Hypercalcemic pancreatitis a rare presentation of sarcoidosis
A case report
Agazi Gebreselassie, MDa,b, Alem Mehari, MDa,c,∗, Rahel Dagne, MDa, Firehiwet Berhane, MDa, Angesom Kibreab, MDa,b

Abstract
Rationale: The usual presentation of sarcoidosis is hilar adenopathy, pulmonary reticular opacities, skin, joint, or eye lesions. Pancreatic involvement is unusual and hypercalcemic pancreatitis as initial manifestation is very rare.

Patient concerns: We present a case that presented with 1-day history of vomiting, diffuse abdominal pain, and altered mental status.

Diagnoses: Initial investigations showed highly elevated calcium levels, acute pancreatitis, and kidney failure. Possible causes entertained were malignancy, hyperparathyroidism, hypervitaminosis D, and granulomatous diseases. Full work-up including a hilar lymph node biopsy revealed noncaseating granuloma. After excluding other diseases capable of producing a similar picture, a diagnosis of sarcoidosis was made.

Interventions and outcomes: The patient was started on aggressive intravenous fluid hydration and intravenous calcitonin, after which her altered mental status resolved and both kidney function and hypercalcemia improved. The patient was discharged on oral prednisone and serum calcium level normalized with progressive improvement of kidney function at follow-up.

Lessons: The current case highlights the need for a high index of suspicion for this condition in patients who present with acute pancreatitis, as steroids are the treatment of choice. Thus, prompt recognition of this entity is of therapeutic significance.

Abbreviations: ACE = angiotensin-converting enzyme, EBUS = endobronchial ultrasound, FNA = fine-needle aspiration, PTH = parathyroid hormone, PTHrP = PTH-related protein.

Keywords: hypercalcemia, pancreatitis, sarcoidosis, steroids

1. Introduction
Sarcoidosis is a multisystem disease of unknown etiology. The usual presentation is bilateral hilar adenopathy, pulmonary reticular opacities, skin, joint, or eye lesions. Pancreatic involvement by sarcoidosis is uncommon and hypercalcemic pancreatitis as initial manifestation of sarcoidosis is rare. Acute pancreatitis in sarcoidosis can be either because of active granulomatous pancreatitis or secondary to hypercalcemia. A high index of suspicion for sarcoidosis in patients who present with hypercalcemia and acute pancreatitis has a therapeutic importance, as steroids, which are generally contraindicated in other forms of pancreatitis, are the treatment of choice.

2. Case presentation
A 53-year-old African American female with a medical history of hypertension, type 2 diabetes mellitus, and dyslipidemia presented with a 3-day history of generalized body weakness, 1-day history of vomiting, diffuse abdominal pain, and altered mental status. She had no history of alcohol intake. Her home medications included amlodipine, losartan, metformin, and vitamin D tablets. Upon presentation, the patient had altered mental status with a Glasgow Coma Scale of 10 out of 15 and had diffuse upper abdominal tenderness. Investigations on admission showed, serum creatinine 3.7mg/dL, calcium 16.7 mg/dL, phosphorus 5mg/dL, amylase 678U/dL, lipase 912U/dL, albumin 3.5gm/dL, triglyceride 139mg/dL, and the rest are shown in Table 1.

She was admitted to medical intensive care unit with the impression of acute metabolic encephalopathy, severe pancreatitis, and acute kidney injury all ascribed to severe hypercalcemia. She was then started on aggressive intravenous fluid hydration and intravenous calcitonin, after which her altered mental status resolved and hypercalcemia improved. CT chest without contrast showed paratracheal, subcarinal, and bilateral hilar adenopathy (Fig. 1). CT scan of the abdomen revealed enlarged pancreatic head suggestive of pancreatitis (Fig. 2). CT scan of the brain was within normal limits.
Further work-up for hypercalcemia revealed a parathyroid hormone (PTH) level of 23 pg/mL (normal value 5–63), PTH-related protein (PTHrP) of 49 pg/mL (normal value 14–27), vitamin D₃ 1,25 (OH)₂ of 174 mg/dL (normal value 18–72), and serum angiotensin-converting enzyme (ACE) level was 175 U/L (normal value 9–67).

