DELAYED DIAGNOSIS OF A HYPER FUNCTIONING PARATHYROID CYST. A CASE REPORT AND GENETIC ANALYSIS

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Abstract

Objective. Parathyroid cyst is a rare disorder of the parathyroid, with a clinical presentation ranging from a nonsymptomatic mass to severe acute parathyroid crisis. We present here a case of a 73-year-old man who had a neck mass for 5 months before presenting to the emergency room with symptoms of severe hypercalcemia. The investigations during his admission led to the suspicion of a hyperfunctioning parathyroid cyst causing the hyperparathyroidism. Total parathyroidectomy was done. The mass was resected and confirmed to be a functional parathyroid cyst. Patient's calcium levels returned to normal after excision. Genetic analysis of the mass showed a single missense mutation c.2164G>A (NM_000215), p.Val722ile (NP_000206) was identified representing the single-nucleotide polymorphism rs3213409 in the JAK3 gene.

Conclusion. Parathyroid cysts, although rare, should be considered in a patient with a neck mass and hypercalcemia. We discussed the findings of our genetic analysis.

Key words: Parathyroid, cyst, functional, hypercalcemia, genetic, analysis.

INTRODUCTION

The parathyroid cyst is a rare disorder where a cyst arises from the parathyroid gland and can be located in the neck or the mediastinum (1). It can be a functional cyst, which will be accompanied by elevated parathyroid hormone levels, or a non-functional with the normal level parathyroid hormone. It is very rare and constitutes less than 0.01% of all neck masses (2). This article presents a patient with a functional parathyroid cyst with an unusual presentation and delayed diagnosis presents the results of the genetic analysis performed on the extracted cyst tissue.

CASE REPORT

A 73-year-old male patient with hypertension who had been on Losartan for the last 3 years presented

to the emergency room complaining of moderate left loin pain for 2 weeks associated with generalized body weakness for the last 3 months and a loss of 12 kg body weight due to loss of appetite. He also had a history of a neck mass for the last 5 months. He had no history of polyuria, polydipsia, or constipation and no symptoms of a thyroid disorder. His remaining history was irrelevant.

The patient was vitally stable. He was in pain, but there was no respiratory difficulty. The neck mass, measuring 3 × 4 × 3 cm, was on the left side of the neck, moved with swallowing, was not tender, and had no overlying skin changes. It was firm and fluctuating. His calcium level was 3.74 mmol/L (normal, 2.12–2.52 mmol/L), parathyroid hormone level 50.91 pmol/L (normal, 1.6–6.9 pmol/L), phosphate level 0.8 mmol/L (normal, 0.81–1.58 mmol/L), thyroid-stimulating hormone level 0.883 mIU/L (normal, 0.27–4.2uIU/L), free triiodothyronine level 3.84 pmol/L (normal, 2.8–7 pmol/L), and thyroxine level 13.74 pmol/L (normal, 12–22 pmol/L).

The patient had been seen in a general surgery clinic where a fine-needle aspiration (FNA) was performed 1 month before this emergency room presentation. The cytology revealed “clusters of follicular cells exhibited a mild nuclear atypia and clear cytoplasm; no colloid was identified, and 65 mL of fluid was aspirated. Diagnosis: follicular lesion with clear cell changes.” A fluid assay for parathyroid hormone was not done at that time.

The patient was admitted to the medical ward for hypercalcemia caused by primary hyperparathyroidism. Anti-hypercalcemic treatment was initiated consisting of intravenous fluids to restore intravascular volume, monitoring of cardiac status, and loop diuretics after fluid replacement. The calcium and parathyroid hormone levels were continuously monitored. His abdominal ultrasound was normal, and the abdominal pain was assumed to be a passing kidney stone.

An ultrasound of the neck showed “the left

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Figure 1. Coronal section computed tomography scan showing the mass.

thyroid lobe is occupied by a large cyst measuring $6.23 \times 2.82 \times 4.82$ cm with a fluid level echogenicity and thick wall. Multiple benign looking submandibular and cervical lymph nodes are present.”

