Pseudotumor of the Mandible as First Presentation of Hemophilia in a 2-Year-Old Male: A Case Report and Review of Jaw Pseudotumors of Hemophilia

D. P. Cox · A. Solar · J. Huang · R. Chigurupati

Received: 24 March 2011 / Accepted: 22 April 2011 / Published online: 13 May 2011
© Springer Science+Business Media, LLC 2011

Abstract Pseudotumor of hemophilia (PTH) is a rare complication seen in approximately 1–2% of cases of hemophilia. Although much more common in long bones, the pelvis, and small bones of the hands and feet than in the jaws, occasionally hemorrhage in the jaws occurs with this result. We present a case in a two-year-old male with a one-month swelling of the right mandible without significant medical history or diagnosis of hemophilia who was subsequently diagnosed as having Factor IX deficiency, or hemophilia B. A review of the literature revealed only 15 reported cases of PTH of the jaws and salient features of PTH in the jaws are discussed. The differential diagnosis of masses occurring in the jaws of children is limited and PTH should be considered when a mass presents with rapid growth and the histopathologic features are not diagnostic for a neoplastic process, even in the absence of a prior diagnosis of hemophilia as PTH may be the initial manifestation of this disease.

Keywords Pseudotumor · Hemophilia · Factor IX deficiency · Jaw

Hemarthrosis, or bleeding into a joint, particularly the knees, ankles, and elbows, is one of the most common complications of hemophilia [1]. These hemarthroses usually develop in childhood [2]. A related complication of hemarthrosis is the exceedingly rare pseudotumor of

hemophilia (PTH), first reported in 1918 by Starker [3]. This complication occurs in ~1–2% of severely hemophilic patients [4], but can be seen in patients with more moderate deficiency of factors VIII or IX [5].

The etiology of these lesions is repeated and unresolved hemorrhage in soft tissue and bone, remote from joints. The classic presentation is painless swelling with subsequent bony destruction [6]. PTH is much more common in the long bones, pelvis, and small bones of the hands and feet, than in the jaws [7]. As the name indicates, the presentation of a rapidly growing swelling with bony destruction is clinically suspicious for malignancy and often results in a misdiagnosis as a tumor.

We have reviewed the literature and found 15 reported cases of PTH of the jaws and we discuss, herein, the clinical presentation and diagnosis of PTH in the mandible of a 2-year-old male without a significant prior medical history.

Case Report

A 2-year-old Afghani American boy developed, over the course of 1 month progressive right jaw swelling, which rapidly increased in size over the last week prior to presentation. He was initially seen at the Oakland Children's Hospital emergency department and was admitted to the pediatric ward for further management of the swelling. A CT scan of the head and neck revealed a well-defined 3 × 2.5 cm unilocular radiolucency in the right body of the mandible with expansion of the buccal and lingual cortices and perforation of the buccal cortical bone (Fig. 1). He was then referred to the University of California San Francisco (UCSF) oral and maxillofacial surgery department.

Upon presentation to UCSF, he was in apparent good health with no prior history of hospitalization, illness,

D. P. Cox (✉) · J. Huang · R. Chigurupati
University of California San Francisco (UCSF),
San Francisco, CA, USA
e-mail: darren.cox@ucsf.edu

A. Solar
Pontificia Universidad Católica de Chile, Santiago, Chile

Fig. 1 CT scan showing a radiolucent lesion of the *right* mandible with marked expansion of buccal and lingual cortices and perforation through the buccal cortical bone

trauma, or dental pain. His mother denied any history of bleeding or bruising and reported that his umbilical cord stump fell off at one-week post parturition without bleeding. Recently, she had noticed that his mandibular right teeth showed some displacement. A panoramic radiograph also showed the 3×2.5 cm radiolucent lesion of the right mandible. Physical examination revealed an expansile mass of the right mandible with visible extraoral bruising of the skin (Fig. 2). The swelling was firm and non-tender, with expansion of the buccal cortex, fullness of the vestibule, and displacement of the right mandibular deciduous molars and canine (Fig. 3). No lymphadenopathy was noted on digital inspection of the bilateral neck.

