Case Report Template

- All case reports MUST be submitted online using this template.
- Tables, images and multimedia files must be uploaded separately on submission.
- Articles should be no more than 2,000 words in length, and include a maximum of 10 references.
- **It is essential that you list the learning points of the case;** these are the messages that readers should remember when dealing with their own patients.
- We strongly encourage authors to comply with the CARE guidelines.
- You must have signed informed consent from patients (or relatives/guardians) prior to publication, using our consent form. Full details of our patient consent and confidentiality policy is available on our author guidelines page. Alternatively, Institutional Review Board approval of the manuscript as containing no identifiable information may be submitted with the manuscript in lieu of written consent by the subject of the report.

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Transient remission of hyperparathyroidism after fine-needle aspiration biopsy

Summary

Primary hyperparathyroidism (PHPT) is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis. PHPT is most commonly caused by a single adenoma of the parathyroid gland, which can have an intrathyroid location in rare cases. The measurement of intact PTH in the washout fluid obtained by ultrasound (US) guided fine needle aspiration (FNA) can be useful in clarifying the aetiology of these lesions. Case report: A 48-year-old man with a background history of symptomatic renal stone disease, was diagnosed with PHPT and referred to our Endocrinology department. A neck ultrasound revealed a thyroid nodule with 21 mm in the right lobe. The patient underwent US-guided FNA of the lesion. The measurement of PTH in the washout fluid was significantly elevated. Following the procedure, he reported neck pain and noticed distal paraesthesias in the upper limbs. Blood test results showed significant hypocalcaemia and supplementation with calcium and calcitriol was started. The patient was closely monitored. Recurrence of hypercalcaemia was later observed and the patient was submitted to surgery. We present a case of FNA induced transitory remission of PHPT in a patient with an intrathyroid parathyroid adenoma. We conjecture that intra-nodular haemorrhage might have occurred, which temporarily affected the viability of the autonomous parathyroid tissue. A few similar cases of spontaneous or induced remission of PHPT after FNA have been previously described in the literature. This remission can be transitory or permanent, depending on the degree of cellular damage, thus follow-up of these patients is recommended.

Learning points

- Hyperfunctioning parathyroid lesions are susceptible to FNA induced damage.
- FNA biopsy is not generally recommended for the evaluation of PHPT, although it might be useful in selected cases, particularly by measuring PTH in the washout.
- Considering its high recurrent rate, close follow-up of patients with FNA-induced remission of PHPT is recommended.

Background

Outline why this case is important and of interest to other clinicians in the field. Does it describe an unusual or novel occurrence, or a common health problem? The types of cases of interest include:

- Findings that shed new light on the possible pathogenesis of a disease or mechanism of therapy
- Unique or rare presentations of a disease
- Novel diagnostic procedures or treatments
- New or unexpected associations between symptoms and diseases
Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia due to an unregulated overproduction of parathyroid hormone (PTH). PHPT is most commonly caused by a single adenoma of a parathyroid gland but can be caused by primary hyperparathyroidism-related multiglandular disease in 10-15% of the cases. Parathyroid carcinoma is rare and occurs in less than 1% of the cases (Dandurand et al., 2021). Parathyroid glands are in close anatomic relationship to the thyroid gland, usually a total of four, though variation in number can be found. Ectopy of one or more glands is relatively common. In rare cases, they can have an intrathyroid location. The imaging techniques most frequently used to detect and locate abnormal parathyroids are $^{99m}$Tc-sestamibi scintigraphy and neck ultrasound. Ultrasound is largely used in these patients as it is widely available, does not involve ionizing radiation and has a high sensitivity to detect these lesions (Bilezikian et al., 2014). In the case of an ectopic gland, especially intrathyroidal parathyroid adenoma, an abnormal gland may be considered as a thyroid nodule. Additionally, cytological differentiation between them is not easy due to overlapping features. Although not widely accepted due to the risk of parathyromatosis, the measurement of PTH in the washout fluid obtained by fine needle aspiration (FNA) can be used in selected cases for clarifying the aetiology of these lesions (Suzuki et al., 2021). Surgery is the only curative therapy for PHPT. However, medical management with pharmacological agents is an option for some patients who have contraindications to surgery or are reluctant to undergo parathyroidectomy (Bilezikian et al., 2014).

