CASE REPORT

Multisystemic sarcoidosis—important lessons learnt from one of the great imitators

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SUMMARY
We report a case of a woman who was admitted with a suspicion of metastatic malignancy of unknown primary origin. A few months prior to her admission, she presented to a rheumatologist with acute anterior uveitis, psoriasisiform rashes and polyarthritis. A diagnosis of psoriatic arthropathy was made and she was treated accordingly. Soon after she presented with persistent back and right upper quadrant abdominal pain for which she had a CT scan done with evidence of hilar lymphadenopathy, liver hypodensities and lytic-sclerotic bone lesions. She was referred to our hospital for further investigations and management. After re-exploring her clinical presentation and further investigations (including a liver biopsy), a diagnosis of multisystemic sarcoidosis with ocular, reticuloendothelial, hepatic and skeletal involvement was made. The patient was started on systemic glucocorticoids and second line immunosuppressants and demonstrated significant clinical improvement with resolution of her liver granulomata on imaging and improvement in her back pain. The case illustrates the importance of a thorough clinical assessment, review of investigations and an open mind in the evaluation of a patient.

BACKGROUND
Sarcoidosis is a rare chronic systemic inflammatory disorder, which is characterised by the formation of non-caseating granulomata. It has a highly variable clinical presentation and disease course, depending on the organ involvement.

Arriving at a diagnosis of sarcoidosis is not a straightforward process. It is important that compatible clinical features are associated with histopathological findings of non-caseating granulomata in affected organs, and that other granulomatous disorders are excluded.1

A wide range of differentials would need to be considered, again depending on patient population and clinical presentation. A rare case of multisystemic sarcoidosis, initially diagnosed as metastatic malignancy of unknown origin, is described here.

CASE PRESENTATION
Four months prior to her presentation to our hospital, the patient—a 56-year-old Indian woman—noted the appearance of left axillary skin thickening associated with dysesthesia. At around the same time, she also developed acute-onset polyarthritis with symmetrical involvement of her elbows, knees and ankles. She reported progressive worsening of her joint pains, which improved with the use of the affected joints, and associated joint swelling and early morning stiffness (lasting more than an hour) over a two week period, and constituted swelling of the affected joints with associated pain, which improved with use of joint, and significant early morning stiffness lasting more than an hour. She self-medicated with paracetamol, with no improvement in her symptoms.

She subsequently developed extensor tenosynovitis of both her feet and swelling and pain over both her Achilles tendons, which significantly limited her mobility and thus led to her presentation to the emergency department (ED) of a hospital near her home. She had plain radiography done, which demonstrated soft tissue swelling with no significant bony pathology and was sent home with oral diclofenac 50 mg twice daily and a referral to orthopaedic surgery. The patient did report some relief in her joint symptoms on diclofenac, but this was partial and non-sustained.

Ten days following her ED visit, she developed redness of both her eyes which was associated with grittiness, blurring of vision and photophobia. She was seen by an ophthalmologist who diagnosed her with bilateral acute anterior uveitis and referred the patient to a rheumatologist for possible seronegative arthritis given her polyarthritis.

At her private rheumatologist review a week later, the patient was noted to have a psoriasisiform rash over her upper limbs, hairline and scalp with florid synovitis in both ankles and knees. A diagnosis of psoriatic arthropathy was made, and the patient was given oral methotrexate 10 mg weekly and prednisolone 5 mg twice daily, to which she had a good clinical response. Prednisolone was subsequently tapered off over a 2-week period.

She returned to the rheumatology clinic a month later with new-onset deep-seated pain over the lower thoracic spine with radiation to both T8 dermatomes, as well as a right hypochondrial ache and fullness, which persisted throughout the day, disturbed her sleep and failed to respond to non-steroidal anti-inflammatory drugs. She was noted to have tender hepatomegaly without any stigmata of chronic liver disease, as well as point tenderness over the T10 and T12 vertebral bodies. An abdominal CT scan demonstrated multiple hypodense lesions in the liver with no enhancement in the resting phase. Lung cuts captured bilateral lymphadenopathy. Methotrexate was stopped immediately.


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The patient was referred to our hospital for further management and evaluation due to suspicions of a diagnosis of metastatic cancer of unknown origin. After admission, she was initially referred to the palliative medicine service for symptom control and consideration of hospice care. As her diagnostic liver biopsy demonstrated non-caseating granulomata, however, decision was made for further evaluation of her lesions and clinical presentation. A rheumatology consultation was sought in view of a possible diagnosis of sarcoidosis, and this subsequently led to further investigations and additional clinical history and physical findings as outlined below.

Past medical history
The patient had no significant past medical and surgical history of note. She denies any personal history of tuberculosis and malignancies in the past. She also denies having had recurrent infections in the past.

Social history
The patient is married and has a son. She is working as a care manager at a children’s home. She has no previous smoking habits and is teetotal. With regards to her sexual history, the patient had only one sexual partner.