A computed tomography (C.T) scan of the neck was performed later, and the report stated that “there is a $5.0 \times 3.6 \times 3.8$ (CC X AP X ML) cm cystic lesion seen in close proximity to the left lobe of the thyroid gland. This lesion is predominantly cystic with low attenuation fluid proximally - hyperdense fluid the dependent position” (See Fig. 1).

Magnetic resonance imaging (M.R.I) of the neck was also performed and revealed the following: “a large left neck peripherally enhancing cyst measuring $4.5 \times 4.7 \times 4$ cm is seen just below the thyroid gland with fluid level, the upper part of the cyst has a crescent-shaped soft tissue that is separated by a thin fat plane from the lower aspect of the left thyroid lobe. Conclusion: A large left side neck cystic mass most likely arising from the parathyroid/thyroid gland.” (See Fig. 2).

Another FNA performed during this admission showed few macrophages and lymphocytes, and no follicles were present. It was declared insufficient for diagnosis.

During his stay in the hospital, the patient’s calcium levels were always above normal, reaching levels up to 3.8 mmol/L. His repeated thyroid function tests were within normal limits.

After consulting with the Head and Neck Surgery Department, it was decided to perform a total parathyroidectomy to restore the patient’s calcium level to normal values.

Intraoperatively, a transverse collar incision was

Figure 2. Sagittal section magnetic resonance image showing the mass extension and its cystic nature.

done above the sternal notch, and the mass was exposed and excised. It was a 4×4 cm cystic mass weighing 45 g. It originated from the left inferior parathyroid gland, was unilocular, and contained a greenish fluid. The cyst had a peripheral rim of solid tissue that was present focally; otherwise, it had a thin wall (Fig. 3). The decision to perform a total thyroidectomy was made in the operating room because the first FNA showed a follicular lesion, and a frozen section could not be evaluated at that time because of a national holiday. Furthermore, the thyroid gland looked suspicious as the mass was attached to it.

Calcium and parathyroid hormone levels were measured immediately after surgery. The calcium level dropped to 2.84 mmol/L (from 3.7 mmol/L before surgery), and the parathyroid hormone level dropped to 2.6 pmol/L (from 58.26 pmol/L before surgery). The patient’s calcium and parathyroid hormone levels were within the normal range in later measurements, with the exception of one reading that showed hypocalcemia (1.9 mmol/L).

Figure 3. The removed mass.

Figure 4. Hematoxylin and eosin-stained section at medium magnification showing the fibrous wall with islands of chief cells.

Figure 5. High magnification showing a nodule of oxyphil cells.

The microscopic histopathological examination of the parathyroid mass showed a “fibrotic cyst wall that contains sheets and nodules of chief cells mostly, with scattered oxyphil cell nodules” (See Figs 4 and 5).

The thyroid gland histology confirmed the presence of a nodular goiter.

Because of the intraoperative findings, the drop in parathyroid hormone and calcium levels after excision of the mass, and the histopathological findings, a diagnosis of a functional parathyroid cyst was made.

The patient was discharged in good condition on thyroxine replacement, and his calcium level remained within the normal range afterward.

To profile the case, we performed targeted sequencing using Ampliseq technology on the Ion Torrent Personal Genome Machine. A targeted sequencing panel, Ion Ampliseq Cancer Hotspot Panel v2 (Life Technologies) was used to amplify 207 amplicons interrogating 2800 COSMIC mutations from 50 oncogenes and tumor suppressor genes from 10 ng of genomic DNA extracted from formalin-fixed and paraffin embedded tissue from the patient in question. Sequencing the amplicons was achieved using the Ion Ampliseq Library Kit v2 and Ion Ampliseq Sequencing Kit 200. Data acquisition and analysis was performed using the Torrent Suite v4 (Life Technologies).

A single missense mutation c.2164G>A (NM_000215), p.Val722Ile (NP_000206) was identified representing the single-nucleotide polymorphism rs3213409 in the JAK3 gene.

