Sequential EGFR mutation and ALK rearrangement in adenocarcinoma lung, with rare metastasis to bilateral breast, ovary and endometrium

V.R. Anjali a,*, Rambha Pandey a, Astha Srivastava a, Madhu Rajeshwari b, Durgatosh Pandey c, M.C. Sharma b

a Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India
b Department of Pathology, All India Institute of Medical Sciences, New Delhi, India
c Department of Surgical Oncology, Artemis Hospital, Gurgaon, India

1. Introduction

Lung cancer is the fourth most common cancer among females, and second leading cause of cancer related death worldwide. Almost 50–60% of patients present with metastatic disease. The most common sites of metastasis are liver, adrenal gland, bone and brain. Metastasis to female genital tract from lung primary is rare. Ovaries are common sites of metastasis for genital primary, but metastasis to endometrium from extra genital primary is extremely rare. Similarly, metastasis to breast is also extremely rare accounting for only 0.4%–1.3% [1,2].

Approximately 60–64% of patients with metastatic NSCLC have EGFR (epidermal growth factor receptor) mutation or ALK (anaplastic lymphoma kinase) rearrangement. Both are usually mutually exclusive [3]. ALK rearrangement can be seen in about 1–1.5% of EGFR mutated NSCLC [4]. Here we present a case report of a young lady who had upfront metastatic adenocarcinoma of lung, both EGFR mutation and ALK rearrangement, with rare sites of distant metastasis to bilateral breast, ovary and endometrium, with 5 years survival.

2. Case report

Thirty-seven years old premenopausal lady presented with complaints of cough and shortness of breath for four months duration. She had associated fatigue, loss of weight and loss of appetite. No other co-morbidities. Patient was evaluated, CXR showed massive left sided pleural effusion. CT-thorax showed massive left sided pleural effusion with nodular deposits in parietal pleura along the chest wall. Multiple subcarinal and hilar lymph nodes were present. Mammogram done was normal study (BIRADS 0-Left and BIRADS 1-Right). MRI(L) Breast revealed peri areolar thickening likely inflammatory. Baseline PETCT scan in July 2013 showed (L) side massive pleural effusion with multiple pleural based nodules in (L) lung. Left breast showed cutaneous thickening with no FDG uptake. Pleural fluid cytology was positive for adenocarcinoma. Pleural biopsy confirmed the adenocarcinoma and tumor cells were immunopositive for CK-7 and TTF, while were negative for ER, PR, HER2NEU and GCDFP-15 Fig. 1. Patient was diagnosed as carcinoma lung with malignant pleural effusion, and started on palliative chemotherapy with Paclitaxel and Carboplatin. Response assessment after three cycles with PET-CT showed partial response and chemotherapy was continued for 3 more cycles. After 6 cycles of chemo PET CT showed disease progression. Mutation analysis by DNA sequencing showed mutation in exon 19 and exon 20 in EGFR gene Fig. 4. Patient was started on Tablet Erlotinib from March 2014. Patient had subjective improvement and radiologically partial response. After 10 months patient had progressive disease, with metastasis to bilateral breast. Biopsy from breast lesion showed metastatic adenocarcinoma, immunopositive for CK-7, TTF-1, while negative for ER, PR, Her2neu, CK 20, consistent with lung primary Fig. 2. ALK mutation study by

* Corresponding author.
E-mail address: dr.anjali.v.ramdulari@gmail.com (V.R. Anjali).

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immunohistochemistry (DSF3) was positive in the breast biopsy Fig. 5. Patient was started on Crizotinib from October 2014. Interim PET CT showed near complete response of the disease. After progression free survival of 1 year and 7 months, patient had progressive disease with brain metastasis. Patient received whole brain radiotherapy 30Gy/10 fractions and was started on Ceritinib in April 2016. After 11 months patient had progressive disease with increase in number of bone and brain metastasis with peritoneal deposits and adnexal mass and uptake in uterus Fig. 6. Serum CA 125 was normal. Endometrial curettage was again consistent with metastatic adeno carcinoma immunopositive for TTF1 (clone 8G7G3/1) Fig. 3. Patient was started on single agent Docetaxel. After 3 cycles of chemotherapy there was partial response and chemo was continued for 3 more cycles, evaluation PETCT showed progressive disease. Patient was started on Tablet Alectinib in November 2017. Patient had progressive disease after 6 months.

3. Discussion

Discovery of driver mutation has started a new era of targeted treatment in metastatic adenocarcinoma lung. Palliative chemotherapy was the only available treatment option for metastatic lung cancer till FDA approved gefitinib in 2003. Up to 60–70% of metastatic NSCLC patients will have oncogenic driver mutations. Molecular studies have shown several oncogenic driver mutations in NSCLC: EGFR mutation, ALK rearrangement, c-ros (ROS1) oncogene 1, rearranged during transfection (RET), mesenchymal-to-epithelial transition (MET), human epidermal growth factor receptor 2 (HER2). The major mutations are seen in KRAS (25%), EGFR (17%), anaplastic lymphoma kinase (ALK) (7%), MET (3%), HER-2 (2%), ROS1 (2%), BRAF (2%), RET (2%) [5]. The targeted therapies have shown to improve PFS and response rate in metastatic NSCLC and is used in first line treatment if mutation is present.

