Glucocorticoid-responsive lymphocytic parathyroiditis and hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor: a case report and literature review

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Abstract

Objective: Autoimmune lymphocytic parathyroiditis and acquired hypocalciuric hypercalcemia associated with autoantibodies against the calcium-sensing receptor (anti-CaSR) are rare and poorly understood conditions. Here, we describe a patient with acquired parathyroid hormone (PTH)-dependent hypercalcemia with associated hypocalciuria, found to have true lymphocytic parathyroiditis on histopathology, and circulating anti-CaSR antibodies in serum. Design and methods: A 64-year-old woman was referred to our clinic for persistent hypercalcemia after a subtotal parathyroidectomy. She was normocalcemic until the age of 63 years when she was diagnosed with primary hyperparathyroidism. She underwent subtotal parathyroidectomy with appropriate intraoperative PTH decline. Two weeks post-parathyroidectomy, she presented with persistent hypercalcemia and hyperparathyroidism. Urine studies revealed an inappropriately low 24-h urine calcium (Ca)/creatinine clearance ratio. Surgical pathology was consistent with true lymphocytic parathyroiditis with lymphoid follicles. The presence of circulating anti-CaSR antibodies was detected by immunoprecipitation of CaSR by the patient’s serum. After a 4-week course of prednisone, serum Ca and PTH normalized, and her anti-CaSR titers declined. She remains normocalcemic 10 months after the discontinuation of glucocorticoid therapy. We present this patient in the context of the relevant published literature on lymphocytic parathyroiditis and acquired hypocalciuric hypercalcemia related to anti-CaSR antibodies. Conclusions: Autoimmune lymphocytic parathyroiditis and acquired hypocalciuric hypercalcemia associated with anti-CaSR antibodies is a very rare yet important condition to be considered in a patient with acquired PTH-dependent hypercalcemia with inappropriate hypocalciuria. Although subtotal parathyroidectomy is unlikely to correct the hypercalcemia, this entity may respond to a short course of prednisone therapy.

Introduction

Autoimmune lymphocytic parathyroiditis is a rare cause of parathyroid hormone (PTH)-dependent hypercalcemia (¹, ²). Non-specific lymphocytic infiltrates in the parathyroid glands are found in 6% of nearly 1000 autopsy cases, whereas true lymphocytic parathyroiditis, defined by more stringent criteria of interstitial lymphocytic
infiltrates with plasma cells or germinal centers with or without tissue damage, is found in no more than 0.5% of autopsies of apparently healthy individuals (3). The mechanism underlying autoimmune lymphocytic parathyroiditis is unclear.

A few case reports have described patients with PTH-dependent hypercalcemia with inappropriate hypocalciuria mediated by autoantibodies against the calcium-sensing receptor (anti-CaSR) (2, 4, 5, 6, 7). This condition is also termed acquired hypocalciuric hypercalcemia. The natural course and management of this entity are poorly understood. Parathyroidectomy and bisphosphonate treatment are usually unsuccessful (2, 4, 7). Glucocorticoids have been reported to reduce anti-CaSR antibody titers and normalize serum PTH and calcium (Ca) in one case (2), but not in another (7). Cinacalcet was shown to be effective in one case (5).

Here, we describe a patient with autoimmune lymphocytic parathyroiditis and acquired hypocalciuric hypercalcemia due to anti-CaSR antibodies whose serum PTH and Ca normalized and anti-CaSR antibodies were reduced after a short course of glucocorticoids; providing support for the pathogenic nature of the autoantibodies.

