Diagnostic Dilemma of Vanishing Bone Disease - A Case Report and Review of Literature

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Abstract

Rationale: Vanishing bone disease (VBD) is a rare bone disorder in which progressive osteolysis may lead to complete disappearance of involved bones. The diagnosis of this disease requires a high degree of clinical suspicion. We present a case of progressive osteolysis of mandible in a patient. **Patient Concerns:** The patient had been without definitive diagnosis and treatment for over a year. **Diagnosis:** Diagnosis was made by exclusion of genetic, traumatic, inflammatory, infective, endocrine and neoplastic aetiologies and by carefully correlating clinical, imaging and histopathological findings of the patient. **Treatment:** Segmental resection of the advancing edge of the lesion was carried out. **Outcome:** The patient is disease free, with no evidence of further osteolysis, after six months of follow-up. **Take-Away Lessons:** This article describes the exclusion-based approach adopted to diagnose a case of VBD, aiming to standardise a workup for the diagnosis.

Keywords: Disappearing bone disease, Gorham disease, Gorham-Stout disease, idiopathic osteolysis, massive osteolysis

Introduction

Vanishing bone disease (VBD) is a rare bone disorder in which lymphatic vessels proliferate, resulting in progressive and massive osteolysis. This disease, first described by Gorham and Stout in 1955, is also known as 'massive osteolysis', 'disappearing bone disease', 'phantom bone disease' and 'progressive osteolysis'.[1]

Case Report

A 35-year-old female patient reported to the dental centre with mobile teeth in the lower left back tooth region and the chief complaint of difficulty in chewing since past one year. Pain was associated with decreased mouth opening. Patchy osteolysis of left condyle was initially noticed on an orthopantomogram (OPG). The patient gradually started to notice mobility of left molars and premolars over a period of a year and a half. Serial OPGs taken during this period revealed continued bone loss from condyle to angle, approaching the body of the mandible on the left side [Figure 1].

At our dental centre, detailed clinical history and all past test results were evaluated. Other than hypothyroidism, for which the patient was on medication since 2014, there was no other associated medical history. Family history was non-contributory, and no hereditary history of bone disease was obtained. No rigidity or restriction of motion in other bones of axial skeleton was noted. Investigations to rule out rheumatoid arthritis, multiple myeloma, eosinophilic granuloma and other systemic diseases were carried out [Table 1]. Serum calcium, vitamin D and intact parathyroid hormone levels were reduced (4.9 mg/dL, 52.14 nmol/L and 14.81 pg/mL, respectively). Full body positron emission tomography scan revealed no lytic lesion in rest of the axial and appendicular skeleton. Cone beam computed tomography (CBCT) with three-dimensional reconstruction disclosed the extent of involvement of the mandible [Figure 2]. Segmental resection of mandible with a margin of normal bone was carried out, and resected tissues submitted for histopathological examination. Plasma cell rich chronic inflammatory infiltrate [Figure 3a and b] was evident

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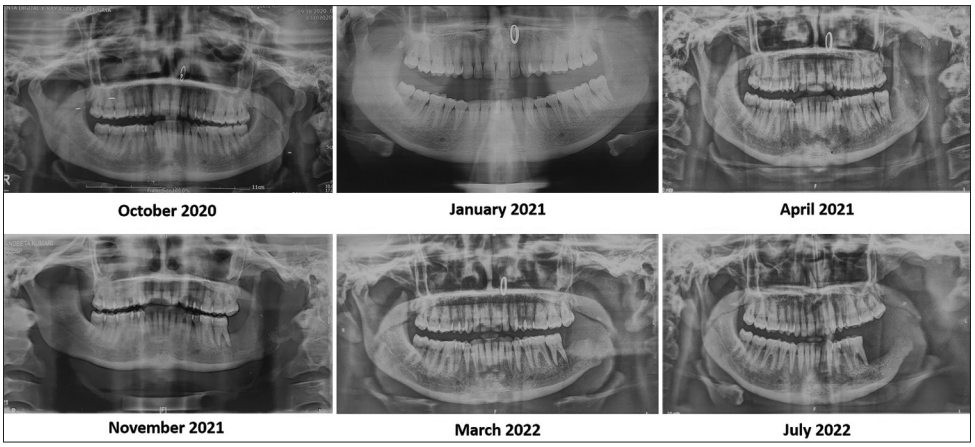

Figure 1: Radiographic and imaging analysis. Serial OPGs revealing slowly progressive osteolysis of the mandible. OPG: Orthopantomogram

