Avances en Biomedicina
Publicación Oficial del Instituto de Inmunología Clínica
Mérida-Venezuela
Volumen 13(2), Julio-Diciembre, p 174-178

Depósito Legal: PPI201102ME3935
ISSN: 2477-9369
PII: S2477-9369(24)130019-CC

Exploring a Rare Case of Hyperparathyroidism-Jaw Tumor Syndrome: A Detailed Case Report

(Análisis de un caso raro de síndrome de hiperparatiroidismo-tumor mandibular: Informe detallado del caso)

Ajitha R[1]✉, Ganesh MT [2], Sushmitha S[1]

[1] Department of Pathology, Sree Balaji Medical College and Hospital, BIHER, Chromepet, Chennai- 600044, Tamil Nadu, India.
[2] Department of Orthopedics, Sree Balaji Medical College and Hospital, BIHER, Chromepet, Chennai- 600044, Tamil Nadu, India.

Received: 22 January 2025.
Accepted: 20 March 2025.
Online publication:28 de Marzo de 2025.

[Case Report]

PII: S2477-9369(24)130019-CC

Abstract(english)

This syndrome is associated with mutations in the CDC73 gene, which encodes the tumor suppressor protein parafibromin. Patients typically present with symptoms in late adolescence or early adulthood, including jaw swelling, hypercalcemia, and renal complications. Early diagnosis is crucial for effective management and surveillance, as the syndrome carries a significant risk of malignancy. This syndrome is both clinically and genetically different from other endocrine neoplasia syndromes and seems to be caused by mutations in a gene associated with endocrine tumors, known as “HRPT2.” This article highlights the clinical features, genetic basis, diagnostic criteria, and management strategies for HPT-JT, emphasises the importance of genetic counseling and regular monitoring for affected individuals and their families. We seek to raise awareness among healthcare providers about this rare but significant differential diagnosis through a detailed case report and a comprehensive review of the literature.

Keywords(english)

Hyperparathyroidism, Jaw neoplasms, Ossifying Fibroma, Tumor suppressor, Mutation, genetic.

Resumen(español)

Este síndrome se asocia a mutaciones en el gen CDC73, que codifica la proteína supresora de tumores parafibromina. Los pacientes suelen presentar síntomas al final de la adolescencia o al principio de la edad adulta, incluyendo hinchazón mandibular, hipercalcemia y complicaciones renales. El diagnóstico precoz es crucial para un tratamiento y una vigilancia eficaces, ya que el síndrome conlleva un riesgo significativo de malignidad. Este síndrome es clínica y genéticamente diferente de otros síndromes de neoplasia endocrina y parece estar causado por mutaciones en un gen asociado con tumores endocrinos, conocido como "HRPT2". Este artículo destaca las características clínicas, la base genética, los criterios diagnósticos y las estrategias de tratamiento para el HPT-JT, y enfatiza la importancia del asesoramiento genético y el seguimiento regular de las personas afectadas y sus familias. Buscamos concienciar a los profesionales de la salud sobre este

✉ **Autor de correspondencia:** Dr. Ajitha R. Assistant Professor, Department of Pathology, Sree Balaji Medical College and Hospital,BIHER, Chromepet, Chennai- 600044, Tamil Nadu, India. e-mail: E-mail:ajitha.pathology@bharathuniv.ac.in

diagnóstico diferencial, poco frecuente pero significativo, mediante un informe de caso detallado y una revisión exhaustiva de la literatura.

Palabras clave(español)

Hiperparatiroidismo, Neoplasias de mandíbula, Fibroma osificante, Supresor tumoral, Mutación, Genética.

