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Case Report .

Hypercalcemic Crisis and Severe Renal Failure Due to Sarcoidosis Followed by Autoimmune Thrombocytopenia on Remission: A Case of Drug-Refractory and Chronic Disease

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ABSTRACT

A 70-year-old woman, with a history of type II diabetes mellitus, presented with a 1-month history of progressive weakness, disorientation and decrease appetite. She was found to have high serum calcium at 3.4 mmol/L and severe renal failure with serum creatinine at 700 umol/L. She had normal kidney ultrasound, vitamin D2, parathyroid hormone and negative Quantiferon and Brucella tests. PET scan showed increase uptake in the paratracheal lymph nodes. Mediastinoscopic lymph node biopsy disclosed non-caseating granulomata. Serum calcium and subsequently her acute renal failure had improved with corticosteroids. She could not tolerate Azathioprine, Cyclophosphamide, and Mycophenolate for severe gastrointestinal side effects. Moreover, her disease did not respond to Cyclosporine A, Methotrexate, Hydroxychloroquine and Rituximab. Ultimately, she was kept on Prednisone 20 mg daily as a long-term maintenance therapy. Eight months after remission, she developed severe thrombocytopenic purpura. Fortunately, the latter was controlled with temporary increase in her corticosteroid dose for 6 weeks. After 2 years of treatment, she had spontaneous remission and Prednisone was discontinued. No relapse was reported 1 year later. In conclusion: Sarcoidosis can induce hypercalcemic crisis, acute renal failure and thrombocytopenia with activity up to 2 years and treatment limited only to Corticosteroids.

Keywords: Hypercalcemia, Prednisone, Renal Failure, Rituximab, Sarcoidosis, Thrombocytopenia.

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INTRODUCTION

Sarcoidosis is a common worldwide disease with an average incidence of 16.5 per 100,000 in men and 19 per 100,000 in women.[1] It is a multi-systemic inflammatory disorder which is characterized by non-caseating granuloma formation.[2] The disease is self-limited in at least half of patients.[3] However, in some, it can progress, relentlessly, to end-stage organ damage especially in the lungs and nervous system.[4] Renal failure is rare in sarcoidosis yet its associated hypercalcemia is a common cause of derangement. The latter was reported in 5-10 % of cases yet was merely described as an incidental finding.[5] Our patient had hypercalcemic crisis with severe renal disease disclosing occult sarcoidosis that was followed by thrombocytopenia during remission. Her presentation is rare and the lessons from management of her chronic disease are worth reporting.

THE CASE

A 70-year-old woman presented with a 1-month history of progressive weakness, disorientation and decrease appetite. Past history was significant for type II DM for 10 years which was controlled with diet and oral hypoglycemic agents. On her initial physical examination, the patient was conscious yet was disoriented X3 and was hardly able to stand from weakness. Her blood pressure and temperature were normal. She did not have lymphadenopathy, goiter, jugular venous distension or edema. Systemic examination did not show abnormality except for low muscle power at 2/5 especially in the proximal ones. Laboratory investigations showed normal peripheral leucocytic and platelets counts. Hemoglobin was 100 g/L with normal MCV. Transferrin saturation% and vitamin B12 were normal. Serum urea and creatinine were elevated at 34 mmol/L and 700 umol/L,

respectively. Serum glucose, electrolytes and liver functions were normal except for corrected calcium at 3.4 mmol/L. Urine routine and microscopy was normal. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound was did not show abnormality. MRI of the brain as well as that of the cervical, thoracic and lumber spines did not show abnormality except for severe osteoporosis. Serum complements, (C3 & C4), IgA and protein electrophoresis were normal. ANA, anti-ds-DNA, ANCA, anti-GBM antibodies, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. CT scan of the chest, abdomen, and pelvis did not show abnormality.

Vitamin D2 and parathyroid hormone levels were normal while vitamin D3 was high at 12 nmol/L (normal: < 2.5). PET scan was done in an attempt to localize tumor or granulomatous disease. However, it showed increase uptake in the paratracheal lymph nodes (Fig.1).

