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Case Report

A Novel Pathogenic *CDC73* Gene Variant in Hyperparathyroidism-jaw Tumor Syndrome

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Abstract

Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare hereditary disorder caused by pathogenic *CDC73* gene variants. We report the case of a patient with HPT-JT who carried a novel germline pathogenic *CDC73* variant. A 27-year-old woman presented with thirst, polyuria, fatigue, constipation, and a history of fibro-osseous mandible lesions and endometrial polyps. Examination revealed hypercalcemia and grossly elevated PTH levels with hypercalciuria accompanied by a right lower parathyroid tumor with concordant imaging, suggesting primary hyperparathyroidism (PHPT). Given that she had early-onset PHPT and a history of fibro-osseous mandible lesions, HPT-JT was suspected. Genetic testing identified a novel frameshift variant in exon 1 of *CDC73*. En bloc resection was planned based on the suspicion of parathyroid carcinoma. However, because no findings suggestive of carcinoma were observed intraoperatively, thyroidectomy was not performed. Despite the surgery, PHPT persisted postoperatively, and further evaluation revealed the presence of a residual ectopic left upper parathyroid adenoma, necessitating additional surgery. High-impact pathogenic *CDC73* variants are linked to a high risk of parathyroid carcinoma and multiglandular disease. In patients with such variants and clinically suspected parathyroid carcinoma, bilateral neck exploration with subtotal parathyroidectomy may be recommended, with en bloc resection added if intraoperative findings suggest carcinoma.

Key Words: *CDC73*, hyperparathyroidism-jaw tumor syndrome, novel germline mutation, parathyroid carcinoma

Introduction

Hereditary hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare autosomal dominant genetic disorder. Over 80% of patients present with primary hyperparathyroidism (PHPT) [1, 2], Ten to thirty percent had jaw tumors [2-4], approximately 6% to 24% had renal lesions [2-4], and over 50% of women had uterine lesions [3, 4]. The *CDC73* gene, which is responsible for HPT-JT, is located on chromosome 1q31.2; it consists of 17 exons and encodes parafibromin (531 amino acids) [3]. *CDC73* functions as a tumor suppressor gene [5]. Over 75% of germline pathogenic variants of *CDC73* are either frameshift or nonsense mutations [6]. Pathogenic variants are primarily concentrated in exons 1 to 7, especially in exons 1, 2, and 7 [7]. We report the case of a young woman with a history of fibro-osseous mandible lesions and endometrial polyps who was diagnosed with HPT-JT following genetic testing, revealing a novel frameshift variant in the *CDC73* gene.

Case Presentation

A 27-year-old woman presented with thirst, polyuria, fatigue, and constipation. She had a history of fibro-osseous mandible lesions at 21 years of age (Fig. 1A), and she underwent surgical mandible tumor resection twice. She also had endometrial polyps at 19 years of age (Fig. 1B and 1C), and she underwent transcervical resection twice. Her parents were divorced, she had no contact with her father, and no genetic diseases were diagnosed in other family members (Fig. 2).

Diagnostic Assessment

The patient's vital signs were within normal limits, and physical examination revealed no significant abnormalities; no cervical mass was palpable. Her laboratory data (Table 1) showed hypercalcemia (12.9 mg/dL [3.22 mmol/L]; normal reference range: 8.8-10.1 mg/dL (2.20-2.52 mmol/L), hypophosphatemia (2.0 mg/dL [0.65 mmol/L]; normal reference range: 2.7-4.6 mg/dL [0.87-1.49 mmol/L]), and elevated intact PTH (318.3 pg/mL [33.7 pmol/L]; normal reference range: 10-65 pg/mL [1.1-6.9 pmol/L]). Serum bone-specific alkaline phosphatase was elevated (32.1 μg/L; normal reference range: 2.9-14.5 μg/L) and 25(OH) vitamin D was low (9.8 ng/mL [24.5 nmol/L]; normal reference range: 20-50 ng/mL [50-125 nmol/L]). Spot urine calcium was 10.4 mg/dL, and her calcium/creatinine clearance ratio was 0.0251. Cervical ultrasound revealed a $19 \times 10 \times 6$ mm hypoechoic nodule rich in blood flow, located posterior to the lower pole of the right thyroid lobe, suggestive of a parathyroid tumor (Fig. 1D). In cervical computed tomography (CT), the nodule was also identified, but ^{99m}Technetium sestamibi scintigraphy did not reveal increased uptake in the nodule. Dual-energy X-ray absorptiometry bone mineral density (HOLOGIC, Discovery Wi, %CV 1.0%) revealed a Z-score of −2.6 at the lumbar spine and −1.9 at the femoral neck,

