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Diffuse Cerebral Infarction Due to Massive Thromboembolism in A Young Male Patient With ALK-Positive Non-Small Cell Lung Cancer: Is the ALK Rearrangement Related to Thrombosis?

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Abstract

The risk of thromboembolism is high in patients with lung adenocarcinoma, especially in patients with ALK rearrangement. The mechanism of thromboembolism due to ALK rearrangement is still unknown. Here, we present a case of diffuse cerebral infarction due to massive thromboembolism in a 25-year-old young male patient with lung adenocarcinoma and ALK rearrangement. Thrombosis, apart from metastasis, should be kept in mind when cranial symptoms develop in patients with lung cancer with ALK rearrangement. In addition, these patients should be followed closely in terms of thrombosis both at diagnosis and during treatment.

Keywords: non-small cell lung cancer; ALK rearrangement; thromboembolism

Introduction

The risk of thromboembolism is increased in cancer patients and its incidence varies in different tumor types [1]. Thromboembolic events are common in lung cancer and are relatively higher in adenocarcinoma than in other subtypes [2]. Driver mutations in lung adenocarcinoma affect the behavior of cancer and the prognosis of the disease. In addition, these different genomic mutations have been found to be associated with thromboembolic events at varying rates. *Anaplastic lymphoma kinase* (*ALK*) rearrangement is detected in approximately 5% of patients with non-small cell lung cancers (NSCLC), and targeted tyrosine kinase therapies can be used in these patients [3]. Patients with ALK rearrangement have an increased risk of both venous and arterial thrombosis [4]. The risk of venous thromboembolism was found to be 3 to 5 times higher in patients with ALK rearrangement [5]. However, there is limited information about arterial thromboembolism risk and mechanism in this patient group with driver mutation. The mechanism of thromboembolism in patients with ALK rearrangement is still unclear. Here, we present a case of diffuse brain infarction due to massive thromboembolism in a young male patient with ALK-positive non-small cell lung cancer.

Case report

A 25-year-old male patient was admitted to our clinic with complaints of pain in the pelvic region lasting more than 3 months. The patient had no recent history of any surgery. The patient's weight according to height was within normal limits. On physical examination, there is tenderness in the pelvic region. Positron emission tomography (PET-CT) imaging reveals a lesion with a high probability of primary tumor obliterating the bronchus in the right hilar region, as well as widespread metastatic lesions including pleural, pancreatic, liver, right adrenal, and skeletal system (**Figure 1**).

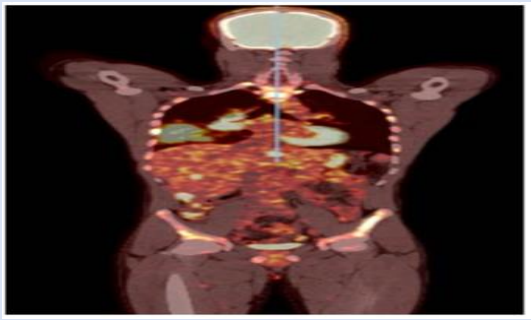

Figure 1: PET-CT image of the patient.

The biopsy taken from the mass in the patient's lung was found to be lung adenocarcinoma. Driver mutation tests were requested to make a treatment decision for the patient. However, cisplatin and paclitaxel chemotherapy were started due to the widespread disease, high tumor burden, and rapid clinical progression. In addition, zoledronic acid treatment was given to the patient due to bone metastasis.

Our patient's leukocyte, hemoglobin, and thrombocyte values were within normal limits. During the follow-up, the patient developed severe headaches, nausea, and blurred vision. In cranial MRI, multiple foci compatible with acute infarction were observed in both cerebellar hemispheres, occipital cortex, white matter, and frontoparietal cortex **(Figure 2)**.

Figure 2: Diffuse areas of acute infarction in both cerebral hemispheres on MRI.

The patient had complaints of pain and temperature increase in the right leg and Homan's sign was positive. Thrombosis causing a filling defect in the right popliteal vein was observed in lower extremity venous Doppler ultrasonography.

In addition, in the thorax CT angiography of patients with dyspnea, there is a filling defect compatible with embolism in both main pulmonary arteries and in the lobar pulmonary artery leading to the lower lobe on the right side **(Figure 3)**.

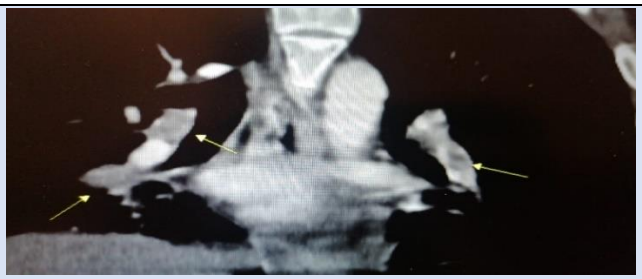

Figure 3: Thorax CT angiography has filling defect compatible with embolism in both main pulmonary arteries, on the right also in the branch of the lobar pulmonary artery leading to the lower lobe.

