Reporte de Caso Clínico

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EXPLORING A RARE CASE OF HYPERPARATHYROIDISM-JAW TUMOR SYNDROME: A DETAILED CASE REPORT

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ABSTRACT

Jaw Tumor Syndrome synonymous for Hyperparathyroidism-Jaw Tumor Syndrome (HPT-

JT), is a 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,

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and hamartomas, with rare occurrences of uterine lesions¹. 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: Hyperparathyroidism; Jaw neoplasms; Ossifying Fibroma; Tumor

suppressor; Mutation; genetic.

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ANÁLISIS DE UN CASO RARO DE SÍNDROME DE HIPERPARATIROIDISMO-

TUMOR MANDIBULAR: INFORME DETALLADO DEL CASO

RESUMEN

El síndrome de tumor mandibular, sinónimo de hiperparatiroidismo-síndrome de tumor

mandibular (HPT-JT), es un trastorno genético poco frecuente que se hereda con un patrón

autosómico dominante. Se caracteriza por la formación de fibromas osificantes en la

mandíbula, así como adenomas o carcinomas paratiroideos. En algunas familias, los

individuos afectados también han presentado problemas renales, como tumores de Wilms,

nefroblastomas, quistes renales, enfermedad renal poliquística y hamartomas, con casos

poco frecuentes de lesiones uterinas¹. Este síndrome se asocia con 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 temprano 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 manejo del HPT-JT,

y enfatiza la importancia del asesoramiento genético y el seguimiento regular de las

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personas afectadas y sus familias. Buscamos concienciar a los profesionales de la salud

sobre este diagnóstico diferencial, poco frecuente pero significativo, mediante un informe de

caso detallado y una revisión exhaustiva de la literatura.

PALABRAS CLAVE: Hiperparatiroidismo; Neoplasias de mandíbula; Fibroma osificante;

Supresor tumoral; Mutación; Genético.

INTRODUCTION

Jaw Tumour Syndrome, also known as

Hyperparathyroidism-Jaw Tumour

Syndrome (HPT-JT), is a 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 charecterised 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

suppression.². tumor regulation and

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 fatigue³. Timely

diagnosis and intervention are key to

avoiding complications and improving





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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 She size. present 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, 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 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. Xray was taken and 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



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the lesion was done extending from canine to 3rd molar. We received multiple

soft tissue curettings and two teeth (Figure 3).

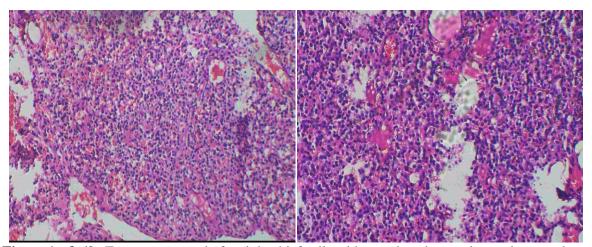


Figure 1a & 1b: Tumor composed of mainly chief cells with round nucleus and granular cytoplasm



Figure 2a and 2b: Xray and axial CT revealed a radiolucent lesion over the right body and ramus region of mandible



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Figure 3.Soft tissue curettings and two teeth

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 4a&b). Hence a fibroosseous diagnosis of lesion-Ossifying fibroma was given. She had then undergone complete surgical resection with 5.5 mm margins and secondary reconstruction (Figure 5). A similar histo-pathological picture was revealed (Figure 6a&b). Mutation

screening of HRPT2 gene with Next Generation Sequencing (NGS) using gene panel targeted showed 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.



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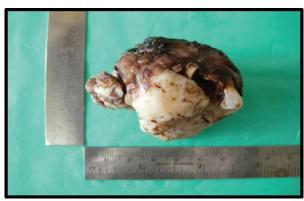


Figure 5. Resected mandible lesion

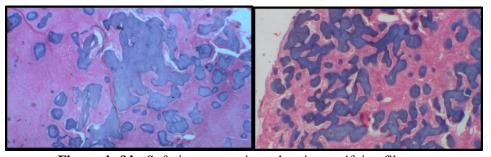


Figure 4a&b: Soft tissue curettings showing ossifying fibroma

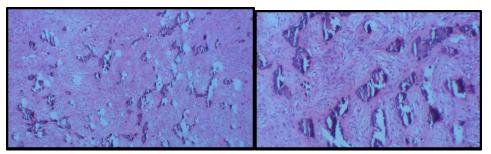


Figure 6a & 6b: Similar picture from Resected lesion

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



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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 generation⁵.

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 parafibromin⁶.

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 untreated⁷.

In a study by Ibrahem et al. on Ossifying fibroma of the bones in iaw hyperparathyroidism-jaw tumor syndrome, 24 cases were analysed and the mean age of presentation was 28.68 years. All the studied presented with cases hyperparathyroidism, most common cause of which was Parathyroid adenoma (66.6%). 16 cases had lesion in the mandible (66.6%).findings These correlate with our report in which the



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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 adenoma⁸.

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 tumors⁹. 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 hypocalcemia¹⁰.

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





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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 cases⁶.

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.

Conclusion

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 function. There is impair 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 recommended¹¹.

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 carcinoma¹².



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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 interests.

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.

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