Approximately 10–15% of Caucasian and 30–62% of Asian population has EGFR mutation. Most common mutation occurs in exon 19 deletion or exon 21 L858R point mutation. EGFR mutation is usually seen in females, younger age group with no history of smoking. Gefitinib and erlotinib are first generation reversible TKIs (Tyrosine kinase inhibitors). Gefitinib is the first TKI to be approved for the treatment of metastatic NSCLC. In the Iressa Pan-Asia Study (IPAS) trial, gefitinib showed improved PFS when compared with standard doublet chemotherapy [6]. Erlotinib has also shown increased PFS when compared with standard chemotherapy in OPTIMAL [7] and EURTAC trials [8]. Afatinib and dacomitinib are second generation irreversible TKIs. The LUX- Lung 3 trial has showed significant increase in PFS of 6.7 months for afatinib when compared with chemotherapy [9]. Osimertinib and rociletinib, are the third generation EGFR inhibitors. Osimertinib was initially approved for patients who developed T790M resistance mutation, later expanded for EGFR deletion 19 or L858R mutations.

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase receptor of the insulin receptor superfamily. Translocation of ALK and Echinoderm Microtubule-Associated Protein-Like 4 (EML4) from an inversion of the short arm of chromosome 2 and results in fusion protein EML4-ALK gene. ALK/EML4 fusion is seen in 3–7% of adenocarcinoma of lung. Usually seen in young age, light or never smokers, central tumors, with increased pleural effusion, extra nodal invasion and lymphangitis. Crizotinib is first generation ALK inhibitor. In PROFILE study, crizotinib had better median PFS and objective response rate than chemotherapy [10]. Ceritinib, Alectinib and Brigatinib are second generation ALK inhibitors approved for patients with ALK rearrangement. Ceritinib was initially approved for patients who had progressed on, or those who had not tolerated crizotinib. Later Ceritinib and Alectinib was approved in first line setting. Alectinib has shown to delay the CNS progression compared to Crizotinib.

The presence of driver mutations EGFR and ALK are found to be mutually exclusive in the same tumor. ALK rearrangement is usually mutually exclusive with EGFR and KRAS mutation. Co-existence of
EGFR mutation ALK rearrangement is seen only in 1–1.5% of patients. The other treatable driver mutations include ROS1 fusion gene, BRAF mutation and MET mutation.

In the study by Guibert et al., out of 17,826 patients, only 165 (0.93%) had multiple genetic alterations involving oncogenic drivers, of which 0.91% was double mutations and 0.02% were three triple mutations. The most common co-mutations occurring de novo with EGFR were PIK3CA, KRAS, ALK and BRAF mutations [11]. Among 1683 NSCLC tumors analyzed by Gainor et al., no co-mutation was detected [12]. These data are concordant with the results of a meta-analysis conducted by Wang et al., in which only 0.75% of patients (three of 399) with EGFR mutations also harbored ALK rearrangement [13].

In our patient EGFR mutation study was done from lung biopsy at presentation and ALK mutation was done later when the patient had disease progression, with breast metastasis. It is difficult to say whether both oncogenic driver mutation were present in same tumor cell or in different subclones of tumor. Patients, who have EGFR mutation, usually do not undergo ALK testing since they are mutually exclusive. But this case report reminds us that there is a subset of patient who benefits from mutational studies for all oncogenic driver mutation and need for repeat biopsy from new metastatic site if possible. There is no consensus regarding the treatment sequencing if both mutations are coexisting. Further studies help us in sequencing the treatment for patients with both EGFR mutation and ALK rearrangement.

The most common metastatic sites are the liver, adrenals, bone and brain. Breast and female genital tract are rare sites of metastasis from lung primary. Ovary and vagina are the usual metastatic sites for genital and extra genital primary [14]. Endometrial metastasis from lung primary is extremely rare, to best of our knowledge only 4 cases have been reported [15–17]. The incidence of metastatic spread to breast from extra mammary sites is also rare accounting for 0.5–3% [1,18]. Here in our case report, a young lady who presented with upfront metastatic adenocarcinoma of lung, having both EGFR mutation and ALK rearrangement. Patient had distant metastasis to rarest sites like bilateral breast, ovary and endometrium. Patient received two lines of TKIs, three lines of ALK inhibitors during the course of treatment and lived with good quality of life for 5 years.

Abbreviations

| Abbreviation | Description               |
|--------------|---------------------------|
| EGFR         | epidermal growth factor receptor |
| ALK          | anaplastic lymphoma kinase  |
| CT           | computed tomography        |
| MRI          | magnetic resonance imaging |
| PET          | positron emission tomography|
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100954.

Fig. 3. Endometrial aspirate showing a similar adenocarcinoma with glandular and solid areas (H&E, x200). Tumor cells are strongly immunopositive for TTF 1 (IHC, x100).

Fig. 4. EGFR mutation detected from lung biopsy by DNA sequencing. E746_A750del mutation in exon 19 and T790M mutation in exon 20 are detected.
Fig. 5. Mutation study from breast biopsy showing ALK D5F3 positive. Test Performed using Ventana anti-ALK (D5F3) Rabbit monoclonal primary antibody along with Ventana detection kit on a Ventana Benchmark XT autostainer.

Fig. 6. FDG-Positron emission tomography – computed tomography (PET-CT) scan showing bilateral breast(A), ovarian and endometrial(B) metastasis.

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