ROS1 positive non-small cell lung cancer with pulmonary embolism in a 22-year woman

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Abstract

ROS1-rearrangement occurs in 1-2% of non-small cell lung cancer (NSCLC). This mutation is predominantly seen in relatively young, non-smoker, female with adenocarcinoma. Association of pulmonary embolism with ROS1-rearranged NSCLC has been suggested. We report a case of a 22-year-old woman with ROS1-positive NSCLC and pulmonary embolism. This case possibly represents the youngest patient in the literature.

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Introduction

Genetic analysis in the field of lung cancer has identified various driver mutations. Although ROS1-rearrangement is relatively rare, it is now being increasingly detected in non-small cell lung cancer (NSCLC). ROS1-positive patients are usually young. Targeted therapy is also available and recommended for this aberration. Studies have suggested a greater association of thrombotic events with ROS1 fusion protein. We present a case of a 22-year-old woman having ROS1 rearranged advanced NSCLC with pulmonary embolism.

Case Report

A 22-year-old never smoker female presented with complaints of non-productive cough and breathlessness for 2 months. Her past history and family history were unremarkable. General physical examination revealed a small right medial supraclavicular lymphnode (1×1 cm). Her pulse rate was 106 per min and respiratory rate was 26 per min. She was maintaining saturation of 93% in room air as measured by pulse oximetry. On respiratory system examination, there was decreased vesicular breath sound on left hemithorax. Breast and other systemic examinations revealed no abnormality. Initial laboratory parameters were as follows: hemoglobin 12.2 gm/dl, total leukocyte count 9650 mm^3, platelet count 315,000 mm^3, urea 21 mg/dl, creatinine 0.7 mg/dl. Liver function test were also normal. Arterial blood gas analysis revealed- pH 7.49, Pco_2 32, Po_2 74 and Hco_3^- 20.9. Chest radiograph showed homogenous opacity in left mid and lower zone with obliteration of costophernic angle with prominence of left hilum (Figure 1). Electrocardiogram was suggestive of sinus tachycardia with heart rate of 109 per min. In contrast enhanced computed tomography (CECT) thorax, there was a heterogenous mass (5.1×4.4×4.2 cm) in left hilar region with mediastinal lymphadenopathy along with left sided pleural effusion. Thrombus was noted in main and descending branch of right pulmonary artery (Figure 2). Ultrasonography guided thoracentesis done and haemorrhagic fluid was aspirated. Pleural fluid analysis showed protein - 5.3 gm/dl, glucose – 36 mg/dl, adenosine deaminase - 33.8 U/l, with cytology having malignant cells. Immunohistochemistry of pleural fluid cell block revealed that the tumour cells were strongly immune-positive for TTF1. The mutation analysis was positive for ROS1, negative for EGFR and ALK. Lower limb doppler study showed no evidence of deep venous thrombosis (DVT). CECT abdomen, contrast enhanced

magnetic resonance imaging of brain and whole body bone scan showed no evidence of metastasis. So a diagnosis of ROS1 positive stage IV adenocarcinoma lung with pulmonary embolism (PE) was made. After completing 4 cycles of conventional chemotherapy, she was switched over to ROS1 targeted therapy along with anticoagulation.

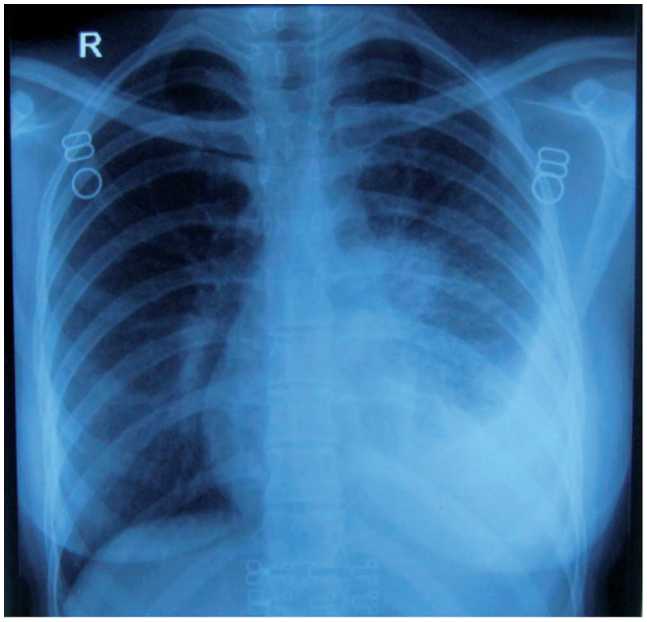

Figure 1. Chest radiograph showing homogenous opacity in left mid and lower zone with costophrenic angle obliteration and left hilar prominence.

