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Hemangioma of the Mandible in a 12-Year-Old Boy

Keywords: *Intraosseous hemangioma; rapamycin; sirolimus; mandibular mass; failed fibular free flap reconstruction*

Intraosseous hemangioma is a benign, rare neoplasm that accounts to 0.5 - 1% of all benign tumors of bones.[1, 2] While most hemangiomas arise from soft tissues, it is uncommon for it to arise from bones.[2] The most common sites of growth are in the vertebral body and the calvarium with frontal bone making up approximately 45% of calvarial cases.[2,3] However, they are also encountered in the head and neck with sites such as the skull (53%), mandible (10.7%), nasal bones (9%), and cervical spine (6%).[4] In the mandible, the body is mostly affected and 65% are found in the molar and premolar region.[1] They are more common in adult females with peaks at the second and fifth decades of life.[1-3]

Hemangioma of the mandible is difficult to diagnose due to its nonspecific clinical presentation and radiographic features. It mimics various mass lesions in the mandible such as giant cell granuloma, fibrous dysplasia, multiple myeloma, osteosarcoma, ameloblastoma and keratocysts. Therefore, a comprehensive history taking and physical examination plus examination of the imaging studies available and tissue biopsy all play important roles in arriving at the final diagnosis.[5]

We present the case of an aggressive mandibular hemangioma in a young boy and our management involving a failed fibular free flap reconstruction.

CASE REPORT

A 12-year-old boy came to our institution due to a 5-month fast-growing right mandibular mass that started after a dental extraction that was followed by heavy bleeding. The mass was described as fleshy and reddish and continued to increase in size with no associated dysphagia or recurrence of bleeding.

Four months prior to admission, an orthopantomogram showed a radiolucent mass with honeycomb appearance and lytic changes in the right mandible, involving the 2nd premolar and 1st molar. *(Figure 1)* A punch biopsy was associated with heavy bleeding and the histopathologic report was hemangioma. The family was advised excision but they were lost to follow up because

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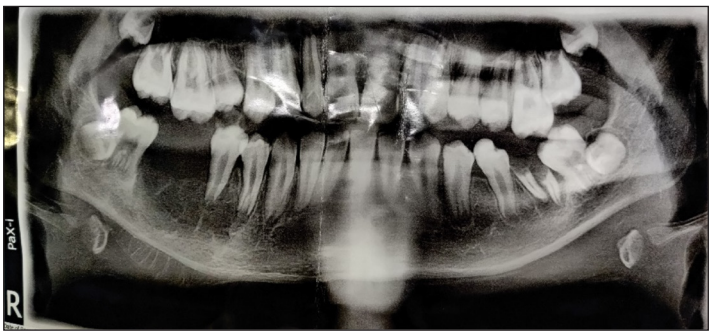

Figure 1. Orthopantomogram of patient obtained 4 months prior to admission showing a radiolucent mass in the right mandibular body

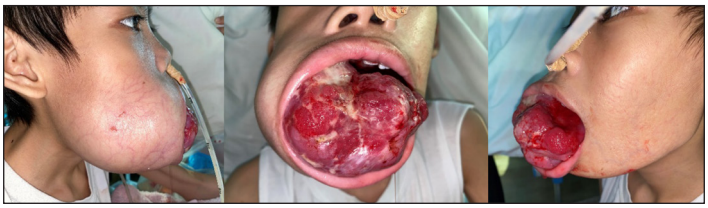

Figure 2. Gross photo of the mass upon admission

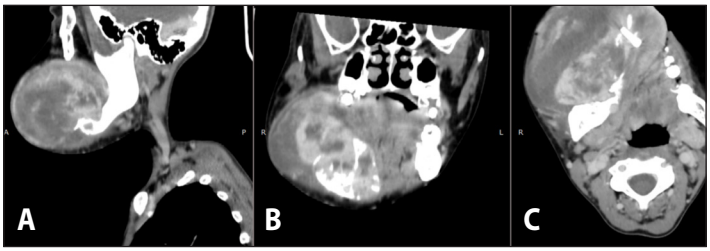

Figure 3. CT scan, soft tissue window, multiplanar view with contrast showing the lytic changes in the right mandible. **A.** lateral view; **B.** coronal view; **C.** axial view

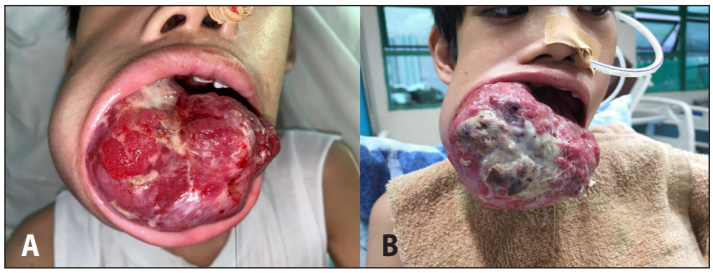

Figure 4. Comparison of decrease in vascularity of mass: **A.** on initial admission; and **B.** after 21 days of rapamycin

