Clinical case

Hyperparathyroidism-jaw tumor syndrome: A case report

Syndrome hyperparathyroïdie primaire – tumeur de la mâchoire : à propos d’un cas

N. Rekik a,∗, B. Ben Naceur a, M. Mnif a, F. Mnif a, H. Mnif b, T. Boudawara b, M. Abid a

a Service d’endocrinologie et diabétologie, CHU Hédi Chaker, route de l’Ain, CP 3029 Sfax, Tunisia
b Service d’anatomopathologie, CHU Habib Bourguiba, route de l’Ain, Sfax, Tunisia

Available online 25 November 2009

Résumé


© 2009 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Hyperparathyroïdie primaire ; Tumeur mandibulaire ; Gène HRPT2

Abstract

We report the clinical and genetic findings in a 23-year-old woman with hyperparathyroidism-jaw tumor syndrome (HPT-JT). The patient had a family history of primary hyperparathyroidism (PHPT) and uterine fibroma in her mother. The patient presented muscle weakness. The diagnosis of PHPT was confirmed by an elevated parathyroid hormone level above 1450 pg/ml with hypercalcemia and hypercalciuria. X-ray radiographies showed a radiolucent lesion in the right body of the mandible. Bilateral neck exploration was performed. An inferior right parathyroidectomy, a left thyroid lobectomy with isthmectomy and thymectomy were carried out. Histopathological examination of the specimen showed a diffuse hyperplasia of the parathyroid principal cells. The association of PHPT with a right jaw tumor and uterine fibroma suggested the diagnosis of HPT-JT syndrome. Mutation screening of HRPT2 gene was carried out and identified a germline mutation, consisting in a base deletion in exon 1, 85delG, inducing a frameshift. The diagnosis of HPT-JT syndrome is clinically important because of its hereditary component and its high risk of parathyroid malignancy, making a genetic inquiry necessary.

© 2009 Elsevier Masson SAS. All rights reserved.

Keywords: Primary hyperparathyroidism; Jaw neoplasm; HRPT2 gene

1. Background

Primary hyperparathyroidism (PHPT) is usually a sporadic disorder, but in a minority of cases (<10%), it is part of hereditary syndromes, namely multiple endocrine neoplasia type 1 (MEN1) and 2A (MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia (FHH), or familial isolated hyperparathyroidism (FIHP).

HPT-JT syndrome was first documented by Jackson who reported multiple cases of PHPT and jaw tumors in three generations of the same family [1]. This syndrome is an autosomal dominant disorder characterized by hyperparathyroidism...
(parathyroid adenoma or carcinoma) (90%), fibro-ossifying jaw tumors (30%), and renal cysts (10%) [2–6].

Uterine tumors are associated in 40% of female cases [7].

The inactivation of the HRPT2 gene is associated with the pathogenesis of hereditary HPT-JT syndrome. The HRPT2 gene is ubiquitously expressed. It consists of 17 exons and encodes a predicted protein of 531 amino acids called parafibromin. Parafibromin is ubiquitously expressed and is a member of the human PAF1 complex, important for histone methylation, transcription elongation and 3’ end processing [2–8]. Parafibromin has three possible nuclear localization signals. Recent data support a possible contribution of parafibromin outside the nucleus through its interaction with actins and actin bundling/cross-linking [3].

Allelic loss at 1q24–q32 have been identified in some but not all parathyroid tumors associated with HPT-JT syndrome, suggestive of a tumor suppressor role for HRPT2 [1–8]. Antiproliferative properties of parafibromin were suggested by its strong effect on the inhibition of cyclin D1 expression [2].

This report describes a case of HPT-JT syndrome found in the investigation of PHPT.

2. Case report

The proband, a 23-year-old woman, was referred for evaluation of muscle weakness.

This patient had a family history of primary hyperparathyroidism and uterine fibroma in her mother. The disease in the mother had been revealed at the age of 35 years, by muscle weakness and walking difficulties. She had been operated for her hyperparathyroidism. Surgical exploration and histopathological examination of the specimen had shown a single left inferior parathyroid adenoma of 2 cm depending on principal cells. The association between PHPT and uterine fibroma suggested the diagnosis of HPT-JT syndrome in the mother. She was not screened for the HRPT2 mutation however, because she died a few years before the exploration of her daughter’s condition.

Our patient had a personal history of left ectopic kidney, in pelvic position, polycystic ovaries treated by bilateral drilling, and uterine fibroma treated by myomectomy.

