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Original Article

Ossifying fibroma of the jaw bones in hyperparathyroidism-jaw tumor syndrome: Analysis of 24 cases retrieved from literatures

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KEYWORDS
Hyperparathyroidism-jaw tumor syndrome;
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Abstract *Background/purpose:* Hyperparathyroidism-jaw tumor syndrome is a rare autosomal dominant disease characterized by parathyroid tumors and ossifying fibroma of the jaw. Disease-causing mutations have been localized in the tumor suppressor gene CDC73. This study is designed to highlight the importance of genetic testing in the diagnosis of ossifying fibroma related to this syndrome.
Materials and methods: The Clinical, histopathological, radiographical, familial and genetic features of 24 patients with Hyperparathyroidism-jaw tumor syndrome were collected by searching the electronic literature PubMed, Medline, Embase, and Science Direct databases combining the MeSH heading terms "Hyperparathyroidism jaw tumor syndrome", with the words "Ossifying fibroma" and "CDC73". The collected features were simply assessed and analyzed.
Results: The average age was 28.68 years old (age range 10–66), with 12 male and 12 female patients (1:1 M/F ratio). Hyperparathyroidism results from parathyroid adenoma in 16/24 cases (66.666%) and parathyroid carcinome in 5/24 (20.833%). Bone pathology occurred most often in the mandible (16/24 cases; 66.666%), while 5/24 cases were in the maxilla (20.883%) and 3 cases in both (12.5%). In 5/24 cases, ossifying fibroma was the first to occur before hypercalcemia. Genetic mutation of CDC73 were positive in 19/24 cases (79.166%).
Conclusion: Since the jaw lesions in Hyperparathyroidism-jaw tumor syndrome could proceed the cardinal signs of hyperparathyroidism, its accurate diagnosis needs to depend on clinical, histological, radiographical, family history and most of all the genetic testing for CDC73 gene.

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Introduction

Primary hyperparathyroidism (PHPT) is usually a sporadic disorder and in less than 10% of the cases, it is part of hereditary familial hyperparathyroidism of autosomal dominant inheritance. Familial hyperparathyroidism occurs either alone or as part of a syndrome accompanied by tumors of other tissues. This comprise of spectrum of disorders that include multiple endocrine neoplasia types 1 (MEN1) and 2A (MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial hypocalciuric hypercalcaemia (FHH) (also known as familial benign hypercalcaemia), and familial isolated hyperparathyroidism (FIHP).[1,2]

HPT-JT syndrome is an autosomal dominant disease characterized by parathyroid tumors and ossifying tumors of the jaw. Some patients also develop renal and uterine tumors. HPT-JT syndrome is due to mutations of CDC73 (cell division cycle 73) gene (Formerly known as HRPT2- Hyperparathyroidism 2 gene), which acts as a tumor suppressor gene, and encodes parafibromin, a protein predominantly expressed in the nucleus.[3]

Ossifying fibromas of the mandible or maxilla occur in 30%—40% of individuals with HPT-JT syndrome.[4] It is a slow-growing benign tumor having the potential of continuous growth if not treated.[5,6] This tumor is thought to arise from the periodontal ligament.[5,6] Generally, it lacks symptoms, but can cause serious cosmetic and functional problems.[7]

The aim of the current study is to reveal the importance of genetic testing for the patients having ossifying fibroma especially young patients and those with family history of this disease.

Materials and methods

An extensive literatures search had been carried out by combing through the Embase, Midline, PubMed, and Science Direct databases. The MeSH keywords applied were " hyperparathyroidism", "hyperparathyroidism-Jaw Tumor", "Ossifying Fibroma", and "CDC73".

Inclusion criteria were met if (1) abstract topic related to HPT-JT, ossifying fibroma and CDC73; (2) article was in English language; and (3) full-text article was available.

Records were then excluded if one of the following criteria pertained: (1) inadequate patients' information was provided (age, sex, type of HPT with its cause, jaw lesion location, genetic test, radiographic findings); (2) no oral involvement was mentioned; (3) co-occurring disorders that might interfere with the results. The collected data organized and analyzed. Table 1 presenting the data of the investigated 24 cases of ossifying fibromas in HPT-JT.

Results

The patients' clinical, radiographical, family history and genetic information are shown in "Tables 1 and 2". The study was based on 24 patients, 12 females (50%) and 12 males (50%) with the ratio of 1:1. The mean age was 28.68 years, with a range of 10—66 years. Age range 10—20 years = 6 (25%), 21—30 years = 8 (33.333%), 31—40 years = 5 (20.833), 41—50 years = 3 (12.5%), 51—70 years = 1 (4.1666%) and N/A = 1 (4.1666%).