Subject and methods

Case report

A 64-year-old woman with type 2 diabetes (T2D), hypertension and depression was referred to our Mineral Metabolism Clinic for evaluation of persistent hyperparathyroidism after a subtotal parathyroidectomy. She had normocalcemia until the age of 63 years (Fig. 1A), when she presented with chronic nausea, constipation and ‘cloudy thinking’, and she was diagnosed with primary hyperparathyroidism with secondary hypercalcemia. She had no history of nephrolithiasis or fractures. Family history was only significant for osteoporosis in her mother. Her pre-operative laboratory studies revealed serum Ca level of 3.08 mmol/L and PTH level of 10.82 pmol/L, which were consistent with PTH-dependent hypercalcemia (Table 1; Pre-op). Her dual-energy X-ray absorptiometry showed osteopenia. Due to the progressive hypercalcemia (highest serum Ca: 3.35 mmol/L), she was referred to endocrine surgery for parathyroidectomy. Her neck ultrasound and Sestamibi scan were non-localizing, so she underwent subtotal parathyroidectomy with resection of three of the four parathyroid glands. Her intraoperative PTH declined from 8.23 pmol/L to 2.29 pmol/L at 15 min. Serum PTH and Ca normalized with symptomatic improvement 1 day after parathyroidectomy, but nausea, constipation and anorexia recurred a few days thereafter accompanied by laboratory evidence of persistent hyperparathyroidism (Table 1; POD 13). Surgical pathology showed hypercellular parathyroid tissue with multiple lymphoid follicles consistent with lymphocytic parathyroiditis in all the three resected glands (Fig. 1B and C). She was referred to our clinic 7 weeks post-parathyroidectomy for further evaluation. Her physical examination was unremarkable except for a well-healed parathyroidectomy scar. Her laboratory studies showed an elevated serum Ca level of 2.70 mmol/L, PTH level of 7.42 pmol/L and 24-h urine Ca to creatinine clearance ratio of 0.005 (Table 1; pre-glucocorticoid).

Lymphocytic infiltrate in the parathyroid glands has been associated with systemic inflammatory conditions such as sepsis, acute myocardial infarction, vascular congestion from heart failure, malignancies and autoimmune conditions. As the patient did not have any evidence of systemic inflammatory conditions, infections, cardiovascular disease or neoplasm, it was thought that her lymphocytic parathyroiditis could be autoimmune in nature. Her serum antinuclear antibody (ANA), thyroid function test and blood counts were unremarkable (Table 1; pre-glucocorticoid). Her inappropriately low 24-h urine Ca to creatinine clearance ratio and high normal serum magnesium level in the setting of acquired PTH-dependent hypercalcemia were suggestive of a potential CaSR abnormality. In combination with the pathological findings of lymphoid follicles in her parathyroid glands, we set out to search for possible anti-CaSR antibodies.

Informed consent for the relevant experiments and publication of this manuscript including the accompanying images was obtained from the patient.

Anti-CaSR antibodies

The presence of circulating anti-CaSR antibodies was detected by immunoprecipitation of CaSR by the patient’s serum. Madin-Darby canine kidney (MDCK) epithelial cells that do not express native CaSR and MDCK cells stably expressing transfected CaSR were lysed and incubated with either normal mouse IgG (Santa Cruz Biotechnology), the patient’s serum or a normal control human serum at a 1:200 dilution at 4°C overnight. The next morning, 100 μg protein A/G beads was added to each sample and incubated at room temperature for 4 h...
followed by elution to separate the immunoglobulin fraction from serum. The eluted samples were run on a 10% SDS-PAGE gel and probed with a specific anti-CaSR antibody (Sigma Aldrich).

The anti-CaSR antibody assay was performed again on the patient’s serum prior to, and after glucocorticoid therapy to assess the response in anti-CaSR antibody titers after the glucocorticoid therapy. MDCK cells stably expressing the CaSR were harvested for the total cell lysate and divided into 10 equal aliquots, which were incubated with different dilutions (1:200, 1:400, 1:600, 1:800 and 1:1000) of the pre-glucocorticoid or post-glucocorticoid serum from our patient at 4°C overnight. The next morning, 50 μg protein A/G beads were added to each sample and incubated at room temperature for 4 h followed by elution. The eluted samples were run on a 10% SDS-PAGE gel and probed with a specific anti-CaSR antibody.
Results

The patient’s pre-glucocorticoid serum showed the presence of anti-CaSR antibodies (Fig. 1D). She was started on prednisone 40 mg daily for autoimmune lymphocytic parathyroiditis. Her serum PTH and Ca normalized after 2 weeks. Further tapering of prednisone to 20 mg daily was associated with continued normal serum PTH and Ca values, and the patient discontinued prednisone completely after 2 weeks of prednisone 20 mg daily. Ten months after the last prednisone dose, the patient’s serum PTH and Ca have remained within the reference range and urine Ca excretion remained low but increased compared to that prior to glucocorticoid therapy (Table 1; post-glucocorticoid). A repeat assay on the patient’s serum showed a decreased serum anti-CaSR antibody titer (Fig. 1E). To date, the patient’s serum PTH and Ca values remain in the reference range (Fig. 1A).