Table 1: Diagnostic flowchart for vanishing bone disease as a diagnosis of exclusion

Clinical history	Radiographs and imaging	Serological and biochemical investigations	Histopathology
1. No history of trauma 2. No hereditary association 3. No pain and rigidity with other joints and bones of axial and appendicular skeleton	1. Slowly progressive atrophy, dissolution of the condyle and ramus; decreased vertical height of the mandibular body with resorption extending towards the basal bone 2. No multilocular cystic appearance 3. No periosteal reaction 4. No punched out radiolucencies in skull and axial skeleton 5. No infective foci in oral cavity 6. Full body PET scan reveals no other osteolytic foci	1. Serum calcium and Vitamin D levels reduced 2. Low or borderline normal parathyroid hormone levels 3. Normal or borderline decreased alkaline phosphatase levels 4. Serum protein electrophoresis, M band, and light chain immune assay did not reveal any monoclonal spike 5. Serum rheumatoid factor within normal range	1. IHC confirmed polyclonal plasma cell (CD 38, kappa, lambda antibodies) predominant chronic inflammatory infiltrate 2. IHC confirmed (D2-40) numerous endothelium-lined lymphatic vessels 3. No osteoclastic activity 4. Viable mature lamellar bone 5. Negative for acid fast bacilli, fungal profile, granulomatous inflammations, and epithelial or mesenchymal malignancies (Ki-67 < 1%)
Exclusion of hereditary multicentric osteolysis, rheumatoid arthritis, osteoarthritis, and osteoporosis	Exclusion of aneurysmal bone cyst, osteomyelitis, multiple myeloma, and osteolytic metastasis	Exclusion of brown tumour of hyperparathyroidism, solitary plasmacytoma, multiple myeloma, rheumatoid arthritis, and chronic inflammatory conditions	Exclusion of primary osteolytic malignancies, osteolytic metastases, eosinophilic granuloma (by way of CD 1a and langerin), odontogenic tumours (by way of calretinin marker), and infective and granulomatous pathologies

IHC: Immunohistochemistry, CD: Cluster of differentiation, PET: Positron emission tomography

on histopathological examination. No osteoclastic activity was evident, and viable bone with osteoblastic rimming and osteocytes was evident on decalcified sections [Figure 3c]. Deep cut sections revealed numerous endothelium-lined vessels along with CD38-positive plasma cells [Figure 3d]. D2-40 or podoplanin marker confirmed proliferation of abundant slit-like lymphatic vessels [Figure 3e]. Histopathological examination was negative for any epithelial and mesenchymal malignancy, and Ki-67 marker was <1% in most proliferative areas [Figure 3f]. Thus, after exclusion of genetic, infective, inflammatory, traumatic, endocrine and neoplastic aetiologies, the patient was diagnosed as a case of VBD. The patient is currently on follow-up, to document any further osteolysis, by way of panoramic radiographs and CT. The patient is disease free after six months of follow-up [Figure 4]. The patient was given both the option of patient-specific implants

and autologous-free fibula graft with dental implants. The patient chose the option of patient-specific implant with fixed prosthesis. The patient will be taken up for rehabilitation post one year of uneventful follow-up.

Discussion

The role of endothelial cells, osteoclasts and osteoblasts in the pathogenesis of the disease has been investigated.[2,3] There is growing evidence that unrestrained growth of lymphatic vessels exerts compression forces, thus causing osteolysis.[4] Numerous endothelium-lined vessels were evident in the present case. The endothelial cells of these vessels were reactive and non-reactive to D2-40 and CD34 antibodies, respectively [Figure 3e]. This validates the observation in previous case reports that VBD is a result of abnormal proliferation of lymphatic vessels. Factors secreted by lymphatic endothelial cells may affect osteoclasts and/or osteoblasts, and macrophage-like mononuclear cells may act as osteoclast precursors. Previous reports have also reported impeded osteoblastic activity on the surfaces of remaining bone fragments.[5] In the present case, however, osteoblastic rimming was seen on the remaining bone fragments, and osteoclasts were not observed on histopathological examination. This observation may be disease-stage dependant (active versus dormant) and may vary during active osteolysis when more osteoclasts may be observed.

