# A Rare Presentation of Pediatric ALK-positive Histiocytosis as Palatal Mass with Response to ALK Inhibitor Crizotinib Treatment: Case report

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## Introduction

ALK-positive histiocytosis is a rare condition distinct from Langerhans cell histiocytosis (LCH) and is most frequently identified in infants and young children. [1,2] However, whereas LCH cells are CD1a and CD207 (langerin) positive, ALK-positive histiocytes are CD1a and CD207 negative.[1,2,4] The histologic differential diagnoses for ALK-positive histiocytosis include juvenile xanthogranuloma (JXG) and Erdheim-Chester disease (ECD).[2,3] Involvement is often systemic; although localized disease has been described, particularly in adults and adolescents. [2,5] Whereas LCH and JXG are traditionally treated with systemic chemotherapy, there is no agreed upon best therapy for ALK-positive histiocytosis. Crizotinib is a first-generation ALK inhibitor known to be used in ALK-rearranged non-small cell lung cancer (NSCLC)[6], ALK-positive rhabdomyosarcoma[7], ALK-positive neuroblastoma [8], refractory solid tumors, and anaplastic large-cell lymphoma[9]. We present a case of a patient with ALK-positive histiocytosis who has been successfully treated with crizotinib.

## Case

***Clinical Presentation.*** *A* 2-year-old male presented with a 2 cm painless hard palate mass, discovered incidentally during routine dental care. He did not have difficulty eating, difficulty breathing, weight loss, headaches, epistaxis, oropharyngeal bleeding, fevers, night sweats, vomiting, diarrhea, polyuria, polydipsia, change in activity level, or other rashes. He did have a remote history of diaper rash thought to be due to cloth diapers, which resolved following change of diaper type and miconazole treatment. There is no known family history of childhood malignancies. There was no evidence of hepatosplenomegaly on exam. Pre-treatment maxillofacial computed tomography (Fig.1A) demonstrated an erosive mass at the anterior palate. Nasal endoscopy and incisional biopsy of hard palate lesion was performed by pediatric otolaryngology team.

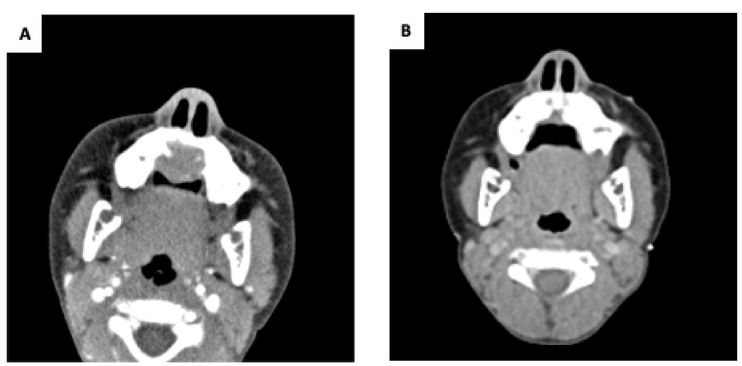


FIGURE 1 A: Computed tomography, pre-treatment, demonstrating an erosive mass at the anterior palate, extending into the inferior nasal cavity. B: Computed tomography, 1.5 months into treatment and approximately 8.5 months from Image A.

## Case

***Pathology.*** Lymphoid infiltrate was noted in the squamous mucosa without evidence of lymphoproliferative disorder and no definite abnormal lymphoid populations. Numerous histiocytes with mild to moderate atypia with rare Langhans and Touton giant cells were reported. ALK stain was brightly positive in histiocytes (cytoplasmic pattern) rather than the lymphocytes which were negative. The atypical histiocytes were positive for CD163, CD68, CD4, lysozyme, S100 (variable), and Factor XIIIa. They were negative for CD1a, langerin, and *BRAF-V600E* mutation-specific antibody. FISH analysis confirmed ALK rearrangement in the 2p23 gene region. There was no morphologic or immunohistochemical evidence of bone marrow involvement by ALK-rearranged neoplasm.

