Primary Intraosseous Carcinoma in the Pediatric Mandible

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Case report

Keywords: odontogenic cyst, primary intraosseous carcinoma, pediatric mandible

Posted Date: February 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-195662/v1>

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Abstract

Background: Primary intraosseous carcinoma (PIOC) is a rare malignant odontogenic tumor that predominantly occurs in males older than 50 years. PIOC can be misdiagnosed as odontogenic cyst because it occasionally shows well-defined border on radiography. In this study, a case of a 14-year-old female with PIOC who was misdiagnosed with odontogenic cyst clinically is reported along with a literature review of pediatric PIOC cases.

Case Presentation: A 14-year-old female patient presented with painful swelling on the mandibular right premolar area. There was a radiolucent lesion with a well-defined border in panoramic view. She was diagnosed with odontogenic cyst, and the cystic mass was enucleated with extraction. However, the biopsy result was consistent with PIOC. After cancer work-up, she underwent partial mandibulectomy, selective neck dissection, and reconstruction with a fibular free flap. Although the surgical resection margins were clear, local recurrence and lung metastasis occurred four months after surgery. She underwent concurrent chemo-radiation therapy, but the prognosis was poor.

Conclusions: PIOC should be diagnosed differentially from odontogenic cyst even in pediatric populations.

Background

Primary intraosseous carcinoma (PIOC) is a rare and infrequently reported malignant odontogenic tumor. In 2005, the World health organization (WHO) divided PIOC into three subcategories according to histogenesis [1]. However, in 2017, WHO reclassified it as a single entity after leaving out unsubstantiated references to histogenesis in 2017 [2]. Approximately 260 cases have been reported [3, 4]. PIOC is more common in males and usually occurs in people 50 years and older [3, 5-11]. PIOC has occurred extremely rarely in pediatric populations: prior to this case, only nine cases had been reported in the English literature [12-20]. PIOC is misdiagnosed frequently as odontogenic cyst because it occasionally shows well-defined borders in panoramic view or on computed tomography (CT) [21-24]. In this study, a PIOC case of a 14-year-old female patient who was misdiagnosed with odontogenic cyst is discussed along with a literature review of pediatric PIOC cases.

Case Presentation

A 14-year-old female patient was referred from a local dental clinic to the Department of Oral and Maxillofacial Surgery at Seoul National University Dental Hospital, Seoul, Korea. She presented with painful swelling on the mandibular right premolar area and complained of intermittent bleeding when she brushed her teeth. A panoramic view showed a radiolucent lesion with a well-defined border (Fig. 1a). Adjacent tooth displacement and external root resorption were noted. There was a radiopaque focus in the upper area of the lesion. The patient was diagnosed with odontogenic cyst, and the cystic mass was enucleated with extraction of the right first premolar under local anesthesia.

Histopathology of the surgical specimen revealed high cellularity and a sheet-like growth pattern with epithelial islands (Figs. 2a,2b). Microscopic examination showed round monotonous shaped tumor cells with high nucleus-cytoplasm ratio and bizarre mitosis (Figs. 2c,2d). On immunohistochemical staining, CK-7 and CK-14 showed focal positive. CK-18, CK-PAN, and Vimentin were positive. Moreover, cells were 40-60% positive for Ki-67. However, CD99, Desmin, S-100 protein, and NSE were negative. A final diagnosis was consistent with PIOC.

Enhanced CT, magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), bone scintigraphy and neck ultrasonography were performed. In enhanced CT, a periosteal reaction was observed on the buccal side (Fig. 3a). In MRI, diffuse enhancement of the soft tissue was observed at the adjacent buccal area (Fig. 3b). There were no significant lymph nodes. In PET-CT, a soft tissue lesion on the right premolar area and a borderline-sized lymph node at the right level IB were observed (Fig. 3c). There was no distant metastasis. In bone scintigraphy, increased uptake in the right mandible was observed (Fig. 3d). In neck ultrasonography, no significant cervical lymph node enlargement was observed. Hand-wrist radiograph and lower extremity angiography were performed for reconstruction surgery with the fibular free flap. In hand-wrist radiograph, that patient's skeletal maturation was estimated as 15-16 years old. On leg angiography, anterior tibial, posterior tibial, and peroneal arteries were intact.