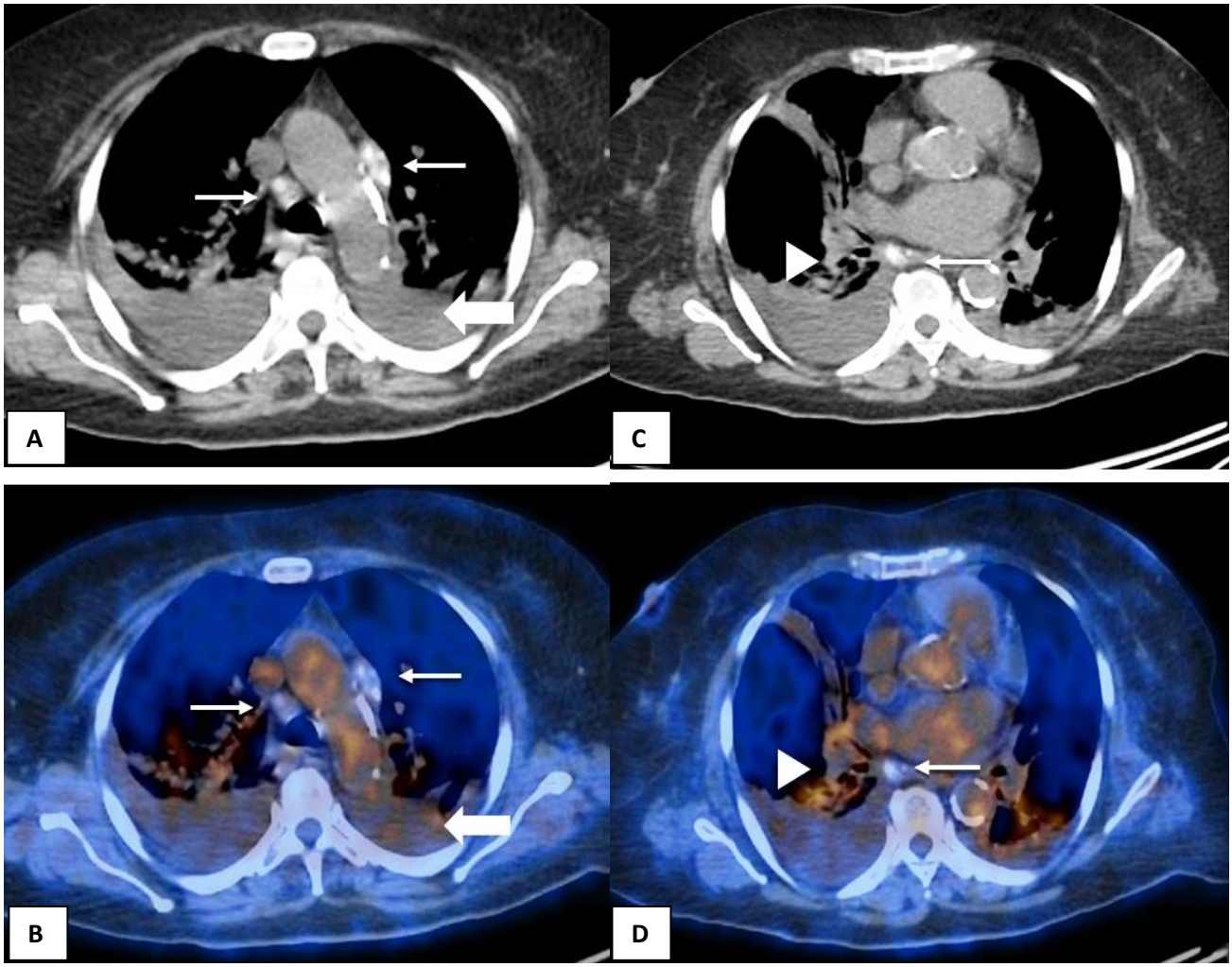

Figure 1: (A) Axial CT images of 18F-FDG PECT/CT scan of the chest; and (B) corresponding fused PET/CT images show calcified perivascular and right paratracheal lymph nodes (thin arrows) with mild FDG uptake; SUVmax is 2.7. (C) Axial CT images of 18F-FDG PECT/CT scan of a lower cut of the chest; and (D) corresponding fused PET/CT images show calcified subcarinal lymph node (thin arrows) with mild FDG uptake; SUVmax is 3.5. Mild FDG activity with SUVmax 4.7 related to bilateral interstitial lung changes (arrowhead) and pleural effusion with SUVmax 3.4 (thick arrow) are seen.