A treatment dose of anti-coagulant was started and a thrombophilia panel was studied. Factor II (G20210A) and V Leiden were homozygous normal, and MTHFR (A1298C and C677T) heterozygous deficiency was found in the thrombophilia panel. Alectinib, a tyrosine kinase inhibitor was administered at a dose of 2x600 mg/day via a nasogastric tube to the patient who was found to have positive ALK rearrangement. Within days, there was an improvement in consciousness, vision problems, and swallowing reflex returned. Partial response to treatment was detected in the control PET-CT

imaging of the patient. Significant regression was detected in the cerebral infarct area in cranial MR imaging (**Figure 4**). The patient's follow-up and treatment continued regularly. Our patient died in the 18th month of follow-up.

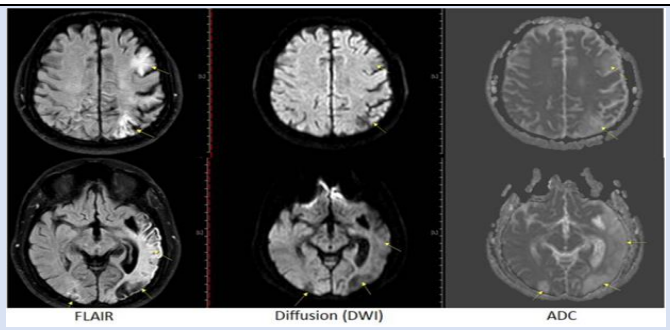

Figure 4: Chronic infarcts and parenchymal malasia areas in the left cerebral hemisphere, temporo occipital, and right occipital on MRI.

Discussion

Thromboembolism is seen between 7-13% in lung cancer, and this risk is about 23% in cases with driver mutations [6]. The rate of thromboembolism in the lung adenocarcinoma subtype is 3 to 4 times higher than in the squamous and small cell subtypes [7]. Venous thromboembolism risks differ according to the type of mutation seen in non-small cell lung cancer. The rates of ALK rearrangement in non-small cell lung cancers range from 2 to 7% [8]. With the new generation ALK tyrosine kinase inhibitors, survival can extend up to 4 to 5 years. However, there is a risk of thromboembolism in the follow-up of these patients with the prolongation of life expectancy [9]. Various views have been proposed regarding the mechanism of thrombosis formation in patients with ALK rearrangement. In one of these views, it has been suggested that ALK rearrangement may activate the NF-kB signaling pathway to increase thromboembolism through tissue factor [10]. According to another view, it has been argued that the predominant thrombotic risk is due to gene alteration and kinase activity [11]. In some preclinical studies, it has been argued that oncogene and tumor suppressor genes increase tissue factor and cause hypercoagulability and thus thromboembolism [12]. In another study, it was stated that increased thrombotic risk in patients with ALK rearrangement was due to increased mucin production [13]. However, the mechanism of thrombosis in patients with ALK rearrangement is still unclear.

Various studies on thromboembolism in patients with ALK rearrangement have had different results. Some studies have reported a higher risk of venous thromboembolism in patients with ALK rearrangement [5,14]. However, in the study of Lee et al., no difference was found in terms of venous thromboembolism in patients with and without ALK rearrangement [15]. There is limited information and studies in the literature, especially regarding arterial thrombosis with ALK rearrangement. Although the rate of arterial thrombosis was found to be numerically higher in a population-based study in patients with ALK-positive NSCLC (7% vs 6.5%), it was not statistically significant [4]. In the study of Al-Samkari et al., an increased risk of arterial thromboembolism was found to be associated with ALK positivity [16]. Cranial infarct, an arterial thromboembolism can be seen in approximately 2.9% of patients with lung cancer [17]. However, limited information is available on cerebral infarction rates in patients with ALK-positive lung adenocarcinoma.

Our patient had deep vein thrombosis, pulmonary embolism and also cranial thromboembolism, an arterial thrombosis. Headache, blurred vision, and altered consciousness were seen as cranial symptoms in our patient. The MTHFR gene was found to be heterozygous in our patient, but the patient had no previous history of thrombosis. In our patient, there was no other risk factor for thromboembolism other than lung cancer, and Khorana risk score was calculated as 1. Although the risk of thrombosis due to lung cancer is high, we think that the increased risk of massive thromboembolism in our case is due to ALK rearrangement, as reported in the literature. According to our knowledge, it is the first case in the literature with ALK-positive lung adenocarcinoma at the age of 25 years and who developed diffuse brain infarction due to massive arterial thromboembolism. Therefore, we think that our case may contribute to the literature.

Conclusion

Thrombosis should be kept in mind, apart from metastasis, when cranial symptoms develop in patients with lung cancer with ALK rearrangement. In addition, patients with ALK rearrangement should be followed closely in terms of thrombosis both at diagnosis and during treatment.

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