CASE REPORT

Concomitant sarcoidosis and papillary thyroid cancer with severe hypercalcaemia as the main symptom

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SUMMARY

A 65-year-old Caucasian man was admitted to our hospital due to incidental finding of plasma ionised calcium=1.83 mmol/L. During the previous months, he had felt more tired and had experienced an unintended weight loss of 6–8 kg. A CT scan revealed an inhomogeneous thyroid gland and enlarged lymph nodes along the cervical vessels and in the mediastinum. The patient underwent total thyroidectomy and, at the same time, two lymph nodes were removed. Histological examination of the thyroid gland revealed papillary thyroid carcinoma (PTC), T1aN0M0, and histological examination of the lymph nodes showed non-caseating granulomatous inflammation. After further investigation, a diagnosis of sarcoidosis (SA) was made.

Coexistence of SA and PTC may yield a diagnostic challenge as both diseases might involve the lymph nodes of the neck. Furthermore, the case illustrates the importance of close follow-up of even moderate hypercalcaemia, since it may evolve into a hypercalcaemic crisis.

BACKGROUND

Sarcoidosis (SA) is an idiopathic multisystem granulomatous disorder most commonly involving the lungs, skin, eyes or lymphatic system.[1] The lungs are involved in more than 90% of the patients, and 30%–50% have extrapulmonary manifestations, which sometimes account for the clinical presentation.[1 2] Hypercalcaemia is seen in 2%–63% of patients with SA and is generally attributed to an excessive production of 1,25-$(OH)_2$-vitamin D in the granulomas.[3 4]

Brincker and Wilbek found that malignancy was more likely to occur in patients with SA (OR=1.42; p<0.02) compared with the general population.[5] Since then, the possible association between SA and different types of cancer has been noted in individual case reports.[6]

We present one of the rare cases in which SA and papillary thyroid carcinoma (PTC) coexisted at the time of diagnosis, and the clinical presentation was symptomatic severe hypercalcaemia.

CASE PRESENTATION

A 65-year-old Caucasian Danish man was admitted to the emergency department at a tertiary care hospital due to incidental finding of a ionised calcium=1.83 mmol/L (normal range: 1.18–1.32 mmol/L). The patient suffered from hypertension treated with losartan (50 mg x 1) and type 2 diabetes treated with metformin (1000 mg x 1), dapagliflozin (10 mg x 1) and Lantus (70 IE x 1). Previously, he had twice been admitted to the emergency department with CT-verified urolithiasis, which both times were treated conservatively with tamsulosin leading to spontaneous stone passage. In both instances, calcium parameters were not assessed.

The patient had felt more tired during the last few months and had experienced an unintended weight loss of 6–8 kg. Apart from this, he was asymptomatic.

INVESTIGATIONS

The physical examination revealed an enlarged thyroid gland, but was otherwise normal. On admission, blood samples were performed including p-D_3 vitamin: 34 nmol/L (50–160 nmol/L), p-parathyroid hormone: 0.5 pmol/L (1.6–6.9 pmol/L), p-thyrotropin (thyroid-stimulating hormone)=0.408 mIU/L (0.300–4.50 mIU/L), and p-creatinine: 168 µmol/L (60–105 µmol/L).

A thyroid scintigraphy was performed showing a multinodular goitre with unequal uptake of iodine-131, but no areas were described with significantly low or high uptake. A whole-body radionuclide bone scan showed no evidence of bone metastases. A CT scan of the thorax and abdomen revealed an enlarged, inhomogeneous thyroid gland causing compression of the trachea and enlarged lymph nodes along the cervical vessels and in the mediastinum. The right lobe of the thyroid gland measured 4×5×11 cm, the left lobe measured 4×4×8 cm and the tracheal diameter was 7–8 mm. A fine needle aspiration from a nodulus in the thyroid gland was performed showing only thyroid tissue. As the patient had obstructive symptoms (exertional dyspnoea), and the cancer suspicion furthermore was considerable, it was decided to offer the patient total thyroidectomy. The patient underwent total thyroidectomy and, at the same time, two lymph nodes were surgically removed. Histological examination of the thyroid gland eventually revealed a 10 mm PTC, T1aN0M0, along with multinodular goitre. Histological examination of the lymph nodes showed non-caseating granulomatous inflammation, suggestive of concomitant SA.

OUTCOME AND FOLLOW-UP

During the admission, the patient was treated with intensive intravenous fluid therapy, 3–4 L per day, causing a reduction of ionised calcium from

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1.83 mmol/L to a level around 1.60 mmol/L, and the patient felt better. However, at the day of discharge, ionised calcium of 1.66 mmol/L was measured, and the patient was discharged to outpatient follow-up nonetheless. No medical treatment was initiated, as the histological examination of the lymph nodes was not completed at the time of discharge. It was planned to measure ionised calcium 2 weeks after discharge.