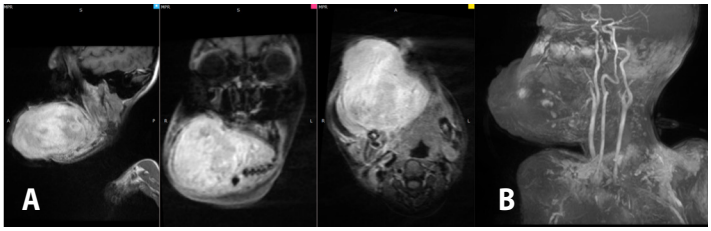

Figure 5. A. MRI, T1 sequence, multiplanar view with gadolinium contrast showing the heterogeneously enhancing mass in the right mandible; **B.** Time-of-flight window of the patient's MRA showing a branch of the external carotid artery going to the mass from the posterior

of the community lockdown implemented during the COVID-19 pandemic.

Upon admission, the patient was underweight with BMI of 13.2 and a mass measuring about 10 cm x 9 cm x 8 cm. *(Figure 2)* A repeat core-needle biopsy of the right mandibular mass showed benign vascular tumor to consider hemangioma vs angiofibroma. A CT scan showed a 7.0 cm x 8.9 cm x 8.5 cm lobulated, soft tissue mass centered at the right mandible associated with an expansile lytic lesion involving the angle and body and displaced adjacent teeth. There were patchy areas of mass that exhibited intense enhancement. *(Figure 3)* The plan for the patient was segmental mandibulectomy with reconstruction using mandibular reconstruction plate and fibular free flap.

While admitted, the patient was quarantined for a positive COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) swab test. Multidisciplinary team meetings were conducted and maximal medical management, nutritional build up, and a magnetic resonance angiography (MRA) of the mass were requested while waiting for a negative RT-PCR swab test result. The patient was adequately fed with 2000 calories per day via NGT based on recommended dietary allowance. He was given propranolol, 20mg/tablet, 1 tablet 3x/day (2.1mg/kg/day) for 3 days and was shifted to rapamycin, 1mg/tablet, 1 tablet once a day for 21 days with rapamycin serum level of 11.38ng/mL (Target: 10 – 15ng/mL). Despite the adequate dosing of rapamycin there was no significant change in the size of the mass but there was decreased vascularity. *(Figure 4)*

Magnetic resonance imaging (MRI) of the oral cavity with MRA done 1.5 months after admission showed an 8.0 cm x 11.3 cm x 10.9 cm fairly-defined, heterogeneously enhancing soft tissue mass seen centered in the right mandible associated with an expansile lytic lesion involving the ramus, body and angle. There were several prominent vessels identified posteriorly which served as collateral vessels arising from the right external carotid artery. *(Figure 5)*

The patient underwent excision of the mandibular mass and segmental mandibulectomy with reconstruction using fibular free flap and mandibular reconstruction plate under general anesthesia. *(Figure 6)* It is important to note that poor arterial flow was observed after anastomosis despite there being no note of thrombosis at the site of the arterial anastomosis. A total of five revision anastomoses were done before adequate perfusion was appreciated. Total amount of blood loss was approximately 1000 cc. The rest of the surgical procedure was uneventful.

Post-operatively, the patient was admitted at the pediatric intensive care unit (PICU) for close monitoring. The immediate post-operative course was uneventful. At this point, sirolimus was already

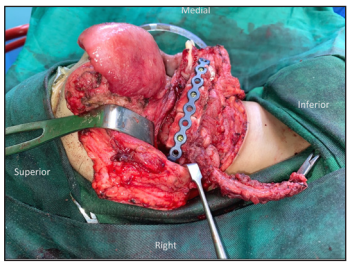

Figure 6. Fibular Free Flap with Mandibular Reconstruction Plate in place

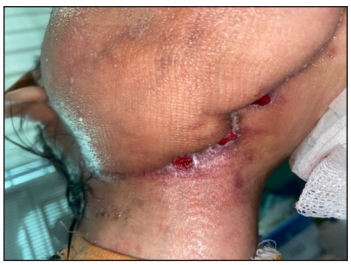

Figure 7. Minimal swelling, hyperemia, dehiscence and granulation tissue on the surgical site in the patient's neck on his first OPD follow-up (26th post-operative day)

