2005 and June 30th 2012. Patients with a pathology report documenting lung carcinoma with an ALK rearrangement and with CT images on the

institutional Picture Archiving and Communication System (PACS, GE Centricity RA100) were included for analysis. The earliest available CT images on the PACS were studied. Clinical parameters documented were age, sex and smoking status. Clinical information was extracted retrospectively from the institutions electronic medical record, following lesion analysis. A cohort of 97 patients with lung adenocarcinoma and EGFR mutation, randomly selected from a separate institutional database were used as a control group.

2.2. Image analysis

All CTs were retrospectively reviewed in an independent fashion by 2 radiologists (D.F.H. and S.H. with 6 and 5 years of radiology experience respectively). Both readers were blinded to the ALK/EGFR status and other clinical details at the time of image interpretation. All images were reviewed on a PACS system. CT imaging protocols varied, as many patients were referred from a range of institutions to our tertiary referral center following their initial imaging. Imaging was performed on a variety of multidetector CT scanners, with slice thicknesses ranging from 1.25 to 5 mm. 61 (48%) CT exams were performed without intravenous contrast, 66 (52%) were performed with contrast.

CT features assessed were: the size and location of thoracic lymphadenopathy; the size, contour, consistency and location of the primary tumor; the presence/absence of a pleural effusion, pleural metastases or lymphangitic carcinomatosis; the presence and location of metastases.

Lymphadenopathy was defined as the presence of a thoracic lymph node ≥ 1.0 cm in short axis. Locations of lymphadenopathy recorded were mediastinal, ipsilateral hilar, contralateral hilar, axillary and supraclavicular. The presence or absence of nodal enlargement at each site was documented. The number of nodal locations (from 0 to 5) was then summed to determine the number of nodal locations involved. Lymphadenopathy was classified as being absent, unifocal (present at 1 thoracic site) or multi-focal (present at >1 thoracic site). The size of lymphadenopathy was recorded as either ≥ 1 cm and <1.5 cm, 1.5 cm and <3 cm, or ≥ 3 cm. For patients with multifocal lymphadenopathy the size of the largest lymph node was recorded.

The contour of the primary tumor was characterized as either: round (spherically shaped lesions with smooth borders that could be clearly outlined radiologically without spiculations into the surrounding parenchyma), lobulated (lesions with smooth borders but without a spherical shape) or spiculated (lesions with linear radiating spicules extending from the border of the lesion in the adjacent lung parenchyma) [12].

The density of the primary tumor was classified as either: solid attenuation (increased density of the lung parenchyma with obscuration of the pulmonary vessels), ground glass attenuation (hazy increased attenuation of lung, with preservation of bronchial and vascular margins) [13], or mixed ground glass and solid attenuation. The presence of air bronchograms, cavitation and calcification was also recorded.

The location of the lesion was classified as either central (tumor involving segmental or larger bronchus) or peripheral (tumor involving subsegmental bronchus or smaller airway).

2.3. Statistical analysis

Lesion size on CT was summarized using median and interquartile range (IQR), and compared between ALK tumors and EGFR tumors using the Wilcoxon rank-sum test. Categorical features were summarized using count and percent, and examined using Fisher's exact test. The inter-reader agreement on lesion size on CT was evaluated using intra-class correlation coefficient (ICC). Log transformation was applied considering the skewed distribution. The inter-reader agreement on categorical feature was assessed using kappa statistic. Agreement of CT features with more than 2 categories was assessed using weighted kappa with quadratic weights. Kappa (κ) values were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [14].

3. Results

3.1. Patient characteristics

30 patients with primary lung tumors harboring an ALK rearrangement were identified from a prospectively maintained institutional database. 97 patients with primary lung tumors harboring an EGFR mutation identified from a separate institutional database were used as a control group. The mean overall age was 61 years (range 33–90). The mean age of patients in the ALK group was 50 years (range 36–76), and the mean age in the EGFR group was 63 years (range 33–90). Additional patient characteristics are summarized in Table 1. There was no difference in sex distribution or smoking status between the ALK and EGFR group. When patients were grouped into those clinical stages [15] that present without lymphadenopathy (Stage 1) and those that present with lymphadenopathy (Stages 2, 3 or 4) there was no significant difference in tumor stage by mutation status ($p = 0.125$) (Table 1).

