RESEARCH ARTICLE

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Primordial Odontogenic Tumor; Archival Review of 19380 Cases in a 55-Year Retrospective Study

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Abstract

Background and Objective: Primordial odontogenic tumor is a rare odontogenic tumor reported for the first time in 2014. It was included in the latest edition of World Health Organization classification of Head and Neck Tumors as a new benign mixed epithelial-mesenchymal neoplasm. To date, 26 cases has been reported in literature. The aim of this study was to determine the possible presence of primordial odontogenic tumor in the previously diagnosed cases with myxoid stroma. **Materials and Methods:** This study was a retrospective descriptive study that was concluded in Oral and Maxillofacial Pathology Department, School of Dentistry, Tehran University of Medical Sciences. We reviewed all 19,380 cases from 19,66 to find the lesions with myxoid stroma which were in differential diagnosis with primordial odontogenic tumor. These cases should be associated with an impacted or unerupted tooth and belong to the patients under 20 years old. **Results:** We find 503 pericoronal lesions with myxoid stroma. Three cases were isolated after recut and reevaluation for finding fulfill histologic features. After immunohistochemical analysis, we find a new case of developing primordial odontogenic tumor associated with odontoma. **Discussion:** Primordial odontogenic tumor a recently described odontogenic tumor has a well-defined clinicopathological and immunohistochemical profile and should be differentiated from the others pericoronal lesions. It is the first time that this archival review has been done to find probable cases of primordial odontogenic tumor.

Keywords: Primordial- neoplasm- odontogenic- tumor

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Introduction

Primordial odontogenic tumor (POT) is a rare lesion reported for the first time in 2014 (Mosqueda-Taylor et al., 2014). POT was included in the latest edition of World Health Organization (WHO) classification of Head and Neck Tumors as a new benign mixed epithelial-mesenchymal neoplasm (El-Naggar et al., 2017; Speight and Takara, 2018). The name Primordial Odontogenic Tumor was suggested because of Its location and process of odontogenesis imply that this lesion may originate from the early stage of tooth development, particularly in the late cap stage to early bell stage (Bologna-Molina et al., 2020). It commonly occurs in the mandible of adolescent and young patients with the age less than 20 years old without gender predilection (Bomfim et al., 2019).

It reveals with an asymptomatic and variably extensive bone cortical expansion (Bologna-Molina et al., 2020). A well-defined, unilocular radiolucency associated to crown of an unerupted tooth is observed in radiographic features. Root resorption at adjacent teeth may be seen especially in large lesions. In histopathologic view, POT consists of cellular to loose myxoid tissue resembling dental papilla. A single delicate layer of columnar to cuboidal epithelium with reverse nuclear polarization resembling the internal epithelium of enamel organ (inner enamel epithelium) is present in the periphery of the lesion (Bologna-Molina et al., 2020; Almazyad et al., 2018).

To date, 26 cases has been reported in literature (Almazyad et al., 2022). The aim of this study was to determine the possible presence of primordial odontogenic tumor in the previously diagnosed cases with myxoid stroma. Based on the best of our knowledge, there is not any accompanying of POT with the other odontogenic lesions. Here we present a new case of developing POT that occurred in the right mandible of 12-year-old girl which is accompanied with an odontoma and discuss clinicoradiographic features of the lesion with immunohistochemical analysis.

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Materials and Methods

This study was an extensive retrospective archive review of the records of 19380 patients in Tehran University of Medical Sciences (TUMS), School of Dentistry, Oral and Maxillofacial Pathology Department. All the reports that belong to under 20 years old patients which have pericoronal lesion around the unerupted or impacted tooth were obtained. This reports also should be have histopathologic diagnosis of the lesions which are in differential diagnosis of primordial odontogenic tumor and the lesion with prominent myxoid stroma. These lesions were included as below: Hyperplastic dental follicle, Dentigerous cyst, Ameloblastic fibroma, Unicystic ameloblastoma, Odontogenic myxoma, Odontogenic fibroma, Fibromyxoma, Ameloblastic odontoma, Odonto-ameloblastoma and Odontogenic myxoma. The exclusion criteria were included: missed pathologic slides, radiographic records and demographic data of the patients, the patients over 20 years old and finally the lesions unrelated to unerupted or impacted tooth. All the complete medical records that had pathologic slides were included. All the microscopic sections were examined by two oral and maxillofacial pathologists.