Introduction

Jaw Tumor Syndrome synonymous for Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT), is an infrequent genetic disorder inherited in an autosomal dominant pattern. It is marked by the formation of ossifying fibromas in the jaw as well as parathyroid adenomas or carcinomas. In some families, affected individuals have also experienced kidney-related issues, including Wilms tumors, nephroblastomas, renal cysts, polycystic kidney disease, and hamartomas, with rare occurrences of uterine lesions (1)

Jaw Tumour Syndrome, also known as Hyperparathyroidism-Jaw Tumour Syndrome (HPT-JT), is an infrequent genetic disorder appreciated by a triad of benign or malignant tumors in the jaw, parathyroid glands, and in some cases, renal abnormalities. First described in the early 1960s, this autosomal dominant condition is characterized by mutations in the HRPT2 (HyperParathyroidism Type 2) gene also referred to as CDC73 (Cell Cycle Division) gene, which encodes the parafibromin protein crucial for cellular regulation and tumor suppression (2). Patients with HPT-JT often have multiple ossifying fibromas in the jaw, leading to facial deformities and dental issues. Additionally, they may develop parathyroid adenomas or carcinomas, resulting in hyperparathyroidism and elevated serum calcium levels. This can lead to various symptoms like bone pain, kidney stones, and fatigue (3). Timely diagnosis and intervention are key to avoiding complications and improving the overall quality of life. Genetic testing and regular monitoring can help identify affected individuals and their family members, enabling timely intervention and treatment.

Case report

A 27-year-old female came to the outpatient department with complaints of painless swelling of the right mandible for 2 months. The swelling was initially smaller and gradually increased to attain the present size. She was previously diagnosed with right inferior parathyroid adenoma and had presented with elevated Parathyroid Hormone (PTH), hypercalcemia, and Vitamin D deficiency before 6 months. She had undergone surgical resection 5 months back, histopathological examination revealed a tumor composed of trabecular,

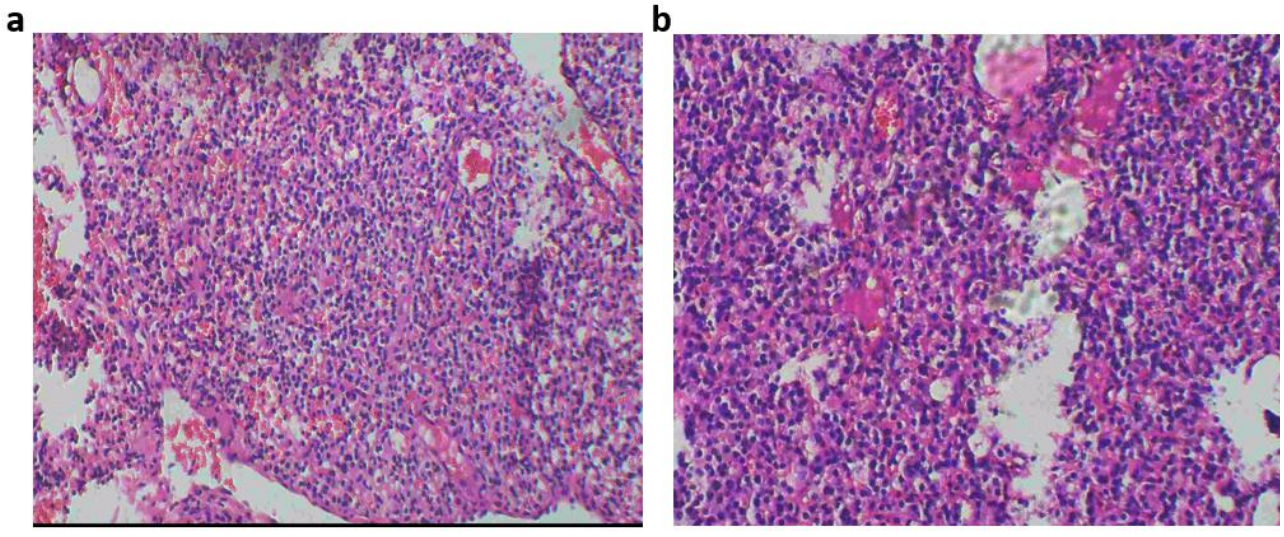

Figure 1. 1a & 1b: Tumor composed of mainly chief cells with round nucleus and granular cytoplasm.

