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Case Series
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Clinical Features of Iatrogenic Hypercalcemia in Sarcoidosis Patients

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Abstract

Severe hypercalcemia is extremely rare in clinical practice and usually arises due to hyperparathyroidism and malignancy or paraneoplastic syndrome associated with malignancy. Hypercalcemia develops in approximately 10% of the sarcoidosis patients while it has also been described in patients with other granulomatous diseases such as tuberculosis. This abnormality of calcium metabolism is caused by the dysregulated production of calcitriol by activated macrophages in the granulomatous foci of sarcoidosis. Undetected hypercalcemia may have deleterious sequela in sarcoidosis patients, especially without a previous diagnosis, such as nephrocalcinosis and renal failure. This metabolic defect may be exacerbated by sun exposure, phosphorus or vitamin D intake.

We present seven cases of sarcoidosis to define the clinical features of such patients who are prone to develop hypercalcemia induced by vitamin D treatment. While only two of our patients had a previously diagnosed sarcoidosis, it was detected in the others while investigating the cause of hypercalcemia. Given the rarity of hypercalcemia due to sarcoidosis and its crucial consequences, it is an imperative that the clinicians should definitely consider the possibility of sarcoidosis before commencing vitamin D treatment to their patients. The sarcoidosis features of our case series reveal the criteria required for clinicians to suspect a possible sarcoidosis disease antecedently and to determine the diagnosis before iatrogenic hypercalcemia develops.

Keywords: Sarcoidosis; Hypercalcemia; Vitamin D; Iatrogenic hypercalcemia

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Introduction

Hypercalcemia is a relatively common clinical problem that results when the entry of calcium into the circulation exceeds the excretion of calcium into the urine or deposition in bone. It has been described mostly in patients with granulomatous diseases [1-3]. Among them, sarcoidosis [4-10] and tuberculosis [11-15] are probably the most common. Sarcoidosis is a chronic granulomatous disorder of unknown origin characterized by the presence of non-classified granulomas in various organs including lung disease in 95% of the patients while eyes, skin and lymph nodes are other commonly involved organs [16-17]. Hypercalcemia occurs in 4% to 11% of the sarcoidosis patients caused by the increased conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D by the enzyme 25-hydroxyvitamin-D-1α-hydroxylase in the macrophages of pulmonary alveoli and granulomas [5-7,18].

We report seven cases of sarcoidosis patients who presented with hypercalcemia due to prior vitamin D treatment. Hypercalcemia is a well-known metabolic feature of sarcoidosis that may lead to serious clinical consequences if undetected. In patients with a previously known or unknown sarcoidosis diagnosis, clinicians should be meticulous for hypercalcemia in regard to its significant challenges before commencing vitamin D treatment to their patients. In this case series, the clinical manifestations of sarcoidosis patients with iatrogenic hypercalcemia are investigated. Our aim is to define the clinical features of sarcoidosis patients who are prone to develop a possible iatrogenic hypercalcemia thereby to predict and prevent the occurrence of high serum calcium levels beforehand in patients with or without a previously known sarcoidosis diagnosis.

Case Series

Case 1

A 42-year-old male presented with a 2-weeks history of fever and dysuria. He was a non-

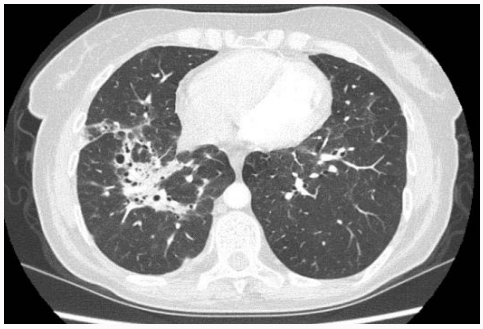

Figure 1: Thorax CT stage III sarcoidosis with parenchymal infiltrations, fibrotic and bronchiectasis lesions in the middle lobe with ground-glass opacities in both lungs.