Gender, age, anatomic location of the lesion, the primary diagnosis of the lesion and the involved tooth were obtained from the medical records of the patients. The descriptive statistics were done to evaluate the registered data.

This study was done under supervision and support of the Tehran University of Medical Sciences, School of Dentistry with grant#1400-2-130-53412. The study was approved by the Ethics Committee of the Tehran University of Medical Sciences, Dental School with ethics code of (IR.TUMS.DENTISTRY.REC.1400.169).

Results

In the first evaluation of the medical records of the 19,380 patients, 503 patients were isolated. All of these cases were associated to an impacted or unerupted tooth, in the under 20 years old patient and have a primary diagnosis of one of these lesions: Hyperplastic dental follicle, Dentigerous cyst, Ameloblastic fibroma, Unicystic ameloblastoma, Odontogenic myxoma, Odontogenic fibroma, Fibromyxoma, Ameloblastic odontoma, Odonto-ameloblastoma and Odontogenic myxoma (Table 1).

The pathologic slides of these 503 cases were reevaluated by two pathologists to assess the presence of the microscopic criteria for diagnosis of primordial odontogenic tumor. These criteria comprised: 1) mesenchymal fibromyxoid tumoral tissue with variable cellularity resembling dental papilla, 2) the periphery surrounded by a columnar to cuboidal epithelium similar to the inner enamel epithelium and 3) subepithelial mesenchymal cells condensation (Bologna-Molina et al., 2020). Occasionally, stellate reticulum-like epithelium in suprabasal areas, partially a thin fibrous capsule and focally invaginations of the epithelium to the underlying tissue may be also observed (Bologna-Molina et al., 2020). Thirty cases were isolated from 503 patients which have the most histopathological similarity (the mentioned criteria) to primordial odontogenic tumor. After recut and reevaluation of the microscopic slides of these 30 cases,

Table 1. Isolated Cases which were in Differential Diagnoses with Primordial Odontogenic Tumor

Lesion	Number (Percentage)
Dentigerous cyst	366 (72.8)
Hyperplastic dental follicle	53 (10.7)
Unicystic ameloblastoma	24 (4.9)
Ameloblastic fibroma	17 (3.3)
Odontogenic myxoma	16 (3.1)
Ameloblastic fibro odontoma	11 (2.4)
Odontogenic fibroma	5 (0.9)
Fibromyxoma	3 (0.5)
Ameloblastic odontoma	5 (0.9)
Odonto-ameloblastoma	0 (0)
Odontogenic myxoma	3 (0.5)
Total	503

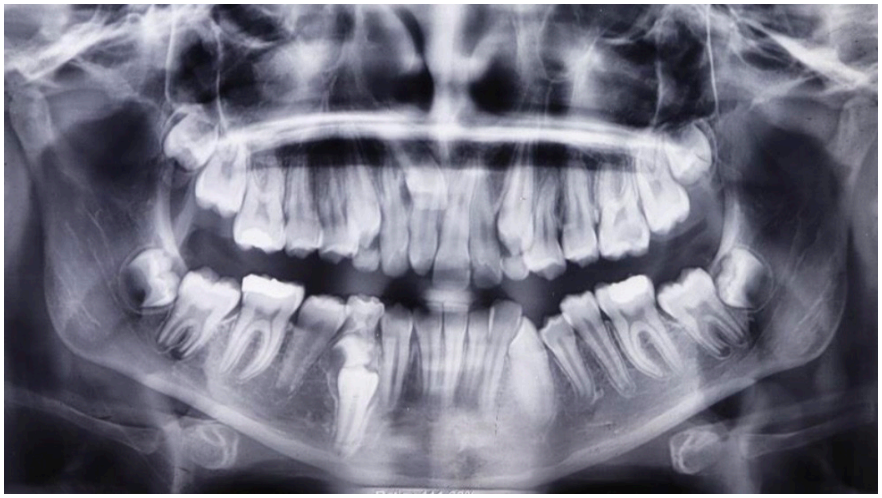

Figure 1. Radiographic View. Panoramic view of the lesion shows admixed lesion in pericoronal area at unerupted right mandibular first premolar tooth.

