Hyperparathyroidism-Jaw Tumor Syndrome

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Contents

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Case Presentation

A 35-year-old woman presented at the emergency room due to confusion and vomiting. Past medical history includes gastritis, femur fracture, and two miscarriages. At physical examination, dehydration signs were observed. The serum calcium was 15.4 mg/dl (normal value, 9–10.5 mg/dl) and was admitted into the internal medicine unit; the PTH level was 969 pg/ml (normal value, 15–70 pg/ml); the vitamin D25OH level was normal; the 24-hour urine calcium and calcium clearance-to-creatinine ratio were within normal range. After 24 hours of initial treatment with rehydratation and loop diuretics, calcium level decreased to 13.6 mg/dl. Neck ultrasound and SestaMIBI scintigraphy were performed, concordantly suggesting the presence of a left parathyroid tumor.

Questions

1. In the operating room, a left lateral minimally invasive approach using a 20 mm skin incision was performed, and a 4 cm superior parathyroid gland was found grossly adherent to the thyroid. What surgical procedure is indicated?
   (a) Continuing with minimally invasive surgery and resection of the parathyroid tumor.
   (b) Continuing with minimally invasive surgery and removal of both left parathyroid glands.
   (c) Enlargement of incision to standard cervicotomy and resection of the parathyroid tumor en bloc with the ipsilateral thyroid lobe and the surrounding lymph fatty tissue.
   (d) Closure of the incision and external radiotherapy.
   (e) Closure of the incision and medical treatment with cinacalcet (30 mg every 12 hours).
2. The definitive histology report described a parathyroid carcinoma with extensive local invasion and negative immunohistochemical staining for parafibromin. Another parathyroid was founded with cystic changes. What is the most probable diagnosis?
   (a) Sporadic parathyroid carcinoma.
   (b) Hereditary parathyroid carcinoma in the context of MEN 1.
   (c) Hereditary parathyroid carcinoma in the context of MEN 2.
   (d) Hereditary parathyroid carcinoma in relation to hyperparathyroidism-jaw tumor (HPT-JT) syndrome.
   (e) Familial hypocalciuric hypercalcemia.
3. The diagnosis of HPT-JT syndrome must be confirmed by genetic testing. The gene responsible for HPT-JT is:
   (a) *SDH-B.*
   (b) *CDC73.*

(c) *RET*.
(d) *BRAF*.
(e) *TP53*.

4. What is the prevalence of jaw tumors in HPT-JT?
   (a) 30%
   (b) 50%
   (c) 60%
   (d) 70%
   (e) 100%
5. Most of the reported jaw tumors in HPT-JT syndrome are:
   1. Ossifying fibromas.
   2. Radiolucent lesions at panoramic X-ray dental imaging.
   3. Malignant.
   4. Located in maxilla or mandible.
   5. Similar to brown tumors.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (2) and (5) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
6. The most common clinical feature of HPT-JT syndrome after pHPT is:
   (a) Jaw tumors.
   (b) Renal involvement.
   (c) Uterine involvement.
   (d) Thyroid carcinoma.
   (e) Colon carcinoma.
7. Women with HPT-JT syndrome often have a history of:
   1. Miscarriage.
   2. Impaired ability to bear children.
   3. Hysterectomy due to menorrhagia.
   4. Benign tumors.
   5. Malignant tumors.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
8. What statements regarding renal involvement in HPT-JT syndrome are correct?
   1. The kidney is involved in 70% of the patients.
   2. Wilms' tumor is usually identified in the fifth decade of life.
   3. Cystic kidney disease is the most common manifestation of this syndrome.
   4. Papillary renal cell carcinoma is frequent.
   5. Surgery usually is not needed.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (2) and (3) and (4) are correct.

(c) Only (2) and (3) are correct.
(d) Only (5) is correct.
(e) All are correct.