All the studied 24 patients were with primary hyperparathyroidism (PHPT) and the cause of this PHPT was adenoma in 16 cases (66.666%), carcinoma in 5 cases (20.833%), no detected lesion in 1case (4.166%) and 2 cases with no available data (8.333%).

Based on the location of the jaw lesions, 16 cases were in the mandible (66.666%), 5 cases in the maxilla (20.833%), and 3 in both (12.5%). Regarding the frequency of the jaw lesions, 19 cases were single (79.166), 4 were multiple (16.666%) and 1 case was with no available data (4.1666%). In 6/24 cases (25%), ossifying fibroma was the first to occur before the onset of hypercalcemia and other symptoms of HPT-JT.

The radiographic appearance was radioopaque in 2 cases (8.333%), radiolucent in 9 cases (37.5%), and mixed in 6 cases (25%), 7 cases were with no available information (29.166%).

CDC73 genetic test information showed that 19 cases (79.166) were with mutated gene while the remaining 5 of 24 were with missing information.

In relation to ossifying fibroma and parathyroid carcinoma, the results of the collected data showed that 5/24 of the patients with ossifying fibroma in HPT-T developed parathyroid carcinoma. Table 2 contains the search algorithms used.

Discussion

The majority of PHPT cases are not inherited, and in 5—10% of cases occurs within familial inherited parathyroid disorders such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 4 (MEN4), familial hypocalciuric hypercalcemia syndrome (FHH), neonatal severe hyperparathyroidism (NSHPT), hyperparathyroidism-jaw tumor syndrome (HPT-JT) and familial isolated PHPT (FIPH) They are mainly sustained by multiglandular disease and often characterized by an earlier age of onset with respect to sporadic PHPT.[8,9]

Hyperparathyroidism jaw tumor syndrome (HPT-JT) is a rare autosomal dominant inherited endocrine neoplasia syndrome, which predisposes carriers to develop a triad of parathyroid adenomas and carcinomas (with consequent hyperparathyroidism), multiple ossifying fibromas of the maxilla and the mandible, as well as renal and uterine tumors.[10]

Mutation in CDC73 gene causes HPT-JT.[11] This gene is located on chromosome 1q25-q31 and encodes parafibromin, a 531-amino acid protein. The latter is expressed in the parathyroid glands, adrenal glands, kidneys, heart, and skeletal muscle. CDC73 is identified as a tumor suppressor gene; thus, the loss of the parafibromin function is considered to lead to tumor development.[11] Mutations of CDC73 are identified in most individuals affected by HPT-JT and many of their asymptomatic family members.[12] This is confirmed y the results of this study which show that all the studied patients were with PHT, OF, and mutation in CDC73 gene.

Table 1 Clinical, radiographical, familial and genetic characteristics of the studied 24 cases of ossifying fibroma associated with HPT-JT syndrome.

Case NO.	Age	Sex	Location	Frequency	X- ray	OF	PHPT	Age at diagnosis of HPT	Cause of PHPT	HRPT2 Mutation	Other lesions	Affected Family members	Reference
1	66	M	Maxilla Mandible	Multiple	N/A	N/A	N/A	56	N/A	N/A	N/A	Grand uncle with jaw tumor and PTG adenoma	Teh et al. 1996[23]
2	37	M	Mandible	Single	N/A	N/A	+ve	24	N/A	+ve	Renal calculi	Father with pHPT and jaw tumor and renal cysts	
3	N/A	M	R. Mandible	Single	N/A	+ve	+ve	50	Adenoma (PTG)	+ve	N/A	Father with HPT and OF	Wassif et al. 1999[24]
4	30	M	R. Mandible	Single	Lucent	+ve	−ve	N/A	No lesion	+ve	N/A	Daughter OF	
5	16	M	R. Mandible R. Mandible	Multiple	Lucent Lucent	+ve	+ve	16	Adenoma (PTG)	+ver	• Kidney stones	N/A	Howell et al. 2004[25]
6	20	M	L. Mandible	Single	Lucent	+ve	+ve	20	Carcinoma (PTG)	+ve	−ve	Father PTG carcinoma	Moon et al. 2005[26]
7	At age 22 At age 28	M	R. Mandible L. Mandible	Single Single	Lucent Lucent	+ve +ve	+ve	28	Adenoma (PTG)	+ve	N/A	Father HPT Sister OF	Aldred et al. 2006[27]
8	At age 17 At age 21	F	R. Mandible R. Mandible (Suggestion, recurrence due to incomplete removal of the lesion)	Single Single	Lucent Lucent	+ve	+ve	15	Adenoma (PTG)	+ve	N/A	Father HPT Brother HPT-JT	
9	18	M	R. Maxilla	Single	Opaque	+ve	+ve	18	Adenoma (PTG)	+ve	−ve	Sister	Yamashiyta et al. 2007[28]
10	26	F	Maxilla	Single	N/A	+ve	+ve	18	Adenoma (PTG)	+ve	• Thyroid carcinoma • Colon adenocarcinoma • Uterine polyps	Father, brother and sister	Masi et al. 2008[12]
11	26	F	L. Mandible	Single	Mixed	+ve	+ve	18	Adenoma (PTG)	N/A	Uterine polype	Father & brother PT lesions; two sisters Parathyroid and uterine lesions	Iacobone et al. 2009[29]
12	37	M	R. Mandible L. Mandible R. Maxilla L. Maxilla	Multiple	Lucent Mixed Mixed Mixed	+ve	+ve	37	Adenoma (PTG)	+ve	−ve	Mother with hypothyroidism	Schmidt et al. 2009[30]
13	36	M	L. Mandible R. Mandible L. Maxilla R. Maxilla	Multiple	All mixed	+ve	+ve	36	Adenoma (PTG)	+ve	−ve	Mother hypothyroidism and aunt hyperthyroidism	Phitayakorn et al. 2010[31]