Fig. 2 Facial image showing swelling of the *right* side of the face in the area of the mandible. Note the slight bruising in the overlying skin

Fig. 3 Intraoral image shows swelling of the *right* mandible with ulceration of the alveolar mucosa and slight displacement of the teeth in that quadrant

The clinical differential diagnosis at the time of presentation included a central giant cell lesion (central giant cell granuloma, aneurysmal bone cyst), ossifying fibroma, desmoplastic fibroma, and other benign and malignant soft tissue neoplasms that may occur in the jaw. He underwent an incisional biopsy under general anesthesia, without incident.

The following day, he returned to UCSF Children's Hospital emergency department with bleeding from the biopsy site and with non-bloody, non-bilious vomiting, watery diarrhea, and abdominal pain. He had a fever of $101^{\circ}\text{Fahrenheit}$. His mother reported that since the biopsy, he had been persistently bleeding from his mouth, as evidenced by small amounts of blood on his pillow. He was admitted to the pediatric service where oral and maxillofacial surgery was consulted to evaluate the wound and determine the cause of bleeding. On examination of the oral cavity, there was a large blood clot at the surgical site that extended to cover the crowns of the erupted deciduous molars. There was oozing of blood from the biopsy site and ecchymosis of the buccal mucosa and overlying skin. The patient was monitored over the next 24 h.

Given these symptoms, a number of bleeding disorders were considered, including Factor VIII deficiency and von Willebrand's disease, and the appropriate investigative laboratory tests were ordered. Further inquiry into the patient's family history revealed that the patient's maternal uncle had been diagnosed with Factor IX deficiency after a fatal hemorrhage following repair of orthopedic injuries.

Fig. 4 **a** Dense and somewhat cellular granulation tissue with a focal benign lymphocytic aggregate. Scattered hemosiderin-laden macrophages are easily identified at this magnification (hematoxylin and eosin, 100 $\times$). **b** The granulation tissue here shows a neutrophilic infiltrate, in addition to marked chronic inflammation. Abundant intracellular and extracellular hemosiderin deposition is noted (hematoxylin and eosin, 200 $\times$)

The biopsy specimen, taken from an intraoral approach to the mandible, measured 0.5 $\times$ 0.2 $\times$ 0.2 cm and was grossly bluish gray in color. A frozen section consultation was negative for malignancy. Permanent sections revealed inflamed fibrous and granulation tissue, with areas of hemorrhage and hemosiderin deposition (Fig. 4a, b). There was no evidence of a neoplastic process; however, a comment was made that the specimen submitted might be a peripheral reactive proliferation and not representative of the true pathologic process. Fresh tissue was submitted for cytogenetic analysis and showed no genetic abnormalities.

Results of blood tests showed the following: PT 13.1 s (normal range 10–15 s), PTT 55.2 s (normal range 30–45 s), Factor VIII 149 (% Activity normal range: 43–168), Factor IX 3 (% Activity normal range: 60–160), Factor XI 174 (% Activity normal range: 72–161). The prolonged PTT and

decreased level of Factor IX, confirmed that the patient suffered from Factor IX deficiency (hemophilia B; Christmas disease), with a moderate phenotype.

He was then treated with 1,500 mg aminocaproic acid, an anti-fibrinolytic agent, every 6 h. This controlled his bleeding and he was discharged pending a decision regarding further surgery. However, 11 days later, he began to bleed again from the biopsy site and was readmitted for administration of recombinant Factor IX (BeneFIX[®]).

The histology of this lesion, combined with the clinical diagnosis of hemophilia, was consistent with a “hemophilic pseudotumor.” Given the risk of bleeding, the decision to forgo surgery was made and he was treated with twice weekly Factor IX for 4 weeks, with resolution of the lesion. At this time, his parents decided to stop the twice-weekly infusions, but would return for Factor IX replacement as needed for trauma or bleeding. Three months later, the family moved out of state and the patient was lost to follow-up.

