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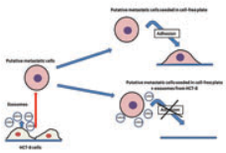

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RESEARCH PAPER

Long time response with chemotherapy in ROS1 NSCLC patient with unusual metastatic site

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ABSTRACT

During the last decade the therapeutic landscape of Non Small Cell Lung Cancer (NSCLC) has profoundly changed with the identification of actionable genetic alterations that defined molecularly selected subgroups of patients with specific clinic-pathological characteristics and increased sensitivity to specific targeted agents. The presence of ROS1 rearrangements defines a small subgroup of lung adenocarcinomas (~1–2%) with peculiar clinic-pathological characteristics and increased sensitivity to Crizotinib. It has been reported that ROS1-tranlslocated NSCLCs may also respond well to Pemetrexed-based chemotherapy. Moreover, patients with oncogene-addicted NSCLC may present peculiar pattern of metastatization and, in some instances, are associated with unusual site of metastases. Herein, we present a case of a young woman with bilateral ovarian metastases from a ROS1-positive adenocarcinoma of the lung with a lengthy progression-free survival on Pemetrexed-containing chemotherapy.

Abbreviations: NSCLC, Non Small Cell Lung Cancer; FISH, Fluorescent In Situ Hybridization; ORR, Overall Response Rate; PFS, Progression Free Survival; OS, Overall Survival; LMP, low malignant potential

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NSCLC; ROS1; ovarian metastases; pemetrexed; long survivor; genetic rearrangements

Introduction

The genetic landscape of Non Small Cell Lung Cancer (NSCLC) has profoundly changed in the last decade with the identification of several molecular subtypes with specific clinic-pathological features and different therapeutic approaches.[1] The presence of ROS1 rearrangements defines a small subgroup of lung adenocarcinomas (~1–2%)[2,3] with peculiar clinic-pathological characteristics: never smokers, young age, adenocarcinoma histology.[2] ROS1-rearranged NSCLCs present high response rate with Crizotinib therapy[4] and seem to respond well also to Pemetrexed-based chemotherapy.[3]

Patients with oncogene-addicted NSCLC may present peculiar pattern of metastatization and, in some instances, may be associated with unusual site of metastases. Herein, we present a case of a young woman with bilateral ovarian metastases from a ROS1-positive adenocarcinoma of the lung with a lengthy progression-free survival on Pemetrexed-containing chemotherapy.

Case report

In April 2013 a 43-years old never smoker woman referred to our hospital suffering of cough, dyspnea and chest pain. The radiological work-up revealed a massive right pleural effusion. Then, a diagnostic thoracoscopy was performed with evidence of a massive metastatic dissemination to the pleura from an adenocarcinoma of the lung (CK7 +, CK20 -, TTF-1 +, Calretinin -, CK 5/6 -, Antimesothelin -). The disease staging revealed an extensive right pleural and ipsilateral involvement of the lung with also an increased FDG uptake in the left parauterine region (Fig. 1A).

Transvaginal ultrasound indicated the presence of dysfunctional cysts in both ovaries. EGFR, KRAS and ALK testing did not found any actionable mutation and hence she commenced in May 2013 first line chemotherapy with Cisplatin-Pemetrexed at standard doses with a partial response after 3 courses (Fig. 1B).

First line chemotherapy was continued for up to 6 cycles (Carboplatin replaced Cisplatin in the last 2 cycles for a better tollerance) and then she started Pemetrexed maintenance with good tolerability and substantial stable disease (SD). In October 2014 a next generation sequencing of the archived tissue specimens with the Sequenom's Lung Carta Panel confirmed the wild type status of the tumor for all the genes tested (EGFR, KRAS, BRAF, NRAS, PI3KCA, TP53, PTEN, AKTl, ALK, DDR2, EPHA3, EPHA5, ERBB2, FGFR4, JAK2, MAP2K1, STK11, MET, NOTCH1, NRF2, NTRK1, NTRK2, NTRK3, PTCH1, PTPN11, PTPRD). However, the FISH assay showed the presence of ROS1 rearrangement (6q22).

In March 2015, after 18 courses of Pemetrexed maintenance, restaging revealed, in the context of a controlled intra-thoracic disease, an increase in size of the non-homogeneous left ovarian lesion, with a substantial stable SUV_{max} at FDG-PET (Fig. 2A).

