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Granulomas With Hypercalcaemia: A Case Report

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ABSTRACT

Granulomatous lung disease encompasses a broad range of differentials, including infection, inflammation and malignancy. The most frequent infective cause is tuberculosis (TB), which commonly presents with cough, fever, weight loss or night sweats [1]. However, it is possible for TB to manifest subclinically [2] without symptomatology in the presence of granulomatous changes, which can pose a diagnostic dilemma. There may be clues that overlap with other differentials, such as hypercalcaemia associated with sarcoidosis and malignancy. Here, we present the case of a patient posthumously diagnosed with TB, who presented with isolated hypercalcaemia and granulomatous lung disease without respiratory symptoms.

CLINICAL RECORD

An 83-year-old female immigrant from Malaysia was reviewed for confusion and hypoglycaemia in the setting type 2 diabetes mellitus. She had a history of hypertension and chronic kidney disease. She was a retired schoolteacher and non-smoker, living independently with her husband. She did not report any significant respiratory or infective symptoms.

On clinical examination, vital signs were within normal limits. Her neurological examination was unremarkable apart from disorientation to time and place. Abnormal pathology results (Table 1) included normocytic anaemia and severe parathyroid hormone (PTH)-independent hypercalcaemia with normal 25-hydroxyvitamin D levels. A whole-body computed tomography (CT) scan was significant for diffuse bilateral spiculated pulmonary nodules without associated mediastinal or hilar adenopathy (Figure 1), and a large right thyroid calcified nodule. A percutaneous biopsy of the largest and most peripheral lesion in the left upper lobe was performed. Histopathology confirmed non-necrotising granulomatous inflammation with negative Ziehl-Neelsen stains for acid fast bacilli (AFB) and mycobacterial culture (Figure 2). The decision was made not to perform a bronchoscopy, as it was felt to be high risk given the patient's age and comorbidities, and low yield due to the peripheral location of the lesions and lack of sputum production.

The constellation of biochemical, radiological and histopathological findings raised the possibility of sarcoidosis. Tuberculosis (TB) was considered unlikely given the absence of infective or respiratory symptoms, negative AFB stain and the presence of non-caseating granulomas. Treatment with prednisolone 0.5mg/kg daily for presumptive

sarcoidosis was initiated, following the acute management of hypercalcaemia with intravenous fluids, calcitonin and pamidronate.

Table 1: Pathology results on admission

Haematology	**Patient**	**Reference**
Haemoglobin	102 g/L	115-155
Mean corpuscular volume	90 fL	80-99
White cell count	8.5 x 10^9/L	4.0-12.0
Neutrophils	6.10 x 10^9/L	2.00-8.00
Lymphocytes	1.46 x 10^9/L	1.00-3.50
Monocytes	0.87 x 10^9/L	0.20-1.00
Platelets	339 x 10^9/L	150-400
Biochemistry	**Patient**	**Reference**
Cr	251 µmol/L	45-90
Corrected calcium	3.24 mmol/L	2.10-2.60
Phosphate	1.82 mmol/L	0.75-1.50
Albumin	34 g/L	34-47
Other	**Patient**	**Reference**
PTH	1.4 pmol/L	1.6-6.9
TSH	0.49 mIU/L	0.27-4.20
Vitamin D 25 OH	73 nmol/L	>50
Vitamin D 1,25 OH	58 nmol/L	>50
ACE	54 units/L	20-70
Proteins and markers	**Patient**	**Reference**
Kappa/lambda ratio	1.32	0.26-1.65
AFP	2 ug/L	<7
bHCG	2 IU/L	<5
CEA	2.6 ug/L	<5.0
Ca-199	12 kunits/L	<27
Ca-153	38 kunits/L	<26
Ca-125	250 kunits/L	<35

Despite steroid treatment, there was persistent hypercalcaemia requiring hospitalisation eight weeks later. Repeat CT chest imaging demonstrated progressive changes (Figure 1), prompting reassessment and withdrawal of steroid therapy. A repeat biopsy of the same lung lesion was performed, demonstrating active inflammation with necrosis (Figure 3) and negative Ziehl-Neelsen stain (Figure 4). The patient rapidly progressed to multi-organ failure with intractable delirium and died despite broad-spectrum antibiotic therapy. The final report of the second tissue culture returned positive for Mycobacterium tuberculosis posthumously.

