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Advanced, Non-Small Cell Lung Cancer with Anaplastic Lymphoma Kinase Rearrangement: Case Report And Literature Review

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ABSTRACT

Non-small cell lung cancer comprises different types of molecular subsets: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and non-otherwise specified. The most common mutation occurs in the epidermal growth factor receptor, particularly in exon 21 and exon 19 deletions. These mutations confer constitutive activation of the epidermal growth factor receptor tyrosine kinase domain. The frequency of epidermal growth factor receptor mutations varies among different ethnic groups. The anaplastic lymphoma kinase gene gained strong clinical interest when it was found to be translocated in anaplastic large cell lymphoma, and subsequently in diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, and non-small cell lung cancer. Activating anaplastic lymphoma kinase translocations dictate favorable and often dramatic responses to anaplastic lymphoma kinase tyrosine kinase inhibitors like crizotinib. Thus, the recognition of this molecular alteration is quite important in clinical practice. Therefore, the main objective of this manuscript is to confirm the relevance of the anaplastic lymphoma kinase tyrosine kinase inhibitors to treat non-small cell lung cancer. Hence, we report a case of advanced non-small cell lung cancer harboring anaplastic lymphoma kinase translocation treated at the Instituto Nacional de Cancerología in Mexico. We conclude that many questions remain unanswered: whether to use first- or second-generation anaplastic lymphoma kinase inhibitors, treatment time, sequencing, order, and the selection of an anaplastic lymphoma kinase inhibitor in clinically specific situations like brain metastasis. We need further investigations to address these problems. (J CANCEROL. 2015;2:34-8)

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INTRODUCTION

Lung cancer is the first cause of cancer-related death worldwide. Annually, 85% of these lung cancer cases are diagnosed as non-small cell lung cancer (NSCLC). Despite efforts and progress in the diagnosis and treatment of this disease, overall survival at five years is only 5%[1].

Adenocarcinoma represents 40.1% of all NSCLC cases, followed by squamous cell carcinoma 21.4%, large cell carcinoma 2.6%, and non otherwise specified 20.2%[2]. Different types of molecular subsets exist in adenocarcinoma, where nearly 50% of patients with this histology have a driver mutation[3].

Epidermal growth factor receptor (EGFR) mutations occur more frequently in adenocarcinoma, non-smoker/light-smoker patients, female gender, and Asian ethnicity. Almost 90% of EGFR mutations comprise punctual mutation in exon 21 (L858R) and exon 19 deletions. These mutations confer constitutive activation of the EGFR tyrosine kinase domain[4,5]. The frequency of EGFR mutations varies among different ethnic groups: Caucasian, Asian, and African American populations harbor 15, 40, and 2-14% of mutations, respectively[6-9]. Latin American countries report an intermediate frequency between Asian and Caucasian patients of 33.2%. The Mexican population has a 31.2% EGFR mutation prevalence[10].

The anaplastic lymphoma kinase *(ALK)* gene gained strong clinical interest when it was found to be translocated in anaplastic large cell lymphoma, and subsequently in diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, and NSCLC[11,12]. To date, ALK overall incidence seems similar in NSCLC unselected series conducted in Asian (4.2%) and Western (3.4%) populations[13]. Activating *ALK* translocations dictates favorable and often dramatic responses to ALK tyrosine kinase inhibitors like crizotinib, as demonstrated by phase I, II, and III clinical trials[14-17]. Thus, the recognition of this molecular alteration is quite important in clinical practice. To confirm it, we report a case of advanced NSCLC harboring ALK translocation treated at the Instituto Nacional de Cancerología in Mexico; likewise, a literature review was carried out to support it.