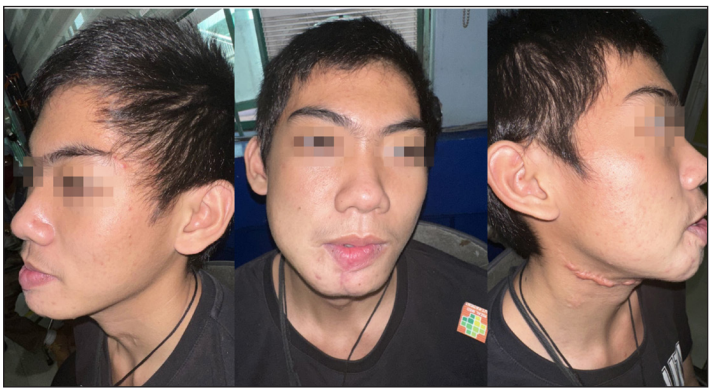

Figure 8. Facial profile of the patient 3 years after surgery with no noted recurrence of the mandibular mass (compare with *Figure 2*)

discontinued. The patient's diet was maintained via nasogastric tube to facilitate adequate intraoral healing. However on the 8th post-operative day, there was an intraoral dehiscence grossly exposing the flap and the mandibular reconstruction plate. Repair of dehiscence under local anesthesia was well tolerated by the patient. There was already suspicion of failure of the fibular free flap but the parents and the patient wanted to delay repeat surgery. A total of 3 repairs of dehiscence under local anesthesia were performed.

On his first follow-up at the outpatient department on the 26th post-operative day, intraoral dehiscence was apparent on examination. Sites of neck wound dehiscence from the surgery were also noted with granulation tissue. *(Figure 7)* The patient and the parents was advised and then agreed to the repeat surgery. Removal and replacement of the failed flap using another fibular free flap from the contralateral leg was done. Surgery and post-operative course were uneventful, and he was well three years later. *(Figure 8)*

DISCUSSION

We presented a case of an aggressive tumor of the mandible in a pediatric patient. Jaw tumors in the pediatric population are uncommon and may be broadly classified into odontogenic or nonodontogenic of which the latter are considered to be common in children.[6] Consequently, jaw tumors may also be classified as benign or malignant of which the benign are more common in the pediatric population.[7] Oftentimes, these benign lesions exhibit locally aggressive behavior.[8]

Our patient presented with a firm, painless lesion that bled intermittently with obliteration of the gingivobuccal sulcus, expansion of the mandible, and mobility and displacement of teeth- - all of which are nonspecific presentations. Hemangiomas of the mandible usually present as an asymptomatic, slow growing, painless mass that affects dentition and has recurrent bleeding due to trauma.[2,5] Papa *et al.* also reported a case of a 12-year-old boy, referred due to intractable gingival bleeding over a period of two months exacerbated by intraoperative manipulation of a loose first premolar.[9] Similarly, Sadain-Urao and Pontejos reported the case of a 20-year-old man with a 3-month history of progressively enlarging right mandibular area associated also with profuse bleeding from a tooth extraction site. Bleeding in the latter case was so severe that the patient had a hypotensive episode and loss of consciousness during exploration and ligation of bleeders.[10]

The radiographic presentation is nonspecific which makes intraosseous hemangioma difficult to diagnose. It has variable appearance such as unilocular, multilocular, reticulated, honeycomb, corduroy-like or sunburst. But some will just present as an expansile lytic mass on imaging.[2] Our patient's radiographic studies did not show pathognomonic features and just exhibited a heterogeneously enhancing fairly defined mass with lytic destruction and prominent vessels coming from the external carotid. Lesions that show ill-defined borders with cortical destruction typically denote an aggressive inflammatory, or neoplastic lesion and those with widening of the inferior alveolar canal may denote vascular or neural origin.[11] Radiographically intraosseous hemangioma has no pathognomonic features and may have similar radiographic features with other bone lesions.[2] A CT scan may visualize the cortical involvement as a "polka-dot" appearance with cortical expansion.[5] Other descriptions include sunburst pattern, tennis racket appearance, soap bubble or honeycomb-like.[1] Even the case series of Chandra *et al.* showed varied radiographic presentations; some were radiolucent while others were radiopaque, some were unilocular and others were multilocular.[12] Angiography allows visualization of feeding vessels, if there are any, which may help in presurgical embolization to minimize surgical bleeding.[5]

Considering the clinical presentation, physical examination findings, and radiographic appearance, differential diagnoses would include vascular anomalies, osteoma, Langerhans cell histiocytosis, fibrous dysplasia, dermoid tumor, and multiple myeloma. A biopsy

may clinch the diagnosis but should be performed cautiously due to possible profuse bleeding.[2]

Our patient underwent biopsy twice preoperatively with results of hemangioma confirmed by final histopathology after excision with a description of a well encapsulated mass with a vast network of varisized blood vessels lined by a single layer of endothelial cells supported by a fibrocollagenous stroma.

