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Case Report

FIP1L1-PDGFRA-Gene Fusion in Patients with Eosinophilia and Spinal Manifestation

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ABSTRACT:

The rapid proliferation of progenitors of blood cells increases the chances of mutations and production of dysfunctional cells that often suppress the normal hematopoietic system. Chronic eosinophilic leukemia, characterized by elevated levels of pink-staining bilobed eosinophils, is one of the known pathological presentation of unregulated proliferation of dysplastic blood cells. Tissue infiltration of heart, lungs, skin, gut and other organs has been observed previously but the formation of a mass, comprising of myeloid and eosinophilic infiltrates, around the spinal cord has rarely been seen. With the spinal mass removed, our reported patient's eosinophilia responded to short course of imatinib however, left him bed bound due to lower limbs paralysis.

Keywords: FIP1L1-PDGFRA, spinal mass, eosinophilia.

Introduction

FIP1L1-PDGFRA gene fusion with chronic eosinophilic leukemia is a rare hematological disorder characterized by excessive production of eosinophils in the bone marrow. This results in elevated levels of eosinophils and subsequent infiltration of these cells into various peripheral organs leading to their dysfunction.1 The involvement of multiple organs including heart, gut, skin and lungs are reported with similar predominance however, the CNS involvement in the form of a paraspinal mass causing spinal cord compression and leading to lower limb paralysis is new to our knowledge and is rarely reported till date.[2]

Case Report

A 44 years old male, teacher by profession, developed sudden bilateral lower limb paresthesia followed by loss of power in both lower extremities the next day. This was also associated with urinary incontinence. He had high grade intermittent fever for the last 2 months which was accompanied by fatigue and night sweats however, weight loss was not reported. According to the patient, in the past few months he once experienced mild interscapular and lower limb pain which he attributed to muscle spasm due to daily strenuous exercise and opted for physiotherapy session for pain relief.

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The patient had no other co-morbidities such as hypertension, diabetes mellitus, neuromuscular disease, joint or cardiovascular disease and any family history of malignancy. There was no history of trauma or any respiratory or gastrointestinal infection that could be associated with his symptoms.

On examination, the power in the right leg was 1/5 and in the left leg was 0/5. He had absent knee and ankle reflexes and there was no response to touch and pain stimulus on sensory examination in both limbs. There were no palpable superficial lymph nodes, no sternal or abdominal tenderness.

An urgent MRI dorsolumbar spine with contrast and CT chest were performed. The MRI reported a paraspinal mass at the level of T5/T6 with heterogenous marrow signals in adjacent vertebra. The CT scan reported mild hepatosplenomegaly. Moreover, his blood tests showed a Total leukocyte count (TLC) of 48,000 cells/µL with an eosinophil count of 26200 cells/µL. An emergency surgical decompression was performed with a midline interscapular incision. The mass was removed and titanium rods were placed to support the adjacent vertebrae as the paraspinal mass damaged the surrounding vertebrae. The mass was sent to lab for histopathology. The patient was commenced on antibiotics and corticosteroids post operatively however the response to steroids was poor. There was no improvement in the symptoms of the patient after surgery. A full body CT was performed the following day, for any signs of metastasis, which was unremarkable. Post op MRI could not be obtained to confirm the complete removal of the mass because of

the unclear images due to metal rods. Histopathology of spinal mass was consistent with myeloid and eosinophilic infiltrate and negative for CD34, CD117, CD10, reactive for CD3, positive for MPO and low for Ki67 marker (1-2%). There was no evidence of granuloma, metastatic carcinoma or lymphoma on histopathology report. Bone marrow biopsy revealed that bone marrow was hypercellular with marked eosinophilia and absence of blast cells. PCR for JAK-2 kinase mutation and BCR-ABL was negative. Fluorescent in situ hybridization (FISH) for PDGFR-B and FGFR was negative while positive for FIP1L1-PDGFRA in 70% of the cells (*gene fusion studies courtesy: Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore*). Blood TLC spiked to 316,000 cells/µL and eosinophils to 34,000 cells/µL. Echocardiography was done to rule out any cardiac involvement and the results were normal. Following poor response to steroids, the patient was started on imatinib 100mg once daily for 14 days which caused marked reduction in his blood cell and eosinophil counts. Furthermore, 2 pints of whole blood and multiple pints of platelets were transfused to the patient to make up for his low Hemoglobin level and platelet count respectively. The patient developed bed sores a week after he was operated. The patient was unable to control his bowels and bladder and had immobility despite being operated and frequent physiotherapy sessions.