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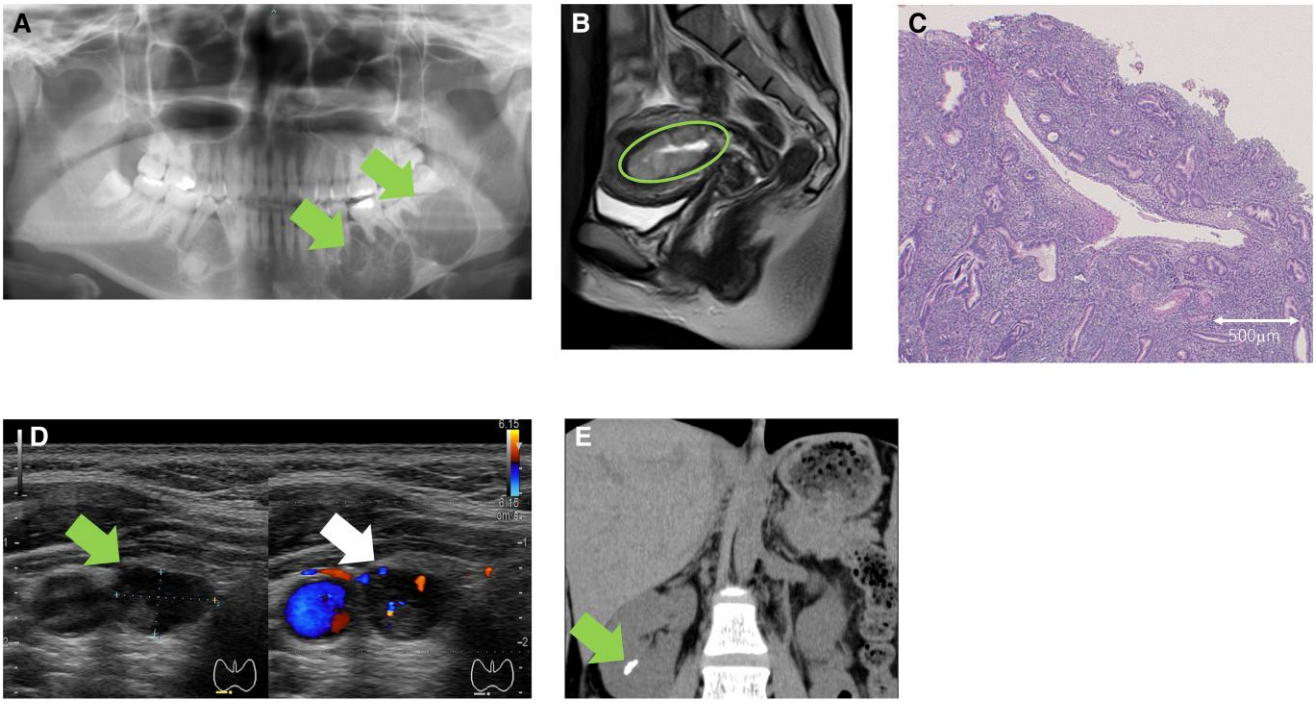

Figure 1. Panoramic X-ray photography (A) showing lytic lesion with thin rim calcification (arrow). Magnetic resonance image (B) showing hypointense intracavitary masses surrounded by hyperintense fluid and endometrium (ellipse). Hematoxylin and eosinophil staining of endometrial polyp, 2× (C) showing fibrous stroma and thick-walled blood vessels. Cervical ultrasound echography (D) showing hypoechoic nodule (green arrow) with increased internal vascularity (white arrow). Computed tomography (E) showing renal stone (arrow).

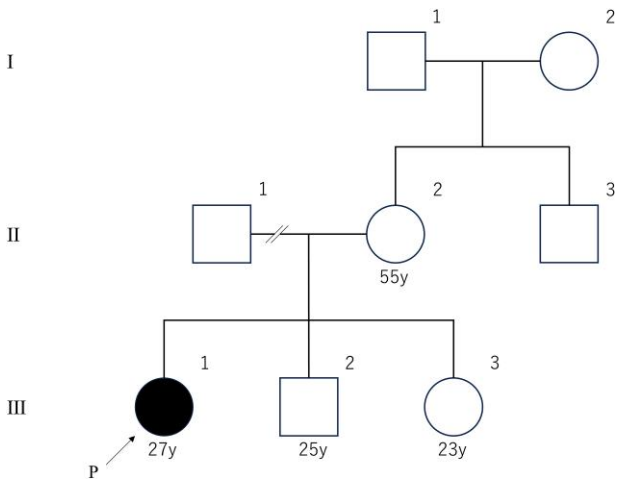

Figure 2. Patient family tree.

with bone densities of 0.701 g/cm^2 and 0.618 g/cm^2, respectively, suggesting osteoporosis. Plain CT from the neck to the pelvis revealed a 10-mm renal stone (Fig. 1E).

