Endocr Pathol (2016) 27:142–146
DOI 10.1007/s12022-016-9427-6

A Novel Mutation in a Patient with Hyperparathyroidism–Jaw Tumour Syndrome

Virginia Bellido[1,2] · **Ihintza Larrañaga**[1] · **Maite Guimón**[1] · **Rafael Martinez-Conde**[3] · **Asier Eguia**[3] · **Gustavo Perez de Nanclares**[4,5] · **Luis Castaño**[2,4,5,6] · **Sonia Gaztambide**[1,2,4,5,6]

Published online: 19 March 2016

Abstract Hyperparathyroidism–jaw tumour syndrome (HPT-JT) is a rare variant of familial hyperparathyroidism, characterized by primary hyperparathyroidism (PHPT) due to one or multiple parathyroid adenomas, and benign tumours of the mandible and maxilla. It has an autosomal dominant pattern of inheritance, and is associated with mutations that deactivate the cell division cycle protein 73 homolog (*CDC73*) gene, also known as hyperparathyroidism 2 (*HRPT2*), located on the long arm of chromosome 1, that encodes for the tumour suppressor protein parafibromin. In the majority of cases, PHPT is the presenting symptom, but up to 30 % of HPT-JT cases initially present with an ossifying fibroma of the maxillofacial bones. HPT-JT may result in severe hypercalcemia-related complications and an elevated risk of parathyroid carcinoma. For this reason, early identification of the disease is important. We present the case of a 23-year-old woman who was found to have jaw tumours and was later diagnosed with PHPT. Genetic analysis revealed a novel mutation in exon 1 of *CDC73*. This report contributes to the understanding of the genetics of this rare syndrome. It also highlights the fact that HPT-JT should be considered and *CDC73* mutation analysis should be performed in cases of early-onset PHPT associated with ossifying fibromas of the jaw.

Keywords Primary hyperparathyroidism · Jaw tumour · Ossifying fibroma · *CDC73* gene · *HRPT2* gene

✉ Virginia Bellido
virginiabellido@gmail.com

[1] Department of Endocrinology, Cruces University Hospital, Plaza de Cruces s/n, 48903 Barakaldo, Vizcaya, Spain

[2] University of the Basque Country, Leioa, Spain

[3] Oral Medicine Unit, Oral and Maxillofacial Pathology Unit, Faculty of Medicine and Dentistry, UFI 11/25, University of the Basque Country, Leioa, Spain

[4] BioCruces Health Research Institute, Vizcaya, Spain

[5] CIBERER (Center for Biomedical Research on Rare Diseases), Carlos III Health Institute, Madrid, Spain

[6] CIBERDEM (Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders), Carlos III Health Institute, Madrid, Spain

Introduction

Hyperparathyroidism–jaw tumour (HPT-JT) syndrome (OMIM no.145001) is genetically and clinically distinct from other endocrine neoplasia syndromes and considered a rare variant of familial primary hyperparathyroidism. It is a rare autosomal dominant syndrome characterized by primary hyperparathyroidism (PHPT) occurring at an early age, ossifying fibromas of the maxilla and mandible and, less frequently, renal lesions and uterine tumours [1–5]. In most cases, PHPT is the presenting symptom, but up to 30 % of HPT-JT cases initially present with an ossifying fibroma of the maxillofacial bones [6–8].

The cell division cycle protein 73 homolog (*CDC73*) gene, located at chromosome 1q31.2, is responsible for HPT-JT and encodes parafibromin [9, 10]. This 531-amino protein is an ubiquitously expressed protein that contributes to the inhibition of cell proliferation and regulation of cell growth [11, 12]. Since the discovery of the *CDC73* gene, there have been a number of different mutations documented in the literature [13].

Here, we report a case of HPT-JT diagnosed by a novel *CDC73* mutation. This report contributes to the understanding

of the genetics of this rare syndrome. It also highlights the importance of early identification in order to reduce associated morbidity and mortality.