3.2. Imaging findings

3.2.1. Lymphadenopathy—For both readers, patients with ALK rearrangements were significantly more likely to have larger volume lymphadenopathy than patients with EGFR mutations (reader 1, $p = 0.009$; reader 2, $p = 0.005$) (Table 2a). Both readers identified 17 (57%) patients in the ALK group with lymph nodes ≥ 1.5 cm (these were the same patients) (Fig. 1). Reader 1 identified 18 (19%) patients in the EGFR group with lymph nodes ≥ 1.5 cm, and reader 2 identified 17 (18%). In addition, for both readers, patients with ALK rearrangements were significantly more likely to have lymphadenopathy at more than one thoracic site (both readers $p = 0.001$). Multifocal thoracic nodal enlargement was identified in 22 (73%) ALK patients versus 35 (36%) EGFR patients by reader 1, and in 20 (67%) ALK patients versus 30 (31%) EGFR patients by reader 2 (Table 2a). There was almost perfect agreement between readers in measurement of lymph node size (kappa 0.969, 95% CI: 0.943, 0.994) count of nodal location (kappa 0.953, 95% CI: 0.924, 0.982) (Table 4). Regarding the location of lymphadenopathy, for both readers ALK patients were more likely than EGFR patients to have lymphadenopathy in the ipsilateral hilum ($p = 0.003$ – 0.005), the contralateral hilum ($p = 0.007$ – 0.013), the mediastinum ($p = 0.001$ – 0.002), and supraclavicular regions ($p = 0.001$) when compared to EGFR patients (Table 2b).

3.2.2. Characteristics of the primary tumor—Both readers found that 17 tumors presented without a measurable pulmonary lesion [ALK 5 (17%), EGFR 12 (12%)]. There was no difference in axial diameter of the primary lesion between the ALK and EGFR groups (ALK median axial diameter 3.0 cm × 2.7 cm, EGFR median axial diameter 3.7 cm × 2.8 cm, $p = 0.203$). When measurable, the density of the primary tumor was most frequently solid (Fig. 1) for both ALK and EGFR groups (Table 3). One reader found that EGFR lesions were significantly more likely than ALK lesions to present with mixed solid and ground glass density ($p = 0.037$) however these findings did not reach significance for the other reader ($p = 0.113$) (Table 3). Both ALK and EGFR lesions were most frequently spiculated (Table 3) however there was no statistical difference between the groups with respect to lesion contour. There was no significant difference between the ALK group and the EGFR group with respect to the location (central versus peripheral). Additional characteristics of the primary lesion studied were: the presence of cavitation, calcification and air bronchograms. There was no significant difference between the ALK and EGFR groups for any of these features (Table 3). No lesion demonstrated calcification.

3.2.3. Ancillary features—There was no significant difference between the ALK group and the EGFR group with respect to the presence of pleural effusion or pleural metastasis. ALK tumors were more likely to be associated with a CT appearance of lymphangitic carcinomatosis (Table 3). 7 (23%) patients in the ALK group had lymphangitic carcinomatosis compared with 8 (8%) in the EGFR group by both readers ($p = 0.046$). Agreement between readers for identification of ancillary features ranged from substantial agreement (pleural disease kappa 0.741, 95% CI: 0.571, 0.912) to almost perfect agreement (pleural effusion kappa 0.975, 95% CI: 0.883, 1.000) (Table 4).

4. Discussion

ALK rearrangement is one of several molecular aberrations involving lung carcinoma that have been described in recent years, but is less common than other frequent mutations such as EGFR and KRAS [4,5]. The presence of ALK rearrangement and EGFR or KRAS mutations are generally mutually exclusive [16]. Although ALK rearrangements only occur in between 2 and 7% of patients with non-small cell lung cancer [2], the existence of a targeted therapy for ALK positive tumors which is superior to conventional treatment [2,8,9] means it is vital to identify patients with this mutation, to ensure appropriate treatment is instituted. The clinicopathological characteristics of ALK-positive lung carcinomas have been extensively described. These tumors tend to occur in younger patients, and in those without a strong smoking history. Histologically they are almost exclusively adenocarcinomas and tend to be found in lesions with signet ring morphology [2].

There have been mixed results in the few studies which have investigated the radiological appearance of the more common genetic subtypes of lung cancer. Glynn et al., for example, did not find any specific CT appearance to correlate with either EGFR or KRAS mutated tumors [17]. Lee et al. used CT and 18-fluorodeoxyglucose positron emission tomography/CT to assess patients with stage 1 non-small cell lung cancer [10]. They demonstrated that EGFR overexpression was associated with tumors >2.4 cm in diameter, a maximum standardized uptake value of >5.0, and a ground glass opacity proportion of the primary

lesion of ~50%. Most recently Lee et al. successfully used the morphology of the primary tumor on CT to differentiate between the two most common subtypes of EGFR mutations, exon 19 deletions and exon 21 mis-sense mutations [11]. They found that the ground glass portion of lesions were higher in lesions with exon 21 missense mutations when compared to both wild type lesions and tumors with exon 19 deletions.

