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SHORT COMMUNICATION

# Myeloid neoplasm with eosinophilia associated with isolated extramedullary *FIP1L1/PDGFRA* rearrangement

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Myeloid neoplasms with eosinophilia associated with *PDGFRA* rearrangement are very responsive to tyrosine kinase inhibitors (TKIs). Herein, we report a case of a 53-year-old man with eosinophilia and a well-differentiated extramedullary myeloid tumor with evidence of *FIP1L1/PDGFRA* rearrangement by fluorescent in situ hybridization in the extramedullary tissue. His bone marrow evaluation revealed a hypercellular marrow with eosinophilia but without evidence of a *FIP1L1/PDGFRA* rearrangement. The patient was treated with imatinib at a dose of 100 mg daily and responded with normalization of his peripheral eosinophil count. The case raises the possibility that an extramedullary myeloid tumor may represent a primary site for *PDGFRA* rearrangement, and highlights the importance of performing cytogenetic testing on extramedullary tissue. Detection of the chromosomal rearrangement is critical for initiation of effective targeted therapy that can improve patient outcomes.

**Keywords** Eosinophilia, extramedullary myeloid tumor, *FIP1L1-PDGFRA*, tyrosine kinase inhibitor, myeloproliferative neoplasm



## Introduction

The natural history of untreated myeloid/lymphoid neoplasms with eosinophilia has been traditionally aggressive with a high mortality rate; and standard, high-dose chemotherapy, as well as allogeneic hematopoietic stem cell transplant, were common treatments. Cytogenetic and molecular testing has generated a better understanding of the pathophysiologic mechanisms of the disease. In the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, the category of eosinophil-related proliferation, termed "myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*" (1,2), constitutes a heterogeneous group of hematologic disorders that result from formation of a fusion gene encoding an aberrant tyrosine kinase, leading to mutations in growth factor receptors. Approximately 20% of patients who present with hypereosinophilic syndrome (HES) have features suggestive of an MPN, and up to 80% of those have a *PDGFRA*-associated myeloproliferative neoplasm (MPN) (3).

The *FIP1L1-PDGFRA* fusion gene is formed as a result of a cryptic microdeletion at 4q12 (4,5). The chromosomal microdeletion at 4q12 includes the *CHIC2* locus and can be detected by fluorescence in situ hybridization (FISH) analysis using a probe for the *CHIC2* gene, which is uniformly deleted (6). The clinical implication of this microdeletion is that the subsequent *FIP1L1-PDGFRA* fusion gene has been identified as a therapeutic target for imatinib mesylate which has altered the natural history of *PDGFRA* and *PDGFRB*-rearranged neoplasms (4).

## Materials and methods

A 53-year-old man with a 2-year history of peripheral blood eosinophilia, with an absolute eosinophil count (AEC) that ranged between 2 K/μL to 4 K/μL presented with acute lower back pain and bilateral lower extremity weakness. Magnetic resonance imaging of the lumbar spine showed a contrast-enhancing mass at the L3-L4 spinous process, which appeared


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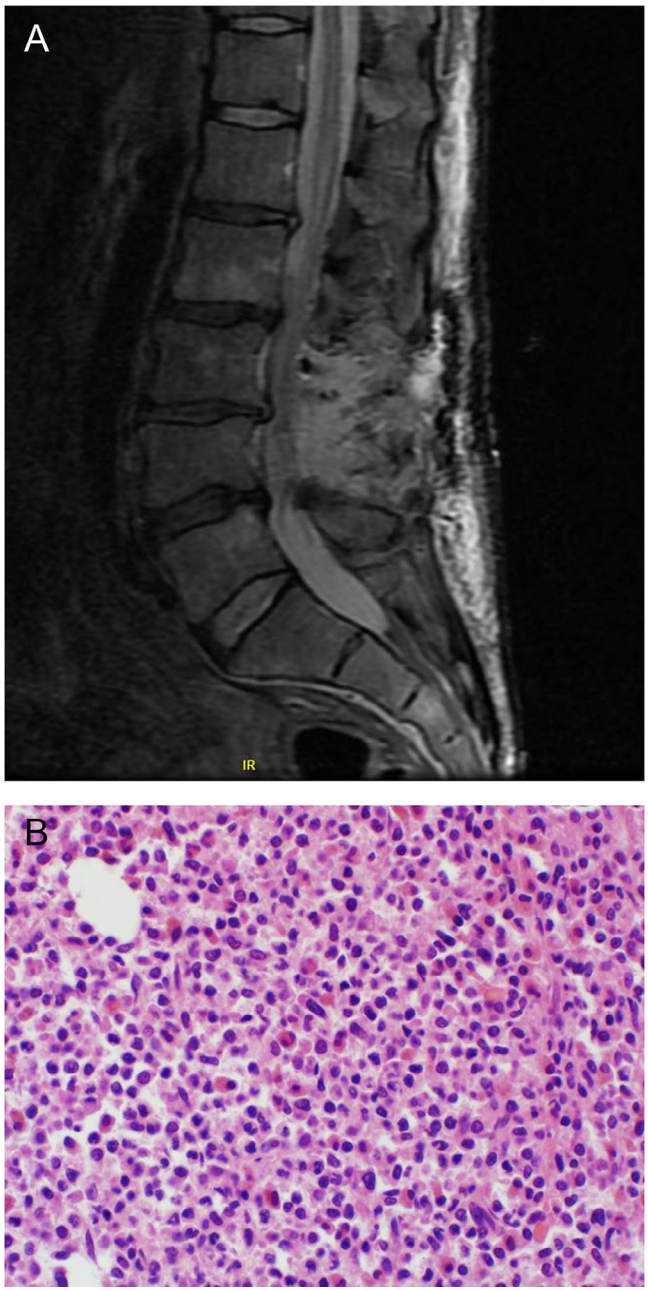