Hemangiomas are usually present at birth but are rarely apparent. They are usually slow growing but infiltrative and may be destructive. Majority may involute in time, but about 40% will eventually need intervention.[13] The origin of hemangioma is debatable as some believe it to be a true benign neoplasm that results from endothelial proliferation which differentiates into blood vessels while others believe that it results from proliferation of mesoderm that undergoes endothelial differentiation and then subsequently canalized and vascularized.[5] In the mandible, some believe that these lesions are congenital while other believe that they arise from the inferior dental canal which subsequently grow into intraosseous lesions.[13] Our patient developed his lesion after a dental extraction; local trauma could also be a possible inciting factor for intraosseous hemangioma.[2, 13]

Our goals of treatment for hemangiomas include control of hemorrhage, complete resection of the lesion, and prevention of recurrence.[1] Indications for intervention are aesthetic disfigurement, repetitive bleeding, and palpable mass.[5] Clinical observation is only indicated for asymptomatic patients or those with minimal facial deformity and is not applicable to our patient considering the size and significant disfigurement.

With hopes of achieving a manageable size of the mass or preventing further progression, we started the patient on medical management while he was being quarantined due to COVID-19. Medical management such as corticosteroids, interferon, and vincristine may also be employed for "problematic" cases and have shown success for massive and life-threatening cases.[13] However, in 2008, propranolol was serendipitously discovered to cause regression of proliferating hemangiomas in newborns receiving treatment for cardiovascular disease.[14] Despite the success of propranolol in reducing hemangioma size, adjuvant therapy may be necessary in up to 50% of patients.[13] There are also studies suggesting the off-label use of rapamycin, a mammalian target of rapamycin (mTOR) inhibitor.[7] Rapamycin is usually given as immunosuppressant for organ transplant patients to prevent rejection because of its antiproliferative and antiangiogenic properties.[7] A systematic review by Freixo *et al*. in 2020 found that there was a decrease in size of the lesions of all patients with vascular tumors that were given rapamycin.[15] Hence, we started the patient initially on propranolol but shifted to rapamycin. While most studies would suggest treatment for 3 months, the lack of significant response from our patient after 21 days of rapamycin made us to decide to halt the therapy and proceed with excision.

Complete excision of the tumor with reconstruction of mandible, alone or in combination with embolization remains the best treatment option for these kinds of tumors.[1] We treated the patient with combined modalities using rapamycin and complete excision of mass via segmental mandibulectomy with reconstruction using fibular free flap. Prognosis after complete excision is thought to be excellent and recurrence is usually rare.[5]

However, 1-month post-operation, signs of flap failure were observed in this patient and re-operation was advised. Total flap success rate for fibula free flap was noted to be 93-99% from large center studies, with an overall postoperative complication rate as high as 48%.[16] This brings us to the question of what might have caused the flap failure. Because post-operative complications may occur at a high rate, the same study noted that the risk of infection was significantly associated with longer operative time and higher amount of blood loss[16] -- two factors that were present in our patient's surgery. Another factor worth looking into is the off-label use of rapamycin to decrease the size of the mass. There have been several reports showing signs of osteonecrosis of the jaw with off-label use of rapamycin for metastatic breast cancer patients.[17,18] Administration of everolimus, a mammalian target of rapamycin inhibitor, showed complications of localized inflammation in the mandibular region.[19] There was purulent discharge and the surrounding gingiva was noted to be edematous and erythematous as well. Ruling out a possible metastatic process, incision biopsy revealed chronic non-specific inflammatory cells with no evidence of metastasis. Osteonecrosis of the jaw (ONJ) was thus diagnosed. Everolimus was discontinued and antibiotic was administered for 2 weeks. Acute inflammation and the exposed bone showed improvement after 2 months. One possible explanation offered was that similar to preclinical studies in mouse models have demonstrated that inhibition of mTOR reduces the maturation and increases the apoptosis of osteoclasts which may be the mechanism in the occurrence of ONJ with mTOR inhibitors.[19] This can also be a factor which might have led to the surgical site infection in an already compromised mandibular bone in our patient leading to wound healing complication and ultimately resulting in flap failure.

In summary, intraosseous hemangioma of the mandible is difficult to diagnose with its nonspecific clinical presentation and variable radiographic features that mimics various disease entities of the mandible. It is important to perform complete history taking,

comprehensive physical examination and thorough analysis of imaging findings to arrive at an accurate diagnosis and provide the appropriate treatment for these patients. A biopsy is necessary to clinch the diagnosis. Medical management with propranolol and rapamycin may be effective for smaller lesions but with a massive mass the best management for patient with hemangioma of the mandible is complete excision with reconstruction. Attention to the possibility of wound healing complications and possible flap failure is also advised in patients administered with rapamycin at the same time undergoing segmental mandibulectomy and mandibular reconstruction surgery.

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