Endobronchial ultrasound (EBUS)-guided fine-needle aspiration (FNA) from hilar lymph nodes revealed noncaseating granulomas (Fig. 3). The diagnosis of sarcoidosis was made and she was started on oral prednisone and discharged from hospital in stable condition with a serum calcium level of 11.4 mg/dL and improved kidney function. Her calcium profile performed 2 months later was normal. The patient is taking prednisolone 20 mg/day and is presently doing well.

### Table 1

| Variable                              | Reference range       | 5 hours before admission | On admission | 50 days after admission |
|---------------------------------------|-----------------------|--------------------------|--------------|------------------------|
| Hemoglobin, g/day                     | 12.1–15.9             | 9.4                      | 8.6          | 7.3                    |
| White cell count, /mm⁢³                | 3.2–10.6              | 9.8                      | 10.7         | 5.2                    |
| C-reactive protein, mg/day            | <0.8                  | 24.2                     | –            | –                      |
| Urea nitrogen, mg/dL                  | 7–25                  | 48                       | 46           | –                      |
| Creatinine, mg/dL                     | 0.6–1.1               | 3.7                      | 3.4          | 1.52                   |
| Estimated GFR, mL/min/1.73 m²         | 15                    | 17                       | 45           | –                      |
| Calcium, µg/dL                        | 8.5–10.6              | 17.1                     | 14.6         | 10.6                   |
| Phosphorus, mg/dL                     | 2.5–4.5               | 5.0                      | 5.5          | –                      |
| Alkaline phosphatase, U/L             | 30–165                | 151                      | 123          | 81                     |
| Amylase, U/L                          | 28–100                | 678                      | –            | –                      |
| Lipase, U/L                           | 22–51                 | 912.0                    | –            | –                      |
| Triglyceride, mg/dL                   | 20–160                | 139                      | –            | –                      |
| ACE, U/L                              | 9–67                  | 175                      | –            | 72                     |
| PTH, pg/mL                            | 5–63                  | 23                       | –            | 10                     |
| PTHrP, pg/mL                          | 14–27                 | –                        | 49           | <0.74                  |
| Vitamin D₃, 25 (OH)₂, mg/dL           | 18–72                 | 174                      | –            | –                      |
| Protein electrophoresis and immunofixation | –                     | No M protein spike       | –            | –                      |
| Free kappa light chain, mg/L          | 158–502               | 477                      | –            | –                      |
| Free lambda light chain, mg/L         | 100–317               | 251                      | –            | –                      |
| Free kappa:free lambda ratio          | 1.35–2.95             | 1.90                     | –            | –                      |
| TSH, µIU/mL                           | 0.4–4.0               | 2.03                     | 2.85         | –                      |
| Urine calcium, mg/dL                  | 24.9                  | 2.85                     | 6.6          | –                      |
| Bronchial washing                     | –                     | –                        | –            | –                      |
| AFB smear and culture                 | Negative              | –                        | –            | –                      |
| Fungal smear and culture              | Negative              | –                        | –            | –                      |
| T-Spot TB                             | Negative              | –                        | –            | –                      |

ACE = angiotensin-converting enzyme, AFB = acid fast bacilli, PTH = parathyroid hormone, PTHrP = parathyroid hormone-related protein, TB = tuberculosis, TSH = thyroid-stimulating Hormone.

3. Discussion

Sarcoidosis is a chronic granulomatous disorder of unknown etiology that affects many organ systems. Even though it primarily affects the hilar lymph nodes, the lung parenchyma, skin, and the eyes, any organ system can be affected including the gastrointestinal system, reticuloendothelial system, musculoskeletal system, exocrine glands, heart, kidney, and central nervous system.⁴⁷ Clinical manifestations of sarcoidosis tend to vary with age, sex, and ethnicity.⁴⁸ Although hypercalcemia and pancreatitis has been reported, these are rare presenting manifestations.

Our patient presented with highly elevated calcium levels associated with encephalopathy and acute kidney failure. Possible causes entertained for the severe hypercalcemia were malignancy including multiple myeloma, hyperparathyroidism, hyper vitaminosis D, and granulomatous diseases.