**Figure 1** A, T2-weighted magnetic resonance image of the lumbar spine shows a contrast-enhancing epidural mass at the L3-L4 spinous process that is compressing the thecal sac with total effacement of the subarachnoid space. B, Histologic evaluation of the epidural tumor (×200) shows diffuse sheets of maturing neutrophil granulocytes and eosinophils at various stages of maturation.

to be compressing the thecal sac, with total effacement of the subarachnoid space (Figure 1A). Complete blood count showed a normal leukocyte count of $7.8 \times 10^9$/L, with an AEC of $3.5 \times 10^9$/L. Chemistry panels, including liver function tests, were normal. He was started on high-dose corticosteroid therapy and urgently taken to the operating room for an L3-L4 laminectomy and resection of the epidural tumor.

Histologic evaluation of the epidural tumor showed diffuse sheets of maturing neutrophil granulocytes and eosinophils

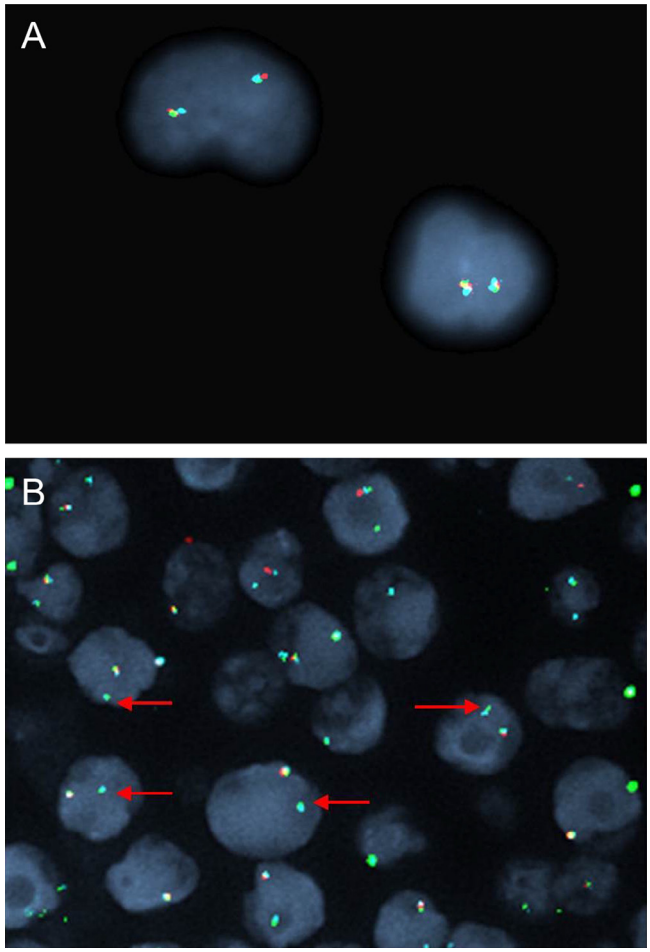


**Figure 2** FISH probes: *FIP1L1*(G)/*CHIC2*(R)/*PDGFRA*(A)[4q12]. A, *CHIC2*, *PDGFRA*, and *FIP1L1* gene regions present within the bone marrow aspirate. B, Loss of *CHIC2* (arrows); *FIP1L1* and *PDGFRA* are present. FISH indicates fluorescence in situ hybridization.

at various stages of maturation (Figure 1B). Scattered individual blasts were present, but sheets or aggregates of blasts were not identified. The tumor contained phagocytic macrophages and frequent apoptotic and mitotic figure. Immunohistochemical stains showed that the tumor cells were positive for CD43 and CD68, as well as CD163 in a subset of cells. They were negative for CD34, CD117, and E-cadherin; and for the lymphoid markers CD3, CD5, CD20, CD23, CD79a, and cyclin D1. Cerebrospinal fluid was negative for malignant cells by cytological evaluation.

A bone marrow aspirate and biopsy revealed a hypercellular marrow (70%), with trilineage hematopoiesis and increased numbers of eosinophils (21%). A reticulin stain showed only scattered linear reticulin, with no intersections present (score of MF-0 by WHO grading). A cytogenetic and molecular genetic workup of the bone marrow showed negative findings for *CHIC2/PDGFRA/FIP1L1* by FISH; and negative results for *JAK2V617F*, *CALR*, and *MPL* mutations by polymerase chain reaction (PCR) amplification (Figure 2A). FISH for *CHIC2/PDGFRA/FIP1L1* was performed on the epidural tumor and revealed *CHIC2* deletion with retention of the *FIP1L1/PDGFRA* gene regions in 83% of cells (Figure 2B).