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CASE REPORTS

The Delicate Balancing of Pros and Cons in the Surgical Management of Hyperparathyroidism in a Young Female with Germline Variant in the *CDC73* Gene

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Abstract
Hyperparathyroidism-jaw tumor syndrome is a rare form of syndromic primary hyperparathyroidism. We describe a young female with a history of common precursor B acute lymphoblastic leukaemia who was diagnosed with overt primary hyperparathyroidism due to a pathogenic *CDC73* variant (c.25C > T). This patient posed several challenging management aspects: the development of nephrocalcinosis, the risk for parathyroid carcinoma, and persistent hyperparathyroidism after two selective parathyroidectomies, leading to the decision to perform a total parathyroidectomy. The latter resulted in permanent complete hypoparathyroidism, with subsequent difficult medical therapy. This case report illustrates the challenge to identify the optimal treatment of parathyroid disease in the context of hyperparathyroidism-jaw tumor syndrome, balancing the risks of hyperparathyroidism and parathyroid carcinoma against the burden of permanent hypoparathyroidism at young age.

Keywords Primary hyperparathyroidism · HPT-JT syndrome · *CDC73* · Parathyroid carcinoma · Parathyroidectomy

Background

Genetics underlie 10% of cases of primary hyperparathyroidism (PHPT). Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is a rare form of syndromic PHPT, due to an autosomal dominantly inherited germline variant in the *CDC73* gene encoding the tumor suppressor protein parafibromin. The syndrome almost always includes PHPT and can be associated with ossifying fibromas of the jaw and benign and malignant tumors of the kidneys and uterus. Typically, parathyroid adenomas arise at a very young age (around the age of 10 years), and progress in an asynchronous manner. Up to 15% develop into parathyroid carcinoma [1, 2]. We describe a young female patient with HPT-JT syndrome with recurrent PHPT, requiring consecutive surgical interventions, finally resulting in permanent hypoparathyroidism (hypoPT) with a challenging medical fine-tuning of the calcium-phosphate homeostasis.

Case Presentation

A 10 year-old female presented with a synchronous finding of hypercalcemia with elevated parathyroid hormone (PTH) and a common precursor B acute lymphoblastic leukaemia. Parathyroid localization studies showed an enlarged parathyroid at the lower pole of the left thyroid gland. However, given the active hematological disease treated with chemotherapy, parathyroid surgery was postponed. One year later, at a time of complete remission of the leukemia, an incidental finding of nephrocalcinosis on ultrasound was diagnosed. A selective parathyroidectomy (PTX) of the lower left pole of the thyroid gland was performed, resulting in normocalcemia. Histological examination showed a parathyroid adenoma without atypical features. At the age of 18, hypercalcemia reoccurred, and an enlarged parathyroid gland at the

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upper left thyroid pole was found. A second selective PTX was performed, again confirming a parathyroid adenoma without atypical features, however hypercalcemia persisted after surgery (Table 1). Gene panel testing (HaloPlex Agilent, custom design v2) targeting coding regions of known cancer predisposition genes was performed on peripheral blood-derived DNA and revealed a heterozygous germline variant LRG_507t1:c.25C > T(p.Arg9*) in the *CDC73* gene. This variant has been reported previously in patients with HPT-JT and was classified as pathogenic [3, 4].

Given the recurrent PHPT, the development of hypertension possibly related to hyperparathyroidism [5, 6], and the *CDC73*-associated parathyroid cancer risk, a totalisation PTX was performed at the age of 19. At pathological examination, an adenoma without atypical features was found in the upper right parathyroid, while the lower right parathyroid was normal. During follow-up, calcium regulation has remained challenging necessitating high doses of calcium and vitamin D analogues in the first 2 weeks post total PTX (suggestive of hungry bones syndrome), followed by multiple episodes of symptomatic hypocalcemia despite compliant intake of calcium supplements and active vitamin D analogues. Dose increases resulted in hypercalciuria. Association of a thiazide to increase renal calcium reabsorption led to hypokalaemia and symptomatic hypotension.

The patient has a history of uterine polyps, which can also be associated with this syndrome. Further screening reveals a fibroadenoma in the mandible.

Discussion

CDC73; OMIM*607393 encodes parafibromin, a ubiquitously expressed nuclear protein that acts as a transcriptional regulator in the RNA-polymerase associated factor-1 complex [3, 7, 8]. Parafibromin functions as a tumor suppressor by inhibiting cyclin D1 expression. In contrast, it may also act as an oncogenic factor by activating Wnt signaling [9].