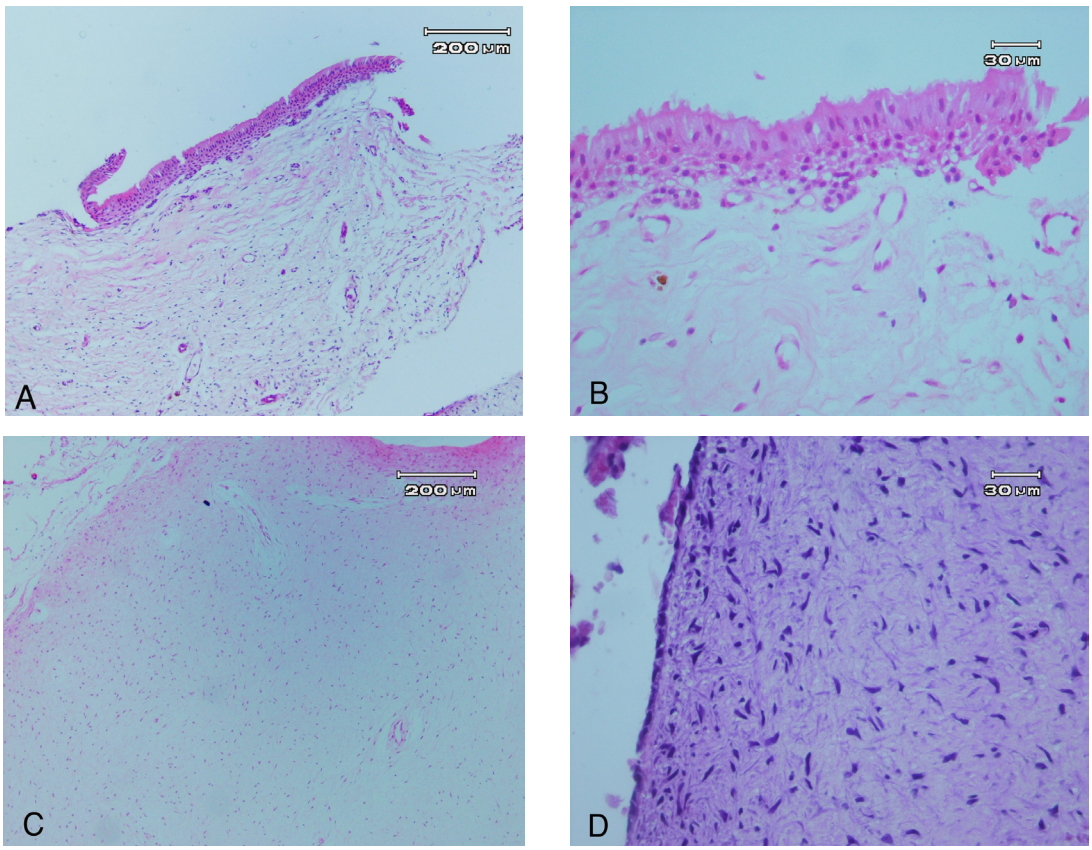

Figure 2. Histopathologic Views (H&E Staining). A, The lesion partially lined by columnar epithelium (×100 magnification); B, Straited columnar epithelium of the lesion (×400 magnification); C, Loosely arranged stellate to spindle cells resembling dental papilla (×400 magnification); D, One layer of cuboidal epithelium of the lesion (×400 magnification).

finally three cases selected for immunohistochemical (IHC) staining based on the most accordance to POT. IHC staining was done for CK14, CK19, CD138, CD34, αSMA, S100, Ki67 and Vimentin according to previously reported cases. Two of three cases had compatible immunohistochemical reaction. One of them was left out because of lack of access to the patient for follow up and radiologic evaluation due to the sample being very old (more than forty years ago).

Here in, we report a case of developing primordial odontogenic tumor associated with a compound odontoma in 12 years old girls.