9. The screening for *CDC73* germline mutations is indicated in:
   1. Familial pHPT.
   2. pHPT with old age onset.
   3. Malignant parathyroid tumors.
   4. pHPT and ossifying jaw tumors.
   5. pHPT and uterine tumors.
   (a) Only (1) and (2) are correct.
   (b) Only (1) and (3) are correct.
   (c) Only (1) and (3) and (4) and (5) are correct.
   (d) Only (5) is correct.
   (e) All are correct.
10. In *CDC73* germline mutation carrier families, the screening for primary hyperparathyroidism should be performed before the age of:
   (a) 4
   (b) 10
   (c) 15
   (d) 20
   (e) 25
11. The initial rate of parathyroid benign single gland involvement in HPT-JT syndrome patients is:
   1. Higher than MEN 1.
   2. Higher than MEN 2.
   3. Lower than MEN 1.
   4. Lower than MEN 2.
   5. Similar to MEN 1 and MEN 2.
   (a) Only (1) is correct.
   (b) Only (1) and (4) are correct.
   (c) Only (3) and (4) are correct.
   (d) Only (2) and (3) are correct.
   (e) Only (5) is correct.
12. The recurrence rate of HPT-JT-related pHPT after surgery is:
   (a) 10%
   (b) 12%
   (c) 15%
   (d) 25%
   (e) 50%
13. The optimal surgical approach to HPT-JT-related pHPT is:
   1. Bilateral exploration with prophylactic total parathyroidectomy.
   2. Bilateral exploration with prophylactic subtotal parathyroidectomy.
   3. Bilateral exploration with selective removal of abnormal gland(s).
   4. Focused exploration with selective parathyroidectomy according to preoperative imaging.

5. If parathyroid carcinoma is suspected wide en bloc resection of the mass with the ipsilateral thyroid lobe, the ipsilateral normal parathyroid, and surrounding lymph fatty tissue.
   (a) Only (1) and (2) and (3) are correct.
   (b) Only (4) is correct.
   (c) Only (4) and (5) are correct.
   (d) Only (3) and (4) and (5) are correct.
   (e) Only (2) and (3) and (4) and (5) are correct.

14. With respect to surgical treatment of tumors associated with HPT-JT, the following is correct:
   1. Complete surgical removal of ossifying fibromas of the jaw is recommended.
   2. For renal tumors, nephron-sparing surgery rather than radical surgery is advocated.
   3. For renal tumors, radical surgery rather than nephron-sparing surgery is advocated.
   4. Renal tumors may be multiple and bilateral, and patients would require multiple surgeries over their lifetime.
   5. Women with menorrhagia may require hysterectomy at early age.
      (a) Only (1) and (2) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (1) and (2) and (4) and (5) are correct.
      (e) Only (1) and (3) and (4) and (5) are correct.

15. Our patient should undergo the following screening:
   1. Biannual serum calcium and PTH and parathyroid ultrasound.
   2. Panoramic X-ray dental imaging at least every 5 years.
   3. Renal ultrasound, RM, or CT scan at least every 5 years.
   4. Colonoscopy at least every 2 years.
   5. Regular gynecologic care including pelvic ultrasound.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (2) and (3) and (5) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.

35.1 Introduction

Primary hyperparathyroidism (pHPT) is a relatively common disease and in 90% occurs as a sporadic form. During the last few decades, different hereditary syndromes causing pHPT have been described, reaching 10% of cases. Most of these familial cases occur in association with multiple endocrine neoplasia (MEN). Other syndromes like

hyperparathyroidism-jaw tumor syndrome (HPT-JT) are very uncommon. The earliest report of some manifestations of the syndrome probably occurred in 1958, when Jackson reported a kindred with autosomal dominant transmission of hypercalcemia with seven pHPT members including four fibro-osseous jaw tumors [1]. Dinnen contributed to a preliminary formulation of the syndrome in 1977 reporting a family with benign and malignant parathyroid tumors and ossifying fibroma of the jaw [2].

In recent years, major advances have been made in the understanding of the molecular pathogenesis of HPT-JT syndrome. Szabo mapped the gene in 1995 to 1q21-q31 [3], and finally Carpten in 2002 identified the gene responsible as *HRPT2* (later named *CDC73*) and its encoded product parafibromin [4].

The present chapter emphasizes clinical characteristics and management of HPT-JT syndrome.