The trasnvaginal ultrasound documented the presence of neoangiogenesis signs within the left ovary lesion with an

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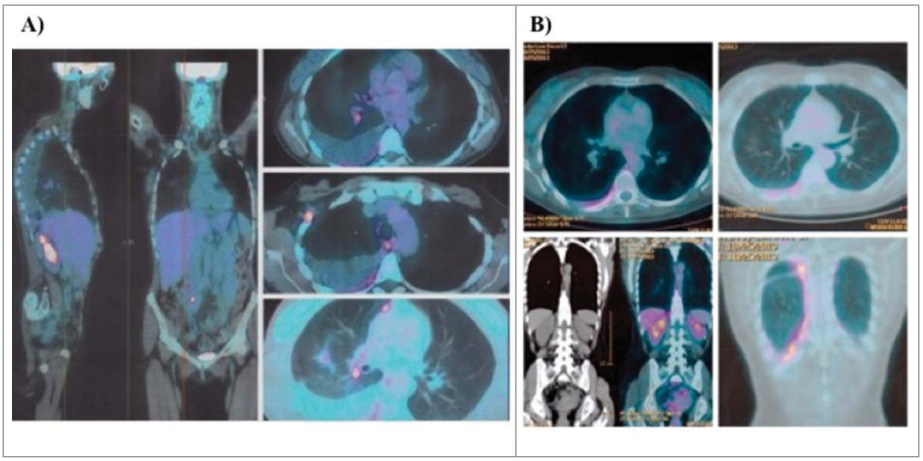

Figure 1. (A) Baseline ^{18}FDG-PET scan; [B] FDG-PET after the first 3 cycles of 1st line Cisplatin-Pemetrexed chemotherapy.

irregular echo pattern. Serum markers of ovary malignancies were within the normal range (CA 125 21 U/ml; HE4 73.5 pM). After a multidisciplinary work-up, suspecting the presence of a complex cyst, the gynecologist proposed a laparoscopic removal of the left ovary. However, after the intraoperative detection of evidence of a poor differentiated adenocarcinoma, the conservative intervention moved to a debulking surgery with a hysterectomy and bilateral salpingo-oophorectomy, omentectomy, abdomino-pelvic lymphadenectomy and peritoneal washing. The histopathological analysis revealed bilateral ovarian metastases from a poor differentiated adenocarcinoma of the lung with a solid growth pattern (CK7 +, TTF-1 +, WT1 -). Peritoneal washing and all lymph nodes removed were negative for the presence of malignant cells. The SPEC ROS1 Dual Color Break Apart Probe (band 6q22.1) FISH assay confirmed the presence of ROS1 rearrangement in the ovarian metastases (Fig. 2B).

After a re-staging with CT and FDG-PET, showing the persistence of disease limited to the right pleura and homolateral lung (Fig. 2C), in May 2015 she restarted Pemetrexed maintenance with substantial SD.

After 27 courses of Pemetrexed maintenance, in January 2016 she started suffering from irregular fever and abdominal swelling and eventually progressed, with evidence of a new hepatic lesion, ascites, peritoneal nodules and re-appearance of right pleural effusion. In February 2016, after re-staging (Fig. 3) and pathological confirmation of the ROS1 translocation, she referred to another Center for enrollment in a phase II study with Crizotinib.

Discussion

During the last decade the therapeutic landscape of Non Small Cell Lung Cancer (NSCLC) has profoundly changed with the identification of actionable genetic alterations that defined molecularly selected subgroups of patients with specific clinic-pathological characteristics and increased sensitivity to specific targeted agents.[1,5]

ROS1, originally discovered as the human homolog of the chicken proto-oncogene c-ros, is a gene located in the chromosome 6, encoding an orphan receptor tyrosine kinase, closely related with ALK and LTK. ROS1 gene fusions have transforming capability and have been reported in several malignancies, including NSCLC.[6,7] In 2012 Bergheton and *coll.* using a FISH (Fluorescent In Situ Hybridization) assay first reported the identification of ROS1 rearrangements, initially identified as a potential driver in NSCLC in cell line assays[8], in a small subgroup of lung adenocarcinoma (1.7%) with peculiar clinic-pathological features that resemble those of ALK-positive NSCLCs: young, never smokers, with high grade adenocarcinomas.[2] Based on preliminary preclinical data of sensitivity to the ALK inhibitor TAE684[9], they also reported data of efficacy