CASE PRESENTATION

A 53 year-old male patient, native and resident of Mexico City. He had a history of being a light smoker, with a tobacco index of three packs/year. The habit was suspended six months before diagnosis. Also he denies asbestos or wood smoke exposure. In the clinical history, he reported that in December 2012 he noticed a lump at the iliac crest, which turned out to be a 5 cm and stony consistency tumor with a rapidly progressive growth up to 15 cm. Also, the patient experienced a more than 10% weight loss and cough with hemoptysis in the previous three months. At the physical examination, a large tumor of 15 × 20 cm was observed at the right hip, and spinal cord compression syndrome was diagnosed.

The patient was hospitalized and underwent extensive staging with computerized tomography (CT) scan, brain and neuro-axis magnetic resonance imaging (MRI), and full blood chemistry with carcinoembryonic antigen. A transthoracic-guided biopsy was performed.

The initial CT scan reported an 88.8 mm right lung lesion, an upper 37 mm paratracheal tumor, an aortopulmonary window nodal conglomerate (24.15 mm), a liver lesion on segment 3 of 34 mm, and an expansive 103 mm lytic lesion to the right iliac bone (Fig. 1 and 2). On brain and neuraxis MRI, tumor infiltration was observed in cervical, thoracic, and lumbosacral regions. Tumoral activity in the left parietal central nervous system and left thalamus was also detected (Fig. 3 and 4). Biopsy results report a moderately differentiated adenocarcinoma with predominantly solid pattern. Immunohistochemistry was positive to TTF1, and CK 7. Direct

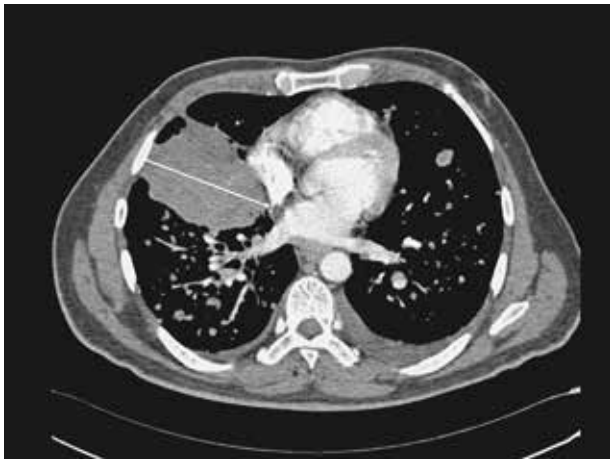

Figure 1. Thorax computerized tomography scan demonstrating bulky tumor on right superior lobe.

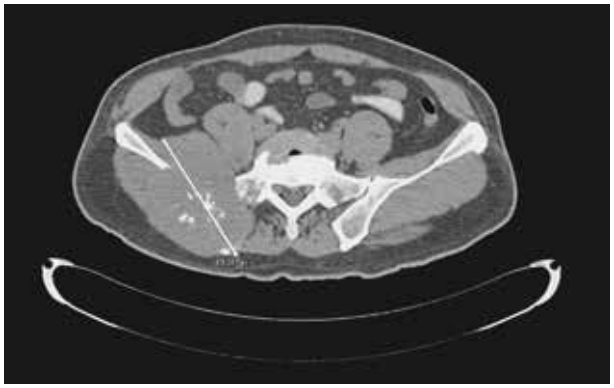

Figure 2. Abdominal computerized tomography scan showing lytic and expansive lesion on right iliac bone.

sequencing was negative to EGFR; however, ALK translocation was positive with FISH break-part dual color test (Fig. 5).

The patient was initially treated with external thoracolumbar spine radiation and holo-cranial radiotherapy, receiving 30 Gy in 10 fractions. In May 2013, crizotinib was given at standard doses. At the first three-month tumor assessment evaluation, a partial response of 41.2% was documented. After a 14-month follow-up, an 80% partial response was achieved (Fig. 6). At his last visit (18-month follow-up), the patient maintains partial response (74%) and remains progression-free, without dose reductions of crizotinib.