35.2 Etiology

HPT-JT syndrome is linked to germline inactivating mutations in the tumor suppressor gene *CDC73*, which contains 17 exons on chromosome *1q31.2* and encodes for a predominantly nuclear, 531-amino-acid protein named parafibromin [5]. Parafibromin is ubiquitously expressed in many organs, including kidney, liver, stomach, renal cortex tubules, and the pars intermedia of the hypophysis [6]. Parafibromin is associated with other proteins in the polymerase-associated factor (PAF1) and induces the downregulation of cyclin D1 expression and direct interaction with ß-catenin, resulting in the activation of transcription of target genes. Studies of the PAF1 complex in yeast and *Drosophila*, as well as in mammalian cells, have revealed that parafibromin induces histone modification, transcription elongation, and chromatin remodeling [7–9].

About 75% of HPT-JT patients have germline *CDC73* mutations within the coding region, and the majority (>80%) are frameshift or nonsense mutations that determine the functional loss of parafibromin by causing a premature truncation of this protein or a rapid loosing of the translated protein via nonsense-mediated mRNA decay. Therefore, the expression of parafibromin is completely lost in HPT-JT-associated tumor tissues. The remaining 25% of HPT-JT patients may have abnormalities in *CDC73* promoter regions, whole exon or gene deletions, mutations in unidentified genes, or epigenetic modifications [10].

As all tumor suppressor genes, the first mutation is usually inherited by one of the parents or, in very rare cases, developed de novo at embryonic level. A second and novel acquired somatic mutation or a loss of heterozygosity in HPT-JT tumor-related tissues is needed, consistent with Knudson's two-hit hypothesis [4–13].

35.3 Clinical Presentation

HPT-JT is a rare autosomal dominant disorder with incomplete penetrance. It is characterized by the development of parathyroid tumors, ossifying fibromas of the mandible and maxilla, cystic and neoplastic renal abnormalities, and hyperplastic and neoplastic uterine involvement [14, 15].

No genotype-phenotype correlations have been fully established to date [16, 17]. However, it has been suggested that missense mutations are more likely to be associated with the disease without typical associated features (familial isolated pHPT), whereas mutations causing gross parafibromin disruption are more likely associated with the classical HPT-JT phenotype [12].

35.3.1 pHPT

pHPT is the main clinical feature and is found in almost 100% of mutation carriers typically in late adolescence or early adulthood. According to the literature review reported by Torresan and Iacobone in 2019 including 154 HPT-JT kindred and 365 patients affected by pHPT, the earliest age of hypercalcemia is 7 years [18, 19]. The median age of diagnosis of pHPT was 27 years, and the mean age ranged between 32 and 36 years [20–22]. In a report of three large kindred, *CDC73*-related pHPT occurred in 87.5% of cases among patients older than 20 years [19], while penetrance of pHPT in a Dutch population was shown to increase with age (8%, 53%, and 75% at age of 25, 50, and 70, respectively) [22].

A single gland parathyroid involvement had been reported more frequently (86.1%) than in other forms of hereditary pHPT like MEN1. Multiglandular involvement occurs rarely at initial surgery (13.9% of cases), but it may affect other glands at long-term follow-up (over decades) in many patients [21–25].

HPT-JT is associated with a higher prevalence of atypical adenomas and parathyroid carcinoma which can be found in 23% of the cases [4, 6–13, 15, 17, 19–22, 24–90], unlike other forms of hereditary pHPT in which parathyroid tumors are typically benign [4, 11]. Cystic changes of parathyroids were originally described as a common histological feature in HPT-JT (previously called familial cystic parathyroid adenomatosis), but it is actually found in only a quarter of the parathyroid tumors (Fig. 35.1) [25]. The adenomas may be cystic, either with micro- or macrocysts, and similar cystic changes can also be present in normal parathyroid glands in these patients [30]. The diagnosis of parathyroid carcinoma in HPT-JT is based on the standard criteria of extensive local invasion and/or metastasis.