As her mother, the patient presented muscle weakness and walking difficulties. Neurologic examination revealed a motor deficiency predominant in the lower limbs without abnormal reflexes or sensorial disorders. Electromyography showed a pure axonal motor deficiency predominant in the lower limbs. Muscle biopsy was normal. The patient weighed 64 kg with a height of 156 cm. The body mass index was 25 kg/m². The rest of the physical examination was normal.

Biochemical screening before surgery is given in Table 1.

The diagnosis of PHPT was confirmed by an elevated parathyroid hormone level above 1450 pg/ml (normal range 11–62 pg/ml), using a radioimmunometric assay. Vitamin D assay was not performed.

X-ray radiographies showed diffuse bone hypertransparence and brown tumors of the right humerus (Fig. 1), the right femur (Fig. 2) and the two clavicles. In addition, a radiolucent lesion in the right body of the mandible was identified corresponding probably to an ossifying fibroma (Fig. 3).

Abdominal ultrasonography revealed the presence of nonobstructive bilateral nephrolithiasis without cysts or tumors in the kidneys. Bone densitometry showed severe osteoporosis, with T score at −5 S.D.

During her stay in hospital, the patient suffered from a pathological fracture of both femoral necks.

Ultrasonography of the neck showed double inferior parathyroid adenomas measuring 27 mm in the right gland and 43 mm in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Time course of biochemical parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>4 days after surgery</td>
</tr>
<tr>
<td>Calcemia</td>
<td>2.8</td>
</tr>
<tr>
<td>N: 2.25–2.55 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Phosphoremia</td>
<td>0.68</td>
</tr>
<tr>
<td>N: 0.5–2 mmol/l</td>
<td></td>
</tr>
<tr>
<td>24 h calciuria</td>
<td>7 mmol/24h</td>
</tr>
<tr>
<td>&lt;0.1 mmol/kg/24 h</td>
<td></td>
</tr>
<tr>
<td>Alcaline phosphatase</td>
<td>1136</td>
</tr>
<tr>
<td>N: 36–120 UI/l</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>&gt;1450 pg/ml</td>
</tr>
<tr>
<td>N: 11–62 pg/ml</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Brown tumor of the right humerus.
Tumeur brune de l’humérus droit.
the left one with cystic and solid components. Adenomas were hypervascular in the Doppler.

Bilateral neck exploration was performed. Surgical exploration showed an inferior right parathyroid adenoma measuring 3 cm and a second one in ectopic position in the left lobe of the thyroid gland. An inferior right parathyroidectomy, a left thyroid lobectomy with isthmectomy and thymectomy were carried out.

Histopathological examination of the specimen showed a diffuse hyperplasia of parathyroid principal cells (Figs. 4 and 5) in both parathyroid and ectopic lesions without indicators of malignancy, and a benign multinodular goiter of the left thyroid lobe. The resected thymus tissue was normal.

After surgery, there was a period of severe hypocalcemia consistent with a hungry bone syndrome (Table 1). In addition, surgery was complicated by septicemia and pulmonary emboli.

The patient took vitamin D and calcium supplementation, antibiotics and anticoagulant treatment. Her condition worsened and she died 38 days after the surgery.

Her death was attributed to a septic shock and a hemorrhagic cerebral accident.

The association of PHPT with a right jaw tumor and uterine fibroma suggested the diagnosis of HPT-JT syndrome. Mutation screening of HRPT2 gene was carried out in the patient, without informed consent taking into account the clinical status of the patient. Peripheral blood leukocyte was studied in the department of molecular genetics of Lyon, Edouard-Herriot hospital group, by professor Calender and his collaborators. The HRPT2 gene (OMIM*607393) mutation, identified as a germline mutation, consisted of a base deletion in exon 1, 85delG. This mutation was predicted to cause premature termination of the protein (GLU39FSX) (607393.0014) leading to impaired parafibromin function due to a frameshift.

3. Discussion

The combination of PHPT and jaw ossifying fibroma is typical of the HPT-JT syndrome. The essential features of
PHPT are a parathyroid adenoma and ossifying fibromas of the jaws with an autosomal dominant pattern of inheritance. Some families also have renal abnormalities or uterine tumors [1,7].

According to Howell et al. [9], 60% of HPT-JT kindreds and up to 7% of familial isolated HPT kindreds have been found to carry germline HRPT2 mutations. In addition, HRPT2 mutations have been detected in 70% of patients with parathyroid carcinomas, almost 20% of which have been found in the germline. These mutations may be de novo germline mutations or inherited mutations with low penetrance.