Case Report

We present the case of a 23-year-old woman who visited the Department of Maxillofacial Surgery in 2011 for a 2-year history of facial asymmetry. Her personal history included an episode of renal colic at 17 years of age. Imaging studies (orthopantomography and computed tomography) showed extended mixed lesions (both radiopaque and radiolucent) in both mandibular bones. Histopathological analysis of an incisional biopsy of one of the lesions was compatible with an ossifying fibroma. Under general anaesthesia, the mandibular lesions and the involved teeth were removed and the mandible was reconstructed with iliac crest bone grafting. Histopathologic examination of the resected tumour showed a proliferation of benign spindle cells, forming a cellular connective tissue intermixed with foci of calcification (Fig. 1), confirming the diagnosis of ossifying fibromas. After surgery, a blood test was requested. The results showed hypercalcaemia, not previously known, and hence the patient was referred to endocrinology.

In addition to hypercalcaemia (total calcium 11.5 mg/dl; normal range of 8.4–10.4 mg/dl), the blood test showed hypophosphataemia (phosphate 2.2 mg/dl; normal range 2.5–4.7 mg/dl), hypercalciuria (24-h urine calcium levels of 400 mg), high levels of parathyroid hormone (PTH) (177 pg/ml; normal range 10–65 pg/ml) and normal levels of vitamin D (32.7 ng/dl). These data indicated PHPT. A neck ultrasound scan revealed a lower left parathyroid nodule (2 × 1.6 × 3.5 cm), while scintigraphy showed increased uptake in the lower pole of the left thyroid, compatible with parathyroid adenoma. Further, we performed an abdominal ultrasound scan, which showed bilateral nephrolithiasis, and bone densitometry, with results compatible with osteoporosis (T scores of −3.9 SD in the lumbar spine and −3.6 SD in the distal radius).

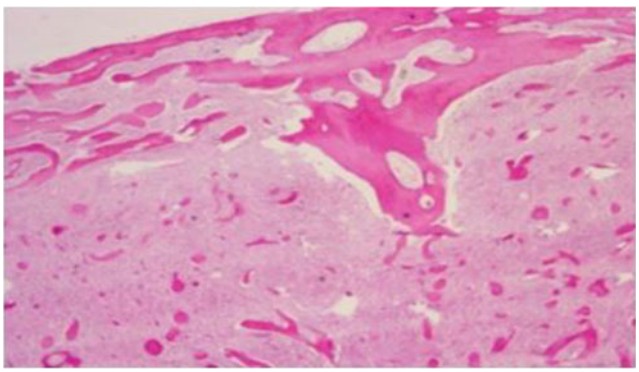

Fig. 1 Photomicrograph of the patient's jaw tumour showing fascicles of uniform spindle cells with small islands of immature bone, consistent with an ossifying fibroma (haematoxylin-eosin stain; original magnification ×20)

The patient was referred for surgery with a diagnosis of PHPT. In April 2013, she underwent bilateral neck exploration and selective parathyroidectomy with resection of a large lower left parathyroid adenoma (3 cm in diameter and 6.033 g in weight). Intraoperative levels of parathyroid hormone decreased from 252 pg/ml preoperatively to a normal level of 26.3 pg/ml at the completion of the procedure, while calcium levels returned to normal 24 h after surgery (8.9 mg/dl). Microscopic examination showed a compressed rim of normal parathyroid tissue adjacent to eosinophilic adenoma cells, without atypical histological features. These findings were consistent with a parathyroid adenoma.

The combination of jaw tumours and PHPT coupled with the early-onset of PHPT suggested HPT-JT syndrome. Given that suspicion, a genetic study of the *CDC73* gene was requested. After informed consent was given, an EDTA-preserved peripheral blood sample was collected for molecular analysis of the *CDC73* gene. Genomic DNA was extracted and all 17 coding exons and all exon–intron boundaries of the *CDC73* gene were analysed by PCR amplification and direct Sanger sequencing (primers and conditions are available on request). Further, copy number quantification and identification of small duplications or deletions at the *CDC73* region was performed using the MLPA (multiplex ligation-dependent probe amplification) technique (SALSA MLPA P466 *CDC73* probemix, MRC-Holland). Sanger sequences were analysed with Sequencing Analysis v.5.2 software (Life Technologies) and compared with the reference sequence (Ensembl reference for the *CDC73* transcript: ENST00000367435) using SeqScape v.2.5 software (Life Technologies).