Report of case

A healthy 12-year-old Iranian girl was taken by her parents to dental faculty of Tehran University of Medical Sciences (TUMS) with chief complaint of crowded teeth for orthodontic therapy. Her past medical history was not significant and contributory. In intra-oral examination, there was not any swelling, unusual discoloration or significant pathologic alteration in the first observation. Past dental history was not noticeable. In panoramic view, an asymptomatic incidental lesion was discovered in the right body of the mandible. A well-defined, unilocular radiolucent lesion circumscribing the crown of the impacted right lower first deciduous molar tooth was

Table 2. Reported most Known Immunohistochemical Antibodies in Primordial Odontogenic Tumor in Comparison with Our Case

Antibody	Pattern in POT	Result in our case
CK14	Positive in epithelium	Strongly positive in all layers of epithelium
CK19	Positive in epithelium	Only positive in basal layer of epithelium
Vimentin	Positive in mesenchymal cells	Strongly positive in mesenchymal cells
αSMA	Negative	Negative
CD34	Variable (negative to strongly positive in subepithelial mesenchymal cells)	Few scant positive in mesenchymal cells
CD138	Variable in mesenchymal cells	Weak scant positive in mesenchymal cells
S100	Variable in mesenchymal cells	Negative
Ki67	Low proliferation index (<5%)	Lower than 2%