Review of Reported Cases of PTH of the Jaws

A summary of all reported cases of PTH of the jaws is seen in Table 1. The left mandible was the site of most frequent occurrence ($n = 8$), followed by the right mandible ($n = 6$) (two cases had both sides of the mandible affected) [8, 9], and left maxilla ($n = 4$). The mean age at presentation was 11.8 years (6 months–34 years). Swelling was the presenting symptom in all 16 cases. The length of onset to presentation ranged from 4 days to 11 months. Thirteen cases, including ours, reported a radiolucent lesion on imaging, with only two suspecting PTH [9, 17]. The mean size of the lesion was 4.9 cm (3–10 cm). In only one other case besides ours [10] was Factor IX deficiency the underlying disorder, with all others reporting Factor VIII deficiency. In cases reporting severity of hemophilia, seven were reported as severe [8–12], two were reported as moderate [13], including our case, and three were reported as mild [9, 14, 15].

Although this series is too small to determine significance of associations, age of onset did not seem to be strongly correlated with severity of hemophilia. Five cases reported an antecedent trauma to the affected region [8–10, 16], with one of these traumatic instances associated with tooth extraction in an 11-year-old male [9].

Factor replacement alone was the treatment in three cases [8, 12, 16], while factor replacement plus additional treatment was given in seven cases, including ours [9–11, 15]. The antifibrinolytic agent aminocaproic acid was used in only one case besides ours as supplemental therapy [18]. Some form of surgery alone (cryotherapy and/or curettage)

Table 1 Reported cases of pseudotumor of hemophilia of the jaws

Author(s)	Age (years)	Sex	Location	Symptom	Duration	Size (cm)	Type	Severity	Prior bone lesions	Hx of trauma	Pre-op Dx	Treatment	Outcome
Lazarovitis and Griem [17]	11	Male	L mandible	Gingival bleeding and swelling	Not known	3	Not reported	Severe	Hemarthrosis/ Pseudotumor of L hand	No	Pseudotumor	Radiation therapy	Resolution
Stoneman et al. [18]	13	Male	L mandible	Swelling	3 months	6	Factor VIII deficiency	Not known	Hemarthrosis	No	Myxoma	Cryotherapy and curettage	Resolution
Marquez et al. [13]	13	Male	L mandible	Swelling	2 years	10	Factor VIII deficiency	2%	N/A	No	Multifocal tumor	Cryotherapy/ aminocaproic acid	Resolution
Mulkey [11]	8	Male	R mandible	Swelling	3 weeks	6	Factor VIII deficiency	1%	None	No	Septated radiolucency	Curettage and Factor VIII therapy	Resolution
	7	Male	L mandible	Swelling	4 days	4	Factor VIII deficiency	Severe	None	No	Trabeculated radiolucency	Aspiration and Factor VIII therapy	Pt died from head injury soon after
	16	Male	R mandible	Swelling	1 month	5	Factor VIII deficiency	Severe	None	No	Osteolytic lesion	Curettage and Factor VIII therapy	Resolution
Martinez-Lage [16]	10	Male	L mandible	Swelling	3 months	3	Factor VIII deficiency	Not given	None	Yes	Not given	Factor VIII therapy	Resolution
Brook et al. [8]	1.25	Male	R/L mandible	Swelling	11 months	Not given	Factor VIII deficiency	1%	None	Yes @ 7 months	Loculated radiolucency	Factor VIII therapy	Resolution
Bryan et al. [20]	2.5	Male	R mandible	Swelling	Not known	4	Factor VIII deficiency	Not given	None	No	Cystic lesion	Curettage, obturator placement and irrigation	Resolution
de Sousa et al. [9]	11	Male	L maxilla	None	Not known	Not given	Factor VIII deficiency	1%	Pseudotumor of tibia	6 years prior	Radiolucency	Curettage	Resolving until death 2 years later
	11	Male	R/L mandible	Swelling	Months	Not given	Factor VIII deficiency	11.50%		Teeth extractions	Pseudotumor versus ameloblastoma	Curettage and Factor VIII therapy	Resolution
Zheng and Zheng [14]	26	Male	L maxilla	None	Not known	Not given	Factor VIII deficiency	11%	Pseudotumor of tibia	No	Pseudotumor	Curettage and tooth extraction	Resolution
Steele et al. [12]	0.5	Male	L maxilla	Swelling and erosion	1 week	4	Factor VIII deficiency	1%	None	No	Rhabdomyosarcoma versus mucocele	Factor VIII therapy	Resolution

