

Identification of anaplastic lymphoma kinase fusion in clear cell renal carcinoma (ALK-tRCC): a precision oncology medicine case report

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Summary. Background. Translocation-associated renal cell carcinoma involving ALK (ALK-tRCC) is a rare subtype of adult renal cell carcinoma (RCC) reported in recent years. **Case presentation.** A new Italian case of ALK-tRCC was reported. The patient was a female 44-year-old with a metastatic and pretreated RCC. The tumor showed a rearrangement of ALK gene in tumor cells detected by targeted next-generation sequencing panel. The patient received oral alectinib therapy and achieved a partial response. **Conclusions.** ALK-tRCC is a rare subtype of adult RCC. Its diagnosis is very difficult because the genomic alteration spectrum is very wide. We suggested that metastatic RCCs should be screened for uncommon genomic alterations especially in good performance status pretreated resistant/refractory patients.

Key words. Alectinib, ALK fusion, molecular biology, NGS panel, precision oncology, renal cancer, target therapy.

Identificazione del riarrangiamento di ALK (ALK-tRCC) in un paziente con tumore renale: report di un caso di medicina oncologica di precisione.

Riassunto. Introduzione. La traslocazione di ALK nel tumore renale (ALK-tRCC) è un raro sottotipo riportato di recente. **Presentazione del caso.** Viene riportata una nuova evidenza di ALK-tRCC in un paziente italiano. La paziente era una giovane donna di 44 anni con diagnosi di tumore renale plurimetastatico e pretrattato. Il tumore mostrava nella sua cellularità il riarrangiamento del gene ALK valutato attraverso un pannello di sequenziamento NGS. La paziente riceveva su tale base terapia orale con alectinib con risposta parziale alla prima rivalutazione. **Conclusioni.** ALK-tRCC è un rara alterazione nel tumore renale diagnosticato nell'adulto. La sua diagnosi è complessa poiché lo spettro delle possibili alterazioni genomiche in tale patologia è molto ampio. Si suggerisce di eseguire nel tumore renale metastatico uno screening per le alterazioni genomiche meno frequenti, in particolare nei pazienti in buone condizioni generali e malattia resistente o refrattaria.

Parole chiave. Alectinib, biologia molecolare, neoplasia renale, oncologia di precisione, pannello NGS, riarrangiamento ALK, terapia target.

Introduction

ALK-tRCC is a provisional entity in the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs. Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that was first discovered as a fusion gene of nucleophosmin (NPM1) in anaplastic large-cell lymphoma (ALCL)¹. Since then, various ALK fusion genes mediated by translocation have been identified in multiple malignancies, including inflammatory myofibroblastic tumor (IMT), non-small cell lung cancer (NSCLC) and ovarian cancer²⁻⁴. The aberration in ALK could be used therapeutically as an 'Achilles heel' for all tumors with this peculiar driver using ALK inhibitors actually approved by the FDA^{5,6}.

Several groups had continuously reported ALK-tRCCs. To date approximately 19 cases of ALK-tRCCs,

which had complete clinic and pathologic information, had been reported from USA, Japan, Korean, France, Canada and China. Although the number of cases reported had increased in recent years, ALK-tRCC still represents a very rare subtype of RCC, especially in adults⁷.

We reported herein a new Italian adult case of RCC with ALK rearrangement with a summary of associated clinicopathologic features, biological behavior and molecular genetic changes that we have discovered.

Case presentation

A 44-year-old female patient with a deeply pretreated metastatic RCC (mRCC) was referred to our hospital (May 2020) because of a rapidly growing left-sided neck mass and neck pain with initial clinical respiratory symptoms due to progressive disease. She had no

accompanying symptoms, such as stridor, hoarseness or dysphagia. In physical examination, a firm and painless 3 cm × 2 cm mass was palpable bilaterally on the thyroid lobes (with a major left extension) and multiple small (1-3 cm) firm laterocervical and supraclavicular masses were palpable bilaterally. She had lost more than 10 kg in weight during the previous four months. She was euthyroid and all of his laboratory evaluations were within normal limits.