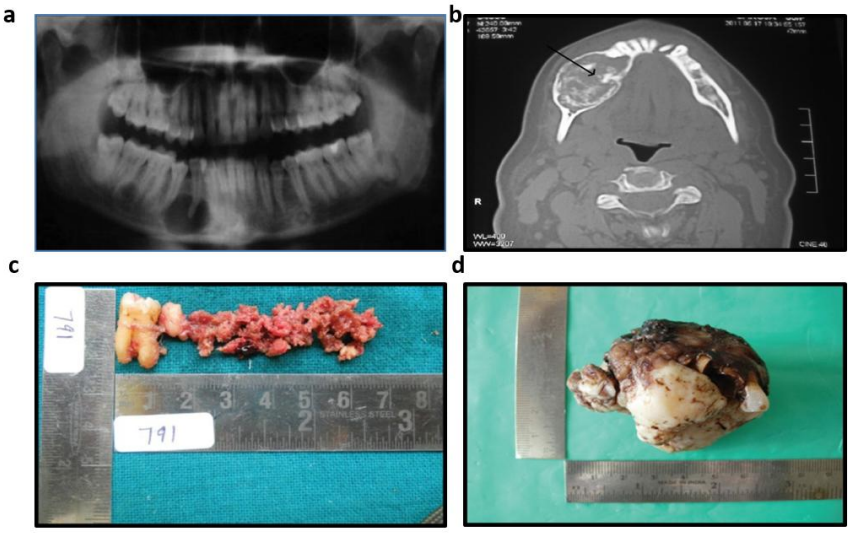

Figure 3. 3a and **3b** Soft tissue curettings showing ossifying fibroma. **3c & 3d.** Similar picture from Resected lesion

follicular and solid pattern with large uniformly arranged cells containing oval nuclei and eosinophilic cytoplasm (chief cells) with minimal stroma. There was no mitosis or invasion. The diagnosis was given as parathyroid adenoma (Figure 1a & 1b). She also gave a family history of similar swelling on the right side of her face in her mother which was left untreated. On extra oral examination, there was no tenderness and a vague, soft swelling of size 3x2 cm was palpable over the right mandible. X-ray revealed a radiolucent lesion in the right mandible (Figure 2a). CT also revealed an expansile lesion in the right mandible of size 2x2 cm with equidirectional expansion (Figure 2b). Pre-operative serum calcium level was slightly elevated at 11 mg/dl (Normal range: 8.4-10.2 mg/dl). Soft curettage of the lesion was done extending from canine to 3rd molar. We received multiple soft tissue curettings and two teeth (Figure 2c).

Sections showed a neoplasm composed of islands and trabeculae of bony fragments in a benign fibroblastic stroma with no mitosis. Bony spicules were seen in the periphery (Figure 3a&b). Hence a diagnosis of fibroosseous lesion-Ossifying fibroma was given. She had then undergone complete surgical resection with 5.5 mm margins and secondary reconstruction (Figure 2d). A similar histo-pathological picture was revealed (Figure 3c&d). Mutation screening of HRPT2 gene with Next Generation Sequencing (NGS) using targeted gene panel showed point mutation in CDC73 gene, autosomal dominant inherited. The patient was given genetic counseling and family members were advised to undergo genetic screening as well. Patient is currently followed up periodically and clinical course is uneventful.

Discussion

Ossifying fibromas often occur in individuals with Hyperparathyroidism-Jaw Tumor Syndrome, a rare genetic condition inherited in an autosomal dominant pattern. This syndrome is distinguished by the formation of parathyroid adenomas and tumors in the jaw that involve both fibrous and bony tissues (4). Most ossifying fibromas are sporadic presenting in 3rd to 4th decade of life. As a part of HPT-JT syndrome, these fibrous tumors present earlier. Jackson et al. first documented this syndrome while studying multiple ossifying fibromas in two members of the third generation, noting similar presentations in four out of five affected individuals from the first generation (5).

