A Unique Case of Hyperparathyroidism – Jaw Tumour syndrome **(HPT-JT)** due to a previously unreported pathogenic duplication mutation of CDC73 gene

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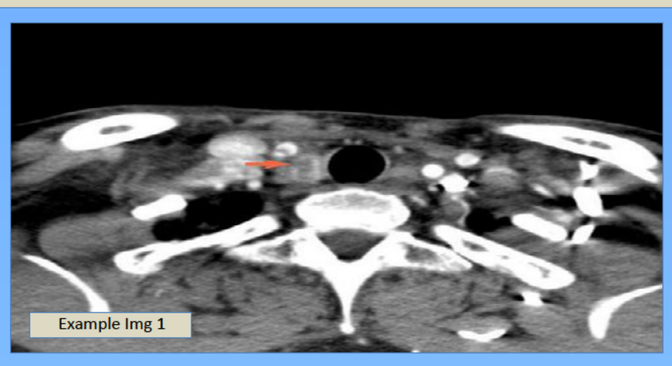
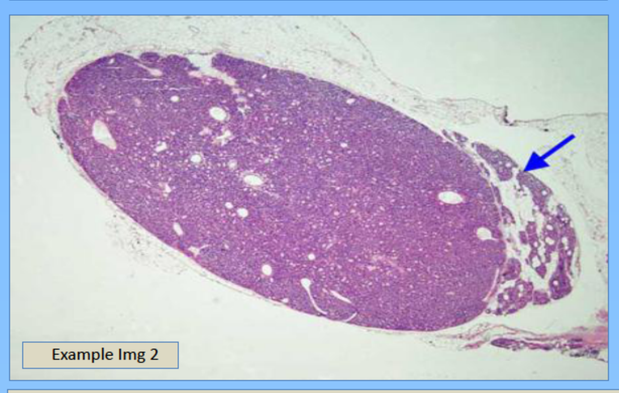
Hyperparathyroidism Jaw – Tumour syndrome (HPT-JT) is a rare autosomal dominant condition characterized by primary hyperparathyroidism (<90%) as a result of parathyroid adenoma or carcinoma (10-15%), ossifying fibromas of mandible and maxilla (30-40%), renal lesions (20%) most commonly cysts and benign and malignant uterine tumours and caused by germline CDC73 pathogenic gene mutations. Currently only 200 cases reported in medical literature.

Case: A 31 year old man presented with polydipsia, fatigue, corrected calcium of 4.3 and PTH 147.
USS and CT neck revealed a left inferior parathyroid adenoma, confirmed by exploration.

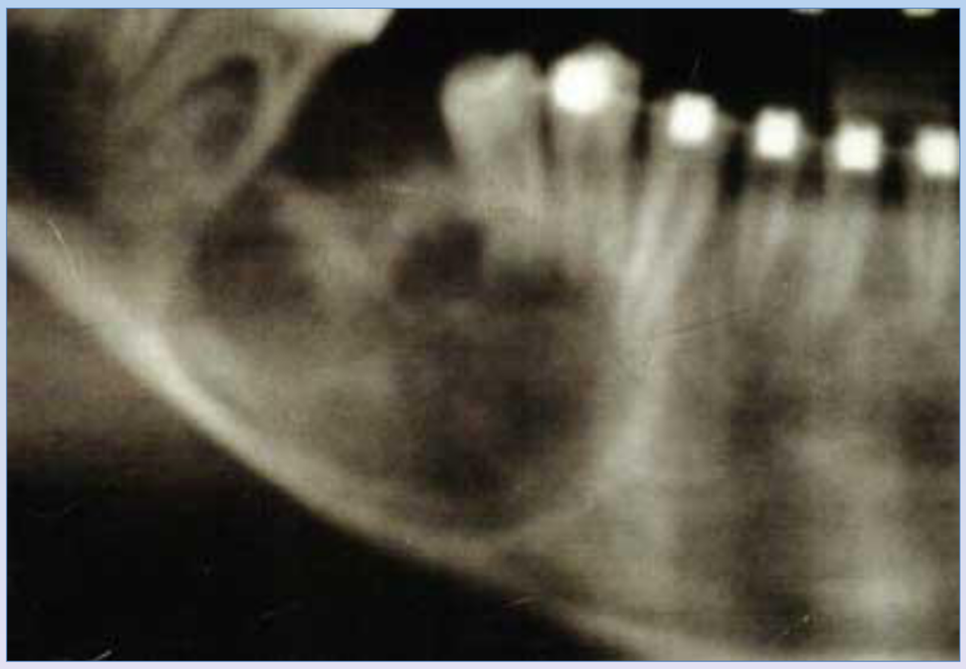

Example Img 1


Example Img 2

Histology showed disruption of the capsule with fibrous tissue extending into the lesion at one pole although no overt malignancy consistent with a benign parathyroid adenoma.

