Three straight forward cases

Dr YC YEUNG, Dr Dave CHAN, Dr YH CHAN

Department of Medicine & Geriatrics,
Princess Margaret Hospital

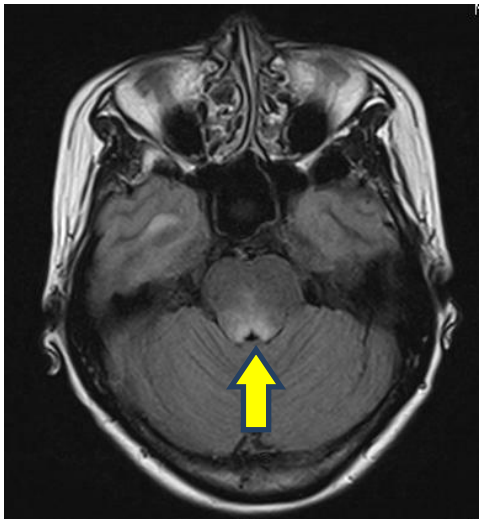
Introduction

When we encounter lung lesions with granulomatous inflammation, they are mostly straight forward pulmonary tuberculosis (TB) given compatible clinical and radiological features. We presented three apparent "straight forward" cases.

Case 1

Miss L was 34-year-old clerk who had history of fibroid. She presented in July 2015 with headache and personality changes. She was admitted to neurosurgical unit and computed tomography (CT) scan of brain showed marked hydrocephalus. Subsequent magnetic resonance imaging (MRI) showing an ill-defined T2 hyper-intense lesion without enhancement at superior-dorsal aspect of pons, suspected low-grade glioma (Fig. 1)

Fig.1: MRI brain (lesion shown with arrow)



Endoscopic third ventriculostomy with brain biopsy and cerebro-spinal fluid (CSF) drainage was performed. CSF showed elevated cell count (411) with neutrophil predominance and CSF culture results were negative. Brain biopsy showed granulomatous inflammation and mycobacterial tuberculosis polymerase chain reaction (MTB-PCR) was negative. Chest radiograph (CXR) showed small nodules over bilateral middle and lower zones suspected military tuberculosis and CT thorax showed numerous tiny pulmonary nodules with extensive mediastinal lymphadenopathy. (Fig. 2a and 2b)

Fig. 2a: CT thorax (lung window)

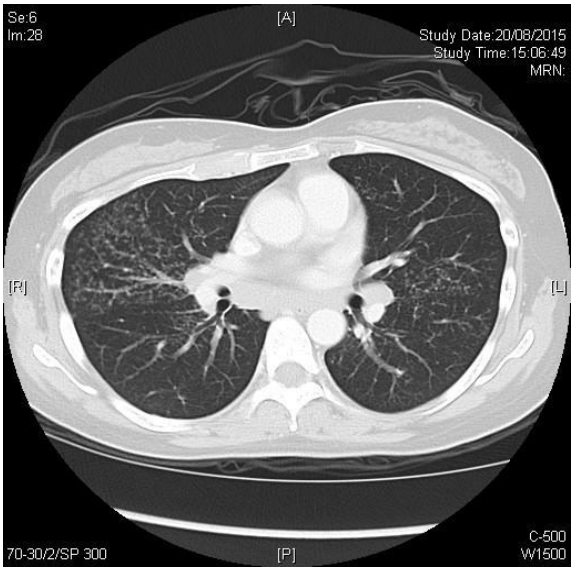
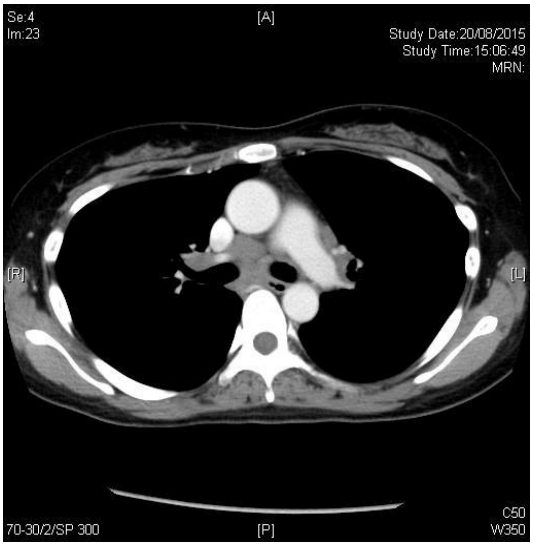