14	23	F	R. Mandible	Single	Lucent	+ve	+ve	23	Adenoma (PTG)	+ve	• Ectopic Kidney • Polycystic overies • Uterine fibroma • Brown tumors	Mother	Rekik et al. 2010[32]
15	41	F	L. Maxilla	Single	opaque	+ve	+ve	Six months later	Adenoma (PTG)	N/A	• Diabetes • Renal failure	−ve	Guerrouani et al. 2013[33]
16	30	F	L Mandible	Single	N/A	+ve	+ve	28	Carcinoma (PTG)	+ve	• Osteoporosis • Renal colics • Lytic lesion in the right tibia	Paternal uncle (PTHG Adenoma)	Chiofalo et al. 2014[34]
17	10	M	R. Maxilla	Single	N/A	+ve	N/A	31	Carcinoma (PTG) diagnosed at age of 31	+ve	• Osteoporosis	N/A	Sriphradang et al. 2014[35]
18	46	F	L. Mandible	Single	Mixed	+ve	+ve	46	Carcinoma (PTG)	N/A Patient refuses	• Hypertension	Brother Jaw tumor	Marchiori et al. 2015[36]
19	33	M	R. Mandible L. Mandible	Multiple	Mixed Mixed	+ve	Previous and treated	27	Previous Carcinoma (PTG)	+ve	Treated generalized osteitis fibrosa cystica	N/A	Parfitt et al. 2015[17]
20	19	F	L. Maxilla	Single	Mixed	+ve	+ve	19	Adenoma (PTG)	+ve	−ve	N/A	Mathews et al. 2016[37]
21	41	M	Mandible	N/A	N/A	+ve	+ve	41	Carcinoma (PTG)	+ve	• Kidney stones • Osteoporosis	−ve (but carrier of mutant HRPT2)	Mele et al. 2016[38]
22	21	F	R. Mandible	Single	Lucent	+ve	+ve	23	Adenoma (PTG)	N/A	Renal calculi	N/A	Redwin et al. 2017[39]
23	31	F	R. Mandible	Single	Lucent	+ve	+ve	32	Adenoma (PTG)	+ve	• Kidney stones	−ve	Rubinstein et al. 2017[40]
24	21	F	R. Mandible	Single	Mixed	+ve	N/A	22	Adenoma (PTG)	N/A	N/A	N/A	Swaminathan, 2017[41]

M = Male, F = Female, PTG = parathyroid gland, OF = ossifying fibroma, PHPT = primary hyperparathyroidism, HPT-JT = hyperparathyroidism-Jaw tumor syndrome, N/A = not available.

Table 2 The distribution of the clinical, radiologic, familial and genetic testing features of the studied 24 cases of ossifying fibroma in HPT-JT syndrome (N/A = not available).