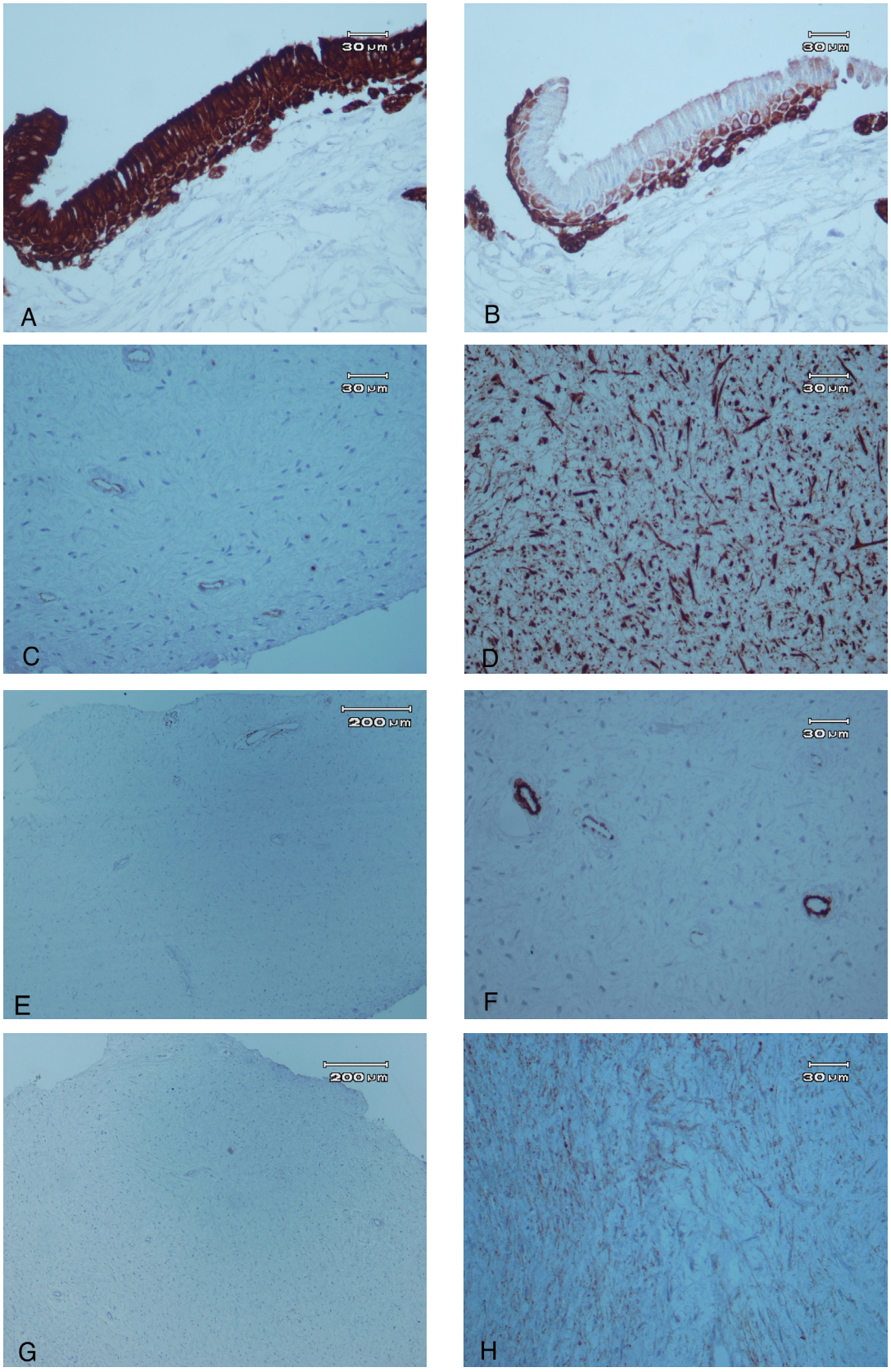

Figure 3. Immunohistochemical views. A, strongly positive immunoreaction for CK14 in epithelial lining (×400 magnification); B, Strongly positive immunoreaction for CK19 only in basal cells (×400 magnification); C, Few scant positive cells for CD34 (×100 magnification); D, Strongly positive immunoreaction for vimentin in stromal cells (×400 magnification); E, Negative immunoreaction for S100 (×100 magnification). F, Negative immunoreaction for aSMA, notice the blood vessels as internal positive control (×400 magnification); G, Lower than 2% for Ki67 (×100 magnification); H, Weak scant positive cells for CD138 (×400 magnification).

Table 3. The Previously Reported Primordial Odontogenic Tumor (F, Female; M, Male; Man, Mandible; Max, Maxilla).

Case Number	Reference	Age (Year)	Gender	Location	Involved Tooth	Treatment	Follow Up	Recurrence
1	Mosqueda-Taylor et al., 2014	18	M	Man	unerupted third molar	enucleation & tooth extraction	20 years	NO
2	Mosqueda-Taylor et al., 2014	16	M	Man	unerupted third molar	enucleation & tooth extraction	13 years	NO
3	Mosqueda-Taylor et al., 2014	16	M	Man	unerupted third molar	enucleation & tooth extraction	10 years	NO
4	Mosqueda-Taylor et al., 2014	3	F	Man	unerupted second deciduous molar	enucleation & tooth extraction	9 years	NO
5	Mosqueda-Taylor et al., 2014	13	F	Man	unerupted third molar	enucleation & tooth extraction	3 years	NO
6	Mosqueda-Taylor et al., 2014	3	F	Max	unerupted second deciduous molar	enucleation & tooth extraction	6 months	NO
7	Slater et al., 2016	19	M	Man	unerupted third molar	excision & tooth extraction	7 months	NO
8	Mikami et al., 2017	5	M	Man	unerupted second deciduous molar	excision & tooth extraction	7 months	NO
9	Amer et al., 2018	2	M	Man	unerupted tooth	excision & tooth extraction	2 years	NO
10	Pardhe et al., 2018	17	M	Man	unerupted third molar	enucleation & tooth extraction	6 months	NO
11	Almazyad et al., 2018	15	F	Man	unerupted third molar	excision & tooth extraction	3 months	NO
12	Almazyad et al., 2018	18	M	Man	unerupted third molar	curettage & tooth extraction	20 months	NO
13	Bomfim et al., 2019	4	M	Man	unerupted second deciduous molar	excision & tooth extraction	---	NO
14	Teixeira et al., 2019	13	F	Man	unerupted third molar	excision	---	NO
15	Poomsawat et al., 2019	17	F	Man	unerupted third molar	partial mandibulectomy	18 months	NO
16	Delgado-Azañero et al., 2020	12	F	Man	unerupted second premolar	enucleation & tooth extraction	15 months	NO
17	Delgado-Azañero et al., 2020	13	F	Man	unerupted third molar	enucleation	5 years	NO
18	Sun et al., 2019	10	M	Max	unerupted third molar	excision & tooth extraction	------	NO
19	Almazyad et al., 2022	19	F	Man	unerupted third molar	excision & tooth extraction and hemi-mandibulectomy after recurrence	4 years	YES
20	Kayamori et al., 2021	10	M	Max	unerupted tooth	excision & tooth extraction	30 months	NO
21	Naina et al., 2021	14	M	Max	unerupted canine	excision & tooth extraction	3 years	NO
22	Zeng et al., 2020	12	F	Max	unerupted second premolar	excision & tooth extraction	13 years	NO
23	Zeng et al., 2020	2	M	Max	unerupted first deciduous molar	enucleation	11 months	NO
24	Ando et al., 2017	8	F	Max	unerupted first deciduous molar	enucleation	16 months	NO
25	Pozuelo Arquimbau et al., 2022	14	M	Max	unerupted third molar	excision & tooth extraction	----	NO
26	Xiaoqin et al., 2022	26	M	Man	unerupted third molar	excision & tooth extraction	5 months	NO