To our knowledge there has been no previous description of the radiological characteristics of tumors with ALK rearrangements. The only paper to address this issue provides a short description of the consistency of the primary lesion, as part of an overview of the clinical characteristics of ALK-positive tumors. The authors demonstrate that ALK positive lesions have a more solid consistency than tumors without ALK rearrangements, however they do not describe any further radiological features [5]. We aimed to provide a more comprehensive radiological overview. Knowledge of the radiological presentation of these tumors, in the correct clinical context, could help to identify patients at risk for ALK-rearrangements.

The results of the current study demonstrate that on CT evaluation, ALK positive lung adenocarcinomas are more likely to be associated with larger volume, multifocal thoracic adenopathy than EGFR mutant lung adenocarcinomas. No feature of the primary tumor on CT correlated with the presence of ALK rearrangement when compared to EGFR mutated lesions. The finding that the majority (92%) of ALK positive lesions are solid in nature correlates with the previously described CT and histological features of these tumors [5,6].

The retrospective nature of this study, resulting in a slightly heterogeneous study population, and its relatively small sample size are inherent weaknesses, both of which could be overcome by larger prospective multi-institutional studies. Although patients were not formally matched, there was no significant difference between the stage of patients when grouped into those stages which present with and without lymphadenopathy. The non-contrast nature of some of the CT studies is another potential limitation. Evaluation of differential lesion enhancement would have been interesting to perform, however because many of these CT studies were performed without contrast such evaluation was not possible. In addition, lack of intravenous contrast can limit the ability to detect lymphadenopathy.

5. Conclusion

Although investigating for ALK rearrangements should be routine in patients with lung adenocarcinoma, ALK testing may not be universal, particularly in areas in which healthcare resources are limited, or where there is a lack of tertiary experience. In this context it is vital for the radiologist to be aware of both the clinical and radiological presentation of this genetically distinct subset of lung cancer. The results of this study suggest that, in the correct clinical context, the presence of large volume multifocal thoracic lymphadenopathy in a patient with lung adenocarcinoma with a solid morphology should prompt testing for ALK rearrangement. However we feel that further prospective studies should be considered to confirm our findings.

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Fig. 1. Axial contrast enhanced CT of the thorax on lung and mediastinal windows, in a patient with lung adenocarcinoma with an ALK rearrangement, demonstrating a typical solid left upper lobe mass with bulky mediastinal lymphadenopathy.

Table 1

Patient characteristics.

	ALK <i>n</i> (%)	EGFR <i>n</i> (%)	Fisher's exact test <i>p</i> -value
Sex			
F	22 (73%)	71 (73%)	1.000
M	8 (27%)	26 (27%)	
Smoking history			
No	23 (77%)	70 (72%)	0.814
Yes	7 (23%)	27 (28%)	
Stage I	3 (10%)	23 (24%)	Stage I vs Stage II + III + IV: 0.125
Stage II	1 (3%)	3 (3%)	
Stage III	8 (27%)	10 (10%)	
Stage IV	18 (60%)	61 (63%)	
	ALK	EGFR	Wilcoxon rank-sum test
	<i>n</i> (%)	<i>n</i> (%)	<i>p</i> -value
Age, median (range)	49.5 (36.0, 76.2)	63.4 (32.6, 89.9)	<0.001

Summary of nodal characteristics. The location of lymphadenopathy was recorded as being mediastinal, ipsilateral hilar, contralateral hilar, axillary or supraclavicular. The presence or absence of nodal enlargement at each site was documented and the largest thoracic node was recorded. The number of nodal locations (from 0 to 5) was then summed to determine the number of nodal locations involved.

Table 2a

	Reader 1				Reader 2			
	ALK n (%)	EGFR n (%)	Fisher's exact test p-value		ALK n (%)	EGFR n (%)	Fisher's exact test p-value	
Short axis measurement of the largest thoracic lymph node	<1 cm	7 (23%)	48 (49%)		7 (23%)	47 (48%)		
	1 and <1.5 cm	6 (20%)	30 (31%)		6 (20%)	32 (33%)		
	1.5 and <3.0 cm	15 (50%)	18 (19%)	0.009	15 (50%)	17 (18%)		0.005
Number of nodal locations involved	3.0 cm	2 (7%)	1 (1%)		2 (7%)	1 (1%)		
	0	7 (23%)	48 (49%)		7 (23%)	45 (46%)		
	1	1 (3%)	14 (14%)	0.001	3 (10%)	22 (23%)		0.001
	>1	22 (73%)	35 (36%)		20 (67%)	30 (31%)		

Summary of nodal characteristics. The location of lymphadenopathy was recorded as being ipsilateral hilar, contralateral hilar, mediastinal, axillary or supraclavicular. The presence or absence of nodal enlargement at each site was documented.