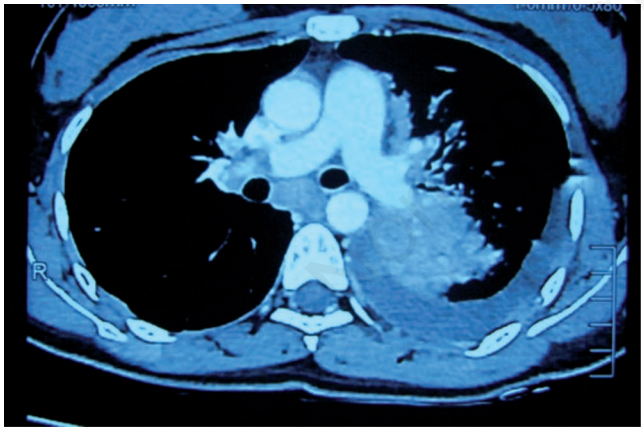

Figure 2. CECT thorax showing a heterogenous mass in left hilar region with mediastinal lymphadenopathy and left sided pleural effusion. Thrombus is present in right main pulmonary artery.

Discussion

ROS1-rearrangements are found in 1-2% of NSCLC. ROS1-positive patients are mostly young, non-smoker and have predominantly adenocarcinoma. The results from PROFILE 1001 have shown that ROS1-rearranged NSCLC patients had a median age of 55 years with the lowest age of 25 years. Fifty seven percent patients were female, 75% were never smoker and 96% had adenocarcinoma in histology [1]. In a retrospective analysis of similar cohort, Park et al. reported that most of these patients were female (68.9%) and never-smokers (75.7%). The lowest age at diagnosis in this study was 28 years [2]. In a single centre study from India, ROS1 positive patients had median age of 54 years with lowest age reported was 45 years [3]. In this case report, the patient was young never smoker female having lung adenocarcinoma. To our knowledge this is the youngest individual having ROS1 positivity till date.

Venous thromboembolism (VTE) is one of the important causes of mortality and morbidity in lung cancer patients. Emerging evidences propose that oncogene-addicted NSCLC may be at a higher risk of thrombophilia in comparison to the general population with NSCLC. Various studies have shown increased incidence of thromboembolism in ROS1 rearranged NSCLC (Table 1). Higher incidence of peridiagnosis thromboembolic events has also been found in ROS1 rearrangement compared to EGFR (odds ratio: 2.24) and KRAS (odds ratio: 2.62) mutant NSCLC [6]. The METROS trial has concluded that patients with advanced ROS1-rearranged NSCLC have 3- to 5-fold more incidence of VTE compared with the general population with NSCLC [5]. The underlying mechanisms of this association are unclear. ROS1-rearranged lung adenocarcinomas commonly have abundant extracellular mucus and this cancer-related mucin results in systemic activation of platelets, aggregation, and subsequent embolization via binding to L-selectin [7,8].

Conclusions

ROS1-rearrangement is predominantly seen in young and non-smoker female and may be considered as a risk factor for VTE. This case report represents the youngest person reported so far with ROS1 mutated NSCLC.

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Table 1. Studies showing association between ROS1 NSCLC and thromboembolic events.

Study	Mean age	Female (%)	Non-smoker (%)	Adenocarcinoma (%)	Median follow up	Thromboembolic events (%)	Pulmonary embolism (%)	DVT (%)
Alexander *et al.* [4] (2020)	53 (31-80)	74	88	96	10.9 months	48	31	29
METROS trial [5] (2019)	50 (24-82)	64.5	56.25	100	36.4 months	41.6	46.4	39.2
Ng *et al.* [6] (2018)	53.83 (±11.76)	53.7	77.7	89	3 months	34.7	10	9

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