evident which due to pushing the unerupted first premolar tooth to the base of the mandible (Figure 1). The roots of the first deciduous molar tooth were absorbed. The second intraoral examination revealed mobility of the second deciduous molar tooth with no pain. Differential diagnosis according to radiographic features were odontoma and ameloblastic fibro-odontoma. Surgical excision of the lesion was performed under local anesthesia. The specimen was fixed in formalin and sent to Pathology department of TUMS.

Macroscopic examination revealed two separate tissues. One piece of irregular, creamy, soft tissue

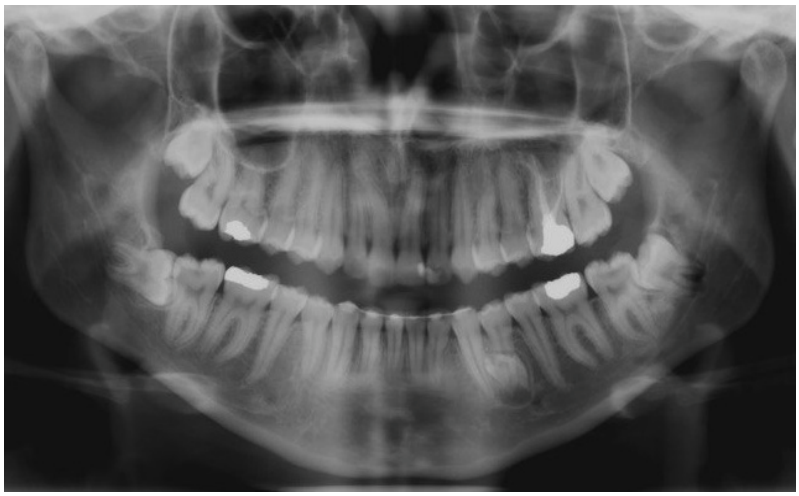

Figure 4. Follow up of the Patient. Tooth eruption and bone formation without any evidence of recurrence.

measuring 1×0.6×0.2cm and a separate piece of creamy hard tissue measuring 0.5×0.5×0.5cm. Cut section reveals solid, creamy, homogenous surface in both pieces.

Microscopic examinations show a tumoral lesion partially lined by two layers of stratified columnar epithelial cells and focal area of cuboidal cells (Figure 2 (A, B and D)). The lesion composed of haphazardly arranged stellate to spindle-shaped cells resembled dental papilla of the tooth germ in loose myxoid stroma, containing nests and cords of inactive-appearing odontogenic rests (Figure2 (C)). Rather condensation of mesenchymal cells was seen in subepithelial region in some areas (Figure2 (D)). Although evidence of hard dental tissue formation such as enamel, cementum or dentin was not found adjacent or among the tumoral tissue, but the separate lesion showed extensive sheets of dentin with areas of cementum-like materials after decalcification.

Immunohistochemical analysis revealed that cytokeratin CK14 was strongly positive in all layers of epithelium whereas CK19 was expressed only in basal layer of cuboidal cells (Figure3 (A, B)). A few scant cells and blood vessels were positive for CD34 (Figure3 (C)). Vimentin marker strongly expressed in mesenchymal tumor cells (Figure3 (D)). S100 protein and alpha smooth muscle actin were negative in tumor cells (Figure3 (E, F)). Ki67 index was lower than 2% in both epithelial and mesenchymal component (Figure3 (G)). Weak scant positive cells was detected for CD138 (Figure3 (H)) (Table 2).