Multiple *CDC73* variants have been described. The p.Arg9* variant in this case induces a stop codon within exon 1 and has been previously described as pathogenic in HPT-JT families. This variant is associated with variable expression and incomplete penetrance [3, 4]. Truncating variants are mainly associated with the classic phenotype of HPT-JT. High-impact pathogenic variants, defined as gross indels, splice site, frameshift, and nonsense variants, affecting the C-terminal domain were found to increase the risk of parathyroid carcinoma. No clear genotype–phenotype correlation has been demonstrated [7, 10]. According to Knudson's 'two-hit' hypothesis of tumor development, a second somatic hit, resulting in loss of heterozygosity, is needed for the development of a parathyroid tumor [8].

Penetrance of PHPT in patients with pathogenic *CDC73* variants at ages 25, 50, and 70 years was reported to be 8, 53, and 75%, respectively [11]. Mostly a single gland involvement is observed, but multiglandular involvement is present in 20% of patients. The risk of parathyroid carcinoma is considered to be 15–20%, which is much higher than in other monogenic forms of PHPT, such as in multiple endocrine neoplasia type 1 [10, 12]. The optimal surgical approach has not yet been established. According to the expert opinion of the 16th International Workshop on Multiple Endocrine Neoplasia in 2019, there is no role for prophylactic (total) PTX to prevent malignancy in carriers of germline *CDC73* variants who have no manifestation of parathyroid carcinoma [13]. Other studies suggest that selective PTX is preferred when imaging is concordant. Alternative approaches include intraoperative exploration of all glands with resection of those that appear abnormal. In general, the approach should be individualized due to inconclusive genotype–phenotype correlations and the lack of specific prognostic markers [2, 14].

The patient described here suffered from persistent PHPT after two selective parathyroidectomies based on concordant imaging, necessitating total PTX at the age of 19. In fact, since PHPT presented at a young age genetic testing was indicated at first diagnosis already. Whether or not this knowledge in an earlier stage would have influenced the surgical approach is not known. Finally, three out of four parathyroids were found to be adenomas without atypical features on histological examination. In case of multiglandular involvement, total PTX is often chosen, combined with auto-transplantation of normal parathyroid tissue into the non-dominant forearm. This latter approach is not advisable in HPT-JT due to the increased cancer risk [2, 15]. This case highlights the challenge the clinician encounters balancing the short- and long-term complications of a disturbed endocrine calcium-phosphate homeostasis against the elevated cancer risk. Nephrocalcinosis, secondary to PHPT-related hypercalciuria, and the development of hypertension (not explained by other causes) were both already evident in our patient at a young age. The persisting PHPT after removal of two parathyroid adenomas led to the multidisciplinary decision for a totalisation PTX, resulting in hypoPT, which in turn was challenging to control. Indeed, the conventional hypoPT treatment with supplementation of calcium and an active vitamin D analogue resulted in a complex balance between targeting low-normal serum calcium levels to avoid symptomatic hypocalcemia on the one hand and avoiding iatrogenic hypercalciuria in a patient with already pre-existing nephrocalcinosis on the other. A trial with a thiazide diuretic, even at low dosage, was not tolerated due to low serum potassium levels and symptomatic hypotension. Thiazides reduce urinary calcium excretion through both a direct tubular effect and by causing volume depletion.

Table 1 Biochemical parameters, imaging and medical treatment before and after repetitive parathyroid surgery

	Alb-corrected sCa	Phosphate	PTH (*intra-operative nadir*)	25-OHD	eGFR	uCa	Ca/creatinine clearance ratio	Imaging/*medical treatment*
	mmol/L	mmol/L	ng/L	µg/L	mL/min		%	
At diagnosis	3.29	1.25	153	17.5	47	2.76 mmol/L (spot urine)		• Neck US: hypoechoic nodule adjacent to caudal pole left thyroid, max. 10 mm • Parathyroid scintigraphy (MIBI/I123): no hot spot
6 m pre PTX	2.67	1.31	162	9.2	149	3.2 mmol/24 h	0.62	• Neck US: hypoechoic nodule adjacent to caudal pole left thyroid, max. 17 mm • Parathyroid scintigraphy (MIBI/I123): hot spot adjacent to caudal pole left thyroid • CT: refused by parents
1st selective PTX (lower left)	2.68	1.30	225 (*23*)		144	ND		
8 m post 1st PTX	2.34	1.44	33	25.1	131	ND		
10 m pre 2nd PTX	2.73	0.75	99	19.7	99	3.94 mmol/L (spot urine)		• Neck US: hypoechoic nodule adjacent to apical pole left thyroid, max. 11 mm • Scintigraphy (MIBI/I123): negative • CT: parathyroid adenoma apical pole left thyroid
2nd selective PTX (upper left)	2.81	0.47	179 (*87*)	18.5	127			
2 m post 2nd PTX	2.64	0.78	123		132	8.6 mmol/24 h	1.91	• Neck US: hypoechoic nodule adjacent to caudal pole right thyroid, max. 14 mm
1 m pre total PTX (lower + upper right)	2.83	0.59	161	17.9	131	ND		• Neck US: hypoechoic nodule adjacent to caudal pole right thyroid, max. 17 mm
Total PTX	2.77	0.58	153 (*11*)	21.7	130	ND		*Postop day 1 onward: Alfacalcidol 1.0 µg/d + CaCO3 2 g/d*
8 days post total PTX	1.83 (postoperative nadir) *Alfacalcidol 3.0 µg/d + CaCO3 5 g/d + Colecalciferol 25 000 U/m*							