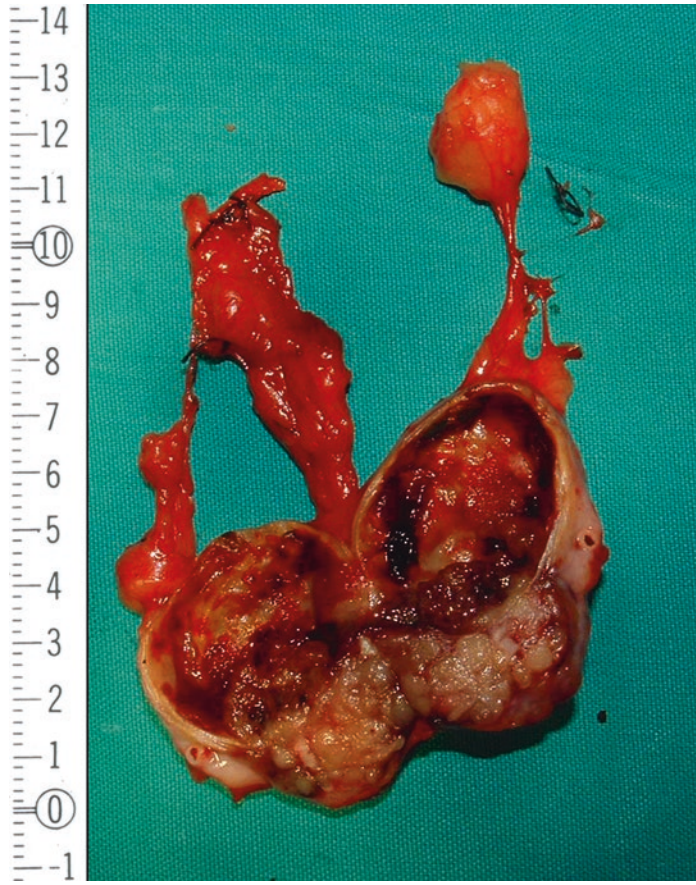


Fig. 35.1 Surgical specimen: parathyroid carcinoma in hyperparathyroidism-jaw tumor syndrome. The parathyroid carcinoma (sectioned) presents cystic and regressive changes. (Reproduced with permission from [91])

pHPT is usually mild or asymptomatic, but, in case of parathyroid carcinoma, severe hypercalcemic crisis may occur [91, 92]. Hence, in the presence of abnormal high serum calcium concentration (>12 mg/dL) and iPTH levels (>3 times the upper limit of normal) and parathyroid lesions larger than 3 cm, parathyroid carcinomas should be suspected. On the other hand, nonfunctioning parathyroid malignancy may very rarely occur in *CDC73*-related disorder [4, 44, 90]. Moreover, parathyroid carcinoma can present as a palpable neck mass associated with hoarseness, difficulty speaking or swallowing, muscle weakness, nausea/vomiting, altered mental status, bone pain, and/or pathologic bone fractures [4, 22, 29, 32, 48].

35.3.2 Jaw Tumors

Despite the nomenclature of the syndrome, jaw tumors may be found only in approximately one third of cases. Jaw tumors in

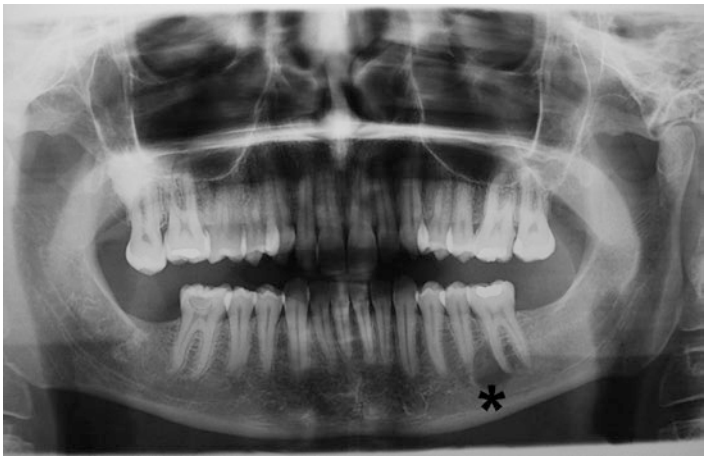


Fig. 35.2 Orthopantomographic X-ray: Ossifying fibroma of the left ramus of the mandible (*) in a young patient with hyperparathyroidism-jaw tumor syndrome. (Reproduced with permission from [91])

HPT-JT are fibro-osseous lesions that typically involve maxilla or mandible often prior to the third decade of life.