Although histopathologic features and immunohistochemical analysis were compatible with a primordial odontogenic tumor, but our case had some clinical and histopathologic characteristics which did not fulfill POT criteria completely. These features were included of: 1) clinically the most reported cases showed swelling in the affected region, 2) histopathologically an area of mesenchymal cells condensation in subepithelial region was commonly seen. Although we had some areas of rather hypercellularity in subepithelial region of cuboidal cells but not classical condensation areas. According to immunohistochemical profile support, it may be showed an early stage of development of the lesion like early stage of tooth development (Bologna-Molina et al., 2020). These two differences were observed in our case in comparison with the other previously reported cases. On the other hand, we have a spectrum of histopathologic changes in many lesions such as ameloblastic fibroma or ameloblastic fibro-odontoma as a developing odontoma. Also based on this fact that a POT is an abortive tooth germ which lose out to develop into a mature and complete dental organ (Speight and Takara, 2018), we suggest that our case can be a developing primordial odontogenic tumor in association with a compound odontoma.

Therefore, a diagnosis of developing primordial odontogenic tumor accompanied with odontoma was made on the basis of microscopic and immunohistochemical analysis. The patient has been followed up for 6 years after surgical excision without any evidence of recurrence till now and complete new bone formation was detected on the panoramic radiograph at the recent follow-up appointment (Figure 4). The patient became aware about the radiopaque lesion in apical area of the mandibular first premolar tooth in the opposite side (compound odontoma is the most probable diagnosis) which requires excision to make a definitive diagnosis.

Discussion

Primordial odontogenic tumor is a benign rare odontogenic neoplasm composed of odontogenic mesenchyme with a dental papilla like loose stroma and internal enamel epithelium like cells (Speight and Takara, 2018). Although this recently described entity has a well- defined clinicopathologic, radiographic and also immunohistochemical profile, but there are not sufficient studies about the possible presence of this lesion among old archive of pathology departments.

We assessed all the medical records from oral and maxillofacial department of TUMS to determine possible presence of POT in the previously diagnosed cases which were under 20 years old and have a pericoronal location and myxoid stroma in histopathologic evaluation. We isolated 503 from 19,380 cases. The most prevalent lesion

with these criteria was dentigerous cyst (n=366,72.8%) followed by hyperplastic dental follicle (n=53, 10.7%). We reported an incidental finding developing POT associated with odontoma in a pericoronal area of unerupted first mandibular premolar tooth according to histomorphologic and immunoreaction profile evaluation.

Today, there are 26 reported cases of POT (table 3). Because of its rarity, this entity does not have any noticeable changes in the new edition of WHO (5th) (Soluk-Tekkesin and Wright, 2022).

Generally, POT is most common in the two first decades of life as our case was. The range was 2-26 with the average of 12.5. The recently reported case is the only case of POT over 20 years (Xiaoqin et al., 2022). POT mostly occurs in posterior site of mandible as our case was. There are only 8 cases of maxillary POT (table 2). All cases except two had swelling or bony expansion (Almazyad et al., 2018; Slater et al., 2016). Our case was the third reported case of asymptomatic and incidental radiographic finding. Radiographically, POT shows a well-defined radiolucent unilocular or less commonly multilocular lesion always associated with unerupted or impacted tooth (Bologna-Molina et al., 2020). Most of the reported cases involved unerupted third molar tooth (61%). There is only one case of involvement of canine tooth (Naina et al., 2021) and two cases of involvement of premolar tooth (Delgado-Azañero et al., 2020; Zeng et al., 2020). We reported the third case of POT with the involvement of premolar tooth. Although the most cases involved the pericoronal area of an unerupted or impacted tooth, but it seems that there are some other relationships between the lesion and the involved tooth (Sun et al., 2019). In addition to pericoronal location of the lesion (Type A), it can appear to completely envelop an embedded tooth (Type B) or it can be very close to the root of the tooth (Type C). Sun et al reported a case of POT in a rare location, mesiolingual area between the roots of mandibular canine and first premolar teeth, with a small tumor size (Sun et al., 2019). It was similar to our case in tumor size. It is worth noting that Bologna et al excluded sun's case due to production of dentinoid materials, subepithelial odontoblastic differentiation, size of the lesion and finally non-relationship with an unerupted tooth (Bologna-Molina et al., 2020).

All the lesions except one were treated with whole lesion excision and extraction of the involved tooth. One POT was treated with more aggressive approach; partial mandibulectomy, because of the diagnosis of odontogenic myxoma in the primary incisional biopsy (Poomsawat et al., 2010). The follow up range was between 3 months to 20 years (Mosqueda-Taylor et al., 2014; Almazyad et al., 2018). There was one case of recurrence of POT after 4 years follow up (Almazyad et al., 2022). We did not see any evidence of recurrence either after more than 6 years follow up of the patient. This only recurrent case of POT is the first epithelium rich variant (Almazyad et al., 2022). The different clinical behavior of this POT may be associated to unusual histopathologic features of the reported case and further evaluation is mandatory.