The HPT-JT gene HRPT2 is located at 1q25 and consists of 17 exons. To date, about 45 different HRPT2 mutations and seven polymorphisms have been identified. Eight of the 17 exons have been found to harbor mutations. Eighty percent of the mutations are located in exons 1, 2, 7 and flanking intronic regions [9,10].

The HRPT2 tumor suppressor gene, mutated in the germline of patients with HPT-JT syndrome, causes truncation, missense or frameshift mutations in the parafibromin open reading frame. The HRPT2 mutation in the present case, identified as a germline mutation, consisted of a base deletion in exon 1, 85delG. This mutation was predicted to cause premature termination of the protein (GLU39FSX) leading to impaired parafibromin function due to a frameshift. Moon et al. [11] have already detected this HRPT2 mutation as a somatic mutation in malignant parathyroid from the affected individuals. We report this 85delG mutation, for the first time, as a germline mutation in our patient in good concordance with the family history. The possible involvement of yet unidentified mutations in the HRPT2 promoter or other regulatory regions may be responsible for HPT-JT in HRPT2 mutation-negative kindreds [10].

The jaw lesions in familial HPT were first described by Kennett and Pollick in 1971. In some families, the jaw lesions predate the diagnosis of PHPT, sometimes by several years; therefore, further screening of such cases and their families would be appropriate. The presence of multiple fibromas and/or the presence of more than one family member having ossifying fibroma should prompt consideration to the possibility of HPT-JT syndrome.

An ossifying fibroma is a well-demarcated benign neoplasm primarily found in the jaw, composed of fibrocellular tissue and mineralized material of varying appearances. In contrast to the brown tumors of PHPT, no giant cells were present. A phenotypically ossifying fibroma is characterized by a slow, progressive enlargement of the affected jaw. Whereas sporadic jaw tumors generally occur in the third and fourth decades of life, jaw tumors in HPT-JT syndrome occur earlier. Non-syndromic ossifying fibromas most often appear radiographically as mixed radiolucent/radioopaque lesions. In syndromic cases, ossifying fibromas appear radiographically as radiolucencies [1]. The case reported here presented a right jaw lesion which appeared as radiolucencies; but the tumor was not removed and no histopathologic examination was performed. A complete surgical removal is the recommended treatment for ossifying fibromas, but there is the possibility of recurrent jaw tumors in patients with HPT-JT syndrome after surgery [1,2].

An analysis of 33 HPT-JT kindreds revealed that affected women in 13 HPT-JT families suffered from menorrhagia in their second to forth decades. This often required hysterectomy, which revealed the presence of uterine tumors. This results in a significantly reduced maternal transmission of the disease. The results of this analysis expand the spectrum of HPT-JT-associated tumors to include uterine tumors and these may account for the decreased reproductive fitness in females from HPT-JT families [7,12].

Most parathyroid tumors in patients with HPT-JT syndrome are mono or oligo-clonal neoplasms, aggressive, occasionally recurrent adenomas, also notable for their cystic histology. Tumors may be in multiple parathyroids with a delayed occurrence, but still at the early age of onset for HPT (average age, 25–35 years) (2, 13, and 14 years) [13,14]. In the present case, the onset of HPT was at the age of 22 years with a multiglandular hyperplasia. One hyperplasic gland was in ectopic intrathyroid position. HPT is revealed by muscle weakness in this case. This clinical presentation reflects the disease’s severity. Indeed, the classic neuromuscular abnormalities of PHPT are based on previous observations at a time when the disease commonly displayed signs and symptoms. In contrast, it is rarely seen among today’s patients with PHPT in whom the vast majority are asymptomatic.

The most widely used localization procedure in PHPT is 99Tc-labelled sestamibi scintigraphy. It identifies a parathyroid adenoma in about 85% of the cases at experienced centers whereas the sensitivity is reduced for multiglandular disease [15].

One of the advantages of sestamibi scintigraphy is its ability to detect ectopic parathyroid adenoma with more than 90% accuracy. In patients with suspected parathyroid adenoma located deep in the neck and ectopic sites, meticulous imaging, including tomodensitometry and acquisition with single photon emission computerized tomography (SPECT), is essential to avoid false-negative results [16,17]. The management of HPT in familial HPT differs from one syndrome to another and is generally complex because of the underlying disease, which predisposes to persistent and recurrent HPT. Due to the rare nature of familial HPT, and its different presentation within and between the familial syndromes and individual kindreds, treatment recommendations based on high levels of evidence cannot be made [18].