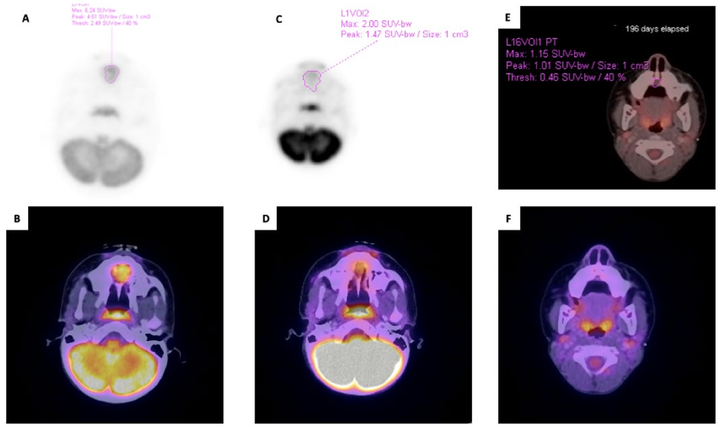


FIGURE 2 Positron emission tomography computed tomography (PET CT). A/B: Pre-treatment demonstrating FDG avidity of lesion. C/D: Approximately 1.5 months into treatment showing some decreased FDG avidity at the lesion. E/F: 6 months into treatment showing barely perceptible residual focal lucency and nearly resolved FDG avidity.

***Staging and Pre-treatment Evaluation.*** His disease was further evaluated and staged according to LCH-III guidelines . Skeletal survey showed no additional osseous lesion and abdominal ultrasound revealed no focal masses, hydronephrosis, or splenomegaly. There was borderline increased echogenicity of the liver, but with normal echogenicity of the portal triads. Positron emission tomography (PET) scan (Figs. 2A and 2B) demonstrated hypermetabolic palatal lesion with adjacent alveolar recess involvement and extension into nasal cavity. Nonspecific bilateral cervical and right external iliac nodes were present which were noted to potentially be reactive given patient's age. No hypermetabolic involvement of the spleen, liver, or additional suspicious skeletal lesions were noted.

Prior to initiation of chemotherapy with crizotinib, baseline laboratory analysis and electrocardiogram (ECG) were obtained, which demonstrated mild polycythemia. He had hypokalemia, hyperglycemia, and transaminitis that improved to normal limits on subsequent labs. ECG revealed sinus arrhythmia and was otherwise normal.

## Case

*Treatment and Response.* Chemotherapy with crizotinib was initiated at 280 mg/m$^2$/dose BID. One month into treatment, it was noted on exam that the palatal mass had significantly decreased in size. A repeat PET scan after completion of 1.5 months (Figs. 1B, 2C, and 2D) and 3 months of crizotinib revealed interval decrease in size and metabolic activity of the erosive anterior palatal mass. There were no new sites of disease or evidence of metastatic disease. Persistent metabolic activity of non-specific cervical lymph nodes and Waldeyer's ring was noted, again with the caveat that this may reflect reactive and physiologic etiology. A PET scan after 6 months of treatment demonstrated further reduction in focal lucency and FDG avidity (Figs. 2E and 2F). Patient has now completed therapy and is doing well in remission with plan for routine monitoring.

Approximately one month into treatment , he had significantly elevated transaminases consistent with grade I hepatotoxicity (asymptomatic). Crizotinib was held until transaminases were less than or equal to 3x ULN (about 2 weeks) and was restarted at 50% of initial dosing. Crizotinib was briefly held for intermittent, pruritic rashes about 2 months into therapy. He was also thought to have vision changes though noted to see generally well overall.

## Conclusion

While ALK-positive histiocytosis represents a minority of histiocytic proliferative disorders, it is histologically distinct from otherwise similar presentations. Its unique immunophenotypic and molecular characteristics provide an opportunity for targeted therapy with ALK inhibitors. This case provides an example of localized ALK-positive histiocytosis with the novel presentation of a palatal mass which was significantly responsive to crizotinib. Given the increasing number of case reports of ALK-positive histiocytosis and the specific treatment options available in ALK inhibitors, we support continued investigation of the clinical, histologic, radiographic, and genetic characteristics of this unique disorder in effort to optimize targeted therapy. Furthermore, we agree with the suggestion of Chan et al[1], Chang et al[2], and others to classify ALK-positive histiocytosis as a distinct entity within the group of histiocytic proliferative disorders.

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