Fig. 2b: CT thorax (soft tissue window)



She was managed as miliary tuberculosis (TB) with lung, lymph node and central nervous system (CNS) involvement with standard HRMZ with short course of steroid for possible TB meningitis (TBM). However, there were persistent cognitive impairment and CXR showed worsening of interstitial involvement with perivascular beading after 8 months of TB treatment. Patient was referred from chest clinic for biopsy. Bronchoscopy on July 2016 showed no endobronchial lesion. Transbronchial lung biopsy (TBLB) taken over right middle lobe and endobronchial ultrasound guided needle aspiration (EBUS-TBNA) of station 7 subcarinal lymph node were performed. Histology from both TBLB and EBUS-TBNA confirmed granulomatous inflammation with negative MTB-PCR.

Case was reviewed with radiologists and pathologists. Diagnosis was confirmed to be sarcoidosis. She was started on oral prednisolone 30mg daily since August 2016 with gradual tapering. Blood for autoimmune markers were negative and serum angiotensin-converting enzyme (ACE) was 55 U/L [normal range (NR) 9-67U/L]. The cognitive impairment settled and patient was able to work again. Repeated CT scan thorax 3 months after steroid treatment showed reduced extent of bilateral lung nodules and thoracic/ upper abdomen lymphadenopathy.

Case 2

Madam C was a 77-year-old lady with history of diabetes mellitus, hypertension, hyperlipidaemia and chronic renal impairment. She was admitted to stroke unit on February 2016 for stroke with mild right-side weakness and slurring of speech. CT brain confirmed lacunar infarcts. There was incidental finding of hypercalcaemia 3.22mmol/L (NR 2.2-2.65mmol/L) with acute kidney injury. Intravenous fluid and pamidronate were given. Further workup showed normal phosphate level and low serum parathyroid hormone level PTH 1.01 (NR 1.30 - 9.30 pmol/L). Erythrocyte sedimentation rate (ESR) was normal (14) and abnormal bands were not detected in serum and urine. Hence the working diagnosis at that time was hypercalcemia related to malignancy.

Positron emission tomography (PET) scan in private showed multiple hypermetabolic (SUV up to 9.5) mediastinal lymphadenopathies bilaterally, with no significant abnormalities over lungs and bones. Bronchoscopy showed no significant endobronchial lesion. Endobronchial ultrasound located stations 7 and 10R lymphadenopathy with needle aspiration done. Histology showed granulomatous inflammation with no organisms identified. MTB-PCR is negative.

She was initially managed as pulmonary tuberculosis with HRMZ, yet there was persisted symptomatic hypercalcemia. There was subsequent development of flat topped

papules over face suggestive of granulomatous lesions, however patient declined skin biopsy after discussion with dermatologist. She also developed bilateral anterior uveitis with progressive visual impairment. All tuberculosis culture was negative. A further blood test showed grossly elevated ACE level to 240U/L with normal parathyroid-hormone related peptide level.

Therefore, the final diagnosis was sarcoidosis. TB medications were stopped and systemic steroid of prednisolone 30mg daily started since November 2016 with gradual tapering. Patient tolerated treatment with normalization of calcium level as well as resolution of mediastinal lymphadenopathy.

Case 3

Mr. C was a 31-year-old man who was chronic smoker and worked as painting worker. He had history of helicobacter pylori associated gastritis in 2009 with eradication treatment given, otherwise unremarkable past health. He first presented with right T5 herpes zoster with bilateral eye redness and visual blurring on August 2015, subsequently diagnosed to have bilateral ankle uveitis by eye specialist. Search of underlying disease showing right hilar prominence on CXR, while autoimmune markers and ESR were normal. Hence, he was referred to our unit for suspected sarcoidosis.