Some patients may also present with renal and uterine tumors. HPT-Jaw Tumor Syndrome results from an inactivating mutation in the CDC73

gene, previously known as the HRPT2 gene. This syndrome is marked by high but incomplete penetrance and involves mutations in a gene encoding a 531-amino acid protein called parafibromin (6).

CDC73 is a tumor suppressor gene, and loss of parafibromin function, a protein encoded by CDC73, is linked to tumor development. Ossifying fibromas affect around 30 to 40% of people with HyperParathyroidism Jaw Tumor syndrome. These slow-growing, benign tumors, arising from the periodontal ligament, can cause cosmetic and functional issues if untreated (7).

In a study by Ibrahem et al. on Ossifying fibroma of the jaw bones in hyperparathyroidism-jaw tumor syndrome, 24 cases were analysed and the mean age of presentation was 28.68 years. All the cases studied presented with hyperparathyroidism, most common cause of which was Parathyroid adenoma (66.6%). 16 cases had lesion in the mandible (66.6%). These findings correlate with our report in which the patient is a 27 year old female who presented with lesion in the mandible and had previously been diagnosed with hyperparathyroidism due to underlying parathyroid adenoma (8).

The origin of ossifying fibroma remains unclear, though it may arise from odontogenic, developmental, or traumatic factors, with a possible connection to the periodontal ligament, which has cells capable of forming both bone and cementum. In individuals with HPT-JT syndrome, mutations in the CDC73 tumor suppressor gene have been linked to the development of these tumors (9). According to Parfitt, ossifying fibromas in HPT-JT syndrome are not directly caused by hyperparathyroidism itself but rather by mutations in the tumor suppressor gene CDC73. This could explain why these tumors often do not regress following parathyroidectomy or correction of hypocalcemia (10).

Ossifying fibromas can be clinically confused with hyperparathyroid brown tumor or central giant cell granulomas. Hence it is important to assess serum calcium and parathyroid hormone level to detect any underlying biochemical issues. Histologically, ossifying fibromas are fibroosseus lesions without giant cells.

Our case was diagnosed based on the presence of jaw tumor, previous history of parathyroid adenoma, similar history in the family and genetic screening with NGS which revealed point mutation involving the CDC73 gene. HPT-Jaw Tumor Syndrome is a complex condition with a wide range of clinical manifestations that can emerge over an extended period, which may contribute to its frequent under-recognition. Patients suspected of having HPT-Jaw Tumor Syndrome should undergo genetic testing for confirmation and are also encouraged to have their family members tested to identify potential hereditary cases (6).

Regular follow up is mandatory as there is a chance for jaw tumors to recur, hyperparathyroidism and possibility of parathyroid carcinomas. Hence, timely diagnosis is required for better patient outcomes.

In HPT-Jaw Tumor Syndrome, mandibular and/or maxillary lesions typically present as ossifying fibromas, which are unlikely to regress on their own. These lesions should be surgically removed if they become symptomatic or impair function. There is limited published guidance on the ideal screening methods or frequency, but at a minimum, it should involve an annual physical examination, periodic measurements of serum calcium and parathyroid hormone levels, and neck ultrasonography. Additionally, annual transabdominal or transvaginal uterine ultrasonography and abdominal MRI every five years are recommended (11).

In conclusion, dentists, oral surgeons and clinicians should consider the possibility of HPT-JT syndrome in adolescents and young adults presenting with jaw tumors, especially when accompanied by primary hyperparathyroidism (PHPT) or even in its absence. Long time follow-up is required because of the risk of recurrent HPT and parathyroid carcinoma (12).

Ethical approval

The authors confirm that all required patient consent forms have been obtained. The patient has provided written consent for the publication of their images and clinical information in this journal. While

the patient's names and initials will not be disclosed and every effort will be made to protect their identity, complete anonymity cannot be guaranteed.