Sanger sequencing revealed a heterozygous deletion of 24 nucleotides affecting the start codon (c.-16:8del; p.Met1?) (Fig. 2). No other alteration was found either by direct sequencing or MLPA.

Previous descriptions of the c.-16:8del variant were checked using Ensembl (www.ensembl.org), 1000 Genomes (www.1000genomes.org/), Human Gene Mutation Database (HGMD, www.biobase-international.com/product/hgmd), Exome Aggregation Consortium (http://exac.broadinstitute.org/) and COSMIC (http://cancer.sanger.ac.uk/cosmic) databases. Pathogenic effect of the variant was assessed using the following prediction pathogenic software: Mutation t@sting (www.mutationtaster.org) and PROVEAN (http://provean.jcvi.org/index.php).

According to the different databases, and to our knowledge, this mutation has not been reported elsewhere, either in germline or in somatic tissues. Analyses by Mutation t@sting and PROVEAN software predict it to be a disease-

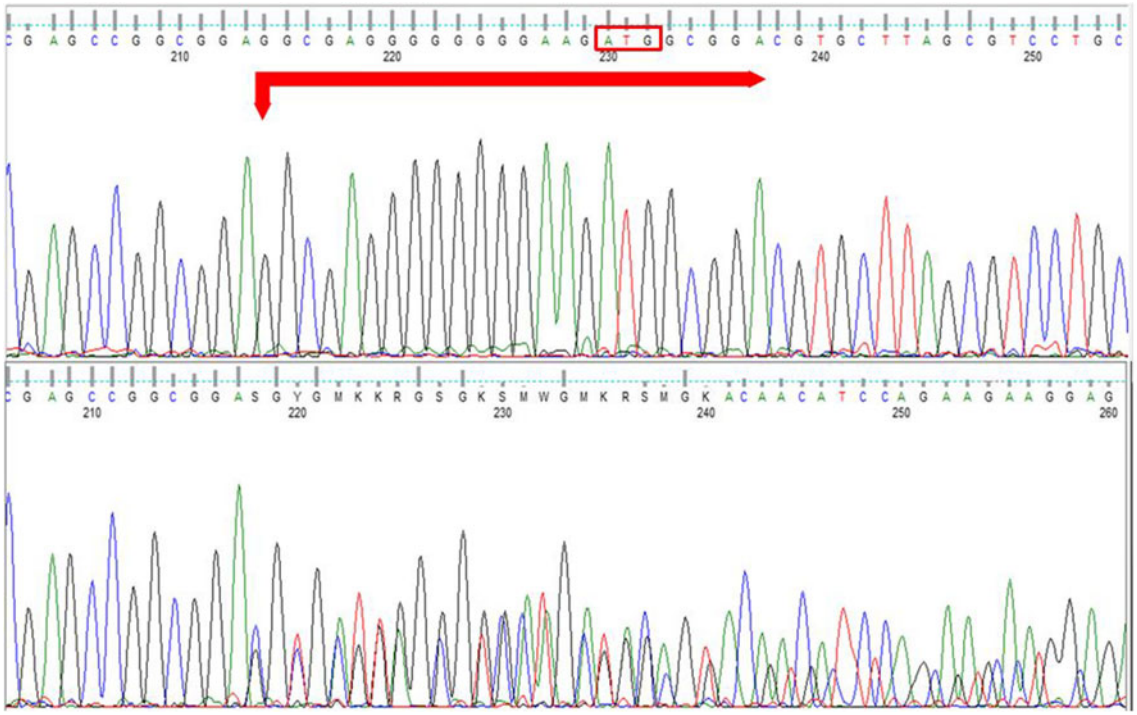

Fig. 2 Electropherogram showing part of the sequence of the *CDC73* gene in a normal control (*upper panel*) and our patient (*lower panel*). *Red arrows* show the 24 nucleotides deleted in the patient, whereas *red square* indicates the location of the start codon

causing mutation, as no protein is created due to the disappearance of the original start codon.