CT thorax was performed on January 2016, showing diffuse numerous sub-centimeter nodules over both lungs, with upper and middle zone predominance. Interlobular septa were mildly thickened. Multiple mediastinal and bilateral hilar lymph nodes were enlarged. Bronchoscopy showed nodule over opening to subsegmental bronchus for right lower lobe (RB9) with contact bleeding (Fig. 3). Endobronchial biopsy was performed. Endobronchial ultrasound located station 7 and 10R lymph node (Fig. 4) with needle aspiration performed.

Fig. 3: endobronchial nodule

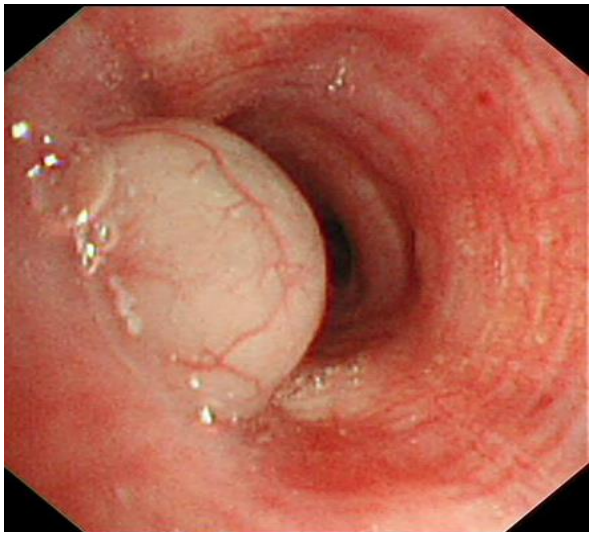
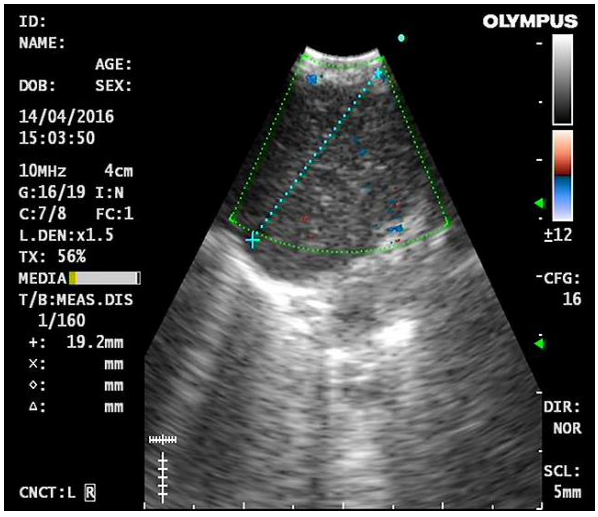


Fig. 4: station 7 lymph node



Both endobronchial biopsy and lymph node aspirate cytology confirmed granulomatous inflammation with negative microbiology. Lung function test was normal and serum ACE level was elevated (149 U/L). PET-CT confirmed more than 10 FDG avid mediastinal LN and small lung nodules with no other

lesion seen over abdomen or bones. He was diagnosed to have radiological stage 2 pulmonary sarcoidosis with eye involvement. Systemic steroid was started as with the previous patients. All acid-fast bacilli culture was negative. CT thorax showed marked improvement after three months of steroid therapy. He had flare up of uveitis after prednisolone dose was reduced to less than 5mg daily; hence the dosage of prednisolone was currently maintained at 5-10mg per day. Summary of various features of our cases is listed in table 1.

Table 1: Summary of our 3 cases (Y= yes)

	Age/ Sex	Symptoms	Organs involved	Pulmonary stage	Given TB drugs	Response to steroid
Case 1	34/F	Personality changes, headache	Lung, mediastinal and upper abdominal lymphadenopathy, central nervous system	2	Y	Resolved in lung lesions, recovered neurological symptoms
Case 2	77/F	Hypercalcaemia	Lung, mediastinal lymphadenopathy, hypercalcaemia with acute kidney injury, bilateral anterior uveitis, skin	2	Y	Normalized calcium level, improved lung lesions
Case 3	31/ M	Visual loss	Lung, mediastinal lymphadenopathy, bilateral anterior uveitis	2	Y	Subsided eye symptoms, improved lung lesions

Discussion

Our cases highlighted the variety of clinical features of sarcoidosis with different organs involvement; hence life is never straight forward. Pulmonologist has an important or even central role in managing this multi-system disorder as lung is the commonest organ to be affected and the most likely site to obtain biopsy in particular with advances in EBUS technique.