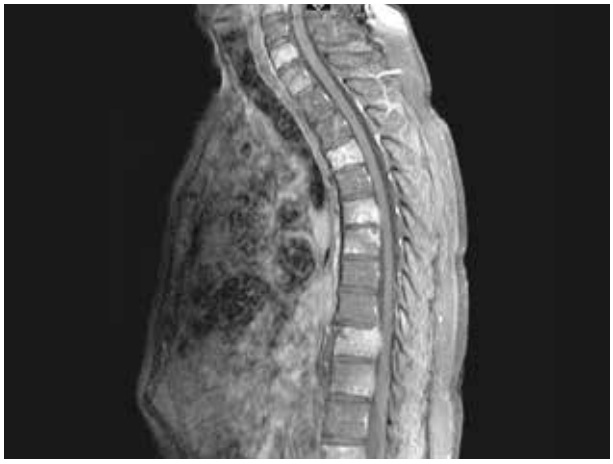

Figure 3. Neuro-axis magnetic resonance imaging with tumor infiltration was observed in cervical, thoracic, and lumbosacral regions.

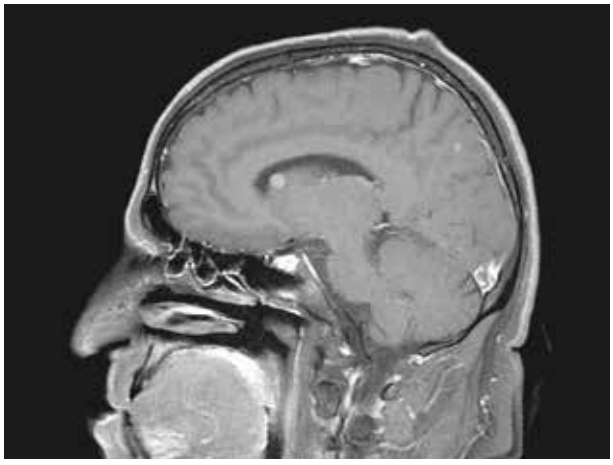

Figure 4. Brain magnetic resonance imaging with tumoral activity in the left parietal central nervous system and left thalamus.

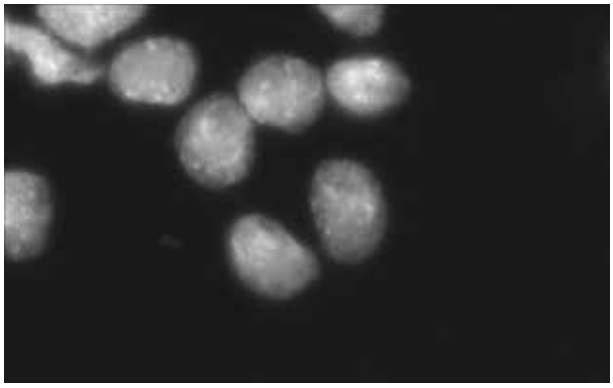

Figure 5. Tissue lung adenocarcinoma sample with positive anaplastic lymphoma kinase rearrangement detected. Positive case showing a break-apart signal pattern, where one fusion signal and a single red and green signal pattern were observed.