Table 1 (continued)

	Alb-corrected sCa	Phosphate	PTH (*intra-operative nadir*)	25-OHD	eGFR	uCa	Ca/creatinine clearance ratio	Imaging/*medical treatment*
4 m post total PTX	2.36	1.14	< 5.5	24.4	101	9.4 mmol/24 h	3.16	*Alfacalcidol 2.5 µg/d + CaCO3 2 g/d + Colecalciferol 25 000 U/m*
16 m post total PTX	1.82	1.39	< 5.5	30.5	119	1.7 mmol/24 h	0.62	*Alfacalcidol 1.5 µg/d + CaCO3 1 g/d + Colecalciferol 25 000 U/2w*
42 m post total PTX	2.13	1.30	< 5.5	28.5	107	6.8 mmol/24 h	8.78	*Alfacalcidol 2.25 µg/d + CaCO3 1 g/d + Colecalciferol 25 000 U/2w*

25-OHD, serum 25-hydroxyvitamin D; eGFR, estimated glomerular filtration (calculated as a child via the creatinine-based "Bedside Schwartz" equation (2009), from PTX A adult age and use of CKD-EPI); ND, not determined; PTH, parathyroid hormone; PTX, parathyroidectomy; sCa, serum calcium; uCa, urinary calcium; US, ultrasonography

There are no studies available studying the effect of thiazides on established nephrocalcinosis in patients with PHPT. In a study involving young rats with established nephrocalcinosis treated with furosemide, chlorothiazide therapy did not result in the resolution of the nephrocalcinosis [16]. In patients with X-linked hypophosphatemia under treatment with vitamin D analogues and phosphate supplements with early-onset nephrocalcinoses, there was no progression of nephrocalcinosis after the initiation of thiazides, while progression was observed during the control period [17].

The development of PTH-analogues represents a significant evolution in the field of hypoPT management. The latest advancements involve prodrug formulations, such as TransCon PTH (palopegteriparatide), which has been recently EMA-approved, in which PTH(1–34) is transiently conjugated to a polyethylene glycol carrier molecule, providing stable PTH levels over 24 h after once daily subcutaneous injection. In adults with chronic hypoPT under conventional treatment, TransCon PTH maintained stable serum calcium levels and reduced the need for supplemental calcium and active vitamin D compared to placebo [18]. A post hoc analysis focusing on the longitudinal effect of palopegteriparatide on renal function revealed an improved renal function (eGFR) and a normalization of the mean 24-h urine calcium excretion. The effect on nephrolithiasis/nephrocalcinosis has not yet been determined [19]. In the patient presented here, with significant fluctuations in serum calcium and important hypercalciuria on conventional therapy, PTH-analogues could represent an elegant treatment but could not be administered in this case due to unavailability in Belgium.

