Case Report

Hypercalcaemia in an idiopathic hypoparathyroidism patient, due to sarcoidosis

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Abstract
We report the case of a female 68 years old patient who appeared in the emergency department (ED) with severe weakness, vomiting and mild confusion with onset 5 days before admission. Previous medical history consisted of idiopathic hypoparathyroidism, diabetes mellitus, hypertension, chronic renal disease and an ischemic stroke. She was previously, in other hospital admitted, multiple times due to hypercalcaemia attributed to high doses of per os calcium and vitamin D, and dosage was adjusted. Physical examination in the ED revealed that patient was lethargic but responsive in sample questions. Rest of clinical examination had no significant findings. The laboratory test showed that corrected calcium levels were elevated 13.3mg/dl. Calcium therapy was withheld and patient was treated with intravenous fluids and dieresis. Further clinical investigation and laboratory investigation, showed that 1.25(OH)₂D₃ was elevated as well as serum ACE. Computing tomography (CT) was performed, revealing thoracic lymphadenopathy. Trans-bronchial biopsy of lymphatic tissue revealed granulomatous disease, compatible with sarcoidosis. Corticosteroid treatment was initiated, with methylprednisolone 32 mg following improvement in calcium levels. Cases of concomitant hypoparathyroidism and sarcoidosis are rare. Treatment of cases of concomitant sarcoidosis and hypoparathyroidism is challenging and requires careful monitoring and collaboration between specialists.

Keywords: Hypercalcaemia, Idiopathic hypoparathyroidism, 1.25(OH)₂D₃, Sarcoidosis

Introduction

Idiopathic primary hypoparathyroidism is an infrequent disease among adults, especially if not associated with genetic disease such as Di George syndrome. Most commonly hypoparathyroidism is a result of surgical removal of the parathyroid glands during operation in the cervical area. Sarcoidosis is a multiorgan granulomatous disease, more frequently encountered than primary hypothyroidism. Hypocalcaemia is the most common finding in hypoparathyroidism. The opposite characterizes, hypercalcaemia is finding, in some cases of sarcoidosis due to 1.25(OH)₂D₃ from granulomas. Concomitant idiopathic hypoparathyroidism and sarcoidosis has rarely been described. Here, we describe a rare case of an elderly woman with idiopathic primary hypoparathyroidism who developed hypercalcaemia attributed to underlying sarcoidosis.

Case report
A female 68 years old patient presented with five day duration of severe weakness, fatigue, nausea, vomiting and mild confusion. Previous medical history consisted of idiopathic hypoparathyroidism diagnosed ten years prior, diabetes mellitus, hypertension, chronic renal disease and an ischemic stroke 7 months prior (resulting in dysarthria). At the time of presentation the patient was treated with per os calcium with cholecalciferol (500 mg + 400 IU) tow times in day, insulin glargine, metformin, a beta-blocker, a calcium channel blocker and a thiazide diuretic (12,5 mg). In the past two years, patient was admitted multiple times due to hypercalcaemia attributed to high doses of calcium with cholecalciferol (1000 mg + 800 IU) tow times in day, and dosage was adjusted.

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At the current presentation, patient was lethargic but responsive in some questions. She was afebrile, with normal vital signs. Rest of clinical examination was impeccable. Initial laboratory examination revealed mild leukocytosis [white blood cell count 10100/μl (normal range: 4600-10200/μl)], elevated C-reactive protein [CRP: 7.15 (normal range: <0.3 mg/dl)], normal procalcitonin test: 0.12 (normal range: <0.5), normal renal function (eGFR: 82 mL/min/1.73m²), elevated alkaline phosphatase [ALP: 56 U/l (normal range: 34-120 U/l)], gamma glutamyl tranferase [γGT: 30 U/l (normal range: 9-35 U/l)], erythrocyte sedimentation rate was elevated (ESR:90). Corrected calcium levels were elevated 13.3 mg/dl. ECG was normal. Chest radiography (Figure 1) appears hilum enlargement. The patient was admitted for further evaluation.

Calcium therapy was withheld and patient was treated with intravenous fluids and diuresis. Calcium levels were improved with treatment (calcium levels 10.3 mg/dl but in 24 hours after fluid replacement was ceased, levels increased rapidly (calcium levels 12.2 mg/dl)).

Clinical investigation was directed to the underlying cause of resistant hypercalcaemia. Renal function was stable with GFR 30 ml/min, PTH was low (2.36 pg/ml) excluding secondary hyperparathyroidism due to renal failure. Phosphorus levels were mildly increased (4.9 mg/dl), a finding incompatible with hyperparathyroidism or paraneoplastic hypercalcaemia. Since the patient was receiving vitamin D supplements, 25(OH)vitD₃ was measured but was found in normal range limits (29 μg/L). Thyroid function was normal. Since alkaline phosphatase levels were normal as were LDH levels, bone metastatic disease was considered unlikely. Imaging studies with CT scan (Figure 2) was performed revealing lymphadenopathy in the axillas, pro-artoritc, paratracheal, sub-carina and mesenteric. PPD test was performed and was unreactive as was quantiferon test. 1.25(OH)₂vitD₃ was elevated (60 pg/ml) as well as serum sACE (91 U/L). Bronchoscopy and bronchial lavage was performed, revealing an elevated CD4/CD8 ratio of 3.8. Trans-bronchial biopsy of lymphatic tissue revealed granulomatous disease, compatible with sarcoidosis. Gallium scan (Figure 3) was performed as well and revealed only the lymphadenopathy noted from CT scan.