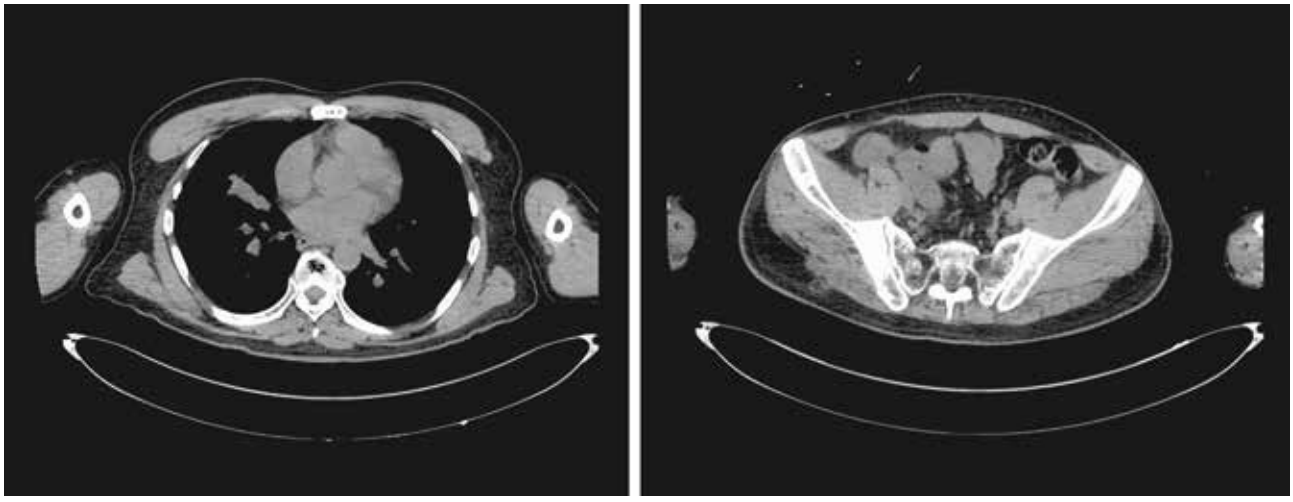

Figure 6. Computerized tomography scan where a 80% partial response by RECIST 1.1 is observed.

DISCUSSION

The discovery of ALK rearrangements in NSCLC took place in 2007 by two independent groups of researchers[18,19]. In one of these studies, Soda, et al. found that an echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion is a driver mutation in NSCLC, independent of EGFR and KRAS. The incidence rates of this molecular abnormality were shown to be 3.8% on average, with a wide range of 0.4-13.4%. Nowadays, we know there are approximately 21 EML4-ALK fusion variants, and EML4 is not the only fusion partner; ALK fusions with TGF, KIF5B, KCL1, and PTPN3 have also been described[13,20,21]. Out of the 21 EML4-ALK fusion variants, the most common are: variant 1 (49.6%), 3a/b (25.6%), and variant 2 (10%)[18]. The NSCLC ALK-rearranged patients are generally associated with never smoking (< 100 cigarettes in a lifetime) or light smoking history (< 15 pack/years), younger age, and male gender[13,22-24]. EML4-ALK is found almost exclusively in adenocarcinomas; no cases have been identified in pure squamous cell carcinoma[13,25,26]; solid, micropapillary-predominant histologic patterns, and tumor cells with a signet ring or hepatoid cytomorphology were found to be related with ALK[27].

Patients with ALK-positive tumors detected by FISH have a favorable clinical response to the ALK inhibitor crizotinib, which has proven to be superior to standard chemotherapy in first- or second-line treatment[14-17]. Nevertheless, progression presented usually after 7.0-10.9 months of treatment.

Acquired resistance in 30% of cases occurred due to a gatekeeper mutation on the tyrosine kinase ALK domain (L1196M). The other 70% of cases are the result of a copy number gain of ALK, expression of a second oncogene, and activation of alternative signaling pathways such as EGFR (9%), KRAS (36%) or KIT[28,29]. Fortunately, second-generation ALK inhibitors, such as ceritinib or alectinib, are active in crizotinib-naive or crizotinib-treated patients, with a seven-month progression-free survival (very similar to crizotinib); they also have a better blood-brain barrier penetration, with an outstanding 50-52% central nervous system response rate[30-32].

Many questions remain unanswered: whether to use first- or second-generation ALK inhibitors, treatment time, sequencing, order, and the selection of an ALK inhibitor in clinically specific situations like brain metastasis. We need further investigations to address these problems.