Most of the reported jaw tumors in HPT-JT syndrome are ossifying fibromas and benign and generally slow-growing tumors arising from the periodontal ligament in molar or premolar areas [3]. Jaw tumors are usually radiographically radiolucent compared to the mixed radiolucent/radiopaque lesions in the sporadic variants [41]. Sometimes they present with an enlarging visible or palpable mass, but, in other cases, they are only detected on dental X-ray imaging (Figs. 35.2, 35.3, and 35.4). Although benign, ossifying fibroma can disrupt normal dentition, impair breathing, and cause functional and cosmetic symptoms. Ossifying fibroma in HPT-JT syndrome may be bilateral or multifocal and may recur.

The ossifying fibromas are composed of a relatively avascular cellular fibroblast-rich stroma, sometimes with a prominent storiform pattern admixed with bone trabeculae and/or cementum-like spherules. The histology is different from brown tumors of osteitis fibrosa cystica associated with pHPT.

35.3.3 Renal Involvement

The kidney is involved in approximately 20% of patients with HPT-JT. Cystic kidney disease is the most common renal manifestation of this syndrome, but some patients often develop hamartomas and rare renal tumors, such as adult Wilms' tumors and mixed epithelial-stromal tumors (MEST). The Wilms' tumors in HPT-JT have been identified in the fifth decade of life, are usually bilateral, are poorly circumscribed, are smaller than in the classical childhood form, and do not usually metastasize. Moreover, they have also distinctive histo-

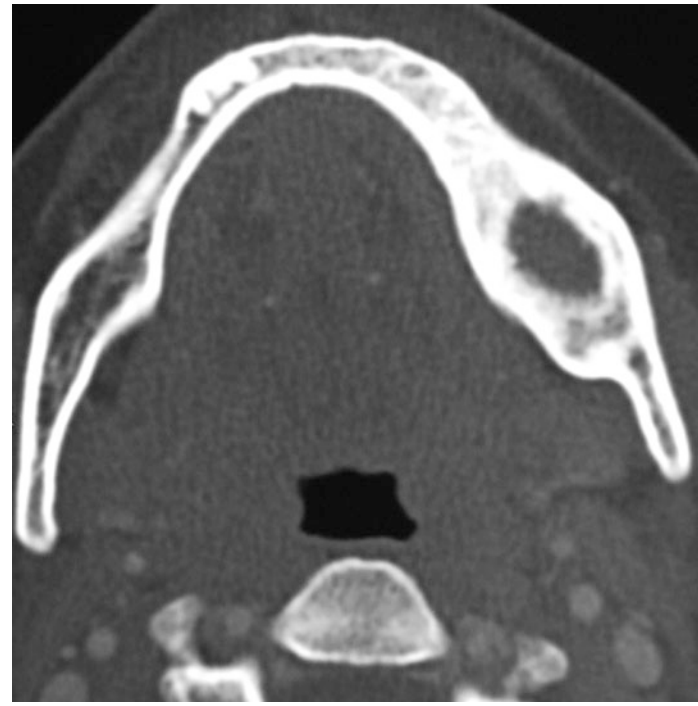


Fig. 35.3 CT scan: Ossifying fibroma of the left ramus of the mandible in a young patient with hyperparathyroidism-jaw tumor syndrome. (Reproduced with permission from [91])

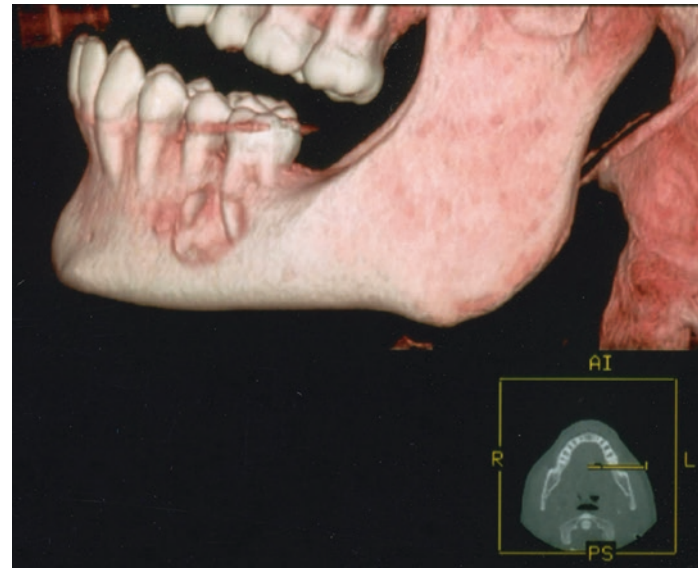


Fig. 35.4 CT scan (reconstruction): Ossifying fibroma of the left ramus of the mandible in a young patient with hyperparathyroidism-jaw tumor syndrome. (Reproduced with permission from [91])