smoker. Past history included sarcoidosis of ten years and a surgical resection for thyroid carcinoma six years ago. His father and brother had sarcoidosis. The patient had been commenced on oral vitamin D treatment for deficiency four weeks ago. His vital signs revealed an intermittent fever of 37.8ºC, blood pressure of 140/70 mmHg, a heart rate of 84 beats/min and a respiratory rate of 14 breaths/min. Serum biochemistry and blood count tests were normal except for an elevated serum calcium (13.6 mg/dl) level. Tuberculin test was negative. Pulmonary function tests revealed a moderate restrictive abnormality with a mild decrease in DLCO/VA [diffusing capacity divided by the alveolar volume (DLCO/VA)]. Chest X-ray showed bilateral infiltrations in the upper and middle zones. Thorax CT [Computed Tomography] revealed bilateral alveolar parenchymal infiltrations and bronchiectasis lesions (Figure 1). BAL [Bronchoalveolar Lavage (BAL)] analysis demonstrated lymphocytosis with an increased CD4/CD8 ratio of 4.2 compatible with active sarcoidosis. BAL culture was negative for bacteria, fungus and mycobacteria. Ocular examination demonstrated anterior uveitis. Final diagnosis was stage III sarcoidosis. The patient was commenced on methylprednisolone for sarcoidosis and persistent hypercalcemia while ciprofloxacin was started for the urinary tract infection.

Case 2

A 48-year-old female was referred for abdominal pain and skin lesions. She had type 2 diabetes mellitus for ten years and polyneuropathy for two years. Physical examination revealed cutaneous scaly lesions (Figure 2) below the knee and a right supraclavicular lymphadenopathy. The patient had been started oral vitamin D 300.000 IU/ml three months ago by her general practitioner for osteoporosis. Laboratory evaluation showed normal results except for a high serum calcium (14.6 mg/dl) and a high urinary calcium (560 mg/day) level. Tuberculin test was negative. Pulmonary function tests revealed a mild restrictive defect and a mild decrease in DLCO/VA. Chest X-ray demonstrated bilateral parenchymal infiltrations. Thorax CT revealed pulmonary infiltrations in upper lobes, middle lobe and lingula. Pathology of the transbronchial, skin and excisional biopsy of the right supraclavicular lymph node biopsy revealed non-classified granulomatous inflammation. BAL cell count, differential cytology and CD4/CD8 ratio was within normal limits while culture was negative for bacteria, fungus and mycobacteria. Ophthalmologic examination did not reveal any pathologic findings. Final diagnosis was stage III sarcoidosis. Methylprednisolone was started for sarcoidosis stage III and zoledronic acid was commenced for hypercalcemia.

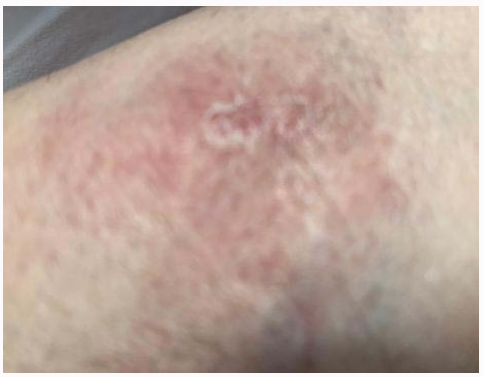

Figure 2: Cutaneous scaly lesions below the knee.

Case 3

A 53-year female was admitted for constipation, polydipsia and polyuria of one month. She had a past medical history of sarcoidosis, chronic HCV infection, a cholecystectomy and a gastric hernia operation. She had been started vitamin D treatment for low serum levels two months ago. Physical examination was unremarkable and did not reveal any pathologic findings. Laboratory evaluation was notable for an elevated serum calcium level at 14.2 mg/dl with a normal complete blood count and serum biochemistry. Tuberculin test was negative. Bilateral parenchymal infiltrations were noted on chest X-ray and thorax CT at the upper, middle lobes and lingula compatible with stage III sarcoidosis. Pulmonary function tests revealed a mild restrictive pattern with a moderate decrease in DLCO/VA. BAL culture was negative for bacteria, fungus and mycobacteria. Ocular examination showed intermediate uveitis. Methylprednisolone was commenced for sarcoidosis and zoledronic acid was given for sarcoidosis associated hypercalcemia.