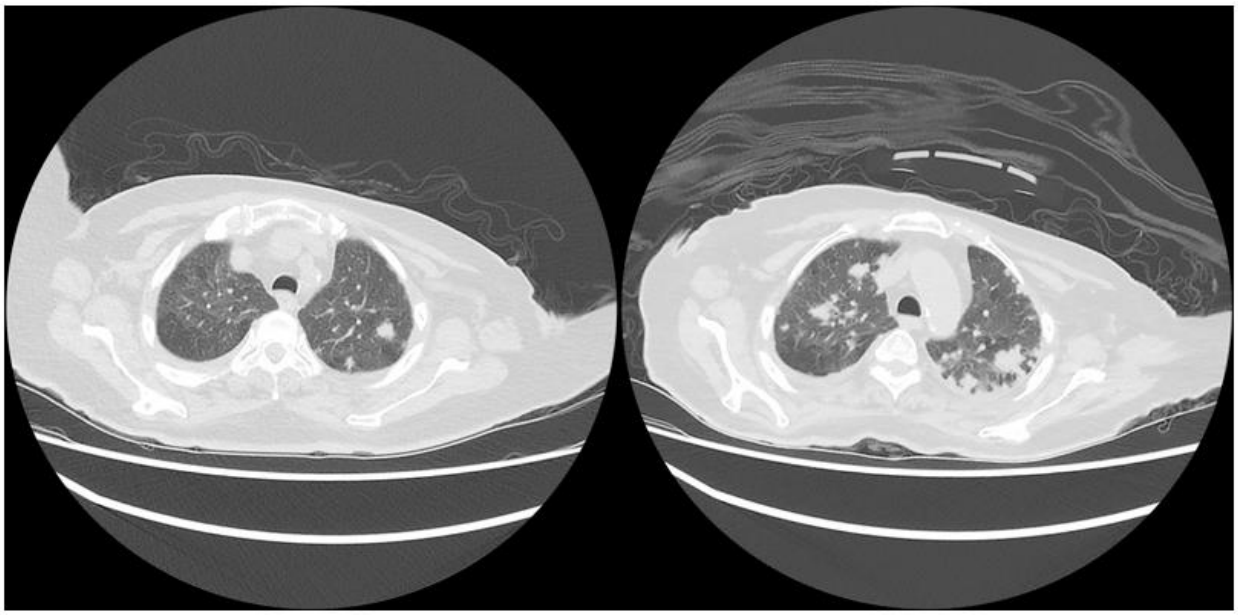

Figure 1: Computed Tomography (CT) Chest images on presentation

Left: CT chest on first admission, demonstrating multiple spiculated lung nodules

Right: CT chest eight weeks later, demonstrating significant interval progression of lung nodules over 3 months