logical features from the childhood form, such as a low number of mitoses, lack of necrosis and hemorrhages, large mesenchymal components, and the presence of cysts [93]. The association between MEST, a predominantly benign tumor characterized by both epithelial and spindle cell stromal components, and HPT-JT syndrome is poorly reported in the literature. Papillary renal cell carcinoma has very rarely been described in HPT-JT [21, 94].

35.3.4 Uterine Involvement

Uterine tumors have been described in association with HPT-JT and are the most common clinical feature after pHPT, affecting more than 50% of HPT-JT female patients in some cohorts [12]. Uterine tumors are frequently accompanied by menorrhagia and often require hysterectomy at an early age (mean 35 years). Affected women often have a history of miscarriage and a significantly impaired ability to bear children when compared with their unaffected female relatives [42].

Histological analysis of the uterine specimens revealed both benign and malignant tumors, such as adenomyosis, adenofibromas, leiomyomas, endometrial hyperplasia, adenosarcomas, or tumors arising from the Müllerian duct system.

35.3.5 Other Features

Thyroid carcinoma, thyrotoxicosis, colon carcinoma, cholangiocarcinoma, chronic lymphatic leukemia, pancreatic adenocarcinoma, and pituitary cyst have also been described, but the association between these tumors and HPT-JT syndrome remains unclear [21, 50, 94].

35.4 Diagnosis

HPT-JT is uncommon, but the exact incidence and prevalence rates are unknown and might be underestimated. In most families, parathyroid tumors are the only lesions at presentation, but when jaw tumors are present in an individual or in a kindred, the diagnosis is strongly suggested [21, 24, 25].

Given the extreme rarity of parathyroid carcinoma in the general population and in other hereditary syndromes associated with hypercalcemia, parathyroid malignancy should be another important clue to the diagnosis of HPT-JT [4]. About 20–30% of patients with apparently sporadic parathyroid carcinomas in fact have germline mutations in *CDC73*, indicating occult HPT-JT syndrome [29, 32].

Parathyroid adenomas and carcinomas and other associated tumors arising in the setting of HPT-JT usually demonstrate negative immunohistochemical staining for parafibromin that is considered a biomarker for *CDC73* or an indirect method to recognize HPT-JT syndrome patients. Nevertheless, *CDC73* immunochemistry should be interpreted with care because some *CDC73* mutations are not associated with loss of *CDC73* expression and therefore normal parafibromin immunohistochemistry does not exclude the diagnosis of HPT-JT [24, 95, 96]. Furthermore, it should be noted that parafibromin is also absent in 60–70% of sporadic parathyroid cancers, 20% of sporadic atypical adenomas, and 1–5% of sporadic parathyroid adenomas.

Finally, the diagnosis of HPT-JT must be confirmed by genetic testing. The screening for *CDC73* germline mutations is indicated in the presence of familial pHPT; pHPT with young age onset (<35 years); multiglandular involvement; cystic, atypical, or malignant parathyroid tumors; or coexistence ossifying jaw fibroma and renal or uterine tumors [12, 29] (▶ Box 35.1).

Box 35.1 Indication for *CDC73* genetic testing

- Personal or family history of HPT-JT.
- Young age onset of primary hyperparathyroidism (<35 years).
- Primary hyperparathyroidism caused by cystic, atypical, or malignant parathyroid involvement.
- Primary hyperparathyroidism due to multiglandular parathyroid involvement.
- Coexistence of primary hyperparathyroidism and ossifying jaw fibroma and renal or uterine tumors.