Discussion

We have presented the case of a patient with primary hyperparathyroidism diagnosed after the finding of maxillary ossifying fibromas. We reached the diagnosis of HPT-JT syndrome based on the clinical presentation and the mutation in the *CDC73* gene. This is a good example of the importance of a multidisciplinary approach to this disease for proper diagnosis and treatment.

The association between hyperparathyroidism and jaw lesions has been reported in the literature since 1971 [14–16]. Jackson et al., who reported several cases of primary hyperparathyroidism and mandibular tumours across three generations in the same family, described in 1990 the hyperparathyroidism–jaw tumour syndrome as a clinically and genetically distinct syndrome [1]. It is a rare endocrine disease, characterized by hyperparathyroidism and benign bone tumours in the mandibular and maxillary bones [1]. The prevalence and incidence of the disease remain unknown, as only approximately 200 cases in less than 40 families have been reported in the literature since it was first described in 1990 [1–3, 7, 8, 17–21]. It has an autosomal dominant pattern of inheritance with incomplete penetrance and variable expression, with 10 % of gene carriers showing no clinical manifestations [22]. The first clinical signs and symptoms tend to occur in late adolescence or early adulthood [2].

About 80 % of patients have PHPT, and in the majority of cases, it is the presenting symptom [23], at an average age of 32 years. Classically, it has been described as more aggressive than primary hyperparathyroidism, often with the involvement of several glands (45–75 %), synchronously or asynchronously, and with a greater risk of persistence and recurrence (20–50 %) [2, 24]. Parathyroid carcinoma, a very uncommon entity (occurring in <1 % of individuals with hyperparathyroidism), has a relatively high incidence in this syndrome, of up to 15 % [25]. It has been suggested that the presence of hypercalcaemia may not have a sensitivity of 100 % for the detection of parathyroid disease in *CDC73* mutation carriers, since some cases of atypical adenomas and parathyroid carcinomas in people with normal blood calcium levels have been reported [26].

The optimal surgical approach of primary hyperparathyroidism for patients with HPT-JT remains controversial. A number of small studies have recommended extensive parathyroidectomy (subtotal) given the syndrome's more aggressive features and higher risk of cancer [27–29]. However, other studies have shown that routine subtotal or total parathyroidectomy confers no benefit in disease-free interval and likely leads to increased risk of permanent hypoparathyroidism. Most authors recommend bilateral neck exploration and surgical excision of the affected gland(s) [30, 31]. Following this recommendation, our patient underwent resection of the

affected gland, after neck exploration. When there is a suspicion of parathyroid carcinoma, en bloc surgical resection is recommended, including ipsilateral thyroid lobectomy and resection of neighbouring tissue [32].

Around 30 % of patients develop fibrous tumours in the mandible or maxillary bones. These tend to occur in adolescence, are histologically different from brown tumours associated with severe hyperparathyroidism, and there is no spontaneous recurrence after parathyroidectomy [3, 8, 33]. A lower percentage of patients (15 %) develop renal complications including Wilms' tumours, hamartomas, renal cell carcinomas, and polycystic kidney disease [17, 34, 35], while up to 75 % of female patients develop benign or malignant uterine tumours [4].

In 1995, the gene locus associated with HPT-JT syndrome was identified on the long arm of chromosome 1, specifically in the 1q21-q31 region [9]. In 2002, the cell division cycle protein 73 homolog (*CDC73*) gene, also known as hyperparathyroidism 2 (*HRPT2*), was definitively localised in this region of chromosome 1 [10]. It contains 17 exons which encode for a 531-amino acid protein called parafibromin, from 'para' (referring to parathyroid) and 'fibro' (referring to fibrous tumours in the jaw). This protein, mainly present in the nucleus, is part of the ribonucleic acid polymerase II-regulatory Paf1 complex. It is believed to act as a tumour suppressor protein, regulating the transcription and the modification of histones, although the exact mechanism remains unknown [22, 36]. Complete absence of immunohistochemical staining for parafibromin occurs frequently in both parathyroid carcinomas and HPT-JT related tumours (adenomas and carcinomas), but not in other benign parathyroid lesions [37]. Unfortunately, this analysis, which would reinforce the pathogenicity of the observed mutation in case loss of parafibromin immunoreactivity was obtained, could not be performed, as our pathology laboratory does not implement parafibromin staining.