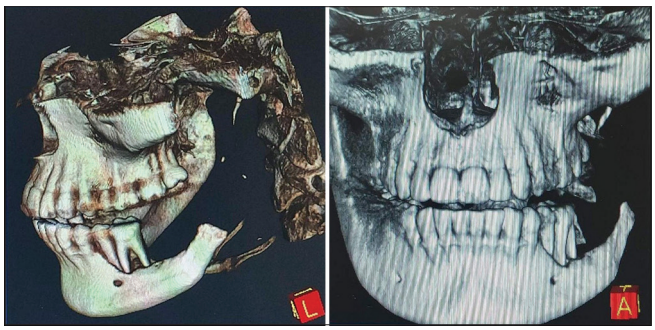

Figure 2: Radiographic and imaging analysis. CBCT with 3D reconstruction showing the extent of bone resorption in mandible. CBCT: Cone-beam computed tomography, 3D: Three dimensional

VBD commonly affects young individuals, and the disease does not display a clear sex predilection or inheritance pattern. Although VBD can affect any bone in the body, it frequently affects the maxilla, mandible, clavicle, ribs, cervical vertebrae, humerus, pelvis and femur. The prognosis of VBD is unpredictable and varies based on the extent of involvement, severity and location of the disease. In cases of thoracic involvement, breathing difficulty due to chylothorax and pleural effusion may be reported. In addition, when vertebrae are involved, severe neurological deficits, paralysis and death are fatal outcomes.

Pain localised to the affected bone is the most common symptom along with swelling and functional deficit of involved limbs. The involved bone may fracture following minor trauma or spontaneously.[6] Our case, however, was a middle-aged female presenting with pain, swelling and functional deficit with hemi-mandible.

On radiographic examination, like the present case, osteolytic lesions in bones affected with VBD appear as small radiolucent foci in initial stages, which later coalesce and enlarge with progression of the disease.[7] Disease follow-up and monitoring by panoramic radiographs and CT are preferred in the maxillofacial region.[1]

VBD is often a diagnosis of exclusion in clinical practice. To enable adequate diagnosis, based on clinical, radiological and histopathological features of the disease, Heffez *et al.*

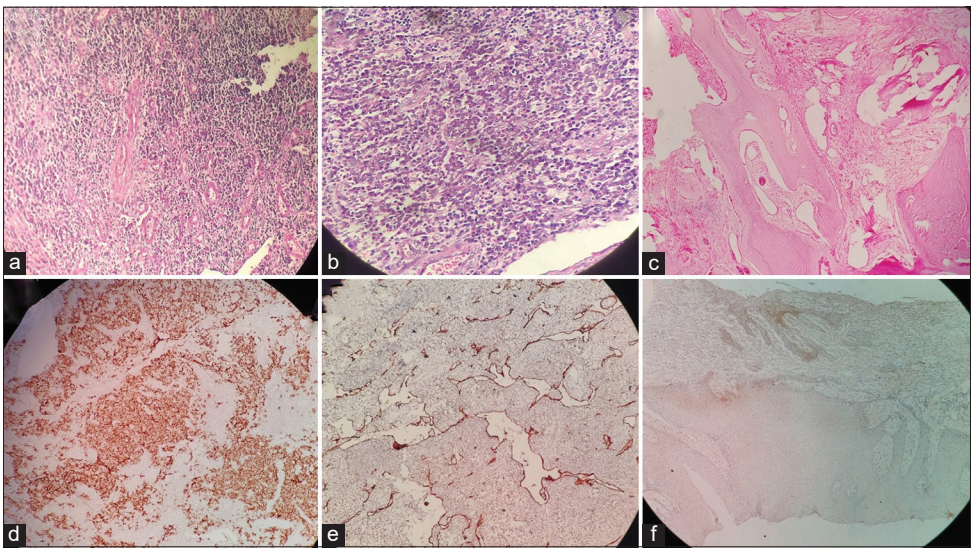

Figure 3: Haematoxylin and eosin-stained histopathological and immunohistochemical analysis images. (a) Inflammatory infiltrate with abundant vascular channels (4x). (b) Dense plasma cell—rich inflammatory infiltrate (10x). (c) Mature, viable lamellated bone with fibrovascular tissue (10x). (d) CD38-positive plasma cells highlighted (10x). (e) D2-40 staining of endothelial cells, highlighting lymphatic vessels. (f) Ki-67 index less than 1% in most proliferative areas