Neck ultrasonography revealed a well-defined marked hypoechoic mass measuring 3 cm × 3 cm on the thyroid lobes without a peripheral halo margin, micro calcification or cystic component. The abdominal ultrasonography was normal. Computed tomography and MRI confirmed the neck low-density mass on the thyroid lobes (3×3×2.5 cm) and laterocervical/supraclavicular lymphadenopathies (1-3 cm) without evidence of others distance metastasis. The patient had no familial history of cancer. The mRCC was pretreated initially with laparoscopic nephrectomy in April 2017 (stage T1bN2M0 poorly differentiated RCC) and due to thyroid metastatic disease after 8 months with several and approved molecularly targeted drugs, including sunitinib, sorafenib, cabozantinib bevacizumab and temsirolimus, which mainly target the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR). A pre-existing severe rheumatic disease prevented the use of any form of immunotherapy.

In June 2020 the patients underwent fine needle agobiopsy (FNA) and surgical biopsy of cervical lymphadenopathies revealing a metastatic carcinoma with rare papillary architecture consistent with carcinoma of renal origin. The immunohistochemical stains were positive for PAX8, vimentin, cytokeratin AE1/AE3, CK7, and CD10. Microscopically, the tumor was composed of bland epithelial cells with scant to moderate amount of amphophilic cytoplasm, round and uniform nuclei, delicate chromatin, and inconspicuous nucleoli, arranged in tightly packed small acini and angulated tubules. Papillary formation, intraluminal glomeruloid tufts, microcysts, and solid nests were focally observed. Psammomatous calcifications were not evident.

Due to deeply pretreatment received and evidence of progressive disease targeted next-generation sequencing (NGS) was performed following microdissection of formalin-fixed, paraffin-embedded tissue from the FNA cell block and resection specimens using the ion semiconductor-based sequencing platform Ion Torrent Personal Genome Machine (Thermo Fisher Scientific) with the Ion AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific). The panel concurrently interrogates 2,800 hotspots/variants with 207 amplicons in 50 cancer-related genes. Sequence data analysis and variant calling were performed with Torrent Suite Software 5.0 (Thermo Fisher Scientific).

The cytology specimen had a visually estimated tumor cellularity (or neoplastic content) of 25 percent, while the surgical pathology resection specimen

had a higher tumor cellularity of 70 percent. Sequencing of the RCC specimens revealed multiple concurrent mutations as follows:

- c.35G>A missense mutation in the NRAS gene
- c.2278C>T nonsense mutation in the ASXL1 gene
- c.3512T > A pathogenic rearrangement in ALK gene

Considering NGS results and no others available therapeutic choices, the patient received oral alectinib therapy in July 2020. After 4 months, a neck CT and MRI scan showed a decrease in tumor size and the patient achieved a partial response to alectinib (figure 1). During alectinib therapy, there were no adverse events, such as rashes, cordis damage, and gastrointestinal reactions. Thus far, the disease remains in response and the patient is under evaluation for radical surgery.

Conclusions

This case report support the theory that metastatic RCC such as others tumors can show uncommon genomic alterations that can be tested by NGS targeted panels. NGS may be an opportunity to better understand cancer biology and treat resistant/refractory patients apparently off approved therapy with existing drugs or in clinical trial.

Conflict of interests: the authors have no conflict of interests to declare.

References

1. 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.
2. Lawrence B, Perez-Atayde A, Hibbard MK, et al. TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. *Am J Pathol* 2000; 157: 377-84.
3. 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.
4. Ren H, Tan ZP, Zhu X, et al. Identification of anaplastic lymphoma kinase as a potential therapeutic target in ovarian cancer. *Cancer Res* 2012; 72: 3312-23.
5. Wong KM, Noonan S, O'Bryant C, Jimeno A. Alectinib for the treatment of ALK-positive stage IV non-small cell lung cancer. *Drugs Today (Barc)* 2015; 51: 161-70.
6. Loong HH, Mok K, Leung LK, Mok TS. Crizotinib in the management of advanced-stage non-small-cell lung cancer. *Future Oncol* 2015; 11: 735-45.
7. Yang J, Dong L, Du H, Li XB, Liang YX, Liu GR. ALK-TPM3 rearrangement in adult renal cell carcinoma: a case report and literature review. *Diagn Pathology* 2019; 14: 112.

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