One month after enucleation surgery, the patient showed abnormal healing (Fig. 4a). Surgical resection and reconstruction with a fibula free flap were prepared. The required bone length was 73 mm, and a resin stent was prepared (Fig. 4b). She underwent partial mandibulectomy from the right retromolar area to the left central incisor and selective neck dissection (right levels I, II, III) under general anesthesia. The mandibular and neck masses were removed en bloc (Fig. 4c) with simultaneous reconstruction using the microvascular fibula free flap (Fig. 4d).

The surgical resection margin was clear, and no metastatic cervical lymph nodes were found in the dissected mass. Perineural or vascular invasion was not seen. However, there was involvement of the underlying bone. The patient's healing was uneventful. However, local recurrence and lung metastasis occurred four months after surgery. She underwent concurrent chemo-radiation therapy (CCRT) for one month; however, a recurred lesion on the right mandibular ramus did not decrease (Fig. 1b). She was lost to follow-up after her visit one month after the end of CCRT.

Discussion

According to the previous case studies, nine PIOC cases have been reported in pediatric populations [12-20]. A summary of all 10 pediatric cases, including this case, is provided in Table 1 and 2. PIOC is more common in adult males [3,5-11]; however, seven of the total 10 pediatric cases were female. PIOC occurs more often in the mandible than maxilla [3,5-11], seen in seven of the pediatric patients. The most common symptom was swelling, followed by pain [3,5,7]. The symptoms of the pediatric patients were consistent.

PIOC can be misdiagnosed as odontogenic cyst because it occasionally presents with a well-defined border in panoramic view or CT [21-24]. Differential diagnosis of PIOC from odontogenic cyst is important because the surgical approach is different. Kaffe et al. [21] reported that 61% of PIOC cases presented

as a unilocular radiolucent lesion. In our review of pediatric cases, six of 10 cases showed unilocular radiolucency. Radiologic borders that were defined but non-corticated were reported to occur in 57% of the PIOC cases and the remaining 43% had diffuse borders. In cases with poorly defined borders, such as those with diffuse margins, the lesions could be unambiguously distinguished from odontogenic cyst. However, since cases with well-defined borders can be misdiagnosed as odontogenic cyst, a differential diagnosis should be thoroughly considered. According to Kaffe et al. [21], a defined but non-corticated border could be a useful feature for differential diagnosis. A well-defined but non-corticated border was observed in five of the 10 pediatric PIOC patients (Table 1). Moreover, tooth displacement and root resorption should be considered as other radiologic features as PIOC tends to grow too rapidly to produce such features [7,19,21,25]. However, four of the pediatric cases in our review showed tooth displacement and five showed root resorption. It was peculiar that these features occurred in the pediatric patients. Although tooth displacement and root resorption are features for slowly growing lesions such as odontogenic cysts, these features should be considered for differential diagnosis of PIOC in pediatric populations. As a rare finding, radiopaque foci were observed in this case and in Punnya et al.'s pediatric case [15]. Although PIOC usually presents as an osteolytic lesion, small radiopaque foci due to calcification or periosteal reaction can be observed, albeit rarely [10,26-28].

Among the 10 pediatric cases we reviewed, the initial diagnosis for five was odontogenic cyst. Huang et al. [7] reported that this diagnostic delay did not show any statistically significant prognostic difference. However, Naruse et al. [25] reported that preoperative dental procedures might be potential prognostic factors and suggested that no intervention before definitive diagnosis could achieve a better prognosis. Therefore, incisional biopsy with obtaining multiple specimens is necessary to rule out an underlying carcinoma [8,9,14,17]. Regardless of patient age, biopsy should be considered for any lesion with any of the unusual radiographic presentations mentioned above. The pediatric patient reported by Charles et al. [17] was accurately diagnosed by biopsy and had the longest follow-up period without recurrence. A biopsy was not considered for definitive diagnosis in the present case although there were atypical radiographic findings. Local recurrence occurred five months after the initial operation, that is, four months after the definitive surgery.

