Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: 5/10/2021
Date of report submission: 9/9/2022

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: A neglected disease entity in Hong Kong

Case history:

A 43-year-old man, a New Zealander, who worked as a pilot and enjoyed good past health. He presented with painful nodules on his bilateral lower limbs and ankles for 1 month. He also had history of left knee pain and calf pain 2 weeks ago which caused walking difficulty. He was seen by a private general practitioner and an Orthopaedic surgeon in the private sector before hospitalisation who had prescribed him with multiple courses of antibiotics since the fourth day of the symptom onset including 2 days of oral amoxicillin-clavulanate 1g twice-daily, followed by 2 days of intramuscular injection of etrapenem 1g once-daily. He had some loose stool after the antibiotic use and was then given 10 days of oral levofloxacin 500mg twice-daily and metronidazole 400mg thrice-daily. 4 days before the admission, he had been being given oral amoxicillin-clavulanate again, into which he developed breakthrough fever and hence he attended the Emergency Department.

He had a florid travel history in the preceding 3 months owing to his job nature. Yet due to restriction in travel during COVID-19 pandemic, his activity was limited in the hotel rooms and airports. He flew to Anchorage, Miami, Los Angeles, Singapore and Jakarta. 4 days before the symptom onset, he landed on Hong Kong. He had been residing in a private residential estate in Hong Kong for 18 years. He did not raise any pets, nor did he remember any recent contact with wild animals. There was no personal or contact history of tuberculosis. He was married for 10 years and his wife was his only sexual partner.

On admission, his temperature was 38.5°C. There was no pulse-temperature deficit. Skin examination revealed tender nodules 1cm around the extensor surfaces of the lower limbs and ankles (see figure 1), compatible with erythema nodosum. There was no discharge from the lesions. There was absence of mucosal involvement. Small-volume non-tender lymph nodes were palpable at the bilateral inguinal areas. The genitalia was clean. The liver and spleen were not palpable. Clinical synovitis was absent.
Examinations on the other system were all normal.
The admission blood test showed that he had leucocytosis with white blood count 10.6 x 10^9/L (normal, 3.89- 9.93) with a high neutrophil count of 9.20 x 10^9/L (normal, 2.01-7.42), low lymphocyte count of 0.64 x 10^9/L (normal, 1.06-3.61). Haemoglobin and platelet count were normal. The liver and kidney function including calcium level, phosphate level and lactate dehydrogenase were all normal. C-reactive protein (CRP) was high at 10.2mg/dl (normal, <0.76), together with erythrocyte sedimentation rate (ESR) 64mm/hour. Blood culture taken 3 times on admission did not have any growth. Anti-parvovirus B19 IgM, Hepatitis B surface antigen (HBsAg), anti-HCV and anti-HIV were negative. In view of travel history and presentation, Borrelia burgdorferi polyvalent antibody and malaria thick and thin smear taken twice with 12 hours apart were done, the results of which were negative. Anti-streptolysin O titre on the first check was 400 IU/ml (normal, < 200 IU/ml). Tuberculosis (TB) workup including early morning, urine and stool for acid-fast stain, culture and polymerase chain reaction for TB (TB-PCR) were negative. As far as loose stool was concerned, there was no suspected pathogen identified on bacterial culture and no ova, cysts and trophozoites were found on microscopic examination. Autoimmune markers including anti-nuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), C3 and C4 were all unremarkable. Chest X-ray showed bilateral clear lung field. There was no apical fibrosis. The mediastinum was not widened. Yet the right hilar opacity was bulky. (see figure 2). X-ray of ankles and knees were unmarkable. Computer tomography (CT) of the thorax with contrast showed multiple enlarged mediastinal and hilar lymph nodes. The right hilar lymph node measured 3.5 x 2.5cm and left hilar 2 x 1.7cm.
In view of the CT findings, dimorphic fungal serology (Blastomyces and Histoplasma) and Cryptococcal antigen were taken, which came back to be negative.
Skin biopsy showed features of septal panniculitis and was suggestive of erythema nodosum. No well-formed epithelioid granuloma or caseous necrosis was found. There were no organisms identified on Ziehl-Neelson and PASD stains.

The patient was continued with amoxicillin-clavulanate and started on prednisolone 0.5mg/ kg for presumed diagnosis of sarcoidosis. Fever subsided afterwards. Skin lesions resolved after steroid therapy. Serum angiotensin converting enzyme (ACE) checked 1

week after steroid use, which was 55 U/L (normal, 16-85 U/L). 2 months later the patient received endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA) of the mediastinal lymph node. The histology showed epithelioid-like histiocytes and granuloma without necrosis. Again, no acid-fast bacilli or fungal organisms identified. Mycobacterial culture and TB-PCR on the lymph node specimen were also negative.