Since its discovery, several mutations in the *CDC73* gene have been described in the literature. A 2010 review identified 68 germline, 38 somatic and 5 unidentified mutations [13]. Approximately 80 % of these mutations are located in exons 1, 2 and 3 [7, 38, 39]. Most of them are frameshift mutations, while a few are nonsense or missense mutations. More than 80 % of mutations predict premature truncation of parafibromin protein [40]. Our patient had a heterozygous alteration in exon 1, consisting of the deletion of 24 nucleotides (c.-16:8del), affecting the start codon. To our knowledge, this mutation has not been previously reported. Prediction software considers no protein would be produced through this allele as a consequence of the disappearance of the original start codon.

Germline-inactivating *CDC73* gene mutations cause HPT-JT by reducing the amount of functional parafibromin which is produced [10]. This results in unregulated cell proliferation, which can lead to tumour formation. Although the rate of tumour recurrence of PHPT seems to be higher in carriers of deletions or frameshift mutations [30, 41], the rarity of the disease makes it difficult to establish a proper genotype–phenotype relationship. In this case, unfortunately, family history could not be performed to reinforce these data as the patient's relatives' clinical information and/or samples were not available.

Whole *CDC73* gene deletion has been already described [30] as a cause of HPT-JT. Although parafibromin staining could not be performed, the c.-16:8del mutation predicts the absence of parafibromin production in the affected allele, resembling the effect of the physical whole deletion of the gene. In this case, the patient will generate lower amounts of the protein. Thus, a theoretical consequence should be the disruption of control of cell division and subsequent tumour creation.

In conclusion, we have presented the case of a patient with HPT-JT syndrome diagnosed after the finding of maxillary ossifying fibromas. The presence of multiple ossifying fibromas in the same individual or in several members of the same family should make us carefully consider this syndrome. Given the high risk of complications associated with hypercalcaemia and parathyroid carcinoma, early detection of the disease is essential. Our identification of a novel mutation in the *CDC73* gene, up to now unaccounted for, increases our understanding of this syndrome.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Jackson CE, Norum RA, Boyd SP, Talpos GB, Wilson SD, Taqqart RT et al. Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. Surgery 1990;108:1006-1012.
2. Iacobone M, Masi G, Barzon L, Porzionato A, Macchi V, Ciarleglio FA et al. Hyperparathyroidism-jaw tumour syndrome: a report of three large kindred. Langenbecks Arch Surg. 2009; 394: 817-25.
3. Aldred MJ, Talacko AA, Savarirayan R, Murdolo V, Mills AE, Radden BG et al. Dental findings in a family with hyperparathyroidism-jaw tumour syndrome and a novel HRPT2 gene mutation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 101: 212-8
4. Braley KJ, Hobbs MR, Buley ID, Carpten JD, Cavaco BM, Fares JE et al. Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome. J Intern Med. 2005; 257: 18-26.
5. McCarthy EF. Fibro-osseous lesions of the maxillofacial bones. Head Neck Pathol. 2013;7:5–10.