Table 1 continued

Author(s)	Age (years)	Sex	Location	Symptom	Duration	Size (cm)	Type	Severity	Prior bone lesions	Hx of trauma	Pre-op Dx	Treatment	Outcome
Lima et al. [15]	12	Male	L maxilla	Gingival bleeding and swelling	2 months	4	Factor VIII deficiency	14%	None	No	Not given	Curettage and Factor VIII replacement	Resolution
Lee et al. [10]	34	Male	L mandible	Swelling	2 months	7	Factor IX deficiency	0.3%	None	Yes	Not given	Excision and Factor IX therapy	Resolution
Cox et al. [This study]	2	Male	R mandible	Swelling	1.5 months	3	Factor IX deficiency	3%	None	No	Bony neoplasm	Aminocaproic acid and Factor IX therapy	Resolution but lost to follow-up

was the treatment in five cases [9, 13, 14, 18, 19]. Radiation alone was the treatment in a single case [17]. Resolution of the lesion was achieved in all cases except for one where the patient died from a head injury soon after presentation [11].

Discussion

Normal levels of factor VIII and IX range from 43–168% and 60–160% respectively, with normal ranges derived specifically for the UCSF reagents and set per the Clinical Laboratory Standards Institute. There are different clinical levels of hemophilia depending on the amount of clotting factor in the blood and the degree of factor deficiency is categorized as mild, moderate, and severe. A mild phenotype, defined by 5–50% of normal clotting factor, is seen in about 25% of patients, who manifest bleeding problems only after serious injury, trauma, or surgery, including tooth extraction. These events are often the first manifestations of hemophilia and will lead to diagnosis. Patients with a moderate phenotype (1–5% of normal clotting factor) account for ~15% of cases and occasionally present with spontaneous bleeding episodes. Patients with a severe phenotype (<1% of normal clotting factor) account for ~60% of all hemophiliacs and have frequent spontaneous episodes of bleeding that often occur into bone, joints, and soft tissue.

In 1918, Starker [3] described the first case of what he termed “hemophilic pseudotumor” in a 14-year-old patient with hemophilia who presented with a swelling of the right thigh and cortical destruction of the femur that had been thought to be osteogenic sarcoma, clinically, but was not confirmed as such on pathologic evaluation. In 1948, Ghormley and Clegg [1] reported on the first large series of “so-called hemophilic pseudotumor”. Although their review did not include any jaw lesions in their series of 44, they did find that there was a large age range of occurrence of hemarthrosis (from 4 months to 35 years), with 30% occurring in children under the age of 10 years. This closely parallels the findings of our review of jaw PTHs.

Ahlberg published on the natural history of PTH in 1975 in which seven cases were followed for 10 years [4]. They showed that adequate and early factor replacement therapy will prevent occurrence of PTHs, with replacement advocated when factor VIII or IX was reduced to 50% of normal levels.

In that same year, Gilbert characterized PTH into two distinct types: proximal and distal pseudotumors, respectively. Proximal pseudotumors are much more common in the long bones and pelvis and are slow growing lesions that begin in the soft tissues and secondarily erode into bone. These are more common in adults and are associated with pathologic fractures. Distal pseudotumors tend to occur as a result of direct trauma and intraosseous hemorrhage, and

are rapidly growing masses in the small bones of the hands and feet. These occur in younger patients and are associated with a better prognosis [7].