Sarcoidosis has been described since the 19th century by pioneering Norwegian dermatologist Caesar Boeck. He used the term “multiple benign sarcoid of the skin” to describe skin nodules characterized by

compact, sharply defined foci of "epithelioid cells with large pale nuclei and also a few giant cells". [1] Subsequently it was found to be a multi-system disease. The exact pathogenesis is unclear, and probably related to interplay among environmental exposure (irritants, mycobacterial antigens, and other organisms), genetic factors and immunological dysfunction leading to the development and accumulation of granulomata, especially the TNF-α pathway. [2] There were two comprehensive overviews of the disease published [2,3] and suggested read-up for interested readers.

Sarcoidosis in Hong Kong: the situation

It affects all ethnic group and ages, with peak incidence of 20-39 years old. [4] It was thought to be rare among Asian patients, with most published literature in Japan, with annual incidence ranges from 1 to 2 cases per 100,000 people and peaks in the third decade of life. [5] Reports in Chinese patients are scarce: estimated annual incidence of sarcoidosis in Singapore was 0.56 per 100,000, [6] and there were 38 incidences over five years among the local Chinese population in Taiwan, with disease-specific rates of 0.027 out of 100,000. [7]

The epidemiology in Hong Kong has not been reported as it was thought to be very rare. However, upon search of literature, there were case reports from many different specialties over the last 20 years; [8-15] showing the many facets of sarcoidosis. (Table 2)

Table 2: Reports of sarcoidosis in Hong Kong over last 20 years

Specialty	Description
Medicine	Report in HKMJ 1998 of a woman who had hilar lymphadenopathy and pulmonary infiltrates resolved without treatment and a review of previous 11 cases over 30 years [8]
Respiratory Medicine	Report on concomitant mycobacterial tuberculosis DNA detected with sarcoid lesion that responded well to 1-year of corticosteroid treatment. [9]
Radiology	Report from radiologists on mediastinal lymph node involvement of sarcoidosis [10]
Ear, nose and throat	Pulmonary and cochlear involvement causing sensorineural hearing loss [11]
Chest Clinic	Report on a lady with skin and pulmonary lesions 4 years after silicone breast prosthesis with multiple biopsy showing TB negative granulomatous inflammation [12]
Cardiology	Three cases of cardiac sarcoidosis with heart failure receiving heart transplantation [13]
Ophthalmology	Case report of ophthalmological sarcoidosis using intravitreal triamcinolone acetonide treatment [14]

Dermatology	Review on five patients (four Chinese) diagnosed of cutaneous sarcoidosis [15]

Challenges in diagnosis of pulmonary sarcoidosis

Diagnosis of sarcoidosis is of no doubt with typical Löfgren's syndrome and Heerfordt's Syndromes but it only happened in a minority of cases. For most cases, sarcoidosis remains a diagnosis of exclusion and diagnosis is difficult to secure. It needs a compatible clinical (including radiological) picture with multi-organ disease, histologic demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histologic or clinical picture. [16] This highlighted the challenges faced by many respiratory physicians, especially in our locality of moderate tuberculosis burden as tuberculosis is a main differential of granulomatous inflammation. What further complicates the picture is that two diseases may overlap. [9] Many cases received TB treatment, as with our patients, before definitive diagnosis was made.