Case presentation

A 48-year-old man with complaints of fatigue and malaise was diagnosed with PHPT (total serum calcium concentration 12.4 mg/dL [reference range, 8.6–10.5 mg/dL]; PTH 462.1 pg/mL [reference range 12–67 pg/mL]) and referred to our Endocrinology department. He presented a background history of symptomatic renal stone disease and had already been submitted to lithotripsy.

Investigation

A neck ultrasound was performed and the only abnormal finding was a 21 mm predominantly cystic thyroid nodule in the right lobe (Figure 1 – image A and B). FNA using 25-gauge needle (two passes) with PTH washout to differentiate between an enlarged parathyroid and a thyroid nodule was undertaken. PTH measurement in FNA washout fluid was significantly elevated (PTH 7,199 pg/mL).

Ten days after the procedure he returned to our department reporting neck pain following FNA and has been noticing distal paraesthesias in the upper limbs. Blood test results showed hypocalcaemia (8.1 mg/dL) and reduction of PTH levels to 124 pg/mL. The patient reported symptomatic improvement after starting therapy with calcium plus vitamin D. Concurrently, a $^{99m}$Tc-sestamibi scan was performed and did not reveal any abnormalities suggestive of parathyroid disease (Figure 2). Sequential ultrasounds revealed an increase followed by a decrease in the nodule’s size from to 29 to 23.5 mm in transverse diameter (Figure 1: image C and D). The patient was kept under close monitoring. Forty-five days after FNA, recurrence of hypercalcaemia (11.5 mg/dL) was observed and the calcium plus vitamin D supplementation was discontinued. Elevated calcium levels persisted over time.

Treatment

The patient was submitted to right thyroid lobectomy. During surgery, serum PTH decreased from 178.8 to 15 pg/mL within 10 minutes of the excision. The postoperative course was uneventful, with the exception of transient hypocalcaemia. Histopathology examination confirmed the presence of an intrathyroid parathyroid adenoma. The lesion had areas of fibrosis and hemosiderin deposition consistent with prior puncture (figure 3).
Outcome and follow-up
Provide follow-up data to enable readers to clearly understand the case outcome. Please specify follow-up period.

Soon after surgery, calcium and PTH levels were within the normal reference range and have remained so ever since (last follow-up seventeen months after surgery). Table 1 shows the biochemical profile changes after FNA and after surgery.

Discussion
This should not be a summary of other similar cases. Authors should describe the points of interest of the reported case and discuss in the context of information available in the literature, with reference to relevant publications.

We present a case of FNA induced transitory remission of PHPT in a patient with an intrathyroid hyperfunctioning parathyroid adenoma. Serum PTH and calcium dropped from 462.1 to 124 pg/mL and 12.0 to 8.1 mg/dL, respectively, following FNA. These unexpected changes along with neck pain suggests that FNA-induced haemorrhage led to remission of PHPT, which temporarily have affected the viability of the autonomous parathyroid tissue. Remarkably the PTH level gradually began to rise one month after the procedure, demonstrating the damage was only temporary. In our case, a $^{99m}$Tc-sestamibi scan was performed during remission of PHPT which may explain the negative result.

Spontaneous remission of PHPT due to nontraumatic necrosis, haemorrhage and infarction of a parathyroid adenoma is extremely uncommon, but it is a previously well-documented event, usually denominated as ‘parathyroid auto-infarction’, ‘autoparathyroidectomy’ or ‘parathyroid apoplexy’. This rare incident may range in presentation from asymptomatic to life-threatening with signs and symptoms of massive cervical or mediastinal haemorrhage, a condition requiring emergency neck exploration surgery. Most of the reported cases presented with acute hypocalcaemia, resulting from the adenoma’s necrosis and ineffectiveness of the remaining parathyroid glands to produce PTH; followed by a period of normocalcaemia at first and finally recurrence of the disease. Surgical treatment was performed in most cases, with only a few cases reported in which regular follow-up was initially chosen. This indicates that the apparent cure that follows necrosis of a parathyroid adenoma is potentially temporary, possibly explained by the presence of non-ischaemic adenomatous tissue having a potential to grow resulting in recurrence of hypercalcaemia at some stage. Therefore, long-term clinical and biochemical surveillance is advised (Novodvorsky et al., 2019).