PTH was later divided into three subtypes [20]: (1) bleeding into muscle with subsequent pressure resorption of the underlying bone followed by necrosis; (2) subperiosteal hemorrhage with stripping of the periosteal bone and pressure necrosis; and (3) intraosseous hemorrhage and necrosis.

The pathology of the PTH is basically an encapsulated hematoma with varying stages of organization [6]. The thick, fibrous capsule itself is highly vascularized; hence, the tendency to continue growing. Moreover, this rich blood supply is the reason that these lesions may bleed significantly after biopsy. Hemosiderin and hemosiderin-laden macrophages are frequently seen, as evidence of chronic bleeding. When bone is involved, both medullary and cortical destruction is common and necrosis may be seen in adjacent tissues [21]. Calcification and reactive peripheral bone formation may be seen in lesions over time.

The most comprehensive review of PTH came from a Spanish multicenter experience over a 25-year period [21]. Of 1,831 total patients with coagulopathies, 21 patients (0.01%) (age range: 8–61; median 40) were found to have PTHs. Of these, 16 had hemophilia A, four had hemophilia B, and one had another coagulopathy. Of the hemophilia cases, nine were severe, seven were moderate, and four were mild. A documented antecedent event was identified in 12 cases, including trauma in 10 (47.6%) and surgery in two (0.1%). Bones were affected in 12 cases (57.1%) and local pain was reported in 17 cases (80.9%). Continuous factor replacement therapy (40–50 U/kg 2–3/week) was administered to 11 patients for 2–36 months (median 4 months) and treatment was successful in two of the 11 cases. The remaining five patients underwent surgical excision. Including these five patients, surgery was performed on a total of 14 cases, and amputation was carried out in one case. Their conclusion was that surgery delivered the best results, particularly in those who did not have prior replacement therapy.

Other findings from this study suggest that patients 40 years or less had a better prognosis ($n = 11$; 8 resolved, 3 did not) than patients over 40 ($n = 10$; 2 resolved, 8 unresolved) ($P = 0.02$). Interestingly, they did not see a significant outcome correlation between mild/moderate cases and severe cases. This is similar to our evaluation of PTH of the jaw. The possible explanation they offered for this is that those with severe hemophilia receive frequent factor VIII transfusions, which may act as a protective mechanism against long lasting PTHs.

In 2002, Rodriguez-Merchan summarized the treatment options for PTH, which include embolization, irradiation,

percutaneous management, and surgical removal [22]. Since embolization has only a temporary effect, the recommendation is that it be used as a preparatory procedure about 2 weeks prior to surgery to allow for mass shrinkage. Irradiation has some benefit in unresectable lesions by causing direct injury to the blood vessels feeding the pseudotumor. Moreover, it can be beneficial, post-excision, if there is any remaining capsule. However, it may not be beneficial *prior* to surgery due to the ensuing fibrosis. Specifically, the recommendation is a range of 600–2,350 Gy in divided treatments of 200 Gy. Percutaneous aspiration and filling with fibrin glue or cancellous bone graft may slow or halt progression in those lesions deemed inoperable. This method has the advantage of being relatively noninvasive and inexpensive and does not require hospitalization. Surgical excision requires close collaboration with the hematologist to carefully monitor factor levels. The recommendation is to maintain factor levels at 100 IU/dl⁻¹ for the first 3 days following surgery and then at 50 IU/dl⁻¹ for the 2 weeks post-surgery. Recurrent lesions can be the result of incomplete excision, or postoperative hematomas that repeat the pathologic process.

In our review of PTH of the jaws, it is evident that treatment decisions are based on many factors, including operability, age of the patient, and location of the lesion. Tailoring the treatment of choice for each patient can have beneficial results, provided that adequate factor levels are maintained.

Although other, more common lesions must be considered in the clinical differential diagnosis of destructive, intra-bony lesions of the jaws in children, particularly malignant neoplasms, it is important to keep PTH in this differential even when there is no prior history or family history of hemophilia, particularly when histopathologic findings are non-specific.