Lung is the commonest internal organ being affected in up to 90% of sarcoidosis patient. However, only less than half of them have symptoms as most cases have incidental finding on chest radiography as hilar lymphadenopathy. Symptoms are also non-specific with fatigue reported in more than half of cases. [17] Shortness of breath or cough is sometimes present and endobronchial disease may present as wheezing. Radiologically, it has been classified into stage I-IV since 1961, [18] with stage I disease (bilateral hilar lymphadenopathy only) reported to have 90% rate of spontaneous resolution within 2 years. Lung function test findings are non-specific either. Restrictive pattern with or without reduction in diffusion capacity is most frequently encountered, especially in those cases with stage II-IV disease with interstitial involvement. [19] Yet concomitant obstructive pattern, and even airway hyperactivity can be present in half of the cases which can mimic asthma in young patients. [20] Therefore high index of suspicion is needed.

Studies have shown that patients need to have symptoms for more than 3 months before diagnosis is made, and require three or more encounters with health care providers. Patients with sarcoidosis presenting with pulmonary symptoms alone often have a relative delay in the diagnosis of sarcoidosis, as these symptoms are nonspecific; while those with skin symptoms have quicker diagnosis. [21]

With the advancement of imaging and biopsy technique in recent years, it is expected there will be less under-diagnosis problem. Of note is the advancement in PET-CT imaging and also endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA). PET-CT is helpful to show up sites with active granulomatous inflammation, in particular organs which are relatively inaccessible (e.g. heart) and also help identifying potential biopsy sites. [22] The drawback of PET-CT is lack of specificity to differentiate from other pathology. For EBUS combining with use of TBNA for tissue sampling of mediastinal or hilar lymphadenopathy, report from Wong M et al. the accurate diagnostic rate is more

than 93% with minimal complications of the procedure. [23] Serum ACE test remained suboptimal in both sensitivity and specificity, but is useful for disease monitoring if it is elevated on presentation. [24]

Management and monitoring of pulmonary sarcoidosis

The principle of management is to preserve organ function, prevent complications (especially with cardiac and neurologic sarcoidosis) and improve quality of life. Therefore, corticosteroid therapy is indicated in symptomatic patients, with radiological and spirometric deterioration. [25] For radiological stage III disease, less than one-third would spontaneous resolve [18] and many would deteriorate within 6 months from diagnosis. The usual recommendation is to start prednisolone 20-40 mg daily with gradual tapering over 12-24 months. [25] Many would need long term maintainence with prednisolone 5-10mg, as in our third patient. For steroid refractory and chronic cases, further immunosuppressant with methotrexate, azathioprine, leflunomide or mycophenolate should be considered. Much interest is now drawn to anti-TNFα therapy especially with infliximab showing promising results. [26]

Brief note on neuro-sarcoidosis

Our first case suffered from CNS involvement of sarcoidosis. It is rare and estimated to affect around 5% of all sarcoidosis patients, but this may be under-reported as biopsy of CNS remained difficult. Fifty to seventy of neurosarcoidosis patients first presented with neurological symptoms before systemic disease. Depending on the site of the lesion, any neurological signs and symptoms are possible. By far, facial nerve palsy is the commonest (especially bilateral). [27]

Imaging findings are also non-specific as well hence it makes concrete diagnosis difficult unless there is involvement of other organs which is accessible for biopsy. MRI brain finding ranges from subtle white matter changes to hydrocephalus. The lesions can mimic demyelination or neoplastic process. Lumber puncture, when suitable, is mainly used to exclude possible infection or malignancy. For sarcoidosis, CSF protein can be elevated and there may be mild to moderate pleocytosis. Usually PET-CT is needed to look for other organ involvement.

Neurosarcoidosis is one the most fearful complications of sarcoidosis as it can carry mortality up to 18% [28] and it can cause irreversible neuronal damage (severe morbidity). Steroid dose may need to be stepped up to 1mg/kg and slower tapering is needed. [29] Cytotoxic treatment or biologics warrant consideration in early part of treatment. Surgery may be needed for complications such as hydrocephalus.

Conclusion

Sarcoidosis is rare in Hong Kong, but is possibly under-recognized and under-diagnosed. Diagnosing sarcoidosis can be challenging, particularly with difficulty in exclusion of tuberculosis. With advances in imaging and endoscopy technique, more cases are likely to be picked up in the future. Treatment with systemic corticosteroid is the cornerstone to preserve organ function.

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