Novel use of imatinib to treat mandibular fibrous dysplasia in Noonan's syndrome

Joshua W. Goldman[1], Sean Edwards[2], Rajen Mody[1], and Rama Jasty[1]

[1]University of Michigan Department of Pediatrics
[2]University of Michigan Department of Surgery

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Abstract

Fibrous dysplasia of the mandible typically begins during toddler years and culminates during puberty. These lesions may cause jaw disfigurement and may not be amendable to surgery. Imatinib successfully has treated cherubism associated with *SH3BP2* mutations, but similar lesions can present in other conditions such as Noonan syndrome. We report diagnosis of Noonan syndrome caused by a *PTPN11* activating mutation and successful treatment of the fibrous dysplasia of the mandible with imatinib.

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Joshua W. Goldman, MD[1*], Sean Edwards, MD, DDS[2], Rajen Mody, MBBS, MS[1], and Rama Jasty-Rao, MBBS[1]

Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA [1]

Department of Oral and Maxillofacial Surgery, University of Michigan Medical School, Ann Arbor, MI, USA [2]

Corresponding author information:

Joshua Goldman, MD

1500 East Medical Center Drive

MPB 4202 SPC 5718

Ann Arbor, MI 48109

734-936-9814 (office)

734-232-8740 (fax)

josgoldm@med.umich.edu

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Abbreviations utilized:

Abbreviation	Full term
SH3BP2	SH3 domain-binding protein 2
PTPN11	Protein-tyrosine phosphatase non-receptor type 11
MAP kinase	Mitogen-activated protein kinase
BRAF	Serine/threonine kinase BRAF
MEK	Mitogen-activated protein kinase 1
SOS1	Son of sevenless homolog 1
cKIT	Proto-oncogene cKIT

Abstract:

Fibrous dysplasia of the mandible typically begins during toddler years and culminates during puberty. These lesions may cause jaw disfigurement and may not be amendable to surgery. Imatinib successfully has treated cherubism associated with *SH3BP2* mutations, but similar lesions can present in other conditions such as Noonan syndrome. We report diagnosis of Noonan syndrome caused by a *PTPN11* activating mutation and successful treatment of the fibrous dysplasia of the mandible with imatinib.

Introduction:

Fibrous dysplasia of the mandible and maxilla, often referred to as cherubism, begins during toddler years and culminates with involution during puberty [1]. The presence of these lesions during the formative years of development leads to significant physical and psychological morbidity. In addition to physical disfigurement, these maxillary and mandibular lesions can cause difficulty with mastication, pain, and airway compromise [2]. Both jaw reconstruction following injury and cosmetic resection and reconstruction can potentiate further fibrous dysplasia and increase morbidity, though successful operative correction also is reported [3]. While intralesional corticosteroids, calcitonin, and alpha-interferon have been used, both response time and overall efficacy vary depending on the cohort studied [4, 5].

Cherubism classically is associated with *SH3BP2* mutations, but similar lesions can be observed in Noonan syndrome, Fragile X syndrome, and neurofibromatosis type I and have been referred to as either cherubism-like lesions or giant cells lesions. MAP kinase pathway activation is implicated in these lesions, with *BRAF, MEK,* and*SOS1* mutations reported [6]. Imatinib has been used successfully in three patients with *SH3BP2* -associated cherubism [1]. We report successful use of empiric imatinib to resolve mandibular fibrous dysplasia in a single patient whose disease was later determined to be caused by Noonan syndrome with a confirmed*PTPN11* activating mutation.

Results:

A 10-year-old male with short stature and mild conductive hearing loss presented to discuss use of imatinib to manage his worsening giant cell granulomas of the mandible that had been present for five years of age and consistent with cherubism on biopsy. He was suffering from difficulty with mastication, frequent bullying by peers, and inability to participate fully in athletics due to concern that any jaw injury would not be amenable to surgical correction. Targeted genetic testing for known *SH3BP2* pathogenic mutations previously was negative, and additional genetic workup had been deferred since the patient phenotypically did not exhibit features of other disorders known to include similar lesions. Therapy was initiated with imatinib at 300 mg daily, rounding the usual pediatric dose to the nearest whole tablet [7]. The patient and his parents noted decreased mandibular size within two months of beginning treatment. He continued imatinib for 15 months with full resolution of the mandibular granulomas both clinically and on computed tomography of the jaw (Fig. 1). Imatinib then was discontinued at patient preference. Therapy was well tolerated with

mild nausea, mild anorexia, and occasional headache. No dose reductions were required. The conductive hearing loss also resolved.