The primary treatment for PIOC is surgical resection [3,8,11,29]. In the present case, because simultaneous reconstruction was necessary, hand-wrist radiography was analyzed for assessment of growth potential. Her skeletal age was assessed as 15-16 years old. Previous research has concluded that the face matures between 12 and 15 years in males and two years earlier in females [30,31]. The vascularized fibular free flap is a reliable option for mandibular reconstruction, even in pediatric patients [32,33]. Therefore, the fibular free flap was employed for this 14-year-old female patient.

Recent reviews reported the rate of cervical lymph node metastasis to be 12.8% [3] and 70.1% [11]. In our case review, three of the 10 pediatric cases showed cervical metastasis. Wenguang et al. [11] reported nodal status to be a significantly poor prognostic factor for survival. However, de Morais et al. [3] reported that lymph node metastasis was not statistically associated with survival. Although these outcomes conflict, it seems reasonable that neck dissection be considered among the surgical procedures for PIOC. In the present case, there were no metastatic lymph nodes on enhanced CT or MRI. However, because there were borderline-sized lymph nodes at the right level IB, selective neck dissection was performed.

In recent literature, de Morais et al. [3] reported a local recurrence rate of 22.1% and Ye et al. [4] reported a local recurrence rate of 24.1%. In this study, local recurrence occurred in three pediatric patients, including the present case, a rate of 30% although the total cases were only 10. In one report, a four-year-old female patient suffered recurrence five months after excision and underwent additional radical excision [3]. However, 10 months later, recurrence recurred, the lesion was removed, and the area was irradiated. She was alive after one year of follow-up. In another case, a 16-year-old male patient suffered recurrence two months after excision and underwent total mandibulectomy after one month. However, he died two months after the surgery [13]. The 14-year-old female patient in the present study suffered recurrence four months after definitive surgery. She underwent CCRT for one month, but the recurred lesion did not decrease. According to de Morais et al. [3] and Ye et al. [4], local recurrence is a significant prognostic factor for survival. Likewise, pediatric PIOC cases with local recurrence showed poor prognosis. The five-year survival rate has been reported as 44.6% [3] and 53.2% [4]. However, the five-year survival rate of the pediatric patients could not be evaluated because of the rarity of the cases and relatively short follow-up periods.

Because PIOC has a poor prognosis, accurate diagnosis and adequate surgical procedures are important. Continuous updates are required to analyze the pathophysiologic mechanism of PIOC, and a recent approach such as genetic analysis [34] could contribute to understanding the pathophysiology of PIOC.

Conclusion

PIOC is a rare malignant odontogenic tumor that can be misdiagnosed as odontogenic cyst because it occasionally presents with a well-defined border on radiography. According to the literature review, 10 pediatric PIOC cases have been reported, five of which were initially diagnosed as odontogenic cyst. PIOC with a well-defined border usually has non-corticated margin. Atypically, tooth displacement and root resorption were observed in approximately half of the pediatric cases. Incisional biopsy with multiple specimens is necessary to rule out PIOC in cases with atypical radiographic findings. PIOC should be differentially diagnosed from odontogenic cyst even in pediatric populations.

Abbreviations

PIOC: Primary intraosseous carcinoma; WHO: World health organization; CT: computed tomography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computed tomography; CCRT: concurrent chemo-radiation therapy

Declarations

Ethics approval and consent to participate

Consent for publication

Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

All authors read and approved the final manuscript. **HJO** read and wrote the manuscript, **DHS** collected the literature data, **HM** designed the article, **HJY** prepared the histopathologic data, and **SMK** prepared the figures and wrote the manuscript.

Acknowledgement

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education(No. 2017R1D1A1B04029339).

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Tables

Table 1. Clinical and radiological characteristics of 10 pediatric patients with primary intraosseous carcinoma in jaw.