Mediastinoscopic lymph node biopsy disclosed non-caseating granulomata (Fig.2). Serum angiotensin converting enzyme level arrived late and was high at 150 U/L (Normal: < 53 U/L). Prior to establishing the diagnosis, her hypercalcemia was refractory to Calcitonin, Biphosphonate and hydration with normal saline. Subsequently, hypercalcemia, acute renal failure improved with high-dose Corticosteroid therapy. Unfortunately, her diabetes was difficult to control as she remained dependent on prednisone 60 mg/day for > 2 months to keep her corrected serum calcium just < 2.7.

Moreover, she developed severe proximal myopathy and severe osteoporosis. To avoid long-term Corticosteroid-use, Azathioprine, Cyclophosphamide, Mycophenolate mofetil, CyclosporineA, Methotrexate, Hydroxychloroquine and even Rituximab were used. The first 3 drugs were not tolerated for severe gastrointestinal side-effects. The latter 4 drugs, failed to induce remission. Hence, she was kept on Corticosteroids and the dose was decreased with time and had required Prednisone 20 mg daily after 6 months. After 8 months of therapy, and while in remission, she developed thrombocytopenic purpura (Fig.3). She did not have splenomegaly and her peripheral blood film confirmed low platelets. EBV and CMV IgM were negative. She responded to an increment of Prednisone to 60 mg daily for 6 weeks followed by gradual tapering to 20 mg daily. Fortunately, by 2 years, she had spontaneous remission and Prednisone was discontinued. One year later, her serum calcium, creatinine and peripheral platelets counts remained normal without any treatment.

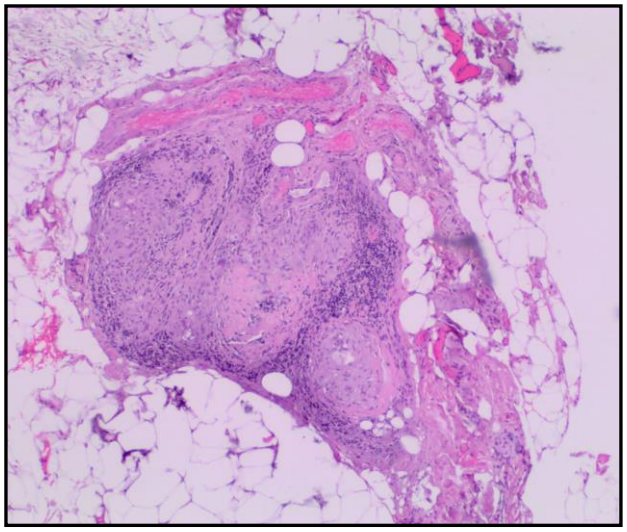

Figure 2: Photomicrograph of a paratracheal lymph node biopsy showing multiple non-caseating granulomata (HE X200).

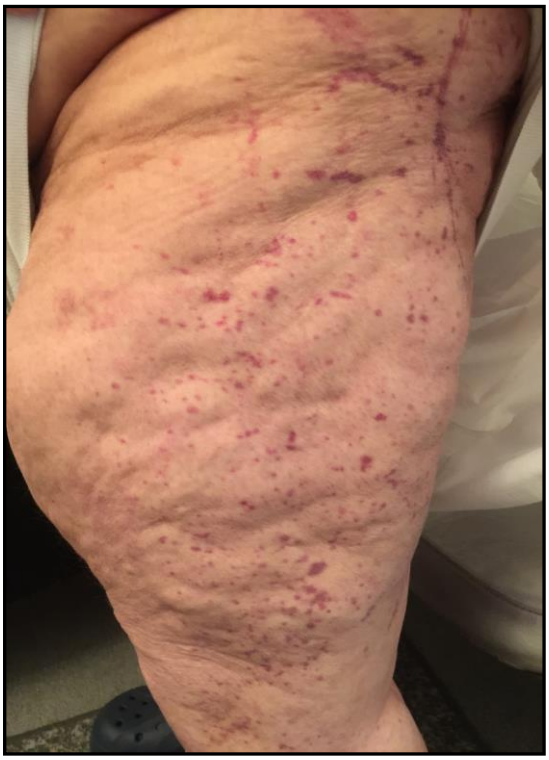

Figure 3: The purpuric rash over the right lower limb.