Discussion

True lymphocytic parathyroiditis, defined by evidence of interstitial lymphocytic infiltrates with plasma cells or germinal centers with or without tissue damage, is a rare clinical entity (3). It has been associated with variable parathyroid functions (Fig. 2) (1, 8, 9, 10), and various conditions including multiple endocrine neoplasia type 1 (3) and IgG4-related diseases (2). Rarely, lymphocytic parathyroiditis is associated with the presence of anti-CaSR antibodies (Fig. 2) (2).

Anti-CaSR antibodies can be activating (11, 12) or inhibitory (4, 5, 6, 7). Neutral anti-CaSR autoantibodies likely exist but will never be searched for. The functional nature of these antibodies will impact on parathyroid function and Ca status: anti-CaSR antibodies have been described in PTH-dependent hypocalcemia (autoimmune polyendocrine syndrome type 1 (11)), and isolated autoimmune hypoparathyroidism (12, 13), PTH-dependent hypercalcemia (autoimmune or acquired hypocalciuric hypercalcemia (2, 4, 5, 6, 7, 14) and autoimmune polyendocrine syndrome type 1 (15)) and normocalcemia with normal PTH in two patients with Graves’ disease (16). The presence of anti-CaSR antibodies does not always correlate with lymphocytic infiltrate in the parathyroid glands (17). This intricate relationship is demonstrated in Fig. 2.

Our patient has true lymphocytic parathyroiditis based on her surgical pathology. Her biochemical profile mimics that of familial hypocalciuric hypercalcemia (FHH) with PTH-dependent hypercalcemia and hypocalcuria. FHH is unlikely in this patient given normocalcemia until the age of 63 years and absence of family history.

Table 1 Timeline of laboratory studies.

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Pre-op</th>
<th>POD 1</th>
<th>POD 13</th>
<th>Pre-glucocorticoid</th>
<th>Post-glucocorticoid</th>
</tr>
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<tbody>
<tr>
<td>Serum Calcium (mmol/L)</td>
<td>2.10–2.63</td>
<td>3.08</td>
<td>3.13</td>
<td>2.70</td>
<td>2.60</td>
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<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.13–1.33</td>
<td>1.68</td>
<td>1.33</td>
<td>1.35</td>
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<tr>
<td>Phosphorus (mmol/L)</td>
<td>0.77–1.45</td>
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<td>7.33</td>
<td>7.42</td>
<td>4.46</td>
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<tr>
<td>PTH (pmol/L)</td>
<td>1.59–6.90</td>
<td>10.82</td>
<td>1.93</td>
<td>1.93</td>
<td>7.42</td>
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<td>25-OH vitamin D (nmol/L)</td>
<td>75–200</td>
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<td>Alkaline phosphatase (U/L)</td>
<td>35–104</td>
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<td>100</td>
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<td>Albumin (g/L)</td>
<td>35–52</td>
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<td>45</td>
<td>46</td>
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<td>Magnesium (mmol/L)</td>
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<td>0.82</td>
<td>0.99</td>
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<tr>
<td>Creatinine (μmol/L)</td>
<td>45.1–84.0</td>
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<td>63.6</td>
<td>69.8</td>
<td>63.6</td>
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<td>Anti-nuclear antibodies (ANA)</td>
<td>Negative</td>
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<td>Negative</td>
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<td>Serum protein electrophoresis</td>
<td>Normal pattern</td>
<td></td>
<td></td>
<td>Normal pattern</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>120–150</td>
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<td>Hematocrit</td>
<td>0.34–0.44</td>
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<td>WBC (×10^9/L)</td>
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<td>Eosinophil (×10^9/L)</td>
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<td>0.24</td>
<td>0.24</td>
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<td>24-h urine Calcium (mmol/day)</td>
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<td>3.90</td>
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<td>Magnesium (mmol/day)</td>
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<td>6.53</td>
<td>7.73</td>
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<td>Phosphorus (mmol/day)</td>
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<td>Creatinine (mmol/day)</td>
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<td>11.7</td>
<td>12.4</td>
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<td>Ca/Cr clearance ratio</td>
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<td></td>
<td>0.005</td>
<td>0.008</td>
<td>0.008</td>
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POD, post-operative day; post-glucocorticoid laboratory studies were after discontinuation of prednisone for about 3 months; 24-h urine calcium to creatinine clearance ratio = (serum creatinine × 24-h urine calcium)/(24-h urine creatinine × serum calcium).
of hypercalcemia. Thus, she most likely has acquired hypocalciuric hypercalcemia. Her serum anti-CaSR antibodies can be presumed to be inhibitory antibodies leading to increased PTH release and increased renal Ca resorption despite hypercalcemia. Despite the detection of antibodies to CaSR in patient’s serum, we were unable to test whether these antibodies truly inhibited CaSR signaling.

