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Systemic Sarcoidosis Presenting as Hypercalcemia-Induced Acute Pancreatitis with Granulomatous Hepatitis: A Diagnostic Challenge in a Tuberculosis-Endemic Region

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Abstract

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by the formation of non-caseating granulomas in affected organs. Hypercalcemia is a recognized metabolic manifestation resulting from increased extrarenal production of 1,25-dihydroxy vitamin D by activated macrophages within granulomas. Acute pancreatitis secondary to sarcoidosis-associated hypercalcemia is uncommon and may present a significant diagnostic challenge, particularly in regions where tuberculosis is endemic. We report a 39-year-old woman who presented with upper abdominal pain, intermittent fever, anorexia, generalized weakness, and significant weight loss of 15 kg over three months. Laboratory evaluation revealed hypercalcemia (12.1 mg/dL), elevated serum lipase (517 U/L), elevated alkaline phosphatase (487 U/L), and suppressed parathyroid hormone levels (5.2 pg/mL), consistent with PTH-independent hypercalcemia. Serum angiotensin-converting enzyme levels were markedly elevated (198.5 U/L), and increased 1,25-dihydroxy vitamin D levels (89pg/ml) suggested active granulomatous disease. The patient was diagnosed with acute pancreatitis (BISAP score 1) secondary to hypercalcemia and was treated with intravenous hydration, calcitonin, and zoledronic acid, resulting in normalization of serum calcium levels and symptomatic improvement. Further evaluation with FDG PET-CT demonstrated hypermetabolic

supraclavicular, mediastinal, abdominal, and inguinal lymphadenopathy with diffuse hepatosplenic uptake. Liver biopsy revealed non-necrotizing epithelioid granulomas with Langhans giant cells, while fine-needle aspiration cytology of an inguinal lymph node showed granulomatous lymphadenitis. Ziehl–Neelsen staining and GeneXpert testing were negative for tuberculosis. Based on the clinical, biochemical, radiological, and histopathological findings, a diagnosis of systemic sarcoidosis was established. Corticosteroid therapy resulted in sustained clinical improvement. This case highlights the importance of considering sarcoidosis in the differential diagnosis of unexplained PTH-independent hypercalcemia presenting as acute pancreatitis and underscores the role of comprehensive multidisciplinary evaluation in establishing the diagnosis.

Keywords: Sarcoidosis, Hypercalcemia, Acute Pancreatitis, Granulomatous Hepatitis, Vitamin D, PTH-independent Hypercalcemia, Granulomatous Lymphadenitis, FDG-PET, ACE, Corticosteroids

Introduction

Sarcoidosis is a chronic multisystem inflammatory disorder characterized by the formation of non-caseating granulomas in affected tissues. First described by Hutchinson in 1877, the disease most commonly affects the lungs and intrathoracic lymph nodes but can involve virtually any organ system. The exact etiology remains unknown; however, an exaggerated immune response to environmental antigens in genetically susceptible individuals is believed to play a major role.[1–3]

The prevalence of sarcoidosis varies globally, with higher rates reported in Northern Europe and African-American populations.[9] Hypercalcemia occurs in approximately 5–10 per cent of patients and results from increased extrarenal production of 1,25-dihydroxy vitamin D by activated macrophages within granulomas.[4,16] Acute pancreatitis is an uncommon manifestation of sarcoidosis and is usually secondary to hypercalcemia.[12]

The diagnosis of sarcoidosis remains challenging in tuberculosis-endemic regions because both conditions may present with constitutional symptoms, granulomatous inflammation, and multisystem involvement.[14] This case is clinically significant because acute pancreatitis was the presenting manifestation of previously undiagnosed systemic sarcoidosis with hepatic and generalized nodal involvement. The diagnosis required integration of biochemical, radiological, microbiological, and histopathological findings to differentiate sarcoidosis from tuberculosis and other granulomatous disorders.

Case Report

A 39-year-old female presented with complaints of upper abdominal pain for three months, intermittent fever, anorexia, generalized weakness, and weight loss of approximately 15 kg over the preceding three months. The abdominal pain was predominantly epigastric, non-radiating, aggravated after meals, and had worsened during the week prior to presentation.

There was no history of jaundice, diarrhea, dysuria, alcohol consumption, smoking, or substance abuse. Upper gastrointestinal endoscopy performed before admission revealed Los Angeles Grade A esophagitis, pangastritis, and bulbar duodenitis. There was no significant past medical history except hemorrhoidectomy.

On examination, pulse rate was 120/minute, blood pressure 140/90 mmHg, respiratory rate 16/minute, temperature 98°F, and oxygen saturation 96 per cent on

room air. General examination revealed no pallor, icterus, edema, clubbing. There was no significant palpable generalized lymphadenopathy. Abdominal examination revealed a soft abdomen without guarding or rigidity.