Given the onset of PHPT at a young age, hereditary PHPT was considered. The presence of fibro-osseous lesions in the mandible and a history of endometrial polyps suggested a high likelihood of HPT-JT. With written informed consent, we extracted germline DNA from her peripheral blood and performed next-generation sequencing using a genetic panel including *MEN1*, *CDKN1B*, *RET*, *CASR*, *GNA11*, *AP2S1*, *CDC73*, and *GCM2*. A novel frameshift variant, c.93del p.Trp32GlyfsTer5, in exon 1 of the *CDC73* gene was identified that has not been previously reported in Clin Var (https://www.ncbi.nlm.nih.gov/clinvar/), Genome Aggregation Database (https://gnomad.broadinstitute.org/), or the Human Genome Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php). The databases were accessed on October 2, 2024. This variant was predicted to be pathogenic by in silico analysis using MutationTaster 2 (https://www.mutationtaster.org).

Treatment

Because of the presence of high PTH, and the high-impact pathogenic *CDC73* germline variant, there were concerns that the parathyroid tumor was a carcinoma; we recommended en bloc resection and obtained consent. We initially planned to remove the right upper and lower parathyroid glands, right peritracheal lymph nodes, and thymus. However, as the parathyroid glands had not infiltrated the surrounding tissues or adhered to the thyroid gland, thyroidectomy was not performed. The right upper parathyroid gland was not clearly identified, and fatty tissue suspected to include the right upper parathyroid gland was excised. Histopathology revealed the right lower parathyroid adenoma, but the right upper parathyroid gland was not identified. Incidentally, metastatic papillary thyroid carcinoma was revealed in the level IV cervical lymph nodes (American Joint Committee on Cancer). Postoperatively, her serum calcium level was 9.6 to 11.1 mg/dL, and her intact PTH level was 94-113 pg/mL, suggesting that PHPT was not completely cured.

Upon reexamination of the neck ultrasound, no nodules raising suspicions for papillary thyroid carcinoma were identified in thyroid; however, a hypoechoic nodule, suspected to be a metastatic lymph node of papillary thyroid carcinoma or an ectopic left upper parathyroid adenoma was detected in the left level III lymph node area. Retrospectively, the nodule was

Table 1. Laboratory values of the patient

Test	Result	Reference range
Albumin	4.3 g/dL (43 g/L)	4.1-5.1 g/dL (41-51 g/L)
Serum Ca	12.9 mg/dL (3.22 mmol/L)	8.8-10.1 mg/dL (2.20-2.52 mmol/L)
Serum IP	2.0 mg/dL (0.65 mmol/L)	2.7-4.6 mg/dL (0.87-1.49 mmol/L)
ALP	137 U/L	38-113 U/L
Serum Cre	0.50 mg/dL (44.2 mmol/L)	0.46-0.79 mg/dL (40.7-69.8 mmol/L)
Intact PTH	318.3 pg/mL (33.7 pmol/L)	10-65 pg/mL (1.1-6.9 pmol/L)
25-(OH)Vit-D	9.8 ng/mL (24.5 mmol/L)	20-50 ng/mL (50-125 mmol/L)
1,25-$(OH)_2$Vit-D	163 pg/mL (391.2 pmol/L)	20-60 pg/mL (48-144 pmol/L)
Bone ALP	32.1 μg/L	2.9-14.5 μg/L
TRACP-5b	847 mU/dL	120-420 mU/dL
Spot urine Ca	10.4 mg/dL	
Spot urine Cre	16.08 mg/dL	

Abbreviations: ALP, alkaline phosphatase; Ca, calcium; Cre, creatinine; IP, inorganic phosphate; TRACP-5b, tartrate-resistant acid phosphatase 5b; Vit-D, vitamin D