Microscopically POT is composed of myxoid mesenchymal tissue demonstrating variable cellularity with stellate to spindle fibroblasts similar to the dental papilla which is lined by thin cuboidal to columnar epithelium resembles the inner enamel epithelium of the enamel organ. This characteristic feature is the hallmark for diagnosis of POT. A stellate reticulum like feature may be seen in suprabasal area. An area of mesenchymal cells condensation is commonly obvious in subepithelial region. Area of ameloblastic fibroma like, thin fibrotic capsule and focal area of intraepithelial calcification may be occasionally seen (Bologna-Molina et al., 2020; Kayamori et al., 2021). In our case, we observed a fibro myxoid tissue partially surrounded by columnar epithelium without significant subepithelial condensation of mesenchymal cells. Because of the rather small size of our reported case, considering the IHC study was compatible with POT, it may be the first stages of the development of the lesion, so we suggested the developing primordial odontogenic tumor.

It is the first time to report a case of developing POT associated with odontoma. Although our case differs in some aspects to classic from of POT, but since the many of odontogenic lesions such as ameloblastic fibroma or ameloblastic fibro-odontoma represent as a part of spectrum of histopathologic changes, it seems that developing POT may be the first level of formation and development of POT. On the other hand, it is obvious that there is an important need for further surveys and case series of POT in association with odontoma to define whether this relationship is a variant of POT or a distinct condition. Also, further molecular and genetic studies are necessary to better understand true nature of this relationship. Although a systematic review reported that POT does not show dental hard tissue production (Bologna-Molina et al., 2020), but recently reported case of POT present abundant enameloid and focal dentinoid deposition (Almazyad et al., 2022). These contradictions are in line with the latest systematic review about POT that reported both peripheral ameloblastic epithelial islands and deposition of hard dental tissue can occasionally happen within the tumor and have been remained arguable (Azzi et al., 2020).

Bologna-Molina (2017) reported a wide useful panel for POT using 23 antibodies. He reported in another study that they are compatible with the normal early stage of tooth development (Bologna-Molina et al., 2020). Immunohistochemical analysis shows low rate of proliferation (less than 5%), positive immunoreaction in epithelial area for CK14, CK18, CK19, Syndecan-1, Glut-1, Vimentin [may be focal positive (Xiaoqin et al., 2022) or negative (Pozuelo Arquimbau et al., 2022)] and Amelogenin. The stromal cells are strongly positive for vimentin and negative for smooth muscle actin, CD34, CD138, S100, P53 and BRAF V600E (Bologna-Molina et al., 2020; Almazyad et al., 2022).

Primordial odontogenic tumor a recently described odontogenic tumor has a well-defined clinicopathological and immunohistochemical profile and should be differentiated from the others pericoronal lesions. It is the first time that this archival review has been done to find probable cases of primordial odontogenic tumor. We reviewed 19380 cases to find the lesions which were

in differential diagnosis with primordial odontogenic tumor. After immunohistochemical analysis, we reported a new case of developing primordial odontogenic tumor associated with odontoma. Recently, Etebarian (2022) presented a case of POT in an 18 years old female in 6th Congress of Iranian Oral and Maxillofacial Pathologists for the first time in Iran. Although our case had some differences with a classic POT, but we suggest that our case can be a developing primordial odontogenic tumor in association with an odontoma. It is clear that there is an important need for further assessment of POT in association with odontoma to define whether this relationship is a variant of POT or a distinct condition. Also, further molecular and genetic studies are necessary to better understand true nature of this relationship.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

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Availabilty of data

The data consists of pathologic and IHC slides are available in Tehran University of Medical Sciences, Dental School, Oral and Maxillofacial Pathology Department from the corresponding author on reasonable request.

Conflict of interest

There is not any conflict of interest. Derakhshan and Ghazi conceptualized research and established methodology. Ranjbar was involved in data gathering. Derakhshan and Moradzadeh conducted examination and evaluated the IHC results. Ranjbar analyzed and interpreted the results. Ranjbar and Derakhshan were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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