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LETTER TO THE EDITOR

Resolution of mandibular fibrous dysplasia following imatinib therapy in Noonan syndrome

To the Editor:

Fibrous dysplasia of the mandible and maxilla, often referred to as cherubism, begins during toddler years and culminates with involution during puberty.[1] In addition to physical disfigurement, these maxillary and mandibular lesions can cause difficulty with mastication, pain, and airway compromise.[2] Mitogen-activated protein kinase pathway activation is implicated in these lesions, and while SH3 domain-binding protein 2 (*SH3BP2*)-associated cherubism is best known, similar lesions

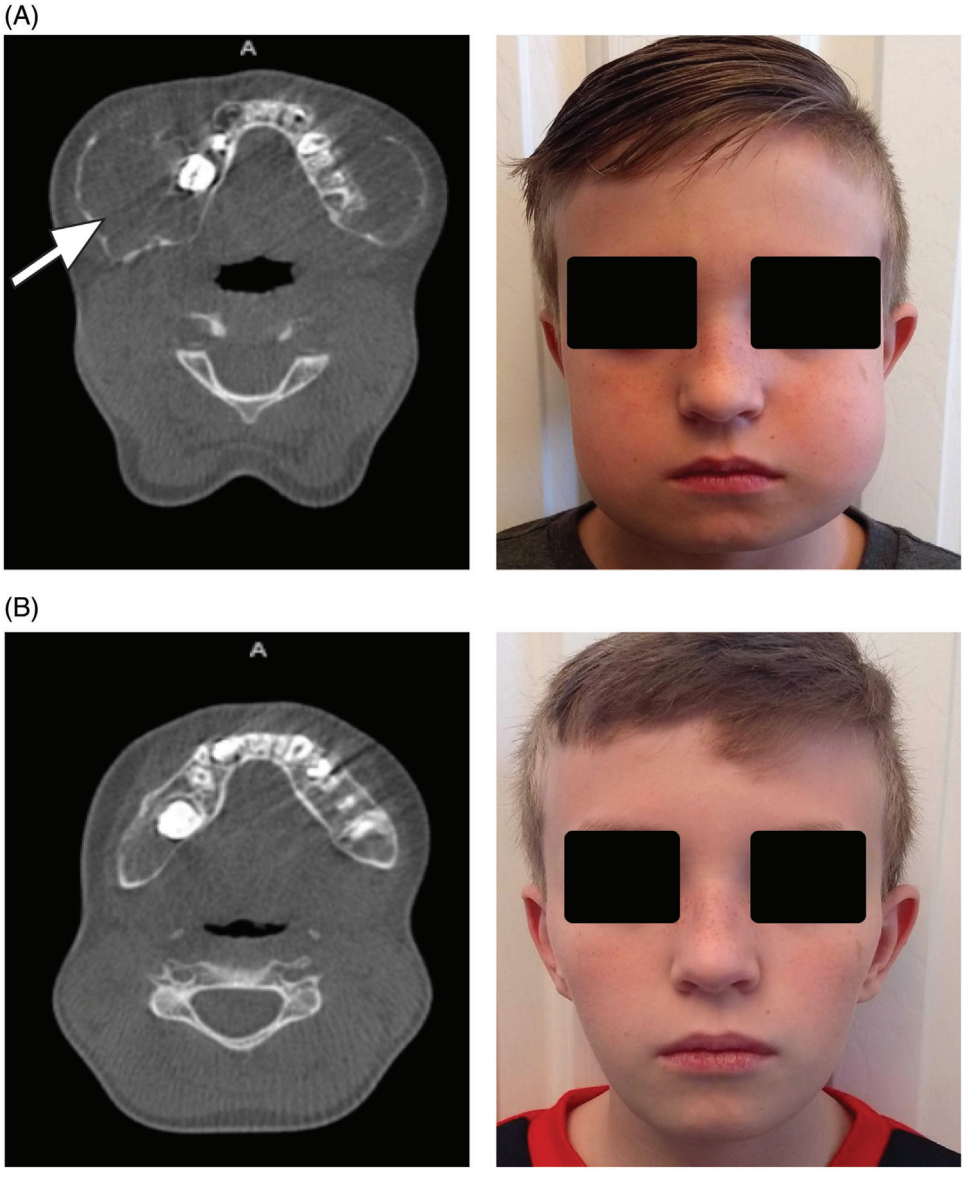

FIGURE 1 (A) Giant cell granulomas of the mandible (see example marked by arrow) were present as shown on computed tomography for 5 years upon patient presentation with clinical cherubism. (B) Full resolution of the granulomas was noted both clinically and on computed tomography following 15 months of therapy with imatinib.

are seen in Noonan syndrome, Fragile X syndrome, and neurofibromatosis type I. *BRAF*, *MEK*, and son of sevenless homolog 1 (*SOS1*) mutations are commonly reported.[3,4] Standardized treatment is lacking for individuals with symptomatic lesions. Jaw reconstruction both for cosmesis and following injury can be successful but also may potentiate further fibrous dysplasia and increase morbidity.[5] Intralesional corticosteroids, calcitonin, and alpha-interferon have been used both with and without surgery, but both response time and overall efficacy vary depending on the cohort studied.[6,7] Imatinib monotherapy successfully has been used without surgery in three patients with *SH3BP2*-associated cherubism, and one patient with Stickler syndrome responded to imatinib with alpha-interferon.[1,8] We report successful use of empiric imatinib monotherapy to resolve mandibular fibrous dysplasia in a 10-year-old male child whose disease was later determined to be caused by Noonan syndrome driven by a protein-tyrosine phosphatase non-receptor type 11 (*PTPN11*) activating mutation.

The patient presented with worsening giant cell granulomas of the mandible present for 5 years and consistent with cherubism on biopsy. Short stature and mild conductive hearing loss also were noted. 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. He suffered from difficulty with mastication that caused mild oral aversions, 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. Therapy was initiated with imatinib at the conventional dose of 340 mg/m^2 daily rounded to the nearest half tablet.[9] The patient and his parents noted decreased mandibular size within 2 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 (Figure 1). The conductive hearing loss also resolved. Imatinib then was discontinued at patient preference. The patient tolerated therapy well with mild nausea controlled with 5-HT3 blockade, mild anorexia, and occasional headache relieved with acetaminophen. No hematologic or hepatic toxicity was observed on serial laboratory assessment, and no dose reductions were required. Integrative sequencing, including matched tumor/DNA and tumor/RNA sequencing, confirmed a germline *PTPN11* p.I56V mutation establishing a diagnosis of Noonan syndrome. While multiple giant cell lesion syndrome is a known characteristic of Noonan syndrome, its presentation without other phenotypic findings is rare.[10] 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. Cascade testing confirmed Noonan syndrome in the patient's mother, who reported a previously unexplained bleeding diathesis.

This report furthers the evidence supporting empiric imatinib treatment for giant cell lesions regardless of the principal genetic driver, a conclusion additionally strengthened by an additional patient with central giant cell granuloma of the jaw in absence of an associated syndrome who responded to imatinib after failing other agents.[11] In both cases, use of imatinib obviated the need for attempted reconstructive surgery. Given the rarity of giant cell lesions, 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.

CONFLICT OF INTEREST STATAMENT

The authors declare that there is no conflict of interest.

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