Discussion and literature review

This case illustrated a typical example of sarcoidosis, in which the patient presented with a classical triad of erythema nodosum, mediastinal lymphadenopathy and joint pain, collectively known as Lofgren's syndrome.

The diagnosis was initially missed and was finally made after a month of symptom onset. It is not surprising as the disease is frequently mistaken as a disease outside Hong Kong and thus not familiar among local clinicians. This is not completely true. Touching on epidemiology, sarcoidosis remains more common in Caucasians. It is most common in the blacks and Scandinavians. Nevertheless, it is not non-existent in other places. It affects all races and all ethnicities, particularly younger age group (30-60 years old) with slight female preponderance.[1] The first local report of case series of thoracic sarcoidosis in Hong Kong was reported in 1981 by Professor GB Ong's team.[2] In the case series, there were a total of 4 Hong Kong cases diagnosed within the same year in the late 1970 based on histopathology of the mediastinal lymph node biopsy using mediastinoscopy. In Hong Kong, formal statistical data is lacking pertaining to the incidence of this disease specific to our population. Yet, one would agree that it is an important disease to remember as sarcoidosis mimics tuberculosis and hence distinguishing it from mycobacterial disease is crucial as the treatment modality is different – steroid is a treatment option for the former but it might exacerbate the latter if it is diagnosed wrongly.

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. It is most often deemed to be a result of exaggerated response to unknown antigen, triggering type 1 T helper (Th1) response. As a result of over-expression of interferon-γ, interleukin-2 and tumour-necrosis factor α, there is formation of non-caseating

epithelioid-cell granulomas, a pathological hallmark of this disease.[3]

For disease presentation, the majority involves the thorax, giving most commonly bilateral hilar lymphadenopathy. Lung involvement is characterized by diffuse interstitial lung diseases. Common respiratory symptoms include cough, chest pain and dyspnoea. Systemic symptoms such as fever, weight loss and pronounced fatigue might be present. It is further classified into 4 stages: stage I disease only involves bilateral hilar lymphadenopathy, stage II bilateral hilar lymphadenopathy plus parenchymal involvement, stage III parenchymal involvement without lymphadenopathy and stage IV fibrotic diseases. Stage III and IV carry poorer prognosis.
Extrathoracic involvement can happen up to 30% of the cases. Every organ can be involved, and the most common organ of involvement is the skin. Papular, nodular and plaque-like lesions on the head and neck regions, particular in the places of previous trauma, are typical of cutaneous sarcoidosis. Erythema nodosum in our case, as a part of the Lofgren's syndrome, is a form of septal panniculitis which usually fails to demonstrate non-caseating granuloma and hence biopsy is not routinely suggested in cases with classical presentations. Renal sarcoidosis is characterized by nephrocalcinosis, cardiac sarcoidosis usually presents with heart block while neurosarcoidosis mostly manifests with cranial nerve palsies.[3]

Diagnosis heavily relies on 3 aspects, namely compatible clinical and radiological features, demonstration of non-caseating granuloma on histology and exclusion of other causes. There are numerous conditions that resemble sarcoidosis including infection (e.g. TB, dimorphic fungal infection), malignancy (e.g. lymphoma) and vasculitis (e.g. Granulomatosis with polyangiitis). They can as well appear similarly on histopathology. Unless very suggestive presentation (e.g. Lofgren's syndrome, lupus pernio), biopsy is often required as it can provide additional clue to the aetiology in addition to demonstration of granulomatous inflammation. Biopsy of the mediastinal lymph node provides the best diagnostic yield. EBUS-FNA yield is not particularly compromised but slightly lower than mediastinoscopy (87% vs 98%). Yet, due to its invasiveness and cost, EBUS-FNA is recommended nowadays.[4] Obtain tissue sample for mycobacterial culture and nucleic acid test is of paramount importance in our locality due to endemicity of tuberculosis. Moreover, in our case, excluding dimorphic fungal infections like histoplasmosis is necessary due to his travel history. Up to one third of the sarcoidosis granuloma show features of caseous necrosis, mimicking tuberculosis. Furthermore, some tuberculous granuloma are non-caseating.[5] Neurological and cardiac involvement rely on imaging.