Lifelong screening of other clinical manifestations related to HPT-JT syndrome is warranted. Ossifying fibromas are found in 5.4–15.4% of patients, and are mostly benign lesions with a low risk of malignant degeneration. Unlike the 'brown tumors', which can be observed in severe PHPT and are composed of multinucleated osteoclasts (giant cells), ossifying fibromas occur only in the maxilla and mandible, are composed of proliferating fibroblast stroma, and do not resolve after PTX. Treatment involves surgery in case of functional and cosmetic concerns. Monitoring is advised with orthopantomograms [2, 14, 20]. Uterine tumors are frequent and mostly benign [14]. In 15% of the cases, renal lesions occur, mostly consisting of cysts. Some patients develop hamartomas and rare renal tumors, such as Wilms's tumors and mixed epithelial-stromal tumors (MEST) [14]. Thyroid carcinoma, colon carcinoma, cholangiocarcinoma, chronic lymphatic leukemia, pancreatic adenocarcinoma, and pituitary cysts have also been described, however the association between these conditions and HPT-JT syndrome remains unclear [2]. In a recent narrative review describing retrospective cohorts and case series, no patients were found to suffer from leukaemia or lymphoma [14]. One case of chronic myeloid leukaemia and parathyroid adenoma has been reported [21]. In common precursor B acute lymphoblastic leukaemia, like in the patient described here, the association with variants in the *CDC73* gene is not clear. B-ALL is often accompanied by somatic chromosomal rearrangements. International disease registers are important to increase our insight in the clinical manifestations, genotype–phenotype correlations, and management of this rare syndrome.

Conclusion

It is important for clinicians to recognise this rare syndrome with high penetrance of both early-onset and recurrent PHPT and increased risk for parathyroid carcinoma.

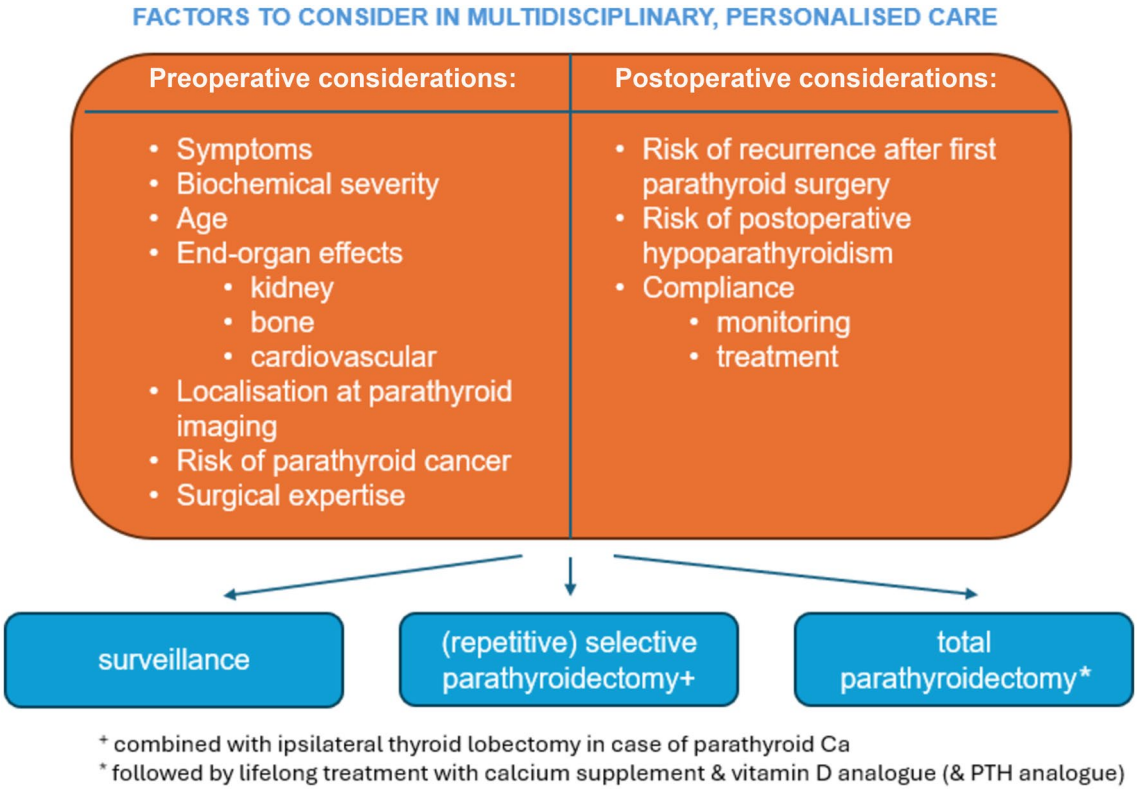

Fig. 1 Management of CDC73-related primary hyperparathyroidism

As shown in Fig. 1, timing and extent of PTX, as well as post-surgical hypoPT management are challenging and require multidisciplinary discussion taking into account factors such as young age, parathyroid cancer risk, risks and complications of PHPT as well hypoPT.

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Declarations

Conflict of interest The authors declare that they have no confict of interest.

Informed Consent The participant has consented to the submission of the case report to the journal.

Ethical Approval Not applicable.

Human and Animal Rights Human and Animal Rights This study did not involve any animals.

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