Primary hyperparathyroidism is one of the common causes of hyperparathyroidism. Patients are usually asymptomatic, have mildly elevated serum calcium levels (around 12 mg/dL) and the PTH levels are usually elevated.⁴⁹ These findings were not evident in our patient and her PTH levels were not fully suppressed despite a highly elevated serum calcium levels which can be explained by a possible some degree of autonomous parathyroid function.⁴⁶

Diffuse mediastinal and hilar lymphadenopathy with elevated PTHrP level would put malignancy at the top of the differential in...
However, vitamin D2 (exogenous vitamin D) levels were low and phosphate levels and hypercalcemia might favor this diagnosis. D. The patient has been taking vitamin D tablets. The initial high however was not in favor of multiple myeloma in this patient.

Kidney failure. Diagnostic work-up with serum electrophoresis which might present with elevated calcium levels and acute malignant process. Another possible cause is multiple myeloma patient EBUS-guided FNA from hilar lymph nodes ruled out a kidney. The other possibility worth entertaining was hypervitaminosis D. The patient has been taking vitamin D tablets. The initial high phosphate levels and hypercalcemia might favor this diagnosis. However, vitamin D2 (exogenous vitamin D) levels were low and the vitamin D3 levels were elevated despite the discontinuation of vitamin D tablets. The hyperphosphatemia also resolved as the kidney function improved implying acute kidney failure as the cause for it.

Granulomatous diseases are also important causes of hypercalcemia. Tuberculosis (TB) and sarcoidosis are the most common granulomatous diseases causing hypercalcemia. Hilar and mediastinal lymphadenopathy with elevated serum C-reactive protein might suggest TB in this patient but the lack of typical TB symptoms, negative T spot test, negative stain and culture for acid fast bacilli from bronchial washing, and absence of caseating lesions on biopsy speak against the TB.

Our patient most likely presented with newly diagnosed sarcoidosis. Biopsy of hilar lymph nodes revealed noncaseating granuloma. The elevated 1, 25 vitamin D3 levels and ACE inhibitor levels also support the diagnosis of sarcoidosis. The central nervous system manifestation and the pancreatitis are most likely the consequences of the severe hypercalcemia as imaging studies did not reveal any lesions in the brain. The clinical improvement with aggressive hydration and calcium correction also suggest the hypercalcemia as the culprit for the altered mental status and pancreatitis.

The hypercalcemia in sarcoidosis is as the result of the increased production of calcitriol (Vitamin D 1,25) by alveolar macrophages in granuloma which contains the enzyme 1-a-hydroxylase, which converts precursor vitamin D to active calcitriol. Another mechanism of hypercalcemia in sarcoidosis as seen in our patient is via increased production of PTHrP which, like PTH, causes upregulation of 1-a-hydroxylase. Unlike PTH, PTHrP is not regulated by calcium but by interleukin-2 and tumor necrosis factor-α, both of which are increased in sarcoidosis.

Pancreatic involvement by sarcoidosis is uncommon. Acute pancreatitis in sarcoidosis can be either because of active granulomatous pancreatitis or secondary to hypercalcemia. Usually, acute elevations of calcium can cause pancreatitis. The mechanism causing hypercalcemic pancreatitis may be calcium deposition in the pancreatic duct and calcium activation of trypsinogen in the pancreas. Prompt resolution of pancreatitis occurs after treatment with glucocorticoids. Only 5 previous case reports have been described as cases of acute pancreatitis with hypercalcemia in patients with sarcoidosis.

The current case highlights the need for a high index of suspicion for this condition in patients who present with acute pancreatitis, as steroids are the treatment of choice. Thus, prompt recognition of this entity is of therapeutic significance.

In summary, the diagnosis of sarcoidosis requires compatible clinical symptoms, radiological findings, pathological demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar picture. Careful assessment particularly applies to cases where extrathoracic or multiple organ involvement is present.

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Figure 2. Computed tomography scan of the abdomen demonstrating pancreatic head enlargement (arrow).

Figure 3. Pathology from hilar lymph nodes showing collection of histiocytes and multinucleated giant cells consistent with noncaseating granulomatous inflammation.
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