Table 2. Laboratory values of the patient's family members

	Mother (II-2)	Brother (III-2)	Sister (III-3)	Reference range
Albumin	4.3 g/dL (43 g/L)	5.1 g/dL (51 g/L)	4.6 g/dL (46 g/L)	3.8-5.2 g/dL (38-52 g/L)
Serum Ca	9.1 mg/dL (2.27 mmol/L)	9.7 mg/dL (2.42 mmol/L)	8.9 mg/dL (2.22 mmol/L)	8.6-10.2 mg/dL (2.15-2.54 mmol/L)
Serum IP	3.6 mg/dL (1.16 mmol/L)	3.7 mg/dL (1.19 mmol/L)	3.9 mg/dL (1.26 mmol/L)	2.5-4.5 mg/dL (0.81-1.45 mmol/L)
Intact PTH	78 pg/mL (8.3 pmol/L)	79 pg/mL (8.4 pmol/L)	41 pg/mL (4.3 pmol/L)	10-65 pg/mL (1.1-6.9 pmol/L)

II-2, III-2, III-3 correspond to the numbers in the family tree in Fig. 2.
Abbreviations: Ca, calcium; IP, inorganic phosphate.

also seen on CT prior to the initial surgery, but at the time it was thought to be a reactive lymph node enlargement. Fine-needle aspiration was performed and revealed a parathyroid adenoma. Given the suggestion of occult thyroid carcinoma and the successful localization diagnosis of the remaining parathyroid adenoma, we performed total thyroidectomy and left upper and lower parathyroid gland resection. Histopathological examination revealed left upper and lower parathyroid adenomas; however, no thyroid carcinoma was detected. After the second surgery, her serum calcium level was 7.4 mg/dL and her intact PTH level was 12 pg/mL, suggesting that PHPT was completely cured, and alpha-calcidol was administered.

Outcome and Follow-up

The patient's mother, brother, and sister showed no apparent signs of PHPT according to laboratory data (Table 2); however, details about the patient's father were unknown because their relationship had been severed. After genetic counseling and obtaining written informed consent from the patient and her mother, brother, and sister, Sanger sequencing was performed to confirm whether the family members had the same variant as the patient. The results suggested the presence of a germline variant only in the patient, with no abnormalities found in the same region of the gene in the other family members (Fig. 3). Subsequently, the patient has undergone regular follow-ups; as of 9 months after the second surgery, neither hypercalcemia nor elevated intact PTH levels have been documented, and no worsening or new appearance of other complications of HPT-JT have been reported.

Discussion

Here we report the case of a patient with HPT-JT carrying a novel germline variant (c.93del p.Trp32GlyfsTer5) in exon 1 of the *CDC73* gene. This frameshift variant results in premature termination of translation within exon 1, causing significant abnormalities in protein structure or loss of protein expression. In silico analysis revealed that this variant was disease-causing. According to the American College of Medical Genetics and Genomics guidelines [8], this variant is categorized as pathogenic; it has been found exclusively in patients who developed PHPT and jaw tumors, whereas other family members without the variant have no history of these diseases, supporting its pathogenic nature.

CDC73-related disorders are inherited in an autosomal dominant manner, although cases of de novo variants have also been reported [9]; however, the proportion of de novo pathogenic variants remains unknown. In this case, the patient harbored a pathogenic *CDC73* variant and had PHPT,

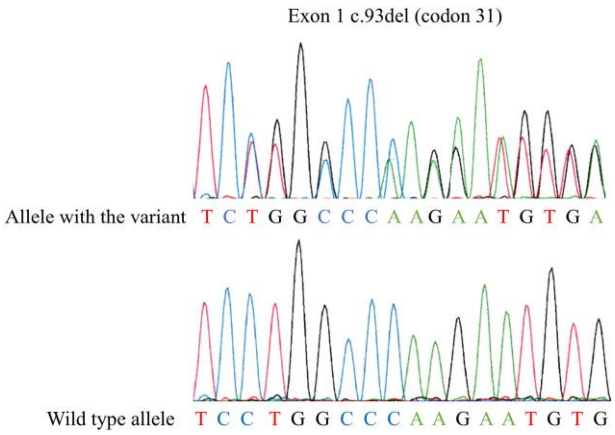

Figure 3. The results of Sanger sequencing of *CDC73* exon 1 using the patient's and the family member`s germline DNA. DNA sequences revealed the deletion of cytosine in 1 allele at nucleotide 93 resulting in a frameshift variant at codon 31 in the *CDC73* gene. The mother, sister, and brother of the patient did not possess the variant.

whereas the mother and siblings who lacked the variant showed no evidence of PHPT. It is possible that the father had a pathogenic variant or that the patient had a de novo variant; however, obtaining the father's medical history or genetic test results is challenging, and the specific situation remains unclear. Sanger sequencing showed that the family members tested negative for the variant. A previous study showed that the penetrance of primary hyperparathyroidism in HPT-JT increased with age (8%, 53%, and 75% at ages 25, 50, and 70 years, respectively) [10]. Confirming the absence of the gene variant in family members has significant implications for exempting them from HPT-JT surveillance.