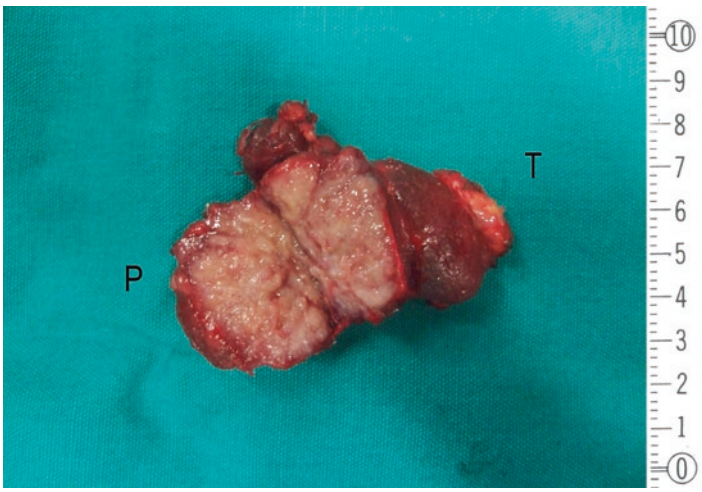
Following the initial diagnosis, it is necessary to establish the extent of the disease by evaluating standard end organ damage of pHPT, but also the associated jaw tumors and renal and uterine lesions should be systematically searched [26, 28].

Genetic screening for identifying gene carriers should be performed in all family members to start a specific HPT-JT screening program [31]. In *CDC73* mutation carrier families, the screening should be performed also in children before the age of 10, since malignant pHPT has been sometimes described at very early age.

35.5 Treatment

Most patients with a diagnosis of parathyroid adenoma can be cured by surgery, but about 25% of cases may recur [21, 24]. Given the rarity of the disease and the heterogeneity of the phenotype, the optimal surgical approach to *CDC73*-related pHPT has not yet been established and remains controversial,

varying between bilateral or targeted neck exploration and extensive or limited parathyroidectomy [12]. In the past, prophylactic total parathyroidectomy has been suggested to minimize the risk of recurrences and parathyroid carcinoma in HPT-JT syndrome and therefore to obtain a definitive cure. However, total parathyroidectomy is clearly not always successful and leads to permanent postsurgical hypoparathyroidism with difficult treatment especially in young patients and increased morbidity. For these reasons, subtotal parathyroidectomy or total parathyroidectomy with autotransplantation has been suggested for HPT-JT-related pHPT as for other variants of hereditary pHPT, even if autotransplantation has been implicated in tumor dissemination in case of malignant involvement [90]. Moreover, in contrast with other variants of hereditary pHPT, a high prevalence of uniglandular involvement at onset has been reported. For that reason, when malignant parathyroid involvement is unlike, targeted approaches (even with minimally invasive procedures with minimal tissue dissection) and selective parathyroid excisions have recently been proposed in the same setting of sporadic pHPT. This strategy is aimed to achieve, whenever possible, the longest possible normocalcemia without permanent hypoparathyroidism, minimizing surgical morbidity and facilitating eventual future surgery for recurrent disease [21]. On the other hand, if parathyroid carcinoma is clinically suspected (large tumor at imaging, palpable neck mass, biochemical and clinical presentation of severe pHPT), wider en bloc resection of the mass with the ipsilateral thyroid lobe (◘ Fig. 35.5), possibly also including the ipsilateral normal parathyroid and the surrounding lymph fatty tissue, should be performed, in order to avoid tumor



◘ **Fig. 35.5** Surgical specimen: parathyroid carcinoma. The parathyroid carcinoma (P, sectioned) has been removed en bloc with the ipsilateral thyroid lobe (T)

seeding and achieve a "complete unilateral parathyroidectomy" and finally minimize the risk of reoperation in a scarred area [21, 88–91].

However, the strategy remains controversial. In 2008, Sarquis et al. observed, in a series of 11 *CDC73* germline mutated patients from three kindred, a synchronous multiglandular involvement at initial operation in 54.5% of cases, parathyroid malignancy in 9%, and an overall persistence/recurrence rate of 80%; thus, a bilateral exploration with subtotal parathyroidectomy was suggested as the initial approach [25].

In 2014, Mehta et al. suggested a bilateral neck exploration with selective removal only of abnormal gland(s) in HPT-JT syndrome patients, given the high frequency of benign single-gland involvement (69%) and relatively low rate of recurrences (20%) found in their multicentric cohort of 16 individuals from seven HPT-JT families [24].