Conflict of interest

The authors declare that there are no conflicts of interest.

Author Contributions

Ajitha R contributed towards histopathological diagnosis and treatment protocol for the patient. Ganesh M T contributed in preparing the case report, editing, drafting case report and collecting follow up data from the patient.

Referencias

1. Hobbs MR, Pole AR, Pidwirny GN, Rosen IB, Zarbo RJ, Coon H, Heath H 3rd, Leppert M, Jackson CE. Hyperparathyroidism-jaw tumor syndrome: the HRPT2 locus is within a 0.7-cM region on chromosome 1q. Am J Hum Genet. 1999; 64: 518-25. [PubMed] [Google Scholar]
2. Zama A, Kruger EC, Zemlin AE, Conradie M. Hyperparathyroidism Jaw Tumor Syndrome, an Unforeseen Diagnosis. JCEM Case Reports. 2024;2: luae020. [PubMed] [Google Scholar]
3. Hyperparathyroidism-jaw tumor syndrome | About the Disease | GARD (nih.gov). [PubMed] [Google Scholar]
4. Szabó J, Heath B, Hill VM, Jackson CE, Zarbo RJ, Mallette LE, Chew SL, Besser GM, Thakker RV, Huff V, et al. Hereditary hyperparathyroidism-jaw tumor syndrome: the endocrine tumor gene HRPT2 maps to chromosome 1q21-q31. Am J Hum Genet. 1995; 56: 944-50. [PubMed] [Google Scholar]
5. Jackson CE, Norum RA, Boyd SB, Talpos GB, Wilson SD, Taggart RT, Mallette LE. Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. Surgery. 1990; 108: 1006-12, discussion 1012-13. [PubMed] [Google Scholar]
6. Jozsef S, Brett H, Virginia M, Charles E, Shem L, Richard J. The Hyperparathyroidism-Jaw Tumor Syndrome in a Portuguese Kindred. QJM: An Int J Med. 2001; 94: 213-22. [PubMed]
7. Chen JD, Morrison C, Zhang C. Hyperparathyroidism-jaw tumor syndrome. J Intern Med. 2003; 253: 634-42. [PubMed] [Google Scholar]
8. Ibrahem HM. Ossifying fibroma of the jaw bones in hyperparathyroidism-jaw tumor syndrome: Analysis of 24 cases retrieved from literature. J Dent Sci. 2020 ; 15: 426-32. doi: 10.1016/j.jds.2019.12.007. Epub 2020 Apr 4. [PubMed] [Google Scholar]
9. Swami AN, Kale LM, Mishra SS, Choudhary SH. Central ossifying fibroma of mandible: a case report and review of literature. J Indian Acad Oral Med Radiol. 2015; 27: 131-5. [Google Scholar]
10. Parfitt J, Harris M, Wright JM. Tumor suppressor gene mutation in a patient with a history of hyperparathyroidism-jaw tumor syndrome and healed generalized osteitis fibrosa cystica: a case report and genetic pathophysiology review. J Oral Maxillofac Surg. 2015; 73: 194.e1-9. [PubMed] [Google Scholar]
11. Roy P, Christopher RM. Jaw tumor: An uncommon presenting manifestation of primary HPT. W J Endo Surg. 2010 Jan-Apr; 2: 45-50.
12. Karin FR,Christine H,Egbert S,Roger K. CDc73- related hereditary HPT:five new mutations and the clinical spectrum. Eur J Endo.Vol 165 2011; 477-83. [PubMed] [Google Scholar]

How to cite this article: Ajitha R , Ganesh MT, Sushmitha S. Exploring a Rare Case of Hyperparathyroidism-Jaw Tumor Syndrome: A Detailed Case Report. ***Avan Biomed. 2024; 13: 174-8***

https://qr.me-qr.com/uN3BgzJC.