Corticosteroid treatment was initiated, with methylprednisolone 32 mg with following improvement in calcium levels (calcium levels 9.7 mg/dl).

She was discharged after 20 days with normal calcium levels and was followed up in sarcoidosis specializing department of our hospital.

**Discussion**

This is a rare case of sarcoidosis in a patient previously diagnosed with idiopathic hypoparathyroidism. Cases of concomitant hypoparathyroidism and sarcoidosis are scarce in literature and all cases have been described more that 40 years prior, and most cases refer to hypoparathyroidism due to surgical removal of the glands during thyroidectomy1-4. In known hypoparathyroidism patients, most cases of hypercalcaemia are attributed to inappropriate excessive
Concomitant hypoparathyroidism and sarcoidosis

Calcium intake or poisoning from vitamin D supplementation. In such patients, diagnosis of an underlying disease causing hypercalcemia can be challenging. In this case, the patient was admitted multiple times due to hypercalcemia, yet suspicion of underlying disease had not been raised.

Sarcoidosis is a systematic disease of unknown etiology. It affects patients of all ages but most cases diagnosed are 25-40 years old, and females are affected most frequently. It is characterized by the formation of granulomatous lesions in many organs. Respiratory symptoms are the most common cause for seeking medical assistance. Peripheral lymphadenopathy is also common. Regarding severe manifestations, pulmonary fibrosis is the most usual. In our case, no respiratory symptoms were present, either at presentation or mentioned in medical history. Although the patient had thoracic and intrabdominal lymphadenopathy in imaging studies, peripheral lymphadenopathy was absent. Disorders in calcium metabolism in sarcoidosis have been noted from early cases, with hypercalcemia being the most noted. However rare cases of hypocalcemia associated with sarcoidosis have been described, in connection to hypoparathyroidism. Hypercalcemia is noted in sarcoidosis but in less than 5% of cases, and is mostly associated with male sex. Our patient was much older than the usual age of diagnosis, female and the presenting symptom was a result of hypercalcemia, even though she had underlying hypoparathyroidism. sACE is linked with sarcoidosis activity and is useful in monitoring the disease rather than diagnosis itself. Elevation of sACE can be noted in cases of tuberculosis, fungal infections, thyroid disease and Gaucher’s. In our case, sACE was elevated, directing investigation towards sarcoidosis, since other causes were excluded. Bronchial lavage is useful in the diagnosis, especially when CD4/CD8 ratio is over 3.5 as was the case in this patient. Gold-standard for the diagnosis however is histopathological findings of noncaseating granulomas on biopsy from affected organs in a patient with compatible clinical and radiological findings, provided that other diagnosis was excluded. In our case,
only lymph nodes could be biopsied, since no other organs were obviously affected. Other causes of hypercalcaemia were thoroughly investigated and were excluded. Treatment with calcium and vitamin D supplements was withheld with no improvement. Secondary hyperparathyroidism was excluded from laboratory testing. Underlying malignancy was not noted from imaging studies. Elevated 1,25(OH)2 D3 levels raised the suspicion of underlying granulomatous disease. Tuberculosis was excluded from laboratory examination.

Presence of compatible clinico-radiological findings, elevated sACE, elevated CD4/CD8 ratio in bronchioalveolar lavage and compatible histopathology raises no doubts in the diagnosis of sarcoidosis in this case.

Treatment of sarcoidosis is based on corticosteroids and symptomatic treatment of hypercalcaemia with intravenous fluids and diuretics initially7,8. However, treatment of hypoparathyroidism consists in calcium and vitamin D supplementation15-17 which in our case resulted in exacerbation of hypercalcaemia. Treatment of cases of concomitant sarcoidosis and hypoparathyroidism is challenging and requires careful monitoring and collaboration between specialists in order to avoid complications from either disease or their treatment.

Conclusion

It is a rare case of sarcoidosis related hypercalcaemia in a patient with previously diagnosed idiopathic hypoparathyroidism. It affects patients of all ages but most cases diagnosed are 25-40 years old. Our patient was much older, had underlying hypoparathyroidism and the presenting symptom was a result of hypercalcaemia. Gold-standard for the diagnosis of sarcoidosis is histopathological findings of noncaseating granulomas on biopsy. Diagnosis of the underlying cause of hypercalcaemia in cases of hypoparathyroidism can be quite challenging and high clinical suspicion is essential. Besides diagnostic challenges, treatment is also complicated and requires careful monitoring and collaboration among specialists.

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