Integrative sequencing, including matched tumor/DNA and tumor/RNA sequencing confirmed a germline *PTPN11* p.I56V mutation establishing a diagnosis of Noonan Syndrome. Subsequent cardiac evaluation was unremarkable, and the patient continues to follow with oncology, oral and maxillofacial surgery, and genetics. There is no evidence for recurrent disease 15 months post stopping imatinib.

Discussion:

While multiple giant cell lesion syndrome is a known characteristic of Noonan syndrome, its presentation without other phenotypic findings is rare [8]. While these lesions may involute during puberty, the benefit in reducing risk for dental malalignment, inoperable jaw injury, and perhaps most importantly, repeat suffering of adverse childhood experiences due to bullying cannot be understated [9]. We report for the first time the successful use of imatinib to treat giant cell granulomas associated with a *PTPN11* activating mutation. Adverse effects were minor and similar to those experienced by pediatric patients receiving tyrosine kinase inhibitors to treat Philadelphia-chromosome-positive acute lymphoblastic leukemia. As Noonan syndrome features MAP kinase pathway activation, use of imatinib over additional agents studied in cherubism is attractive mechanistically since imatinib is known to inhibit downstream activity of the MAP kinase pathway through inhibition of cKIT [10].

It is unknown both whether the patient will require repeat therapy for recurrent disease and if a second course of imatinib will be effective. Recurrence could be mitigated by continuing maintenance imatinib through puberty, but prolonged therapy may not be desired by patients or families, especially for a self-limiting process. Additional reports on the use of imatinib with similar disease hopefully can address if imatinib should be offered to all patients with symptomatic fibrous dysplasia both due to *SH3BP2* -associated cherubism or due to other underlying causes such as Noonan syndrome.

Ethics Statement:

All patient images and results were obtained with patient assent and parental consent, and both the patient and his parents support their publication.

Conflict of Interest:

All authors deny any conflicts of interest.

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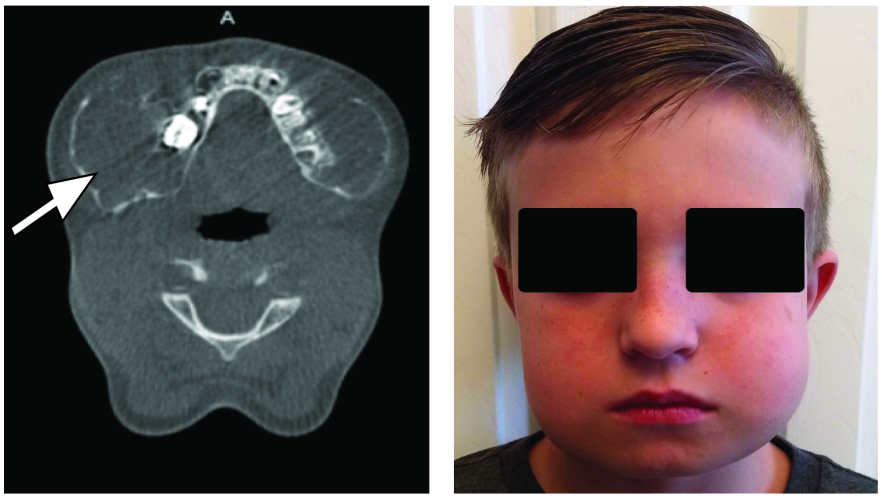
Figure Legends

Figure 1.

A. Giant cell granulomas of the mandible (see example marked by arrow) were present as shown on computed tomography for five years upon patient presentation with clinical cherubism. B. Full resolution of the granulomas was noted both clinically and on computed tomography following 15 months of therapy with imatinib.

A



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