CASE FOR DIAGNOSIS

A “respiratory” cause of abdominal pain

D. Gupta*, R. Agarwal*, A. Singh* and K. Joshi#

CASE HISTORY

A 52-yr-old female presented with complaints of upper abdominal pain, nausea and vomiting. There was no history of prior abdominal pain, abdominal distension and constipation. In June 2003, the patient had presented to her general practitioner with pain and swelling in multiple joints, both small and large. She was diagnosed to have seronegative rheumatoid arthritis and had received diclofenac, vitamin D, calcium supplements and methotrexate (7.5 mg *p.o.*·week⁻¹) for the same. She had partial response, and methotrexate was stopped for the last 6 months of treatment up until June 2005;

however she was continued on diclofenac and calcium supplements.

On examination the patient was conscious and afebrile with a pulse rate of 96 beats·min⁻¹, blood pressure of 130/84 mmHg and respiratory rate of 18 breaths·min⁻¹. Examination of the abdomen showed epigastric tenderness and normal bowel sounds. Otherwise, the physical examination was unremarkable. There were no joint deformities or joint tenderness.

A summary of investigations is shown in table 1, and these included a chest radiograph (fig. 1) and computed tomography of the chest (fig. 2). Fibreoptic bronchoscopy was carried out, and transbronchial biopsies were performed which showed characteristic histological findings (fig. 3).

TABLE 1 Summary of investigations	
Investigation units	Result
Initial investigations	
Complete blood count coagulation profile	Normal
Serum electrolytes	Normal
Urea nitrogen, creatinine mmol·L ⁻¹	14.3, 221
Calcium, phosphate mmol·L ⁻¹	3.7, 1.4
Amylase U·L ⁻¹	1050
Liver function tests, blood glucose	Normal
Chest radiograph	Figure 1
Ultrasound abdomen	Normal
24-h urinary calcium mmol·L ⁻¹	116.5
Parathormone levels pg·mL ⁻¹	1.8
Subsequent investigations	
Computed tomography of abdomen	Normal
Computed tomography of chest	Figure 2
Liver function tests, lipid profile	Normal
Serum electrolytes, renal function tests	Normal
Serum amylase and calcium profile	Normal
Mantoux test (intradermal, 1 TU, read after 72 h)	Negative (no erythema or induration)

TU: tuberculin unit.

FIGURE 1. Chest radiograph of the patient.

*Depts of Pulmonary Medicine, and #Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
CORRESPONDENCE: D. Gupta, Dept of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. Fax: 91 1722745959. E-mail: dheeraj@indiachest.org

FIGURE 2. Computed tomography scan of the chest.

FIGURE 3. Photomicrograph of the transbronchial lung biopsy specimen (haematoxylin and eosin). Scale bar=50 µm.

BEFORE TURNING THE PAGE, INTERPRET THE HISTORY, INVESTIGATIONS, CHEST RADIOGRAPH, COMPUTED TOMOGRAPHY SCAN AND BIOPSY AND SUGGEST A DIAGNOSIS.

INTERPRETATION

The patient had severe hypercalcaemia, acute renal failure and raised amylase, suggesting a diagnosis of acute pancreatitis secondary to hypercalcaemia. The chest radiograph (fig. 2) shows bilateral hilar lymphadenopathy. The computed tomography scan of the chest (fig. 3) shows bilateral hilar and mediastinal lymphadenopathy. Transbronchial biopsy showed noncaseating granulomas (fig. 1). A Ziehl-Neelsen stain for acid-fast bacilli was negative.

Diagnosis: Sarcoidosis with joints and lymph node involvement. Severe hypercalcaemia and hypercalciuria, secondary to sarcoidosis, and contributed to by calcium and vitamin D supplements. Acute renal failure, prerenal; secondary to hypercalcaemia, dehydration. Acute pancreatitis, secondary to hypercalcaemia and sarcoidosis.

TREATMENT AND CLINICAL COURSE

The patient was kept nil per mouth and given intravenous fluids and intravenous proton pump inhibitors. She was managed conservatively for acute pancreatitis and the renal failure improved with intravenous fluids. She was started on oral prednisolone ($40 \text{ mg} \cdot \text{day}^{-1}$) and all her calcium supplements were stopped. With this, her calcium levels started decreasing and normalised in the next 3 days. She was discharged on oral prednisolone.

A repeat chest radiograph, computed tomography scan of the chest and calcium profile performed 2 months later were normal. The patient was taking prednisolone ($15 \text{ mg} \cdot \text{day}^{-1}$) and will continue to take steroids to complete 1 yr of therapy; she is presently doing well.

DISCUSSION

Sarcoidosis is a disorder of unknown aetiology characterised by the presence of noncaseating granulomas. Although most patients present with respiratory, skin or ocular involvement, autopsy studies have shown that virtually any organ system in the body can be affected, including joints, kidney, liver, gastrointestinal, heart and nervous system [1]. Pulmonary involvement in the form of hilar lymphadenopathy, parenchymal infiltrates and fibrosis occurs in more than 90% of patients, but less than half are symptomatic [2]. The diagnosis is often delayed because of the nonspecific nature of the symptoms, as was seen in the current case [3]. Hypercalcaemia has been variably reported to occur in 2–63% of patients [4], and pancreatic involvement in 2.1% [4], although these are rarely the presenting manifestations.