DISCUSSION

Our patient presented with hypercalcemic crisis as manifested by altered mental status, gastrointestinal manifestations, and generalized weakness. There was no clinical evidence of milk-alkali syndrome, hypervitaminosis D, hyperparathyroidism, chronic granulomatous infections or malignancy. Despite the lack of gross abnormality in her initial chest x-ray and CT, PET scan was suggestive of activity in the paratracheal lymph nodes. Mediastinoscopic biopsy of the latter, established the diagnosis of sarcoidosis. High levels of angiotensin converting enzymes confirmed the diagnosis. Though lung involvement is the most common manifestations of sarcoidosis, chronic renal disease with or without hypercalcemia have been described. Sarcoidosis nephropathy usually manifests as chronic renal impairment due to interstitial nephritis more commonly than glomerular disease. Granulomatous inflammation or other pathologic manifestations may be seen, including membranous nephropathy, minimal change disease, proliferative or crescentic glomerulonephritis, focal glomerulosclerosis and even IgA nephropathy.[6] In sarcoidosis, the chronic hypercalcemia is due to an increase in 1, 25 cholecalciferol (vitamin D3) production from pulmonary macrophages and granulomata which leads to increased absorption of calcium.[7] This can eventually result in hypercalcemia, seen in up to 5 percent of patients with sarcoidosis, as well as hypercalciuria, nephrocalcinosis and nephrolithiasis which may contribute to their chronic renal disease. Our patient presented with hypercalcemic crisis and acute renal failure which is rarely reported as the first sign of an occult sarcoidosis. Currently, there is no US Food and Drug Administration (FDA) approved treatment for sarcoidosis.[8] However, Corticosteroids are efficacious, at most times, and are commonly used for short-term management of progressive cases.[8] Unfortunately, long-term Corticosteroid therapy is associated with multiple side effects especially infections, osteoporosis and uncontrolled diabetes mellitus. Multiple agents were reported to be useful in treatment of the chronic disease viz. Azathioprine, Cyclophosphamide, Mycophenolate mofetil, CyclosporineA, Methotrexate, Hydroxychloroquine and Rituximab.[9] Unfortunately, such steroid-sparing agents were not useful in our patient. Our patient had developed thrombocytopenia after remission of his sarcoidosis. The latter has been reported in less than 2% of patients with sarcoidosis.[10] The etiology is an antibody-mediated destruction, analogous to that seen in idiopathic autoimmune thrombocytopenic purpura.[11] Our patient was off immunosuppressive treatment for > 2 months prior to development of thrombocytopenia. Moreover, she did not receive new drugs prior to it and did not have evidence of infections and malignancy. Fortunately, it responded to corticosteroid treatment confirming the diagnosis of an autoimmune-mediated etiology. Review of the recent data on the pathogenesis of sarcoidosis may provide a plausible explanation of our findings. Sarcoidosis is an autoimmune disease associated with increase CD4 (helper) T-cells leading to inflammation (accumulation of monocytes, macrophages, TNF, INF-γ, multiple interleukins and TGF-β. Moreover, the regulatory T-lymphocytes in the periphery of sarcoid granulomata appear to suppress IL-2 secretion, which is hypothesized to cause the state of anergy by preventing antigen-specific memory responses.[12] Hence, to treat sarcoidosis, broad-spectrum immunosuppressive agent viz. corticosteroids (able to suppress T-lymphocytes) are more efficacious than Cyclosporine A which is an interleukin-2 blocker (the cytokine from T to activate B-lymphocytes) and Rituximab which is a B-lymphocyte blocking agent.[13] Moreover, the development the autoimmune thrombocytopenia, after the induction of remission and hence release of B-cell inhibition by IL-2, is a “rebound phenomenon” similar to that seen after rebound of immune system after treatment of HIV (immune reconstitution syndrome).[14]

In conclusion, a hypercalcemic crisis and acute renal failure can be the sole presentation of an occult sarcoidosis and temporary immune thrombocytopenia can develop during therapy. The disease is self-limited despite a chronic course yet corticosteroids remain a cornerstone in its management.

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