Case 4

A 54-year-old female presented with mild arthralgia, bone pain and weight loss. Her medical history included diabetes mellitus and hypertension. She had been commenced on vitamin D for osteoporosis four months ago. Physical examination was normal other than a high blood pressure of 170/100 mmHg. Serum laboratory results showed an elevated serum calcium (12.8 mg/dL) and a high ACE [Angiotensin-Converting Enzyme (ACE)] level (94 IU/ml). Tuberculin test was negative. Chest x-ray showed infiltrative lesions in the upper and middle zones of both lungs. Pulmonary function tests demonstrated a mild restrictive defect with a mild DLCO/VA decrease. Chest CT revealed alveolar infiltrations in the upper lobes. Histopathology of the transbronchial lung biopsy revealed non-classified granulomatous inflammation compatible with sarcoidosis. BAL cell count, differential cytology and CD4/CD8 ratio revealed normal findings. BAL culture was negative for bacteria, fungus and mycobacteria. Ophthalmologic examination demonstrated anterior uveitis. Final diagnosis was stage III sarcoidosis. Methylprednisolone 24 mg/day was commenced for sarcoidosis, associated uveitis and hypercalcemia.

Case 5

A 39-year-old female was referred for dry cough and blurred vision. There was no relevant past medical and family history. The patient had been treated with 300.000 IU/ml with vitamin D for osteoporosis that was started six months ago. Physical examination was unremarkable with normal vital findings. Laboratory results demonstrated a high serum calcium (13.9 mg/dL) level with a normal

blood count and normal serum biochemistry. Chest X-ray showed infiltrative lesions in the upper and mid zones. Tuberculin test was negative. Pulmonary function tests revealed a mild restrictive abnormality with a mild decrease in DLCO/VA. Thorax CT revealed parenchymal infiltrations, fibrotic and bronchiectasis changes in the right middle lobe with mild ground-glass opacities in both upper lobes. Pathology of the transbronchial biopsy samples revealed non-classified granulomatous inflammation. BAL cytology showed lymphocytosis with a high CD4/CD8 of 4.1 while BAL culture was negative for infectious agents. Ocular examination revealed anterior uveitis. Final diagnosis was stage III sarcoidosis. Methylprednisolone was initiated for sarcoidosis and sarcoidosis associated hypercalcemia and uveitis.

Case 6

A 56-year-old male was referred for dry cough, fatigue and weight loss. His personal history did not include any significant disease. His father had myocardial infarction and her sister was under treatment for lymphoma. Physical examination and vital findings were normal except for a erythematous and popular rash on the anterior right forearm. Laboratory results showed high serum calcium of 12.8 mg/dl and a urine calcium level (260 mg/day) above normal. Tuberculin test was negative. Chest X-ray showed fibrotic parenchymal lesions in the middle lung. Pulmonary function tests revealed a mild restrictive defect. Thorax CT demonstrated fibrotic and bronchiectasis lesions in the upper and middle zones of both lung parenchyma. BAL cytology demonstrated normal cell and differential count. BAL culture was negative for bacteria, fungus and mycobacteria. Transbronchial and cutaneous biopsy revealed non-classified granulomatous infiltration. Ocular examination demonstrated bilateral anterior uveitis. Methylprednisolone was started for the treatment of sarcoidosis and associated anterior uveitis, hypercalcemia and cutaneous disease.

Case 7

A 46-year-old male presented with a maculopapular rash, constipation and fatigue of two weeks. Personal and family history was excellent. He had been commenced vitamin D six months ago. Physical examination demonstrated maculopapular rash on the anterior chest wall (Figure 3) with otherwise normal physical and vital findings. Laboratory results were within normal levels except for a high serum calcium (13.8 mg/dL) level and a high serum ACE (92 IU/L) level. Tuberculin test was negative. Chest X-ray showed bilateral parenchymal infiltrative lesions in the upper lung zones. Pulmonary function tests revealed a mild restrictive abnormality and a moderate decrease in DLCO/VA. Parenchymal infiltrations, bronchiectasis lesions and a thin walled cyst in the right lung with

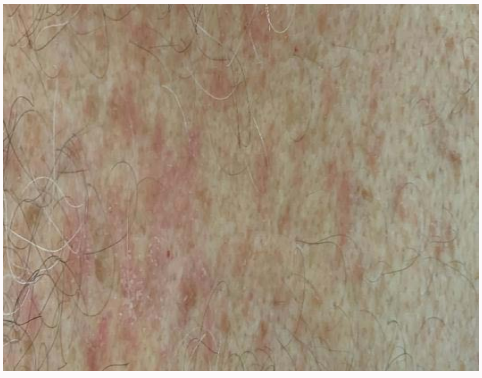

Figure 3: Maculopapular rash on the anterior chest wall.