However, 2 weeks after discharge, the patient was readmitted with fatigue, renal impairment (p-creatinine: 335 µmol/L) and a severely elevated ionised calcium of 2.35 mmol/L. On the day of admission, the patient was treated with intensive fluid therapy, calcitonin (600 IE) and zoledronic acid (4 mg). Treatment with prednisolone 50 mg per day was initiated the day after admission, and the patient's condition rapidly resolved. Blood samples revealed s-interleukin-2 receptor: 1430 ku/L (223–710 ku/L). Based on non-caseating granulomatous inflammation, blood samples and radiological findings, the patient was diagnosed with SA. The patient was once again discharged to outpatient follow-up, and prednisolone dose was gradually reduced to 2.5 mg per day over the following 1.5 years, but after reduction from 5 to 2.5 mg per day, he experienced relapse of hypercalcaemia (ionised calcium=1.69 mmol/L), and prednisolone was increased to 5 mg per day with a satisfying clinical and biochemical response. Chest X-rays were performed regularly showing regression of mediastinal lymphadenopathy. The patient had no relapse of thyroid cancer after 3 years of follow-up.

DISCUSSION

The hypothesis that there might be a link between SA and malignancy is supported by results from cross-registry studies[1 7] which show increased incidence rates of cancer in patients with SA. The largest study,[7] to our knowledge, retrospectively followed 9015 patients with a diagnosis of SA and found a relative risk of 1.3 ($p<0001$) for cancer compared with population-based incidence rates matched on sex, age and calendar period. A great effort was done to minimise bias. On the other hand, another cross-registry study[8] found no excess incidence of malignancy in patients with SA, although this might partly be due to lack of power. Overall, the current literature on the subject is conflicting, and causality remains unproven. Due to the observational design of the studies, bias cannot be entirely ruled out.

Concomitant PTC and SA have previously been described in less than a dozen case reports,[9–14] with a wide range of clinical presentations, and a possible association has been proposed. In the present case report, however, the patient underwent total thyroidectomy due to obstructive symptoms and multinodular goitre, and the finding of PTC may be seen as incidental. Incidental finding of small PTC (≤10 mm) is common in patients undergoing thyroidectomy for a presumably benign thyroid disease with incidence rates ranging from 2% to 24% in different studies.[15] From this perspective, it is most likely that the coexistence of PTC and SA in the present case report represents a random association. Nonetheless, this question remains unanswered. It should be mentioned that autoimmune thyroid diseases are also seen with an increased prevalence in patients with SA.[16]

Coexistence of PTC and SA can cause a diagnostic challenge, especially because both diseases might involve the lymph nodes of the neck. As such, SA can mimic metastatic PTC[10 11] and, on the other hand, cervical lymphadenopathy might lead to insufficient investigation in a patient with known SA implying the risk of overseeing a metastatic PTC. Furthermore, a so-called sarcoid reaction with non-caseating granulomas can be seen in lymph nodes and primary tumours as a non-specific reaction to malignancy,[6 9] a condition that complicates the interpretation of the histological investigation. In the present case report, various circumstances support that the patient had indeed SA, and not 'just' a sarcoid reaction in the lymph nodes caused by the thyroid cancer. First, a sarcoid reaction in lymph nodes is not known to cause hypercalcaemia. Second, sarcoid reaction in lymph nodes caused by malignancy appears in the lymph nodes draining the primary tumour.[17] The patient had mediastinal lymphadenopathy, a key finding in SA, and the mediastinal lymph nodes do not drain the thyroid gland. Finally, a sarcoid reaction is not known to cause elevated interleukin-2 receptors. However, it should be mentioned that investigations on this subject are sparse.

This is the first report of severe hypercalcaemia in a patient with coexisting SA and PTC. The patient's symptoms in this rare case were primarily caused by hypercalcaemia, which evolved into hypercalcaemic crisis. According to the literature, hypercalcaemic crisis due to SA is rare,[4 18–20] and in fact, an ionised calcium level of 2.35 mmol/L is, to our knowledge, one of the highest reported.

Acute treatment of hypercalcaemic crisis, no matter what course, should consist of aggressive fluid therapy and bisphosphonate therapy, even though bisphosphonates are mainly effective in lowering calcium in hypercalcaemia attributable to bone metastasis. Calcitonin and loop diuretics should be considered under certain circumstances.[18] In the case of hypercalcaemia caused by SA, however, bisphosphonates are with sparse or no effect, and hypercalcaemia will tend to recur if the patient is not treated with anti-inflammatory drugs since hypercalcaemia is caused by excessive 1,25-$(OH)_2$-vitamin D production in the granulomas.[4] Therefore, the most important treatment of SA-related hypercalcaemia is in fact prednisolone until disease control is achieved. When the patient in this case was initially admitted with moderate hypercalcaemia, he was only treated with fluid therapy, and he was discharged with ionised calcium=1.66 mmol/L. Shortly after discharge, he developed hypercalcaemic crisis. It is the impression of the authors of the present case report that the severity of hypercalcaemia was underestimated at the time of the first discharge, because the patient felt better and was clinically well. Retrospectively, it was irresponsible to discharge the patient with ionised calcium as high as 1.66 mmol/L and with no medical treatment initiated.

The present case provides an example of severe hypercalcaemia and the rare coexistence of SA and PTC. Clinicians should be aware of this, since concomitant SA and PTC may yield a diagnostic challenge. Finally, clinicians should be aware not to underestimate moderate hypercalcaemia as it may evolve into a hypercalcaemic crisis.

Learning points

- The rare coexistence of sarcoidosis and papillary thyroid cancer may yield a diagnostic challenge.
- Sarcoidosis can present with severe hypercalcaemia as the main symptom.
- Moderate hypercalcaemia should not be underestimated as it may evolve into a hypercalcaemic crisis.

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