More recently, Iacobone et al. reported a 95% rate of single gland involvement at initial diagnosis, in a cohort of 20 HPT-JT syndrome patients from five large families. Therefore, in case of concordant results of preoperative functional and anatomical tests suggesting a single gland involvement and in the absence of suspicion of parathyroid malignancy, a focused approach with selective parathyroidectomy was proposed. A subtotal parathyroidectomy was recommended in case of absent or discordant preoperative localization because of the increased risk of multiglandular involvement and recurrent pHPT [88]. However, long-term follow-up is indicated for all patients because of the risk of recurrent disease.

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Cinacalcet hydrochloride, a calcimimetic that binds to the calcium-sensing receptor, has been approved for the long-term control of hypercalcemia secondary to pHPT in individuals who are unable to undergo parathyroidectomy and for the treatment of parathyroid carcinoma-related hypercalcemia, in case of unresectable or metastatic disease. For severe or symptomatic hypercalcemia, an infusion of bisphosphonates, steroids, or dialysis can be necessary for acute management [18].

In relation to ossifying fibromas of the jaw, a complete surgical removal is the recommended treatment based on the size, location, and symptoms of the lesion. Individuals with a history of jaw tumors should be followed closely because of the possibility of recurrence [97].

With respect to renal involvement, HPT-JT patients may be at risk for multiple and bilateral renal tumors potentially requiring multiple renal surgeries over their lifetime. Sarcomatoid differentiation and metastatic spread is rare. Surgery represents the treatment of choice [98]. Nephron-sparing surgery rather than radical surgery should be preferred, whenever possible, in order to preserve renal function.

Finally, no treatment guidelines for uterine manifestations associated with HPT-JT syndrome have been proposed to date [18]. Given the occurrence of both benign and malignant

involvement, individuals with evidence of a uterine tumor should be managed by a gynecologist with a tailor-made treatment. In case of malignancy or in case of severe recurrent menorrhagia, hysterectomy even at an early age (mean 35 years) may be required.

35.6 Surveillance

Even if there are no well-established surveillance guidelines, it has been suggested that *CDC73* mutation carriers should undergo a specific screening [18] including an evaluation of serum calcium and PTH for pHPT screening at least every 6 months, possibly after the age of 5 with periodic parathyroid ultrasound examination; panoramic X-ray dental imaging at least every 5 years; and monitoring for kidney lesions by periodic renal ultrasound examination, magnetic resonance imaging, or computed tomography scan at least every 5 years, starting at age of diagnosis. Moreover, starting at reproductive age, women with a *CDC73*-related disorder should undergo regular gynecologic care, including pelvic ultrasound examination with eventually further imaging studies if clinically indicated (Table 35.1).

Table 35.1 Clinical features, treatment, and follow-up of HPT-JT

Phenotype	Treatment	Follow-up (frequency)
Primary hyperparathyroidism	Focused parathyroidectomy (in case of preoperatively suspected uniglandular involvement); subtotal or total parathyroidectomy (with/without autotransplantation, in case of suspicion of multiglandular involvement); en bloc resection of the parathyroid tumor with the ipsilateral thyroid lobe, including the ipsilateral normal parathyroid and the surrounding lymph fatty tissue (in case of suspicion of parathyroid carcinoma)	Serum calcium and PTH evaluation, possibly starting after the age of 5 and periodic parathyroid ultrasound examination (every 6 months)
Ossifying jaw fibroma	Radical excision	Panoramic X-ray dental imaging or computed tomography at least every 5 years
Uterine tumors	Uterine polyps excision, hysterectomy	Regular gynecologic care, including pelvic ultrasound examination with eventual further imaging studies if clinically indicated, starting at the reproductive age, at least every 5 years
Renal tumors	Variable	Kidney lesions monitoring by periodic renal ultrasound examination, magnetic resonance imaging, or computed tomography scan at least every 5 years

Answers to the Questions

1. (c); 2. (d); 3. (b); 4. (a); 5. (b); 6. (c); 7. (e); 8. (c); 9. (c); 10. (b); 11. (a); 12. (d); 13. (e); 14. (d); 15. (c).

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