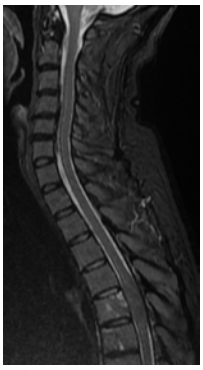
Figure 1: STIR

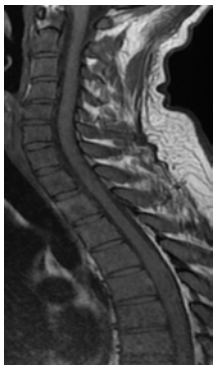
Figure 2: T1 Sag

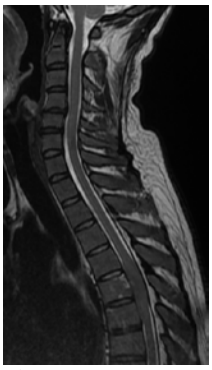
Figure 3: T2 Sag

Figure 1,2,3 shows Pre-Op mass at T5/T6

Discussion

FIP1L1-PDGFRA fusion gene results from interstitial deletion of 800kb on chromosome 4q12 and it is most commonly found in dysplastic eosinophils leading to hyper eosinophilia characterizing Chronic eosinophilic leukemia (CEL).1-3 However, the fusion gene is also detected in other cells including neutrophils, mast cells, T-cells, B-cells and monocytes. This suggests that this mutation occurs in pluripotent hematopoietic precursor cells that can give rise to multiple lineages. The mechanism for preferential expansion of eosinophils and mast cells in chronic eosinophilic leukemia is still unknown.4 The genetic product of the novel gene FIP1L1-PDGFRA, formed as a result of fusion of FIP1L1 gene and PDGFRA gene, is a continuously activated tyrosine kinase that causes uncontrolled and persistent proliferation of eosinophils. The fusion gene can be detected accurately with 3 color probe and FISH technology.5 The pathophysiologic mechanism leading to organ damage is a multistep process. Initially, eosinophils cause necrosis which is followed by local platelet thrombi that may have the potential to embolize. The damage is induced by contents of eosinophilic granules, which mainly include major basic protein and eosinophilic cationic protein that causes endothelial damage and promotes hypercoagulability.[6] Multiple peripheral organ involvement has been reported with hematologic, cardiovascular, dermatologic, neurologic, pulmonary and splenic manifestations being the most common.

Cases of thromboembolism, peripheral neuropathy, dementia, epilepsy, cerebellar disease and eosinophilic meningitis has been reported in patients with neurological involvement6, however, a paraspinal mass causing compressive symptoms leading to lower limb paralysis has rarely been reported as clinical manifestation of CEL.

Imatinib is the preferred drug of choice in CEL having FIP1L1-PDGFRA. Being target specific for FIP1L1-PDGFRA, studies reported a dramatic response to low dose (100mg/day-200mg/day) imatinib therapy with about 3-log reduction in fusion transcripts compared to pre-treatment levels.[2,7] Most of the patients treated with imatinib achieved complete molecular remission. Very few patients were reported with relapses that were treated with long term imatinib therapy. Other treatment options for CEL include steroids, pegylated interferon alpha, hydroxyurea, cladribine, anti-thymocyte globulin, methotrexate, cyclosporine A and allogenic stem cell transplantation but they show partial to no response, frequent relapses and multiple adverse side effects. Alemtuzumab therapy is another treatment option which showed complete hematological response in CEL patients however, with this drug most patients relapsed. Further studies are required to evaluate the efficacy of Alemtuzumab in patients with CEL refractory to standard therapy.[8]

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