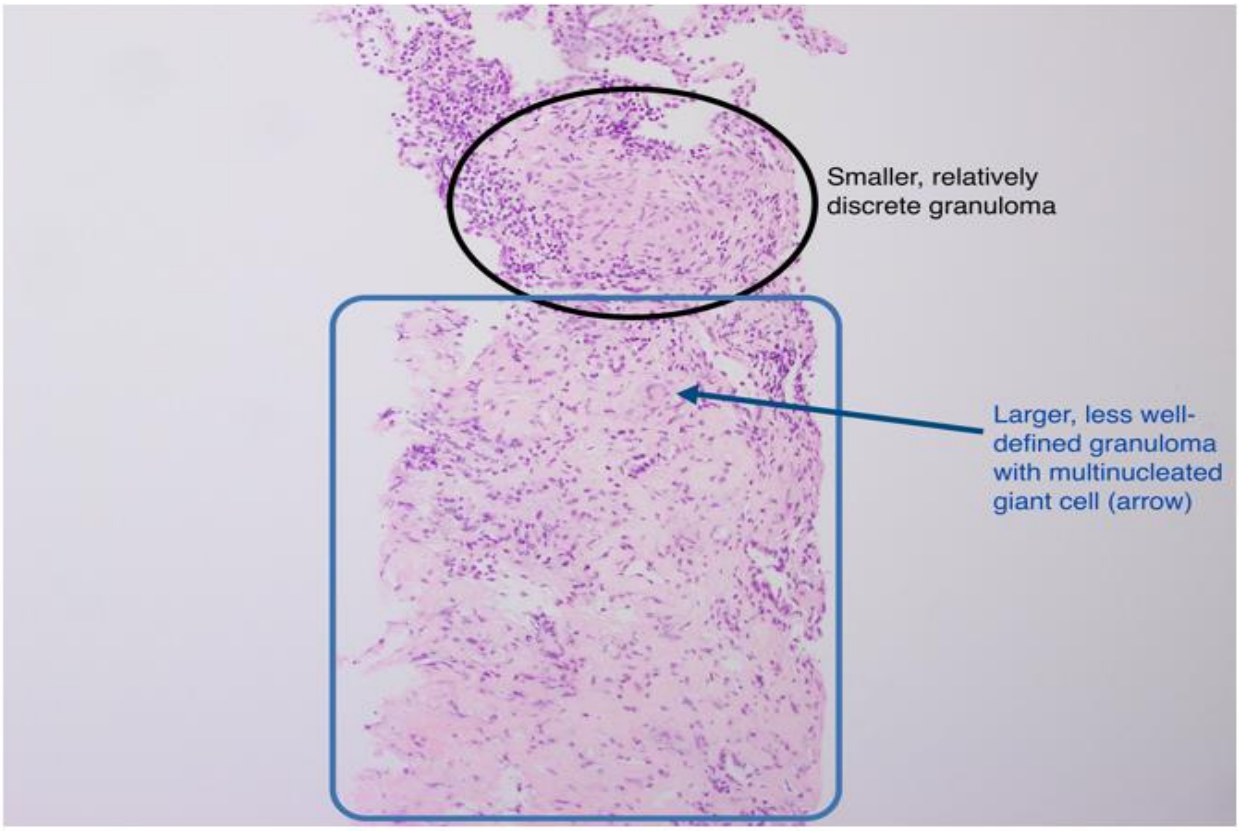

Figure 2: First percutaneous lung biopsy of left upper lobe

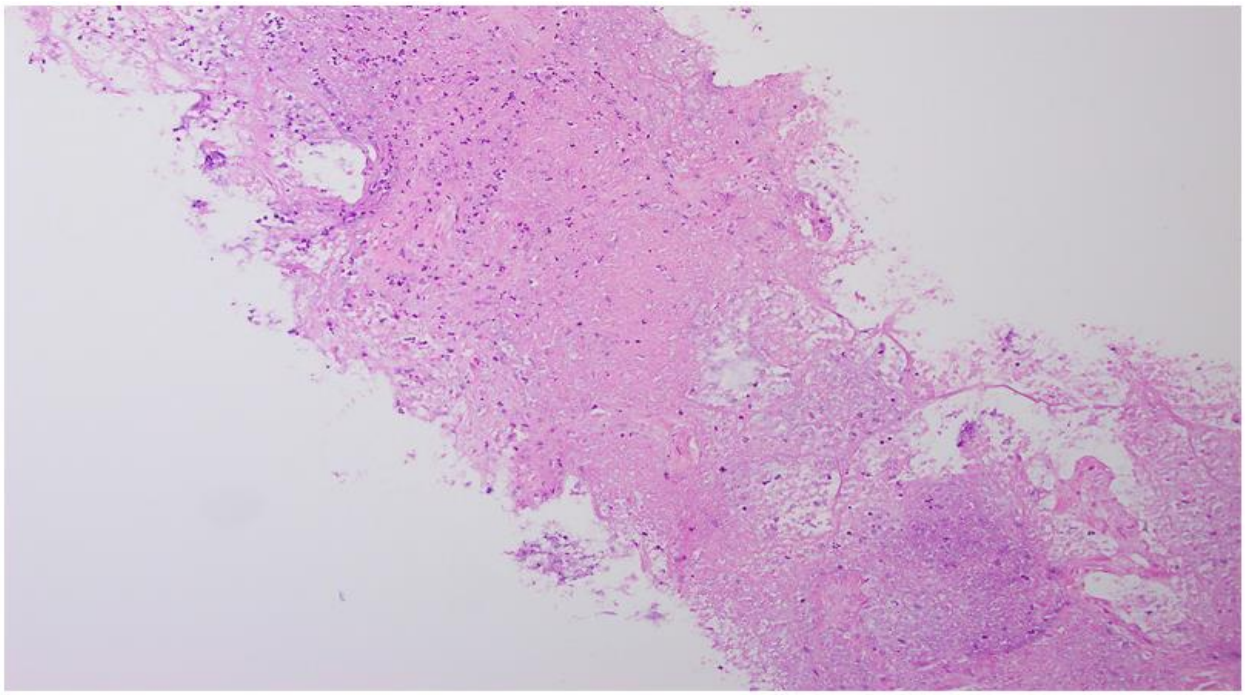

Figure 3: Second percutaneous lung biopsy of left upper lobe

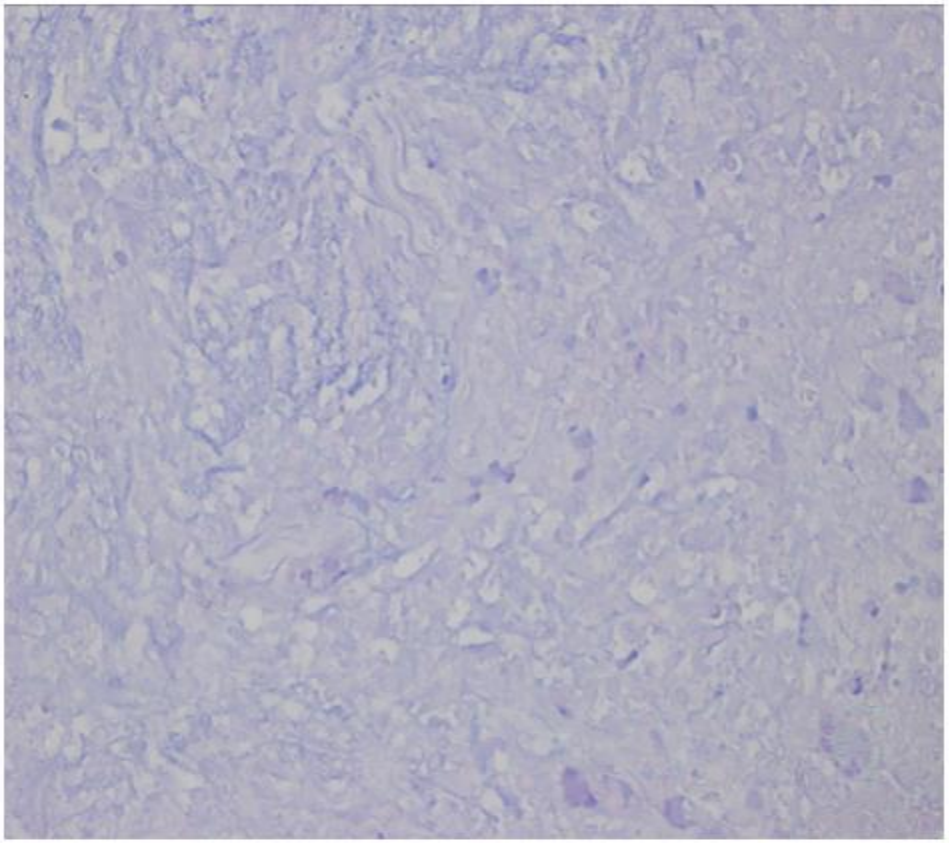

Figure 4: Negative Ziehl-Neelson stain of second percutaneous lung biopsy

DISCUSSION

Pulmonary granulomatous disease comprises an array of aetiologies, such as infections, inflammatory conditions, and toxin exposure [1]. Granulomatous diseases cause hypercalcaemia through production of 1a-hydroxylase by macrophages and giant cells [3], converting 25-hydroxyvitamin D to calcitriol, independent of PTH suppression. Calcitriol is responsible for increasing calcium absorption and bone resorption through stimulation of receptor activator of NF-kB (RANKL) ligand effects on osteoclasts [4].

Pulmonary TB is typically confirmed by detecting Mycobacterium tuberculosis via culture, acid fast bacilli smear or nucleic acid amplification of a respiratory specimen. This can be challenging in subclinical TB with lack of sputum production. An alternative is tissue biopsy of the lung, which was performed in this case. Histopathology may show granulomas composed of epithelioid macrophages, Langerhan's giant cells and lymphocytes with caseating or non-caseating necrosis. However, this is non-specific [1] and culture is ultimately required for bacteriological confirmation and identification of drug resistance, which requires up to eight weeks.