References

1. Ghormley RK, Clegg RS. Bone and joint changes in hemophilia; with report of cases of so-called hemophilic pseudotumor. *J Bone Joint Surg Am.* 1948;30A(3):589–600.
2. Caffey J, Schlesinger ER. Certain effects of hemophilia on the growing skeleton. *J Pediatr.* 1940;16:549.
3. Starker L. Knochensur durch ein hamophiles, subperiostales hamatom. *Mitt Grenzgeb Med Chir.* 1918;31:318.
4. Ahlberg AK. On the natural history of hemophilic pseudotumor. *J Bone Joint Surg Am.* 1975;57(8):1133–6.
5. Abell JM, Bailey RW. Hemophilic pseudotumor. Two cases occurring in siblings. *Arch Surg.* 1960;81:569–81.
6. Rodriguez-Merchan EC. The haemophilic pseudotumour. *Haemophilia.* 2002;8(1):12–6.
7. Gilbert MS. Characterizing the hemophilic pseudotumor. *Ann NY Acad Sci.* 1975;240:311–5.
8. Brook AH, Bedi R, Lui WY, et al. Haemophilic pseudotumours of the mandible: report of a case in a one-year-old child. *Br J Oral Maxillofac Surg.* 1985;23(1):47–52.

9. de Sousa SO, de Piratininga J, Pinto Junior DS, de Araujo N. Hemophilic pseudotumor of the jaws: report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;79(2):216–9.
10. Lee DW, Jee YJ, Ryu DM, et al. Changes in a hemophilic pseudotumor of the mandible that developed over a 20-year period. *J Oral Maxillofac Surg.* 2009;67(7):1516–20.
11. Mulkey TF. Hemophilic pseudotumor of the mandible. *J Oral Surg.* 1977;35:561.
12. Steele NP, Myssiorek D, Zahtz GD, et al. Pediatric hemophilic pseudotumor of the paranasal sinus. *Laryngoscope.* 2004; 114(10):1761–3.
13. Marquez JL, Vinageras E, Dorantes S, et al. Hemophilic pseudotumor of the inferior maxilla. Report of a case. *Oral Surg Oral Med Oral Pathol.* 1982;53(4):347–50.
14. Zheng K, Zheng P. Hemophilic pseudotumor involving maxilla and tibia. *Chin Med J (Engl).* 1997;110(3):233–5.
15. Lima GS, Robaina TF, de Queiroz Chaves Lourenco S, et al. Maxillary hemophilic pseudotumor in a patient with mild hemophilia A. *J Pediatr Hematol Oncol.* 2008;30(8):605–7.
16. Martinez-Lage JL, Sanchez H, Garcia JS, et al. A pseudo-tumour of the mandible in a haemophiliac patient. A case report. *J Maxillofac Surg.* 1983;11(4):171–3.
17. Lazarovits P, Griem ML. Radiotherapy and haemophilia pseudotumors. *Radiology.* 1968;91(5):1026–7.
18. Stoneman DW, Beierl CD. Pseudotumor of hemophilia in the mandible. Report of a case. *Oral Surg Oral Med Oral Pathol.* 1975;40(6):811–5.
19. Bryan GW, Leibold DG, Triplett RG. Hemophilic pseudotumor of the mandible. Report of a case. *Oral Surg Oral Med Oral Pathol.* 1990;69(5):550–3.
20. Correria A, Buckley J, Roser S, et al. Radiotherapy of a pseudotumor in a hemophiliac with Factor VIII inhibitor. *Am J Pediatr Hematol Oncol.* 1984;6(3):325–7.
21. Magallon M, Monteagudo J, Altisent C, et al. Hemophilic pseudotumor: multicenter experience over a 25-year period. *Am J Hematol.* 1994;45(2):103–8.
22. Rodriguez-Merchan EC, Gomez-Cardero P. Pathological fracture of a true tumour mimicking a haemophilic pseudotumor. *Haemophilia.* 2005;11(2):188–90.