Age	Average age = 28.68 Youngest = 10, Oldest = 66 10–20 = 6 (25%), 21–30 = 8 (33.333%), 31–40 = 5 (20.833), 41–50 = 3 (12.5%), 51–70 = 1(4.1666%), N/A = 1 (4.1666%)
Sex	Female = 12 (50%) Male = 12 (50%)
HPT	23 cases (+)ve = (95.8333%), N/A = 1 case (4.1666%)
OF first presentation	6 cases (25%)
HPT first presentation	17 cases (70.833%)
CDC73 (HRPT2)	19 cases (79.166%)(+)ve, N/A = 5 cases
X-Ray appearance	Radioopaque = 2 (8.333%) Radiolucent = 9 (37.5%) Mixed = 6 (25%) N/A = 7 (29.166%)
Frequency	Single = 19 (79.166) Multiple = 4 (16.666%) N/A = 1 cases (4.1666%)
Location	Mandible = 16 (66.666%) Maxilla = 5 (20.833%) Both = 3 (12.5%)
Parathyroid lesion	Adenoma = 16 (66.666%) Carcinoma = 5 (20.833%) No detected lesion = 1 (4.166%) N/A = 2 (8.333%)
Other lesions	(+) ve = 13 (54.166%) (−) ve = 5 (20.833%) N/A = 6 cases (25%)
Affected Family members (Father, mother, brother, or sister)	(+) ve = 16 (66.666%) (−) ve = 2 (8.333%) N/A = 6 cases (25%)

In HPT-JT syndrome patients, the onset of PHPT occurs in relatively young age (< 20 years) than those with sporadic PHPT (>30 years). Of the HPT-JT families previously studied, the youngest patient was 10 years of age,[13] which is the same in this study, indicating that this disorder starts earlier than the sporadic non-familial HPT.

PHPT is observed in 80–90% of patients with the HPT-JT syndrome, parathyroid carcinoma is seen in 10–15%, and ossifying fibromas of the maxilla or mandible are seen in approximately 40% of the cases; furthermore, some patients have renal or uterine abnormalities in female patients.[14]

Earlier studies showed that parathyroid carcinoma may occur in approximately 10–15% of affected individuals.[15,16] While the present study shows that parathyroid carcinoma occurs in 20% of the affected individual and this discrepancy in percentage may be related to the larger sample of the present study.

Approximately 25–50% of patients with HPT-JT have ossifying fibromas of the jaws. This estimate is likely on the low side because the syndrome is relatively rare and there may be a failure to correlate patients in whom the ossifying fibromas develop before the hyperparathyroidism with the syndrome.[17]

The World Health Organization currently defines ossifying fibroma as a benign fibro-osseous neoplasm which often presents well demarcated borders and is composed histologically of fibrocellular stroma and variable amounts of mineralized material showing different morphologic appearance.[18]

Generally, sporadic ossifying fibromas of the jaw occur in the third and fourth decades of life,[4] whereas jaw tumors in HPT-JT syndrome occur earlier to 13 years of age.[3] In the current study the youngest age is 10 years old which means that, in HPT-JT, ossifying fbroma may appear early at the beginning of the second decayed of life.

The bone lesions specific to HPT-JT are restricted to the maxilla and mandible.[19] The jaw tumors can precede the development of hypercalcemia by several decades,[14] and this may mislead the diagnosis, ending with improper diagnosis of the case.

The collected data of this study reveals that in 25% of the cases the jaw tumor precede the development of HPT. Also, it shows that the jaw lesions is more frequent in the mandible (66.666%) indicating that it has a predilection for the mandible than the maxilla.

The etiology of ossifying fibroma is unknown but odontogenic, developmental and traumatic origins have been suggested and thought to be of periodontal ligament origin. The multipotential mesenchymal cells of periodontal ligament are able to form both bone and cementum. Although the precise pathogenesis is still unknown, genetic studies for HPT-JT syndrome reveal that a mutation in the tumor suppressor gene CDC73, leads to tumor formation.[20]

In this study, no isolated lesion was found in the angle and ascending ramus of the mandible, indicating that these jaw lesions are restricted the tooth bearing area. This could support the theory of its origin form the pluripotent mesenchymal cells of the periodontal ligaments that are capable of forming bone tissue and cementum.[21,22]

Parfitt, 2015,[17] suggested that, in HPT-JT the ossifying fibromas are not a result of the direct effect of hyperparathyroidism, but are due to the mutation of the tumor suppressor gene CDC73 and this might explain why this tumor does not regress after parathyroidectomy and the correction of the hypocalcaemia status of the patient.

In conclusion, dentists and oral surgeons should be aware of the possibility of HPT-JT syndrome in adolescents and young adults presenting with jaw tumors and PHPT

together or separately. Intensive history taking and the need for assessing CDC73 mutations in patients with ossifying fibromas, especially in young patients and in those with family history of the same lesion, is an important step before starting treatment. Patients with ossifying fibroma in HPT-JT syndrome should be followed closely due to the possibility of recurrence of jaw tumors and high risk of parathyroid malignancy.

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Declaration of Competing Interest

None to declare.

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