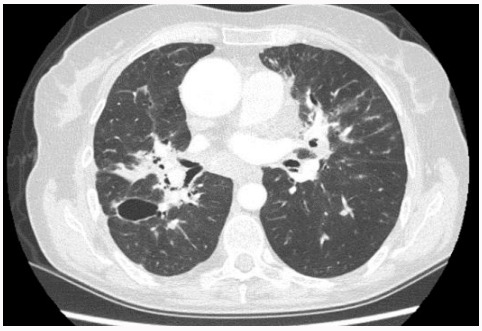

Figure 4: Thorax CT revealing stage III sarcoidosis with a cystic lesion and fibrotic parenchymal changes.

ground-glass opacity in the left upper lobe (Figure 4) were observed in the thorax CT. Pathologic examination of the transbronchial biopsy specimen revealed non-classified granulomatous inflammation while BAL demonstrated lymphocytic alveolitis with a 4.6 CD4/CD8 ratio. BAL culture was negative for infectious organisms including bacteria, fungus or mycobacteria. Histopathology of the cutaneous biopsy demonstrated non-classified granulomas in the dermis with epithelioid histiocytes and CD4+ T lymphocytes. Ophthalmologic examination revealed anterior uveitis. Final diagnosis was stage III sarcoidosis with associated hypercalcemia ocular and cutaneous involvement. Methylprednisolone 32mg was commenced for sarcoidosis treatment.

Discussion

Hypercalcemia is an uncommon medical condition that primarily occurs due to primary hyperparathyroidism and malignancy associated with bone metastasis or paraneoplastic syndromes. It has also been described in granulomatous disorders such as sarcoidosis, tuberculosis, berylliosis and leprosy [1-4]. Sarcoidosis is a chronic disease characterized by granulomatous inflammation and the presence of non-classified granulomas in the involved organs, mainly the lungs, lymph nodes and skin [16-18]. Hypercalcemia is detected in approximately 10% of the sarcoidosis patients due to the abnormal calcium metabolism secondary to increased synthesis of calcitriol by macrophages [4-7]. We present seven cases of iatrogenic hypercalcemia due to vitamin D treatment in patients with or without a previously known sarcoidosis diagnosis.

The most crucial feature of these patients was the presence of sarcoidosis associated hypercalcemia that was exacerbated due to the prior vitamin D treatment commenced for osteoporosis or vitamin D deficiency. The second point was the presence of advanced sarcoidosis designated as stage III in all patients. The third hallmark was the existence of three organ sarcoidosis in these cases. Following steroid treatment, the clinical course of sarcoidosis became stable while the calcium levels returning to normal in each patient. The triangulation point of these cases was the necessity to undergo a thorough evaluation in terms sarcoidosis, that may lead to iatrogenic hypercalcemia, for all patients who are be treated with vitamin D since it is well-known that unnoticed or in discriminable hypercalcemia may lead to deleterious effects. As the results of our study indicate, some clinical features of sarcoidosis appear to be useful in predetermining the probability of iatrogenic hypercalcemia that may develop following vitamin D treatment in sarcoidosis patients with or without a previous known diagnosis.

Harrell and Fisher have first reported the occurrence of

hypercalcemia in sarcoidosis [19]. Albright et al. have shown that hypercalcemia and hypercalciuria in sarcoidosis was due to the elevated levels of vitamin D [20]. Bell et al. have revealed that levels of 1,25-dihyroxy vitamin D was the cause for abnormal calcium metabolism in sarcoidosis patients [21]. Since vitamin D production is substrate-dependent, the development of hypercalcemia due to vitamin D treatment in patients with sarcoidosis is a great possibility. It is well-known that special care is required in sarcoidosis patients who are to be supplemented with vitamin D or calcium [22] and thereby close monitoring of serum calcium levels is required to prevent the occurrence of hypercalcemia in these patients. Seven cases developed hypercalcemia due to the vitamin D treatment while only one of these had a previously diagnosed sarcoidosis in our case series. Presence of unidentified sarcoidosis in patients to be treated with vitamin D appears to be a crucial risk for iatrogenic hypercalcemia. Such a possibility should always be considered by clinicians.