Sarcoidosis should be considered as an aetiology in all patients presenting with hypercalcaemia, especially when common conditions have been excluded. Hypercalcaemia may fluctuate in patients with sarcoidosis, depending on the activity of the disease; moreover, hypercalciuria is three times more common than hypercalcaemia [5]. Therefore, serum and urine calcium levels should be measured regularly over the whole course of the illness. The mechanism of hypercalcaemia in sarcoidosis is due to excess extrarenal calcitriol production. The alveolar macrophages present within the granulomas contain the enzyme 1α -hydroxylase, which converts precursor vitamin D to active calcitriol [6]. High levels of calcitriol normally cause feedback inhibition of 1α -hydroxylase; likewise, calcitriol also

causes upregulation of $25(\text{OH})\text{D}_3$ 24-hydroxylase (where D is vitamin D), which converts $25(\text{OH})\text{D}_3$ to $24,25(\text{OH})_2\text{D}_3$, the metabolically inactive form of vitamin D. Both the feedback mechanisms are lost in alveolar macrophages, leading to continuous production of calcitriol [7]. Another recently described mechanism is excess production of parathyroid hormone-related peptide [8], which, like parathyroid hormone, causes upregulation of 1α -hydroxylase. Unlike parathyroid hormone, parathyroid hormone-related peptide is not regulated by calcium but by interleukin-2 and tumour necrosis factor- α , both of which are increased in sarcoidosis [9]. It is possible that, when released by alveolar macrophages, these cytokines act in a paracrine fashion to upregulate parathyroid hormone-related peptide production by macrophages [7].

Pancreatic involvement by sarcoidosis is uncommon; in fact, gastrointestinal tract involvement by sarcoidosis is unusual, and the liver is the most frequently involved organ, followed by the stomach [10]. Pancreatic sarcoidosis can present as acute pancreatitis, chronic pancreatitis, or nonspecific abdominal pain as a result of granulomatous involvement of the pancreas [11]. Acute pancreatitis in sarcoidosis can be either because of active granulomatous pancreatitis or secondary to hypercalcaemia [12]. Only eight cases of acute pancreatitis secondary to sarcoidosis have been reported in the literature, and three patients out of the eight had hypercalcaemia [5]. Prompt resolution of pancreatitis occurs after treatment with glucocorticoids.

Prednisone is the drug of choice and causes a decrease in circulating calcitriol and serum calcium within 3–5 days. A decrease in urinary calcium excretion rate occurs in 7–10 days. Failure to normalise the serum calcium after 2 weeks should lead the clinician to exclude the possibility of a coexisting disorder, including hyperparathyroidism, myeloma, *etc.* Chloroquine and hydroxychloroquine can be attempted in patients who develop adverse effects with glucocorticoid therapy [13]; however, the role of ketoconazole is not clear [4]. Patients should avoid a high calcium diet, calcium supplementation and exposure to sunlight, as even normocalcaemic patients with sarcoidosis may develop hypercalcaemia, renal stones and renal failure [4].

In the current patient, the diagnosis of sarcoidosis was delayed for almost 2 yrs; this is not an uncommon occurrence [3]. Moreover the institution of methotrexate also changed the clinical picture in this patient. Once methotrexate was withdrawn and calcium supplements were continued, the sarcoid activity flared up, with presentation as severe hypercalcaemia and pancreatitis.

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

REFERENCES

- 1 Longscope WT, Freiman DG. A study of sarcoidosis. *Medicine* 1952; 31: 1–132.

- 2 Hunninghake GW, Costabel U, Ando M, *et al.* The American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) statement on sarcoidosis. *Am J Respir Crit Care Med* 1999; 160: 736–755.
- 3 Judson MA, Thompson BW, Rabin DL, *et al.* The diagnostic pathway to sarcoidosis. *Chest* 2003; 123: 406–412.
- 4 Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med* 2000; 6: 442–447.
- 5 Siavelis HA, Herrmann ME, Aranha GV, Garcia G, Eubanks T, Reyes CV. Sarcoidosis and the pancreas. *Surgery* 1999; 125: 456–461.
- 6 Bell NH, Stern PH, Pantzer E, Sinha TK, De Luca HF. Evidence that increasing circulating 1 alpha, 25-dihydroxy-vitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. *J Clin Invest* 1979; 64: 218–225.
- 7 Conron M, Young C, Beynon HLC. Calcium metabolism in sarcoidosis and its clinical implications. *Rheumatology* 2000; 39: 307–313.
- 8 Zeimer HJ, Greenaway TM, Slavin J. Parathyroid-hormone related peptide in sarcoidosis. *Am J Med* 1998; 152: 17–21.
- 9 Muller-Quernheim J. Sarcoidosis: immunopathogenic concepts and their clinical applications. *Eur Respir J* 1998; 12: 716–738.
- 10 Crystal RG. Sarcoidosis. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 15th Edn. New York, McGraw Hill, 2001; pp. 1969–1973.
- 11 Siavelis HA, Herrmann ME, Aranha GV, Garcia G, Eubanks T, Reyes CV. Sarcoidosis and the pancreas. *Surgery* 1999; 125: 456–461.
- 12 McCormick PA, Malone D, Fitzgerald MX, Fitzgerald O. Pancreatitis in sarcoidosis. *BMJ* 1985; 290: 1472–1473.
- 13 O'Leary TJ, Jones G, Yip A, Lohnes D, Cohanum M, Yendt ER. The effects of chloroquine on serum 1, 25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; 315: 727–730.