The optimal surgical approach to PHPT in HPT-JT has not yet been established and remains controversial [11]. In a report [12], 95% of the cases involved a single gland lesion but 23.5% of the cases relapsed post-surgery. Of the relapse cases, 75% occurred with preoperative discordant imaging results. Therefore, in patients with preoperative concordant single-gland localization, targeted unilateral exploration with selective parathyroidectomy was suggested, and in patients with absent or preoperative discordant localization, subtotal parathyroidectomy was suggested. In contrast, HPT-JT has a relatively high incidence of parathyroid carcinoma (23.5% and 31% [1, 2]), especially when high-impact pathogenic variants, such as frameshift, gross indel, splicing, and nonsense variants are present [13]. If parathyroid carcinoma is clinically suspected, en bloc resection should be performed to avoid the risk of reoperation in a scarred area [3]. Preoperative indications for suspected parathyroid carcinoma include markedly elevated PTH levels (5-10 times the upper normal limit), severe hypercalcemia (>14 mg/dL), parathyroid crisis, and a palpable neck mass [14]. In the present case, the patient was suspected to have concordant single-gland disease before the first surgery. She also had a high-impact pathogenic frameshift *CDC73* variant and significantly elevated intact PTH levels, which raised concerns about parathyroid carcinoma. Therefore, en bloc resection was initially planned. However, intraoperative findings did not suggest parathyroid carcinoma, so thyroidectomy was not performed, and histopathology also did not indicate parathyroid carcinoma. However, as a result, PHPT persisted postoperatively, and it was found to be a multiglandular disease. This suggests that the presence of ectopic parathyroid adenoma may be a pitfall in localization diagnosis. In cases with pathogenic variants of CDC73, the risk of parathyroid carcinoma is relatively high. Therefore, it may be reasonable to consider that bilateral neck exploration should have been performed from the outset to check for findings suggestive of parathyroid carcinoma, followed by subtotal parathyroidectomy. HPT-JT is clinically suspected not only when a combination of PHPT and fibro-osseous lesions of the jaw are present but also when PHPT appears at a young age (<40 years) or with multiglandular involvement; with cystic, atypical, or malignant involvement of the parathyroid gland; or in the case of coexisting ossifying jaw fibroma and renal or uterine tumor [15]. In such patients, genetic testing of *CDC73* should be performed preoperatively to determine the appropriate surgical procedure. If a high-impact pathogenic variant is identified and parathyroid carcinoma is clinically suspected, bilateral neck exploration and subtotal parathyroidectomy should be performed. In cases where intraoperative findings are suggestive of parathyroid carcinoma, en bloc resection should be considered.

In 85% of cases of HPT-JT, the initial manifestation is PHPT [2], whereas in 20.8% of cases, jaw tumors precede PHPT [16]. In the present case, the fibro-osseous mandible lesions developed before primary hyperparathyroidism. Most fibro-osseous lesions associated with HPT-JT are reported to be ossifying fibroma [17], and an analysis of 19 children and 21 adults with sporadic ossifying fibroma did not identify any germline pathogenic variants of *CDC73* [18]. Because of this, diagnosing HPT-JT at the time of onset of fibro-osseous mandible lesions was challenging in this case.

Learning Points

- If HPT-JT is clinically suspected, genetic testing should be conducted; if the result is positive, genetic testing for family members should be pursued. Although the penetrance of HPT-JT is not high in younger individuals, if genetic testing of family members is negative, the need for subsequent follow-up is considered to decrease.
- Some *CDC73* variants are associated with a relatively high incidence of parathyroid carcinoma and multiglandular disease. In patients with PHPT suspected of HPT-JT, genetic testing should be performed preoperatively to guide surgical decision-making. If a high-impact pathogenic variant is identified and parathyroid carcinoma is clinically suspected, bilateral neck exploration with subtotal parathyroidectomy should be performed, and en bloc resection should be added if intraoperative findings suggest parathyroid carcinoma.
- HPT-JT often presents with PHPT as the initial symptom; however, fibro-osseous lesions of the jaw can precede PHPT.

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Contributors

All authors have made individual contributions to authorship. Y.I., R.H., and M.N. were involved in the diagnosis and management of the patient and family; M.N was responsible for the patient's surgery; Y.I. and R.H. wrote and edited the manuscript, and Y.T. supervised the process. All authors reviewed and approved the final draft of the manuscript.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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