Laboratory investigations demonstrated hemoglobin 12.9 g/dL, total leukocyte count 8.59 $\times 10^3/\mu L$, platelet count 160 $\times 10^3/\mu L$, serum creatinine 0.9 mg/dL, sodium 130 mEq/L, serum calcium 12.1 mg/dL, AST 43 U/L, ALT 24 U/L, alkaline phosphatase 487 U/L, amylase 52 U/L, and lipase 517 U/L. Based on characteristic abdominal pain and elevated lipase levels, acute pancreatitis with a BISAP score of 1 was diagnosed.[20]

Further evaluation revealed suppressed intact parathyroid hormone levels (5.2 pg/mL), indicating PTH-independent hypercalcemia. Serum angiotensin-converting enzyme level was markedly elevated at 198.5 U/L. Serum 25-hydroxy vitamin D level was low (12.9 ng/mL), whereas 1,25-dihydroxy vitamin D level was (89pg/dL), suggesting extrarenal activation of vitamin D due to granulomatous disease.

The patient was treated with aggressive intravenous hydration, subcutaneous calcitonin, intravenous zoledronic acid, proton pump inhibitors, analgesics, and supportive care. Her symptoms improved significantly, and serum calcium decreased to 9.9 mg/dL before discharge.

Because of persistent constitutional symptoms and unexplained hypercalcemia, further investigations were undertaken. FDG-PET/CT demonstrated hypermetabolic right supraclavicular, mediastinal, internal mammary, abdominal, and inguinal lymphadenopathy. Diffuse heterogeneous uptake was noted in the liver and spleen, along with diffuse uptake in bilateral tonsillar fossae and bone marrow.

Ultrasound-guided liver biopsy revealed multiple non-necrotizing epithelioid granulomas composed of epithelioid histiocytes and Langhans giant cells. No evidence of malignancy or caseous necrosis was identified. Background liver parenchyma showed ballooning degeneration and focal fatty change. Fine-needle aspiration cytology of the right inguinal lymph node demonstrated granulomatous lymphadenitis with epithelioid granulomas and multinucleated giant cells. Ziehl–Neelsen stain for acid-fast bacilli was negative, and GeneXpert testing for Mycobacterium tuberculosis was also negative.

Following multidisciplinary discussion involving gastroenterology, endocrinology, pathology, and nuclear medicine teams, tuberculosis was considered unlikely. Based on the elevated ACE levels, increased 1,25-dihydroxy vitamin D levels, characteristic PET-CT findings, histopathological evidence of non-necrotizing granulomas, and microbiological exclusion of tuberculosis, a diagnosis of systemic sarcoidosis was established.

The patient was initiated on oral prednisolone 30 mg daily with proton pump inhibitor prophylaxis. On follow-up, she demonstrated marked symptomatic improvement with sustained normalization of serum calcium levels and improvement in appetite and general well-being.

Discussion

The present case highlights an unusual presentation of systemic sarcoidosis as acute pancreatitis secondary to PTH-independent hypercalcemia. Although hypercalcemia is a recognized complication of sarcoidosis, pancreatitis resulting from sarcoidosis-associated hypercalcemia remains rare[4,12]. Pancreatitis

secondary to hypercalcemia occurs in less than 0.5% of cases.[8]

The diagnosis was particularly challenging because the patient presented with constitutional symptoms, generalized lymphadenopathy, and granulomatous involvement of the liver, all of which are common features of tuberculosis in endemic regions.[13,14] However, the absence of caseous necrosis, negative acid-fast bacilli staining, negative GeneXpert testing, elevated ACE levels, elevated 1,25-dihydroxy vitamin D levels, and characteristic PET-CT findings strongly favored sarcoidosis.[2,11]

Hypercalcemia in sarcoidosis results from unregulated expression of 1-alpha hydroxylase by activated macrophages within granulomas, leading to increased synthesis of active vitamin D.[4,16] The resulting hypercalcemia suppresses parathyroid hormone secretion and may rarely precipitate acute pancreatitis through calcium-mediated pancreatic acinar cell injury and premature enzyme activation.[12,15]

Another important aspect of this case was the presence of significant extrapulmonary disease with hepatic and generalized nodal involvement. Histologically proven granulomatous hepatitis together with generalized FDG-avid lymphadenopathy supported a multisystem disease process.[10,13] Hepatic involvement is common histologically but is often clinically silent, making this presentation particularly noteworthy.[8,18]

The elevated ACE level, diffuse hepatosplenic uptake on PET-CT, and non-necrotizing granulomas on histopathology provided important diagnostic clues. Similar presentations have been described only rarely in the literature, where sarcoidosis-associated hypercalcemia preceded the diagnosis of systemic disease.[12]

Current international guidelines recommend corticosteroids as first-line therapy for symptomatic sarcoidosis and sarcoidosis-associated hypercalcemia.[11] The favorable response observed in our patient following corticosteroid therapy further supports the diagnosis and highlights the importance of early recognition and treatment. Delayed diagnosis may result in unnecessary anti-tubercular therapy and prolonged morbidity.[11,14]

Conclusions

Sarcoidosis should be considered in the differential diagnosis of unexplained PTH-independent hypercalcemia presenting with acute pancreatitis, particularly when accompanied by constitutional symptoms, granulomatous histopathology, and multisystem involvement.[4,11] Careful integration of biochemical, histopathological, microbiological, and radiological findings is essential for distinguishing sarcoidosis from other granulomatous disorders, especially tuberculosis.[11,14] Early recognition and corticosteroid therapy can result in excellent clinical and biochemical outcomes.[11] This case emphasizes the importance of considering sarcoidosis as a potentially reversible cause of hypercalcemia-induced acute pancreatitis.

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