Our patients remain progression free and at time of progression will be sequenced with a second-generation ALK inhibitor.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. CA Cancer J Clin. 2008;58:71-96.
2. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD Available from: http://seer.cancer.gov/csr/1975_2010/ based on November 2012 SEER data submission, posted to the SEER web site, April 2013. [Accessed 15/09/2013].
3. Morgensztern D, Campo MJ, Dahlberg SE, et al. Moleculary targeted therapies in non-small cell lung cancer annual update 2014. J Thorac Oncol. 2015;10(Suppl 1):S1-63.
4. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005;5:341-54.
5. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from never smokers and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA. 2004;101:13306-11.
6. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304:1497-500.
7. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. New Engl J Med. 2009;361:958-67.
8. Leidner RS, Fu P, Clifford B, et al. Genetic abnormalities of the EGFR pathway in African American patients with non-small-cell lung cancer. J Clin Oncol. 2009;27:5620-6.
9. Cote ML, Haddad R, Edwards DJ, et al. Frequency and type of epidermal growth factor receptor mutations in African Americans with non-small cell lung cancer. J Thorac Oncol. 2011;6:627-30.
10. Arrieta O, Cardena AF, Bramuglia GF, et al. Genotyping Non-small cell lung cancer (NSCLC) in Latin America. J Thorac Oncol. 2011;6:1955-9.
11. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994;263:1281-4.
12. Ou SH, Bartlett CH, Mino-Kenudson M, et al. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. Oncologist. 2012;17:1351-75.
13. Solomon B, Varella-García M, Camidge DR. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol. 2009;4:1450-4.
14. Shaw AT, Hsu PP, Awad MM, et al. Tyrosine kinase gene rearrangements in epithelial malignancies. Nat Rev Cancer. 2013;13:772-87.
15. Kwak EL, Bang YL, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small cell lung cancer. N Eng J Med. 2010;363:1693-703.
16. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012;13:1011-19.
17. Kim DW, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). J Clin Oncol. 2012;30(Suppl):7533 [Abstract].
18. Sato M, Shames DS, Gazdar AF, Minna JD. A translational view of the molecular pathogenesis of lung cancer. J Thorac Oncol. 2007;2:327-43.
19. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. CA Cancer J Clin. 2011;61:91-112.
20. Wong DW, Leung EL, Wong SK, et al. A novel KIF5B-ALK Variant in Non small Cell Lung Cancer. Cancer. 2011;117:2709-18.
21. Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a Novel Fusion Oncokinase Identified by an Immunohistochemistry-based Diagnostic System form ALK-positive Lung Cancer. Clin Cancer Res. 2009;15:3143-9.
22. Choi YL, Takeuchi K, Soda M, et al. Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. Cancer Res. 2008;68:4971-6.
23. Horn L, Pao W. EML4-ALK: honing in on a new target in non-small-cell lung cancer. J Clin Oncol. 2009;27:4232-5.
24. Perner S, Wagner PL, Demichelis F, et al. EML4-ALK fusion lung cancer: a rare acquired event. Neoplasia. 2008;10:298-302.
25. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561-6.
26. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signalling identifies oncogenic kinases in lung cancer. Cell. 2007;131:1190-203.
27. Nishino M, Klepeis VE, Yeap BY, et al. Histologic and cytomorphologic features of ALK-rearranged lung adenocarcinomas. Mod Pathol. 2012;25:1462-72.
28. Iwama E, Okamoto I, Harada T, et al. Development of anaplastic lymphoma kinase (ALK) inhibitors and molecular diagnosis in ALK rearrangement-positive lung cancer. Onco Targets Ther. 2014;7:375-85.
29. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer**.** Clin Can Res. 2012;18:1472-82.
30. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-Rearranged Non-small cell lung cancer. N Engl J Med. 2014;370:1189-97.
31. Seto T, Kiura K, Nishio M, et al. CH5424802 for patients with ALK-rearranged advanced non-small cell lung cancer (AF-001JP study): a single arm, open label, phase 1-2 study. Lancet Oncol. 2013;14:590-8.
32. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK rearranged non-small cell lung cancer (AF-002JG): results from the dose finding portion of a phase 1, 2 study. Lancet Oncol. 2014;15:1119-28.