6. Yamashita Y, Akiyama T, Mizusawa N, Yoshimoto K, Goto M. A case of hyperparathyroidism-jaw tumour syndrome found in the treatment of an ossifying fibroma in the maxillary bone. Int J Oral Maxillofac Surg 2007;36(4):365-9.
7. Mathews JW, Winchester R, Alsaygh N, Bartlett AM, Luttrell LM. Hyperparathyroidism-jaw tumour syndrome-an overlooked cause of severe hypercalcemia. Am J Med Sci. 2015 [Epub ahead of print]
8. Bradley KJ, Thakker RV. The Hyperparathyroidism-jaw tumour (HPT-JT) syndrome. Clin Cases Miner Bone Res 2006;3:167–174.
9. Szabó J, Heath B, Hill VM, Jackson CE, Zarbo RJ, Mallette LE et al. Hereditary hyperparathyroidism-jaw tumour syndrome: the endocrine tumour gene HRPT2 maps to chromosome 1q21-q31. Am J Hum Genet 1995; 56: 944-50.
10. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J et al. HRPT2, encoding parafibromin, is mutated in hyperparathryroidism-jaw tumour syndrome. Nat Genet 2002; 32: 676-80.
11. Bradley KJ, Bowl MR, Williams SE, Ahmad BN, Partridge CJ, Patmanidi AL et al. Parafibromin is a nuclear protein with a functional monopartite nuclear localization signal. Oncogene 2007; 26: 1213–1221.
12. Hahn MA, Marsh DJ. Identification of a functional bipartite nuclear localization signal in the tumour suppressor parafibromin. Oncogene 2005; 24:6241–6248.
13. Newey PJ, Bowl MR, Cranston T, Thakker RV. Cell division cycle protein 73 homolog (CDC73) mutations in the hyperparathyroidism-jaw tumour syndrome (HPT-JT) and parathyroid tumours. Hum Mutat 2010; 31: 295-307.
14. Kennett S, Pollick H. Jaw lesions in familial hyperparathyroidism. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1971; 31:502-10.
15. Rosen IB, Palmer JA. Fibro-osseous tumours of the facial skeleton in association with primary hyperparathyroidism: an endocrine syndrome or coincidence? Am J Surg 1981;142:494-8.
16. Warnakulasuriya S, Markwell BD, Williams DM. Familial hyperparathyroidism associated with cementifying fibromas of the jaws in two siblings. Oral Surg Oral Med Oral Path Oral Radiol Endod 1985;59:269-74.
17. Cavaco BM, Barros L, Pannet AA, Ruas L, Carvalheiro M, Ruas MM et al. Hyperparathyroidism-jaw tumour syndrome in a Portuguese kindred. QJM. 2001; 94: 213-22.
18. Cavaco BM, Guerra L, Bradley KJ, Carvalho D, Harding B, Oliveira A, Santos MA, Sobrinho LG, Thakker RV, Leite V. Hyperparathyroidism-jaw tumour syndrome in Roma families from Portugal is due to a founder mutation of the HRPT2 gene. J Clin Endocrinol Metab 2004; 89:1747–1752.
19. Haven CJ, Wong FK, van Dam EW, van der Juijt R, van Asperen C, Jansen J et al. A genotypic and histopathological study of a large Dutch kindred with hyperparathyroidism-jaw tumour syndrome. J Clin Endocrinol Metab 2000; 85:1449–1454.
20. Rekik N, Ben Naceur B, Mnif M, Mnif F, Mnif H, Boudawara T. Hyperparathyroidism-jaw tumour syndrome: a case report. Ann Endocrinol (Paris). 2010; 71(2):121-6.
21. Carlson AL, Smith CL. Primary hyperparathyroidism and jaw tumour syndrome: a novel mutation of the HRPT2 gene. Endocr Pract 2008;14(6):743-7.
22. Abdulla AG, O'Leary EM, Isorena JP, Diaz MF, Yeh MW. Recurrent hyperparathyroidism and a novel nonsense mutation in a patient with hyperparathyroidism-jaw tumour syndrome. Endocr Pract 2013; 19: 134-7.
23. Sharretts JM, Simonds WF. Clinical and molecular genetics of parathyroid neoplasms. Best Pract Res Clin Endocrinol Metab. 2010; 24: 491-502.