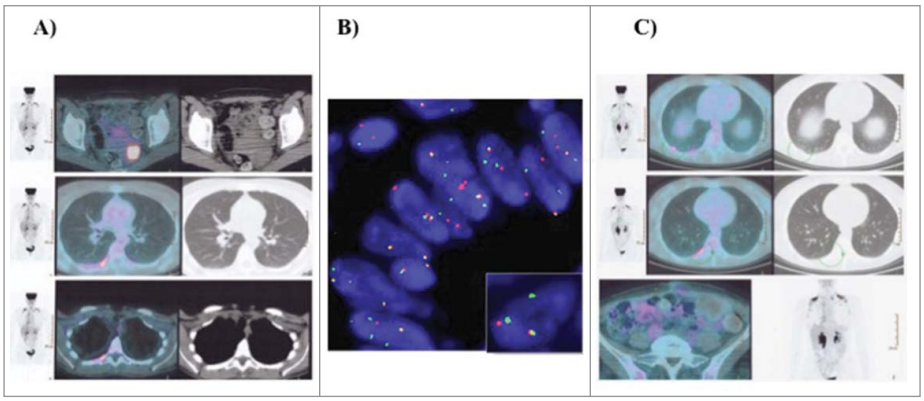

Figure 2. (A) FDG-PET after 18 courses of Pemetrexed maintenance; (B) ROS1 FISH assay performed on ovarian metastases with the SPEC ROS1 Dual Color Break Apart Probe (band 6q22.1); (C) FDG-PET after surgery removal of ovarian metastases, documenting the persistence of disease limited to the right lung and homolateral pleura.

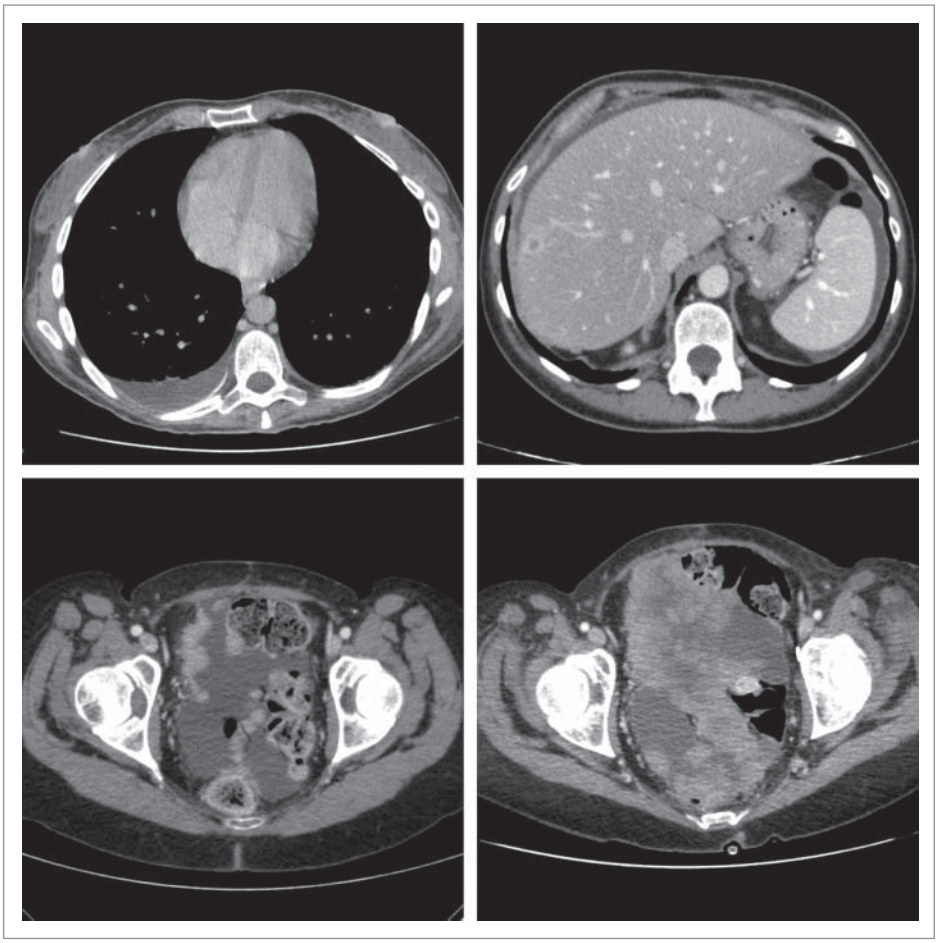

Figure 3. CT scans showing progressive disease with emergence of pleural effusion, an hepatic lesion, ascites and peritoneal nodules.