DISCUSSION

Parathyroid cyst is a rare disorder that usually affects the neck but can also occur in the mediastinum

(1). Functional and nonfunctional cysts are the two types of parathyroid cysts (2). Nonfunctional cysts are more common in women and are not associated with changes in parathyroid hormone levels. Functional cysts are associated with primary hyperparathyroidism and constitute the smaller proportion of the two types; they are more common in the mediastinum and affect men 1.6 times more than women (2). Parathyroid cysts are very rare and constitute less than 0.01% of all neck masses (2). They usually arise from the inferior glands, although 20% of the mediastinal cysts arise from the superior glands (3).

Numerous theories have been suggested regarding the etiology of parathyroid cysts, including (i) degeneration, infarction, or hemorrhage of a parathyroid gland or parathyroid adenoma or very rarely a parathyroid adenocarcinoma; (ii) retention of parathyroid secretions within colloid vesicles; (iii) coalescence of vesicular-canalicular or glandular-like rudiments (Kursteiner canals) that are present during fetal life in the parathyroid glands; (iv) enlargement of a microcyst or fusion of several microcysts that are normally present in the parathyroid glands; and (v) the remnants of the third and fourth branchial clefts (4).

A nonfunctional parathyroid cyst usually presents as a nonsymptomatic neck mass or as an incidental finding during neck surgery or imaging procedure performed for an unrelated issue (1). Even though these cysts range in size from 3–5 cm, some cases were reported to have huge cysts reaching 15 cm that applied pressure on the trachea and esophagus causing symptoms of dyspnea and dysphagia (3). Mediastinal masses grow faster and reach larger sizes than those of the neck 2.5 and have been reported to cause hoarseness due to vocal cord paralysis in some

cases (3). Functional cysts, on the other hand, present as primary hyperparathyroidism causing hypercalcemia, which is mild in most of the cases, although there were reports of cases with severe hypercalcemia, including the case presented here, (6) as well as innominate artery thrombosis (7). Parathyroid cysts can occur with concomitant diseases, such as thyroid multinodular goiter, parathyroid adenoma, and thyroid mass (2).

In this case report, the patient had primary hyperparathyroidism based on his biochemical results and, alongside with the neck mass, should have raised the suspicion toward a functioning parathyroid cyst. However, the diagnosis was delayed since the condition is rare compared to other neck masses.

Cysts can be visualized using ultrasound or CT scans, but these methods are not sufficient to define the origin of the cyst, whether it is from the thyroid or parathyroid glands, as in this case, and sestamibi scans are not reliable (8). It should be noted that in accordance with the guidelines of the European Association of Nuclear Medicine guidelines, sestamibi scan should have been performed in the case of a neck mass with signs of hyperparathyroidism (9). Unfortunately, the patient presented to the Emergency Room on a national holiday where the nuclear scans facilities were not available.

A diagnosis can be achieved correctly by performing FNA where a clear fluid is found; the fluid might be bright red or chocolate-colored in the case of associated hemorrhage. Assays for parathyroid hormone in the aspirated fluid should be done and will show parathyroid hormone concentration from a few hundred up to 400,000 pg/L in nonfunctional cysts, in functional cysts the concentration can reach millions (10). The first sample that was taken from our patient should have been analyzed for PTH level but, unfortunately, it was missed.

In functional cysts grossly, the mass will appear to be cystic, thin-walled, and filled with clear fluid. Histological examination of an excised cyst will reveal islands of chief cells and occasionally oxyphil cells within a thin fibrotic cystic wall lined by a single layer of flattened cuboidal epithelium (2). The preferred treatment for symptomatic nonfunctional and functional cysts is surgical removal (11). A cervical approach is helpful for neck masses and some mediastinal cysts. Thoracotomy might be needed in some cases (3). It should be noted that after the resection of a functional parathyroid cyst, the patient is susceptible to have hungry bone syndrome, and his/her calcium levels should be monitored closely and managed accordingly (12). For nonfunctional nonsymptomatic cysts, aspiration

of the fluid is beneficial in most cases (1). In the case of recurrent cyst formation after several aspirations, sclerotherapy using tetracycline or ethanol can achieve complete resolution (13, 14).

Conflict of interest

None of the authors have any competing interests.

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Ethical approval

The authors declare that they have no conflict of interest concerning this article.

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