Serum ACE is a famous marker for sarcoidosis and its elevation is associated with

sarcoidosis. ACE is produced by epithelioid cells which are highly activated in sarcoidosis. Many other Th1-driven diseases like leprosy and tuberculosis undoubtedly can give similar serum ACE elevation as in sarcoidosis and hence serum ACE elevation is not pathognomonic of sarcoidosis. As demonstrated in a study in the USA evaluating the performance of serum ACE, the sensitivity of high ACE for diagnosis of sarcoidosis were 41.4% (95% CI, 35.3%-47.8%), which is very poor, and specificity 89.9% (95% CI, 88.8%-91.0%).[6]

For clinical course, not all patients require treatment because most patients are asymptomatic or have acute symptoms with spontaneous resolution. Only 1⁄3 run into a chronic course. Our local review also concurred with the disease pattern, in which 7 out of 12 patients were asymptomatic on presentation. The majority of them had spontaneous regression of the diseases (80%).[7]

Therefore, treatment is not mandatory for all patients. Whether to treat a patient or not depends on the risk of organ failure and extent of affecting quality of life. Outcome estimation is based on various factors including the age, stage and/or organ involvement, genetics etc. In general, higher stage of pulmonary involvement (III or IV) and extrapulmonary involvement are associated with poorer prognosis. Of note, Lofgren syndrome and isolated cranial nerve involvement are the exceptions. More than 50% of non-Lofgren's syndrome will have remission.[3]

If treatment is indicated, steroid is the mainstay and usually given in a rapid tailing course. For patients with need of prolonged steroid use, like other rheumatological diseases, steroid sparing agents (e.g. Methotrexate) and biologics (e.g. TNF-α inhibitors) are of options.[8]

Tables and figures (where applicable) (no more than two figures)

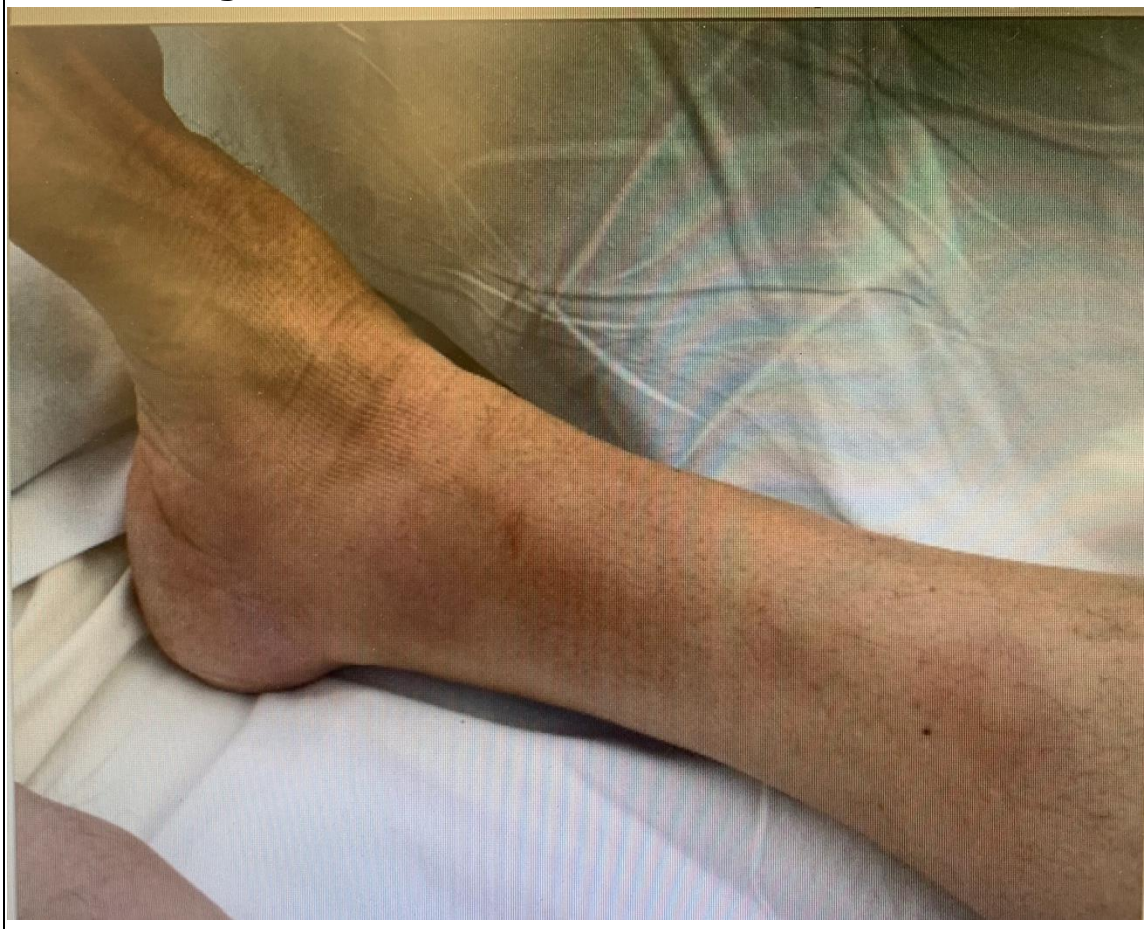

Figure 1. Papulonodular lesions at the extensor surface of the patient's right lower limb