24. Marx SJ, Simonds WF, Agarwal SK, Burns AL, Weinstein LS, Cochran C et al. Hyperparathyroidism in hereditary syndromes: special expressions and special managements. J Bone Miner Res 2002; 17: 37-43.
25. B Veiguela, ML Isidro, S Jorge y B Ruano. Una causa rara de hipercalcemia: carcinoma sincrónico de dos paratiroides en el contexto del síndrome de hiperparatiroidismo familiar-tumour mandibular. Endocrinol Nutr. 2010; 57: 391-399.
26. Vito G, Alfredo S, Lucia Anna M, Claudia B, Nazzareno B, Michele B et al. Diagnosis of Parathyroid Tumours in Familial Isolated Hyperparathyroidism with HRPT2 Mutation: Implications for Cancer Surveillance. J Clin Endocrinol Metab. 2006; 91: 2827-2832.
27. Sarquis MS, Silveira LG, Pimenta FJ, Dias EP, Teh BT, Friedman E, et al. Familial hyperparathyroidism: surgical outcome after 30 years of follow-up in three families with germline HRPT2 mutations. Surgery. 2008; 143(5):630–40
28. Barry MK, van Heerden JA, Grant CS, Thompson GB, Khosla S. Is familial hyperparathyroidism a unique disease? Surgery. 1997; 122(6):1028–33
29. Huang SM, Duh QY, Shaver J, Siperstein AE, Kraimps JL, Clark OH. Familial hyperparathyroidism without multiple endocrine neoplasia. World J Surg. 1997; 21(1):22–8.
30. Mehta A, Patel D, Rosenberg A, Boufraqech M, Ellis RJ, Nilubol N et al. Hyperparathyroidism-jaw tumour syndrome: Results of operative management. Surgery. 2014; 156(6):1315-24.
31. T. Carling, R. Udelsman. Parahyroid surgery in familial parathyroid disorders. J Intern Med. 2005; 257: 27-37.
32. Sharretts JM, Kebebew E, Simonds WF. Parahyroid cancer. Semin Oncol. 2010; 37: 580-90.
33. Chen JD, Morrison C, Zhang C, Kahnoski K, Carpten JD, Teh BT. Hyperparathyroidism-jaw tumour syndrome. J Intern Med. 2003; 253: 634-42.
34. Tan MH1, Teh BT. Renal neoplasia in the hyperparathyroidism-jaw tumour syndrome. Curr Mol Med 2004;4(8):895-7.
35. Teh BT, Farnebo F, Kristoffersson U, Sundelin B, Cardinal J, Axelson R et al. Autosomal dominant primary hyperparathyroidism and jaw tumour syndrome associated with renal hamartomas and cystic kidney disease: linkage to 1q21-q32 and loss of the wild type allele in renal hamartomas. J Clin Endocrinol Metab. 1996; 81: 4204-11.
36. Kutcher MR, Rigby MH, Bullock M, Trites J, Taylor SM, Hart RD. Hyperparathyroidism-jaw tumour syndrome. Head Neck. 2013; 35: 175-7.
37. Gill AJ, Clarkson A, Gimm O, Keil J, Dralle H, Howell VM et al. Loss of nuclear expression of parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw tumour (HPT-JT) syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. Am J Surg Pathol. 30(9):1140-9.
38. Frank-Raue K, Haag C, Schulze E et al. CDC73-related hereditary hyperparathyroidism: five new mutations and the clinical spectrum. Eur J Endocrinol. 2011; 165: 477-483.
39. Khadilkar KS, Budyal SR, Kasliwal R, Lila AR, Bandgar T, Shah NS. HRPT2- (CDC73) related hereditary hyperparathyroidism: a case series from western india. Endocr Pract. 2015; 21:1010-6.
40. Shibata Y, Yamazaki M, Takei M, Uchino S, Sakurai A, Komatsu M. Early-onset, severe, and recurrent primary hyperparathyroidism associated with a novel CDC73 mutation. Endocr J. 2015; 62:627-32.
41. Silveira LG, Dias EP, Marinho BC, Gomez RS, De Marco L, Sarquis MS. HRPT2-related familial isolated hyperparathyroidism: could molecular studies direct the surgical approach? Arq Bras Endocrinol Metabol. 2008; 52:1211-20.