In HPT associated with the HPT-JT syndrome, the suggested therapeutic approach is the resection of all grossly enlarged parathyroid glands unless parathyroid carcinoma is suspected during exploration [15,18–20]. Sarquis et al. [19] and Guarnieri et al. [21] suggested a more aggressive approach: subtotal parathyroidectomy, because of multiglandular involvement, high recurrence and persistence rate, difficult reoperation, and risk of parathyroid carcinoma.

All the patients should undergo bilateral neck exploration and should have all four or more parathyroid glands identified [15,20]. According to Carling et al. [15], minimally invasive parathyroidectomy (MIP) may prove to have a limited role in specific instances of familial HPT. For instance, MIP may be considered in HPT associated with MEN2A, HPT-JT where
uniglandular uptake is noted on preoperative imaging. MIP has the advantage of causing minimal tissue trauma facilitating resections. Intraoperative PTH measurements may guide the extent of parathyroid resection (14, 15, and 18). Resection is adequate if a decline (>50%) in PTH is seen five or 10 min after excision. The failure of the PTH level to decline adequately suggests remaining hyperfunctioning parathyroid tissue and therefore additional surgery is indicated. However, some authors have advocated obtaining delayed measurements (20 min or more after excision), especially in the case of slight or frank renal impairment, cystic parathyroid tumors, where there is a significant manipulatory rise in the intact PTH and multiglandular hyperplasia [18].

To reduce the risk of false-positive results in MEN1 patients with multiglandular disease, it has been suggested that more stringent criteria should be applied, such as an 80% reduction in PTH prior to concluding that it is an adequate excision of parathyroid tissue [15,18]. This notion may be extrapolated in HPT-JT syndrome patients with multiglandular involvement.

In the present case, bilateral neck exploration was performed. Surgical exploration revealed multiglandular disease with an inferior right parathyroid adenoma and a second one in ectopic position, in the left lobe of the thyroid gland. An inferior right parathyroidectomy and a left thyroid lobectomy with isthmectomy were carried out. A thymectomy was performed because of the possibility of a supernumerary gland or another ectopic parathyroid gland.

Outcomes of parathyroidectomy in HPT-JT syndrome remain suboptimal. Recurrent hyperparathyroidism is reported in 22% of cases, after a mean disease-free interval of 11.1 years [22]. In contrast to Icobone et al. [22], Sarquis et al. [19] observed a very high prevalence of recurrence or persistence of the disease after less than subtotal parathyroidectomy, 80% after eight to 30 years of follow-up. Therefore, given these data, Sarquis et al. [19] suggest that subtotal parathyroidectomy should become the initial approach for patients harboring HRPT2 gene mutations. The increased risk for parathyroid carcinoma in HPT-JT requires special attention.

Indeed, somatic inactivating mutations of HRPT2 gene were described in the majority of sporadic parathyroid carcinomas. Mutations in HRPT2 are probably an important precursor for increased risk of parathyroid carcinoma. It is noteworthy that, whereas parathyroid carcinomas are rare in sporadic disorders, their occurrence increases to about 15% in patients with HPT-JT syndrome [2].

The diagnosis of parathyroid carcinoma is histologically extremely difficult and there are no gold standards except for metastatic disease and perhaps locally aggressive disease based upon surgical or clinical findings [23]. The surgical management of parathyroid carcinoma, when recognized intraoperatively as a large grey-white invasive mass, requires an initial aggressive surgical approach employing en bloc tumor resection, ipsilateral thyroid lobectomy and resection of adjacent soft tissues (everything but recurrent nerve, trachea and esophagus) [15,23,24].

Given the risk of recurrence and the parathyroid carcinoma, patients with HPT-JT syndrome should be followed up lifelong with annual examination and blood tests measuring serum ionized calcium and intact parathyroid hormone levels [15,21,23]. There are no recommendations for reoperative parathyroid surgery in HPT-syndrome.

For lesions in the maxilla and mandible, orthopontography of the face should be performed, perhaps once in every three years. For kidney lesions and uterine tumors, annual abdominal ultrasound or computed tomography scan with and without contrast is advisable [23].

4. Conclusion

The diagnosis of HPT-JT syndrome is clinically important because of the possible involvement of other family members and the high risk of parathyroid malignancy.

The endocrinologist should be alerted to the possibility of HPT-JT syndrome in adolescents and young adults presenting jaw tumors and PHPT together or separately.

The uterine involvement represents also a clinical manifestation of the syndrome.

The identification of germline HRPT2 mutations is essential in these cases, so that carriers can receive appropriate follow-up. Early identification of parathyroid and other HRPT2-associated neoplasms, earlier operative management and possibly prevention or cure of parathyroid carcinoma should be considered in these families.

References