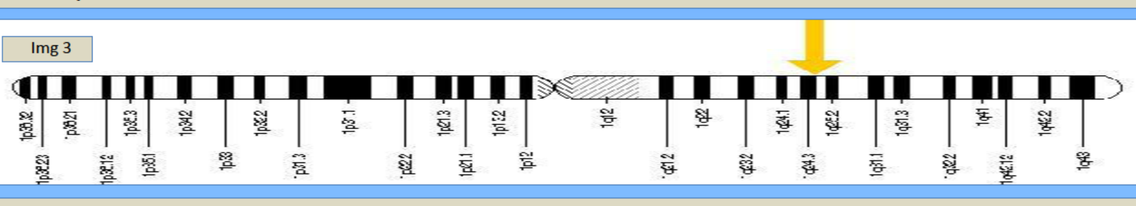
Months later he had recurrence of symptoms, further hypercalcaemia and a right inferior parathyroid adenoma was excised. Genetic testing detected a novel pathogenic duplication mutation of CDC73 gene leading to premature termination of translation.
Further genetic testing of the family for the familial CDC73 pathogenic mutation and genetic investigations in the proband is in progress. He presented a third time with hypercalcaemia. No adenoma was identified on imaging however he declined selective venous PTH sampling. His case was extensively discussed with multiple specialists with differing opinions as to total parathyroidectomy +/- auto transplantation. Patient elected for total parathyroidectomy and no auto transplantation due to his germline CDC73 pathogenic gene mutation and 10-15% risk of parathyroid carcinoma development.

Case conclusion: This unique case illustrates consideration of genetic testing in primary hyperparathyroidism under 45 years, with challenges in rarity and management including implications for biopsy and surgical intervention, multisystem lifelong screening of proband and relatives which is recommended from 5-10 years and availability of predictive genetic testing for the familial CDC73 gene mutation. This indicates a significantly more complex case where previous literature has been unable to guide on management and may help advise other endocrinologists.


Example Img 4: Cemento-ossifying fibroma of bone in a 10-year-old male with hyperparathyroidism-jaw tumor syndrome.

Genetics: The CDC73 (cell division cycle 73) gene (OMIM 607393) is located on the long (q) arm of chromosome 1, 1q25, position between base pair 193,121,957 to base pair 193,254,814.

Img 3



Pathophysiology: CDC73 (previously known as HRPT2 gene) provides instructions for making a protein called parafibromin (thought to play a role in cell growth and division)
CDC73 gene mutations cause HPT-JT syndrome by:

- Reducing the amount of functional parafibromin that is produced. Most of these mutations result in a parafibromin protein that is abnormally short and nonfunctional resulting in regulatory difficulties with cell proliferation leading to tumor formation.
- It is unknown why only certain tissues seem to be affected by changes in parafibromin.
- There are a range of different mutation including nonsense, missense, frameshift and splice site as well as deletions and insertions with mutations found predominantly in exons 1, 2 and 7. Most are unique however a founder mutation in exon 8 in Roma families from Portugal has been detected.

Table 1: Familial hyperparathyroid disorders, genetic characteristics, presentation of hyperparathyroidism and associated features

Disorder	*Inheritance*	*Responsible gene*	*Chromosomal location*	*HPT*	*Associated tumors*
MEN1	AD	*MEN1*	11q13	High penetrance (~ 90%), Multiglandular	Pituitary, EPT adrenocortical, carcinoid
MEN1-variant	AD	*CDKN1B/p27*	12p12-13	Multiglandular	Pituitary
MEN2A	AD	*RET*	10q21	Low penetrance (~ 20%), Multiglandular/Adenoma	MTC, pheochromocytoma
HPT-JT	AD	*HRPT2*	1q21-q32	Cystic parathyroid tumors, 15% risk of carcinoma	Jaw tumors, renal lesions
FIHPT[a]	AD	*HRPT2*	1q21-q32	Adenoma/multiglandular	-
	AD	*MEN1*	11q13	"	-
	AD	*?*	*2p13.3–14*	"	-
ADMH	AD	*CASR*	3q13-21	Multiglandular/Adenoma	-
FHH	AD	*CASR*	3q13-21	Mildly hyperplastic	-
NSHPT	AR/AD	*CASR*	3q13-21	Markedly hyperplastic	-

Diagnosis/testing:

- Biochemical findings of primary hyperparathyroidism
- Identification of ossifying fibroma(s) of the maxilla and/or mandible on imaging studies
- Family history, and detection of a heterozygous germline *CDC73* pathogenic variant on molecular genetic testing.

Evaluation of relatives at risk:

- If the family-specific *CDC73* pathogenic variant is known, molecular genetic testing of at-risk relatives is recommended between age five to ten years.

Surveillance:

- Starting at age five to ten years, recommendations are serum testing for biochemical evidence of primary hyperparathyroidism annually and dental panoramic x-ray with neck shielding at least every five years.
- Those who have undergone surgery for a jaw tumor require closer follow-up for possible tumor recurrence.
- To monitor for kidney lesions, renal ultrasound examination is recommended at least every five years
- For women, reproductive age, lifelong imaging (enhanced MRI) and monitoring for uterine tumors ultrasound examination as clinically indicated.

Management: For single benign parathyroid tumour, a minimally invasive approach to remove the abnormal parathyroid gland followed by close monitoring for recurrent primary hyperparathyroidism has been suggested.
Parathyroid Carcinoma: an *en bloc* resection of the parathyroid gland with surrounding, adherent tissue and the ipsilateral thyroid lobe should be considered.
Jaw tumors should be treated surgically as indicated by size, location, and symptoms; treatment of choice is complete resection, which may not be possible in all cases.

References: Img 1 http://synapse.koreamed.org/DOIx.php?id=10.3342/ceo.2008.1.1.46&vmode=PUBREADER, Img 2 http://www.endocrinesurgery.net.au/primary-hpth-causes/, Img 3 http://ghr.nlm.nih.gov/gene/CDC73 , Img 4 http://www.surgicalrestorative.com/articles/2014/02/hyperparathyroidism-jaw-tumor-syndrome-hptjt-report-of-a-family.html, Clinical info: http://ghr.nlm.nih.gov/condition/hyperparathyroidism-jaw-tumor-syndrome

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Endocrine tumours
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DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16–20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY
PosterSessionOnline.com