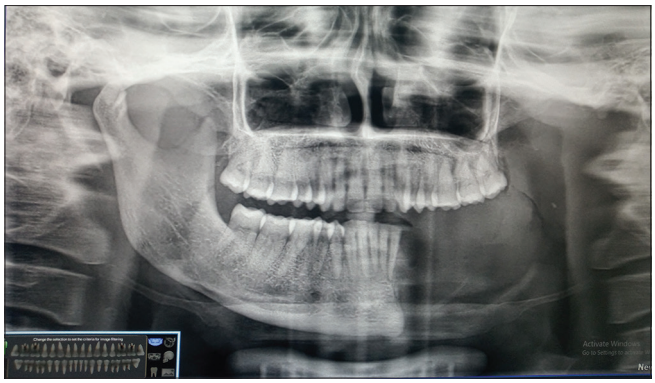

Figure 4: Follow-up OPG (6-month post-operative). OPG: Orthopantomogram

proposed diagnostic criteria for VBD: (1) biopsy-proven angiomatous tissue, (2) absence of cellular atypical features, (3) absence of dystrophic calcifications with minimal to no osteoblastic response, (4) localised progressive bone resorption, (5) non-expansile and non-ulcerative lesion, (6) no visceral involvement, (7) osteolytic pattern on radiographic examination and (8) negative hereditary, infectious, metabolic, immunologic and neoplastic aetiologies.[8] These diagnostic criteria were met to validate the present case as VBD.

Targeted therapy is lacking due to the unclear pathogenesis of the disease. Pharmacological, surgical and radiotherapeutic options have been tried to arrest disease progression. Pharmacological treatment options include targeted inhibition of osteoclast activity, immune response or angiogenesis. Recently, restriction of growth factor-mediated lymphangiomatous proliferation by mTOR inhibitors (sirolimus and everolimus) was effective in stabilising the disease. However, for localised disease in the operable region, surgery (marginal resection or curettage) is considered the preferred therapeutic modality.[5]

Patients with recurrences, multifocal lesions and lesions in inoperable areas are prime candidates for radiation therapy. Primary reconstruction for rehabilitation should be avoided as extension of disease into grafts has been documented. Thus, after surgical intervention, primary reconstruction should be delayed until dormancy of the disease and arrest of osteolysis is confirmed.[9,10]

In the present case, pharmacological and surgical modalities were utilised for therapy. Patient was started on oral calcium and Vitamin D supplements. Considering the localisation of the disease in the mandible, segmental resection was planned. Reconstruction of the defect would be delayed until arrest of osteolysis is confirmed by regular reviews.

Conclusion

The present case was a report of progressive osteolysis in a middle-aged female with no history of trauma. The diagnosis required a high degree of clinical suspicion, which had to be supported with adequate investigations. After review of serial radiographs, major differential diagnoses with the presentation of massive osteolysis were listed. We then systematically ruled out various causes of osteolysis based on history, examination and investigations. Histopathology and IHC were especially useful in this exclusion-based workup [Table 1]. Furthermore, the finding of D2-40 reactive lymphatic vessels highlighted the role of uncontrolled lymphangiogenesis in pathogenesis. Accordingly, agents inhibiting lymphangiomatous proliferation in VBD may be investigated further through future research.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Foster BL, Ramnitz MS, Gafni RI, Burke AB, Boyce AM, Lee JS, *et al.* Rare bone diseases and their dental, oral, and craniofacial manifestations. J Dent Res 2014;93:7S-19S.
2. Tanoue N, Moedano L, Witte M, Montague M, Lukefahr A, Bernas M. Primary versus trauma-induced Gorham-Stout disease. Lymphology 2018;51:18-27.
3. Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis. J Bone Joint Surg Am 1955;37-A(5):985-1004.
4. Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham-Stout disease. Bone 2014;63:47-52.
5. Ricci KW, Hammill AM, Mobberley-Schuman P, Nelson SC, Blatt J, Bender JL, *et al.* Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. Pediatr Blood Cancer 2019;66:e27614.
6. Takaya K, Sakamoto Y, Miwa T, Yoshida K, Kishi K. Gorham-Stout disease with parietal bone osteolysis: A case series and review of literature. Br J Neurosurg 2021;35:27-31.
7. de Keyser CE, Saltzherr MS, Bos EM, Zillikens MC. A large skull defect due to Gorham-Stout disease: Case report and literature review on pathogenesis, diagnosis, and treatment. Front Endocrinol (Lausanne) 2020;11:37.
8. Heffez L, Doku HC, Carter BL, Feeney JE. Perspectives on massive osteolysis. Report of a case and review of the literature. Oral Surg Oral Med Oral Pathol 1983;55:331-43.
9. Gulati U, Mohanty S, Dabas J, Chandra N. "Vanishing bone disease" in maxillofacial region: A review and our experience. J Maxillofac Oral Surg 2015;14:548-57.
10. Saify FY, Gosavi S, Jain S, Sood M. Vanishing bone disease: An enigma. J Oral Maxillofac Pathol 2021;25:S7-10.