Table 2b

	Reader 1			Reader 2		
	ALK n (%)	EGFR n (%)	Fisher's exact test p-value	ALK n (%)	EGFR n (%)	Fisher's exact test p-value
Ipsilateral hilum			0.003			0.005
Yes	20 (67%)	34 (35%)		18 (60%)	30 (31%)	
No	10 (33%)	63 (65%)		12 (40%)	67 (69%)	
Contralateral hilum			0.013			0.007
Yes	7 (23%)	6 (6%)		7 (23%)	5 (5%)	
No	23 (77%)	91 (94%)		23 (77%)	92 (95%)	
Mediastinal			0.001			0.002
Yes	23 (77%)	40 (41%)		23 (77%)	42 (43%)	
No	7 (23%)	57 (59%)		7 (23%)	55 (57%)	
Axillary			0.054			0.054
Yes	2 (7%)	0 (0%)		2 (7%)	0 (0%)	
No	28 (93%)	97 (100%)		28 (93%)	97 (100%)	
Supraclavicular			0.001			0.001
Yes	15 (50%)	12 (12%)		14 (47%)	9 (9%)	
No	15 (50%)	85 (88%)		16 (53%)	88 (91%)	

Table 3

Summary of the morphological CT characteristics of the primary tumor and ancillary imaging features. Characteristics of the primary tumor are described in patients with a measurable primary lesion (ALK patients, $n = 25$; EGFR patients, $n = 85$).

	Reader 1			Reader 2		
	ALK n (%)	EGFR n (%)	Fisher's exact test p -value	ALK n (%)	EGFR n (%)	Fisher's exact test p -value
Solid density of primary tumor			0.350			0.513
Yes	23 (92%)	70 (82%)		23 (92%)	72 (85%)	
No	2 (8%)	15 (18%)		2 (8%)	13 (15%)	
Ground glass density of primary tumor			0.222			0.318
Yes	2 (8%)	2 (2%)		2 (8%)	3 (4%)	
No	23 (92%)	83 (98%)		23 (92%)	82 (96%)	
Mixed solid/ground glass density of primary tumor			0.037			0.113
Yes	0 (0%)	13 (15%)		0 (0%)	10 (12%)	
No	25 (100%)	72 (85%)		25 (100%)	75 (88%)	
Cavitation			0.129			0.129
Yes	2 (8%)	1 (1%)		2 (8%)	1 (1%)	
No	23 (92%)	84 (99%)		23 (92%)	84 (99%)	
Air bronchogram within the tumor			0.999			0.999
Yes	3 (12%)	13 (15%)		5 (20%)	19 (22%)	
No	22 (88%)	72 (85%)		20 (80%)	66 (78%)	
Contour			0.716			0.331
Lobulated	7 (28%)	29 (34%)		5 (20%)	26 (31%)	
Round	0 (0%)	1 (1%)		1 (4%)	1 (1%)	
Spiculated	18 (72%)	55 (65%)		19 (76%)	58 (68%)	
Lymphangitic carcinomatosis			0.046			0.046
Yes	7 (23%)	8 (8%)		7 (23%)	8 (8%)	
No	23 (77%)	89 (92%)		23 (77%)	89 (92%)	
Pleural effusion			0.121			0.113
Yes	13 (43%)	27 (28%)		13 (43%)	26 (27%)	
No	17 (57%)	70 (72%)		17 (57%)	71 (73%)	
Pleural disease			0.133			0.765

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	Reader 1				Reader 2			
	ALK <i>n</i> (%)	EGFR <i>n</i> (%)	Fisher's exact test <i>p</i> -value		ALK <i>n</i> (%)	EGFR <i>n</i> (%)	Fisher's exact test <i>p</i> -value	
Yes	7 (23%)	11 (11%)			5 (17%)	13 (13%)		
No	23 (77%)	86 (89%)			25 (83%)	84 (87%)		

Table 4

Agreement on CT features between two readers.

CT features	Kappa (95% CI)
Short axis measurement of lymphadenopathy ^a	0.969 (0.944, 0.994)
Number of nodal locations involved ^a	0.953 (0.924, 0.982)
Ground glass density of primary tumor	0.884 (0.660, 1.000)
Mixed solid/ground glass density of primary tumor	0.855 (0.694, 1.000)
Air bronchogram within the tumor	0.697 (0.525, 0.869)
Contour	0.733 (0.600, 0.867)
Central or peripheral location	0.892 (0.799, 0.984)
Cavitation	Perfect
Effusion	0.945 (0.883, 1.000)
Pleural disease	0.741 (0.571, 0.912)
Satellite nodules	0.890 (0.810, 0.969)
Lymphangitic carcinomatosis	0.924(0.821, 1.000)

^aWeighted kappa with quadratic weights was used.