A handful of cases of acquired hypocalciuric hypercalcemia associated with anti-CaSR antibodies have been reported (2, 4, 5, 6, 7), and only one case with both anti-CaSR and pathological evidence of lymphocytic infiltrate in the parathyroid gland in the setting of IgG4-related diseases (2). To the best of our knowledge, there is no case reported to date of a patient with both acquired hypocalciuric hypercalcemia and pathological evidence of true lymphocytic parathyroiditis with lymphoid follicles associated with anti-CaSR antibodies as described in our patient.

The inciting event for autoimmunity to the parathyroid glands, the natural course of this condition, its potential complications and the optimal treatment are poorly understood due to the rarity of the condition. Based on the few case reports, parathyroidectomy and bisphosphonate treatment are usually unsuccessful (2, 4, 7, 18). Glucocorticoids have been shown to normalize serum PTH and Ca (2, 14, 18) and reduce the titers of anti-CaSR (2) in three cases, but not in another (7). Two of the three glucocorticoid-responsive cases described patients with underlying IgG4-related diseases (2, 18) with one patient with predominant anti-CaSR IgG4 antibody subclass (2). Responsiveness to glucocorticoids in patients with acquired hypocalciuric hypercalcemia has been suggested to reflect the fact that IgG4-related diseases typically respond to glucocorticoids (2). The parathyroid glands of our patient did not have the histopathological or immunohistochemical-staining pattern typical for IgG4-related diseases with an IgG4/IgG plasma cell ratio <40% and no storiform fibrosis. Thus, IgG4-related disease is unlikely in our patient, and serum IgG4 level was not measured. Nonetheless, she responded to a short course of glucocorticoids with normalized serum Ca and PTH levels and decreased anti-CaSR antibody titers. Thus, it is still unclear what predicts glucocorticoid responsiveness in this condition. In addition, the duration of remission after the glucocorticoid therapy in this condition is unclear. Long-term follow-up data was only available in one of the three glucocorticoid-responsive cases (2, 14, 18), which reported normal serum PTH and Ca levels at least 2 years after the cessation of glucocorticoid therapy (18). Glucocorticoid use is not an optimal long-term solution for our patient given its adverse effects on bone health with her pre-existing osteopenia and T2D. Fortunately, she remains normocalcemic to date, more than 10 months after the discontinuation of glucocorticoids. Cinacalcet, an allosteric activator of CaSR, was shown to be effective in one case (5) and may be a potential option for our patient if her hyperparathyroidism recurs.

Conclusions

Autoimmune lymphocytic parathyroiditis and acquired hypocalciuric hypercalcemia associated with anti-CaSR antibodies is a very rare, yet important condition to be considered in a patient with acquired PTH-dependent hypercalcemia with inappropriate hypocalciuria. This entity may respond to a short course of prednisone therapy, whereas parathyroidectomy is unlikely to correct the hypercalcemia.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Figure 2
Association of parathyroid function, anti-CaSR antibody and parathyroiditis.
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References

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