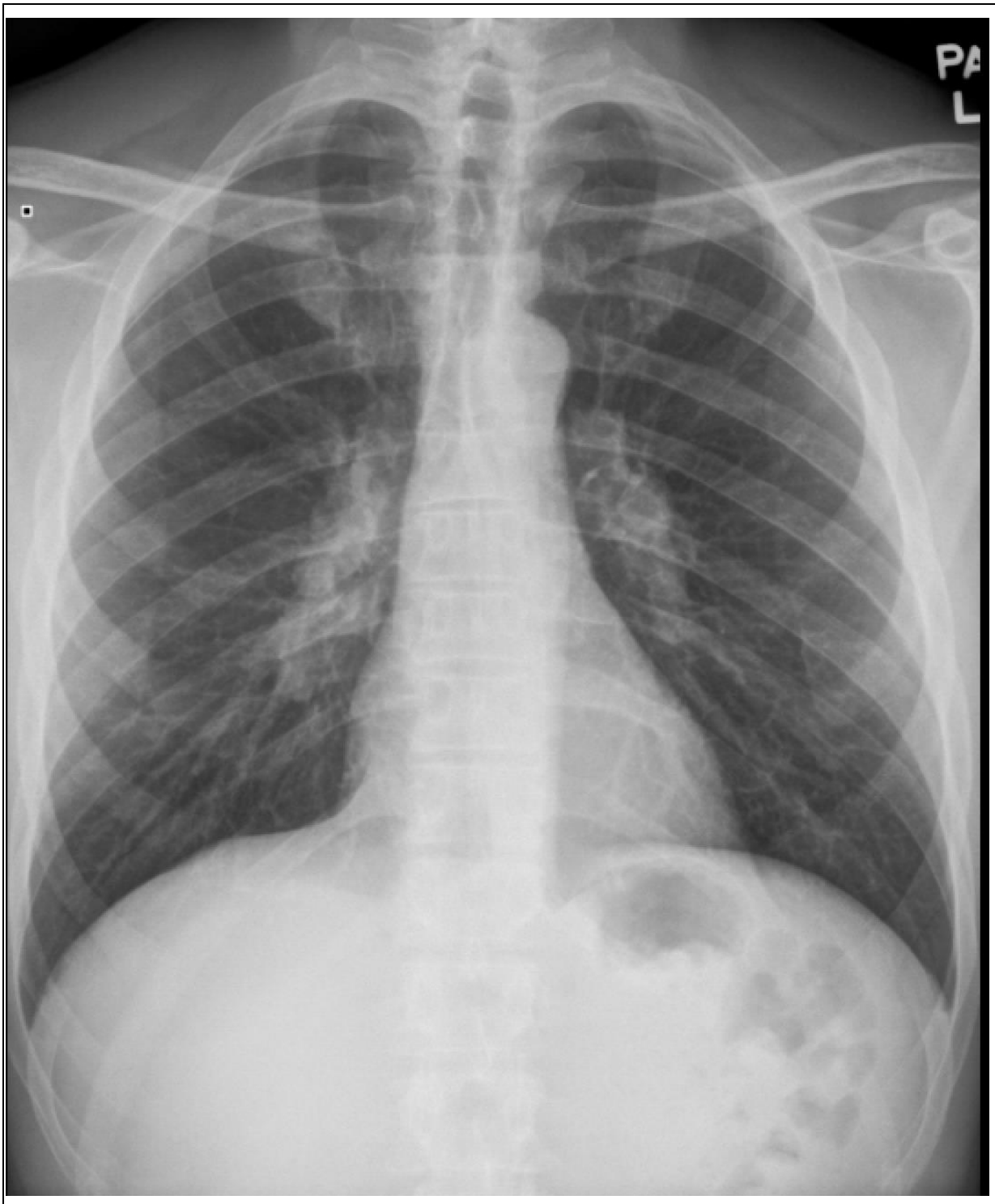

Figure 2. Chest X-ray of the patient showing right bulky hilum.

Reference (not more than 10)

1. Arkema EV, Cozier YC. Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. Curr Opin Pulm Med. 2020;26(5):527-34.
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3. Drent M, Crouser ED, Grunewald J. Challenges of Sarcoidosis and Its Management. N Engl J Med. 2021;385(11):1018-32.
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6. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin-Converting Enzyme in Sarcoidosis: A Population-Based Study. Lung. 2016;194(1):91-5.
7. Leung WK, Lei KI, Yim A, Sit YK, Lai CK, Leung R. Sarcoidosis in a Hong Kong Chinese woman. Hong Kong Med. J. 1998; 4: 333–6.
8. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and Management of Sarcoidosis. Am Fam Physician. 2016;93(10):840-8.

No of words in Case History and Discussion (excluding references):_____1722_____

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

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