Case	Year	Author	Country	Age	Sex	Location	Symptom	Locularity	Density	Border	Tooth displacement	Root resorpti
1	1966	Jones [12]	Ireland	4	F	Mandible	Swelling	N/S	N/S	N/S	Yes	N/S
2	1973	Sirsat et al. [13]	India	16	M	Mandible	Swelling	Not loculated	Mixed	Diffuse	Yes	N/S
3	2002	Gulbranson et al. [14]	America	16	F	Mandible	Swelling	Unilocular	Radiolucency	Cortical thinning	N/S	N/S
4	2004	Punnya et al. [15]	India	18	F	Maxilla	Swelling	N/S	Radiolucency, multiple radiopaque foci	Well defined, non-corticated	N/S	Yes
5	2006	Chaisuparat et al. [16]	America	18	F	Maxilla	Swelling	Unilocular	Radiolucency,	Well defined, non-corticated	N/S	N/S
6	2008	Charles et al. [17]	Canada	5	F	Mandible	Swelling	Unilocular	Radiolucency, enlarged crypt,	Well defined, non-corticated	Yes	Yes
7	2010	Sengupta et al. [18]	India	16	M	Mandible	Swelling, pain	Unilocular	Radiolucency	Well defined, non-corticated	N/S	Yes
8	2016	Boni et al. [19]	Italy	14	M	Maxilla	Swelling	N/S	N/S	N/S	No	No
9	2018	Nokovitch et al. [20]	France	15	F	Mandible	Swelling, pain, intermittent bleeding	Unilocular	Radiolucency, supernumerary tooth	Lingual cortex lysis	N/S	Yes
10	2020	Present study	Korea	14	F	Mandible	Swelling, pain, intermittent bleeding	Unilocular	Radiolucency, a radiopaque focus	Well defined, non-corticated	Yes	Yes

N/S not specified

Table 2. Treatment outcomes of 10 pediatric patients with primary intraosseous carcinoma in jaw.

Case	Initial diagnosis	Initial treatment	Confirmed diagnosis	Definitive treatment	Cervical metastasis	Local recurrence	Salvage treatment	Follow-up duration	Survival status at the last F/U
1	N/S	N/S	N/S	Excision	Yes ^a	Yes	Radical Excision / SND, RT ^a	27 months	alive
2	N/S	N/S	N/S	Excision	Yes ^b	Yes	Mandibulectomy, SND	8 months	dead
3	Dentigerous cyst	Incisional biopsy	Carcinoma	Mandibulectomy, SND	No	No	No	8 months	alive
4	Odontogenic cyst	FNAC	Odontogenic cyst	Enucleation	N/S	No	No	16 months	alive
5	N/S	N/S	N/S	Maxillectomy, RT	No	No	No	44 months	alive
6	More aggressive lesion than odontogenic cyst	Incisional biopsy with extraction	PIOC	Mandibulectomy, mRND, Reconstruction with plate, RT	Yes	No	No	7 years	alive
7	OKC	Enucleation with extraction	PIOC	Refer	N/S	N/S	N/S	N/S	N/S
8	N/S	N/S	N/S	Maxillectomy	N/S	No	No	5 years	alive
9	OKC	Incisional biopsy	OKC	Enucleation with extraction	No	No	No	18 months	alive
10	Odontogenic cyst	Enucleation with extraction	PIOC	Mandibulectomy, SND, Reconstruction with FFF	No	Yes	CCRT	9 months ^c	alive

F/U follow-up, *N/S* not specified, *OKC* odontogenic keratocyst, *FNAC* fine needle aspiration cytology, *P/IOC* primary intraosseous carcinoma, *SND* selective neck dissection, *mRND* modified radical neck dissection, *RT* radiation therapy, *CCRT* concurrent chemo-radiation therapy, *FFF* fibular free flap

^a at second recurrence
^b at recurrence
^c recurred but lost to follow-up.

Figures

Figure 1
Panoramic view findings. a Two days before initial treatment. b One month after the end of concurrent chemo-radiation therapy.

Figure 2
Histopathologic findings. a Epithelial islands (H&E, x40). b High cellularity and a sheet-like growth pattern (H&E, x100). c Round monotonous shaped tumor cells (H&E, x200). d High nucleus-cytoplasm ratio and bizarre mitosis (H&E, x400).

Figure 3
Pre-operative imaging. a Enhanced CT showing periosteal reaction at the buccal side. b MRI showing diffuse enhancement of soft tissue at the adjacent buccal area. c PET-CT showing a soft tissue lesion at the right premolar lesion. d Bone scintigraphy showing increased uptake in the right mandible.

Figure 4

Surgical procedures. a Abnormal healing one month after enucleation surgery. b The 73-mm resin stent for reconstruction with fibula free flap. c En bloc resection of the right mandible and neck mass (right level I, II, III) d Intraoperative fibular contouring using the stent.