In our case, remission of PHPT was caused by FNA of the parathyroid adenoma. This phenomenon is exceptional and to the best of our knowledge, only six cases have been published so far (Ing et al., 2008, Maxwell et al., 2011, Kara et al., 2017, Falcetta et al., 2021, Ho et al., 2021). The cause remains unclear, but has been suggested to be related to autoinfarction (necrosis without haemorrhage) or acute haemorrhage of the lesion after FNA, which can lead to an acute and dramatic reduction of calcium and PTH levels (Maxwell et al., 2011), while in some cases, the decrease is much less noticeable and entirely asymptomatic (Ing et al., 2008).

This remission can be transitory or permanent, depending on the degree of cellular damage. The patients reported by Kara et al., 2017 and more recently by Falcetta et al., 2021 experienced a long-term remission, in 9 years and 1 year follow-up, respectively. In Ing et al., 2008 the complete aspiration of cystic fluid resolved hypercalcaemia for at least 16 months of post-FNA follow-up.

Fine-needle aspiration is usually not recommended for parathyroid suspected tumours due to the chances of serious complications, such as massive haematoma, parathyromatosis, and misdiagnosis as malignancy during pathological diagnosis. However, when the localization is unusual or parathyroid adenoma is mistaken for a thyroid nodule, FNA may be indicated or performed erroneously. Although cytomorphology alone may help distinguishing between parathyroid and thyroid lesions, it has remained a great challenge due to overlapping features (Suzuki et al., 2021). Some studies have reported that FNA with PTH measurement is helpful in diagnosing parathyroid disease (Ho et al., 2021). The performance of PTH washout only without cytology could be considered. However, this technique is mostly restricted to reoperative patients. In a study conducted by the Mayo Clinic Rochester, parathyroid FNA procedures were performed in 75% of 2,265 parathyroid surgeries. For patients with PHPT referred because of difficulties with preoperative localization of their parathyroid adenoma, parathyroid FNA with PTH washout had a superior performance in comparison with parathyroid scanning or ultrasonography alone, exhibiting a positive
predictive value of 100%, a sensitivity of 84%, a specificity of 100%, and an accuracy of 84% (Bancos et al., 2012). However, further studies are needed to confirm the risk or justification of FNA for parathyroid adenomas and its importance in routine parathyroid localization.

In conclusion, our case, together with a literature review, suggests that hyperfunctioning parathyroid lesions are susceptible to FNA induced damage. This procedure is not generally recommended for the evaluation of PHPT, although it might be useful in selected cases. Close follow-up of patients with FNA-induced remission of PHPT is recommended, considering its high recurrent rate.
Funding statement
Please detail all of the sources of funding relevant to the research reported in the following format:
‘This work was supported by the Medical Research Council (grant numbers xxxx, yyyy); the Wellcome Trust (grant number xxxx); and Tommy’s Baby charity (grant number xxxx).’
Where research has not been funded please state the following: ‘This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.’

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Declaration of interest
Actual or perceived conflicts of interest for all authors must be declared in full. Please either (a) declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported; or (b) fully declare any financial or other potential conflict of interest.

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient consent
Include a statement confirming that written informed consent has been obtained from the patient (or patient’s guardian) for publication of the submitted article and accompanying images. Authors must also include a signed copy of our consent form in the patient’s notes for future reference. For full details, please refer to our patient consent and confidentiality policy within the author guidelines.

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Author contributions and acknowledgements
Please include a statement specifying the contribution of each co-author. If the author is not the named physician of the patient please clarify involvement in the oversight of the reported case, or confirm you have permission of the physician who is responsible for the patient.