In patients with a medical history of sarcoidosis in their background, the effects of vitamin D treatment can be easily monitored. The problem arises in patients with a previously undiagnosed sarcoidosis when exogenous vitamin D supplementation is commenced. The deleterious outcome of high serum calcium may occur through organs such as the heart. Drawback becomes extremely crucial especially if patients are in an asymptomatic clinical profile for sarcoidosis that may lead to severe consequences if unnoticed or if a delay occurs for diagnosis. In our case series of seven patients, the greatest problem was that only two of the patients had a previously identified sarcoidosis while all of the patients were completely asymptomatic and did not even show the slightest clue relevant to sarcoidosis. The hallmark of these cases is that it may be necessary to evaluate patients for sarcoidosis before starting vitamin D treatment to avoid the serious clinical side effects of iatrogenic hypercalcemia.

There are some points associated with the weakness of our case series size. The first is the small sample size consisting of only seven patients. This is probably related to the low incidence of hypercalcemia in sarcoidosis patients. The other point is that all patients in our series were of Caucasian origin. It is well-known that sarcoidosis may exhibit many different manifestations according to race or genetic differences in terms of the clinical profile, involved organs, treatment response and disease course. Consequently, studies including a large number of patients from different races with distinct genetic characteristics are required to achieve more precise and explicit results. Whether the patients had a previous diagnosis of sarcoidosis or not, it would be extremely useful to define the clinical criteria to predict the probability of iatrogenic hypercalcemia in such cases, as only two of the patients had a previously identified sarcoidosis.

The important hallmark of our case series is the common features and the mutual clinical profile shared by all of our sarcoidosis patients who developed hypercalcemia due to vitamin D treatment. The first is that they had advanced sarcoidosis compatible with stage III disease. Second, each subject had a chronic and persistent sarcoidosis profile that required steroid treatment. The third point was that the patients had three organ involvement including lung, eye, skin or lymph node. The fourth and perhaps the most interesting aspect of our cases was that the patients presented with atypical symptoms or with a bizarre clinical profile that were not easily to be attributed to sarcoidosis although they had stage III disease. Hypercalcemia in sarcoidosis is caused by the abnormality of the calcium metabolism induced by the increased synthesis of calcitriol or vitamin D by macrophages of the granulomatous lesions. High levels of active vitamin D due to hydroxylase activity in macrophages is the most probable cause of hypercalcemia but overproduction of bone resorbing cytokines and parathyroid-related peptide may also play a role [23-25]. As hypercalcemia is due to the abnormal calcium metabolism secondary to increased synthesis of calcitriol by macrophages that are abundant in granulomas, patients with multiple organ involvement appear to carry a more significant risk of hypercalcemia due to the high load of granulomatous tissue. As clearly seen from our cases, the risk of hypercalcemia in sarcoidosis may have arisen due to the high granuloma load due to three organ involvement. The hazard of may also be associated advanced sarcoidosis stage. The presence of these two aforementioned criteria appears to be extremely helpful to anticipate hypercalcemia in such patients. Sarcoidosis associated hypercalcemia can present with an insidious clinical picture that may cause a diagnostic challenge for the clinician and thereby requires a great suspicion for its identification. Existence of previously undiagnosed sarcoidosis should always be considered for patients for whom vitamin D treatment is to be commenced. Common clinical features of sarcoidosis patients in our case series appear to be useful in predicting or identifying the patients who carry a risk of iatrogenic hypercalcemia.

Conclusion

Sarcoidosis may occur unnoticed due to its asymptomatic and insidious clinical nature. In patients with a previously diagnosed or undiagnosed sarcoidosis, clinicians should bear in mind the possibility for the existence of this disorder because vitamin D treatment may lead to significantly high serum calcium levels that may cause deleterious effects. Hypercalcemia of sarcoidosis is due to the abnormal calcium metabolism secondary to increased synthesis of calcitriol by macrophages that are abundant in granulomatous lesions or tissues. Consequently, advanced disease and triple organ involvement in sarcoidosis patients appears to carry a significant hazard for vitamin D induced hypercalcemia due to the higher burden of granulomas comprising numerous macrophages that lead to increased synthesis of calcitriol. Clinical features of sarcoidosis identified among our sarcoidosis case series can be useful to identify patients that carry a high risk of developing iatrogenic hypercalcemia who are to be treated with calcitriol whether or not they present with a prior diagnosis of sarcoidosis. Clinicians should also bear in mind that patients may be completely asymptomatic, may appear with symptoms or a clinical profile that cannot be easily predicated to sarcoidosis.

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