in vivo with a remarkable response in a ROS1-positive patient enrolled into the phase I trial of Crizotinib PROFILE 1001.[2] Results of the expanded ROS1-positive cohort of that study were recently reported[4]: Crizotinib treatment was associated with an Overall Response Rate (ORR) of 72%, a median Progression Free Survival (PFS) of 19.2 months and a 1-year Overall Survival (OS) rate of 85%. Interestingly, median duration of response with Crizotinib was longer than that previously reported in ALK-positive NSCLC suggesting a more effective blockage on ROS1 or a more indolent nature of ROS1-rearranged tumors.[4] These data are preliminary and deserve further evaluation, since a recent European retrospective study (EUROS1) reported only a modest 9.1 months median PFS.[10]

It has been reported that ROS1-positive NSCLCs may be associated with increased sensitivity to Pemetrexed-based chemotherapy.[3,11]

Here we report a case of a lengthy progression-free survivor on Pemetrexed-based chemotherapy who was on treatment for about 30 months from treatment start with 27 courses of Pemetrexed monotherapy. The reasons of this outstanding sensitivity to Pemetrexed, exceeding by far the median PFS observed in registrative trials with Pemetrexed maintenance (mean number of maintenance cycles 7.9 and a median PFS of 4.1 months in the PARAMOUNT trial),[12,13] may be related to an increased sensitivity to a Pemetrexed-based regimen or to a more indolent outcome associated with this rare genetic abnormality or both.[3]

Oncogene-addicted NSCLCs may present peculiar patterns of metastatization[14] and, in some instances, it has been reported an increased incidence of unusual site of metastases. Ovarian metastases from solid tumors account for ~5–10% of all malignant ovarian tumors, but it is an extremely rare complication in lung cancer (0.4% of metastatic ovarian cancers). Among lung cancers, adenocarcinoma is the most common histology after small cell carcinoma.[15] The histological type of adenocarcinoma of the lung more frequently associated with ovarian metastases was acinar in a large retrospective study,[15] a histotype commonly observed in patients with ALK and ROS1 rearrangements.[16-18] Moreover, ovarian metastases were more commonly among young women with lung cancer, another feature usually common in ALK- and ROS1-positive patients. A few cases reported ovarian involvement from ALK-positive NSCLCs,[19-21] but not in patients with other genetic rearrangements, including ROS1. To our knowledge this is the first report of bilateral ovarian metastases in a ROS1-translocated adenocarcinoma of the lung.

We recognize that TTF-1 expression may be occasionally found in primary ovarian cancers, but the concomitant presence of other features associated with lung malignancies may help the pathologist (histopathological features, use of other immunohistochemical markers, clinical data).[22] Moreover, the presence of ROS1 rearrangements has been also reported in ovarian low malignant potential (LMP) tumors.[23] However, in

the present case the diagnosis of ovarian metastases was based on the history of lung adenocarcinoma, the pathological and immunohistochemical findings (TTF-1 +, CK7+, WT1 -) and finally the genomic testing results (ROS1 rearrangement revealed by FISH). All these data were necessary to confirm the clinical suspect of metastases.

These findings highlight the importance of an accurate radiological work-up in patients with lung cancer, especially in those with oncogene-addicted tumors, such as ROS1-rearranged NSCLCs. The enlargement of ovaries or the development of ovarian masses may be expression of treatment failure of a systemic therapy rather than the development of a second concomitant tumor. Therefore, physicians should be aware of this rare event and pathologists may be informed on the clinical history of patients undergoing surgery in order to prevent misdiagnosis of ovarian metastases in this rare NSCLC subtype.

Disclosure of potential conflicts of interest.

No potential conflicts of interest were disclosed.

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