ARE drafted the manuscript. JC and FJCR were involved in critical revision of all drafts of the manuscript. JC, BM, RCM, JS, TM and JG were involved in patient care. All authors have approved the final version of the manuscript.
References
All references cited in the text must be included in the reference list and vice versa. Cite references in the text in numerical order. References should be formatted as follows:


Legends to tables/figures/videos
Insert text of legends to any figures or tables. Tables, images and videos should be uploaded separately during online submission.

Figure 1: (A) Transverse and anteroposterior and (B) longitudinal diameters of the intrathyroidal nodule in the ultrasound images of the neck performed at the time of FNA-US guided. Image of the nodule three (C) and ten days (D) after FNA.

Figure 2: (A) Early and (B) delayed images of $^{99m}$Tc sestamibi scintiscan.

Table 1: The biochemical profile changes after FNA and after surgery.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>a</td>
<td>Reference range for intact parathyroid hormone, 18-80 pg/mL</td>
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<tr>
<td>b</td>
<td>Reference range for serum calcium, 8.6-10.5 mg/dL</td>
</tr>
<tr>
<td>c</td>
<td>Reference range for ionized calcium, 1.14-1.29 ng/mL</td>
</tr>
<tr>
<td>d</td>
<td>Reference range for phosphate, 2.5-5mg/dL</td>
</tr>
</tbody>
</table>
Patient’s perspective
We welcome comments from your patient; their own description of their experience may help other patients or clinicians who are dealing with a similar problem. If your patient would like to contribute please ensure they include only relevant personal details. Patients may describe their symptoms, how any tests and treatments affected them, and how the problem is now.
Figure 1: (A) Transverse and anteroposterior and (B) longitudinal diameters of the intrathyroid nodule in the ultrasound images of the neck performed at the time of FNA-US guided. Image of the nodule three (C) and ten days (D) after FNA.

85x65mm (144 x 144 DPI)
Figure 2: (A) Early and (B) delayed images of 99mTc sestamibi scintiscan.

87x53mm (220 x 220 DPI)
Figure 3: Intrathyroid parathyroid adenoma, with fibrosis and hemosiderin deposition.
<table>
<thead>
<tr>
<th>Date</th>
<th>PTH, pg/mL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ionized calcium, mmol/L&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total calcium, mg/dL&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Phosphate, mg/dL&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Time of follow-up</th>
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<tr>
<td>15-07-2019</td>
<td>462.1</td>
<td>1.55</td>
<td>12.4</td>
<td>2.0</td>
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<td>19-07-2019</td>
<td>97.9</td>
<td>1.20</td>
<td>9.2</td>
<td>2.9</td>
<td>Three days after FNA</td>
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<tr>
<td>25-07-2019</td>
<td>124.0</td>
<td>1.09</td>
<td>8.3</td>
<td>3.3</td>
<td>Ten days after FNA</td>
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<tr>
<td>01-08-2019</td>
<td>107.6</td>
<td>1.16</td>
<td>9.5</td>
<td>3.6</td>
<td>During supplementation with calcium</td>
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<tr>
<td>29-08-2019</td>
<td>90.9</td>
<td>1.51</td>
<td>12</td>
<td>2.7</td>
<td>During supplementation with calcium</td>
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<tr>
<td>08-05-2020</td>
<td>173.1</td>
<td>1.49</td>
<td>11.6</td>
<td>2.9</td>
<td>Preoperative results</td>
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<td>14-05-2020</td>
<td>15.5</td>
<td>1.14</td>
<td>8.8</td>
<td>2.3</td>
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<tr>
<td>15-05-2020</td>
<td>38.2</td>
<td>1.1</td>
<td>8.7</td>
<td>3.6</td>
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<tr>
<td>02-11-2020</td>
<td>61</td>
<td>1.21</td>
<td>10.2</td>
<td>3.6</td>
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<td>1.16</td>
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<td>12-10-2021</td>
<td>104</td>
<td>1.16</td>
<td>9.6</td>
<td>2.9</td>
<td>Seventeen months after surgery</td>
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