Without bacteriological evidence, it is difficult to distinguish TB from other granulomatous diseases, such as sarcoidosis. This can have major implications on treatment outcomes, especially pertaining to commencement of immunosuppressive therapy. Sarcoidosis is a multisystem disorder that is diagnosed based on clinical presentation, histopathological evidence of non-necrotising granulomatous inflammation in at least one tissue site, and exclusion of alternative granulomatous diseases [5]. Both TB and sarcoidosis typically present with respiratory and constitutional symptoms associated with upper lung parenchymal changes. Sarcoidosis is also associated with adenopathy, however less common findings of multiple bilateral lung nodules or mass-like opacities with minimal adenopathy can occur [4]. Our patient's immigration history placed her at risk for TB, whereas sarcoidosis has a greater prevalence in African and Scandinavian ethnicities. However, 30% of sarcoidosis cases do occur in elderly populations with overall greater prevalence in females [6]. Ultimately, our patient's presentation was atypical for both sarcoidosis and TB, with radiological and histopathological findings compatible with either differential. A diagnosis of sarcoidosis was favoured due to initial negative mycobacterium culture from percutaneous lung biopsy.

This case highlights the diagnostic challenges of an unusual presentation of TB where the patient presented without infective or respiratory symptomatology. It should act as a cautionary tale for clinicians given the implications for both the patient and broader community when TB is missed.

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