Family history
The patient’s mother has a history of psoriasis. During her admission, she discovered that her identical twin sister, who is residing in USA, had been diagnosed with sarcoidosis with lung involvement and acute anterior uveitis 4 years prior.

There is no known family history of malignancy, autoimmune disorders, tuberculous infection.

Review of systems
The patient developed anorexia with an unintentional weight loss of 4 kg 3 months before her admission. She denied any history of recurrent or persistent fever and night sweats. She also experienced dryness of her eyes and mouth in the 2 months leading up to her admission. While she still experienced some aching and early morning stiffness in the small joints of her hands, wrists, elbows, knees and ankles, these have largely improved compared with her initial presentation. She no longer had any skin rashes and denied any history of brittle or deformed nails in the past.

She denied any yellowing of her sclera, change in her stool consistency and calibre as well as change in her bowel habits. She also denied any tea coloured urine and clay coloured stools.

The rest of her review of systems was unremarkable.

Physical examination
The patient was afebrile and normotensive. She appeared comfortable.

There were no rashes, subcutaneous nodules and postinflammatory skin changes, including over the axillae where the patient noted skin thickening and dysesthesia initially. No psoriatic nail changes were seen. Salivary pooling was decreased, but there were no enlarged salivary glands. No ocular redness was noted.

Multiple mobile, non-tender subcentimetre cervical and supraclavicular lymph nodes were found. There were no palpable axillary and inguinal lymph nodes.

Cardiovascular and respiratory examinations were unremarkable. Neurological examination of the central and peripheral nervous system was normal. A formal ocular examination by an ophthalmologist was requested that showed no evidence of active uveitis, any sequelae of the previous episode of anterior uveitis and retinal vasculitis.

On abdominal examination, there was tender hepatomegaly with smooth edges. There was no splenomegaly nor any stigma of chronic liver disease.

There was no dactylitis, synovitis, tenosynovitis and enthesitis. There was tenderness over the spinous processes of the T9–T12 vertebrae and pain on rotation of the thoracic spine. Examination of the sacroiliac joints and cervical spine was unremarkable. Examination of the lumbar spine was limited by pain over the thoracic spine.

The rest of her physical examination was unremarkable.

INVESTIGATIONS
Laboratory evaluation
The official reports of previous blood investigations performed by her previous rheumatologist were not available for review. The rheumatologist’s referral letter stated that the patient had no previous elevations in her transaminases and no abnormalities in her blood count. It also stated that as part of the workup for the patient’s inflammatory arthropathy, Human Leukocyte Antigen B27 (HLAB27), hepatitis C and HIV screening were performed and showed negative results. Throughout her previous follow-up appointments, her erythrocyte sedimentation rate (ESR) ranged between 40 mm/hour to 50 mm/hour.

The patient’s laboratory work at the point of admission for her inpatient stay is shown in table 1.

No further evaluation was performed for the patient’s hypercalcaemia as repeat serum calcium levels throughout her admission were within normal values (2.30–2.50 mmol/L).

After having obtained the histological and radiological findings during the course of the admission, further blood investigations were requested for the patient (table 2).

Radiological evaluation
Extensive radiological evaluations were performed.

Quadriphasic CT of the thorax, abdomen and pelvis (figure 1A,B) showed significant findings of:

► Paratracheal, prevascular, subcarinal and bilateral hilar lymphadenopathy measuring up to 1.1 cm in the short axis. The lungs are clear apart from atelectasis in the lung bases, mediastinal structures are unremarkable. No pleural effusion or pericardial effusion is noted.

► Multiple hypodensities in both hepatic lobes, largest measuring 2.2 cm × 1.7 cm. They do not demonstrate significant arterial enhancement and are rather inconspicuous in the delayed phase. These are suspicious for metastases.

► Mottled lytic-sclerotic appearance of T9 and T12 vertebral bodies.

► Bulky cervix. No adnexal masses. No intra-abdominal lymphadenopathy. Spleen, pancreas, adrenal glands and gall bladder are normal in appearance.

Further evaluation of bony lesions was done with an MRI of the whole spine (figure 2) and bone scan (figure 3). MRI findings include that of a heterogeneous abnormal marrow signal with abnormal enhancement in the T9 vertebral body as well as focal lesion in the T12 vertebral body, both of which were suspicious for metastatic lesions. Indeterminate abnormal marrow signal without enhancement at T8. There were no pathological fractures or paraspinal soft tissue masses. Bone scan findings also demonstrated focus of moderately increased tracer uptake at the right half of T9 vertebra, as well as mildly increased tracer uptake in T12 vertebra were seen. Findings were thought to
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be suspicious of metastatic disease. As such a bone biopsy was arranged for the patient.

A pelvic ultrasound was performed to assess the bulky cervix further and showed no suspicious cervical bulkiness nor any adnexal masses. The only abnormal finding was that of a uterine fibroid.

Mammography was done as part of malignancy screening and did not show any suspicious features.

Histological evaluation

In pursuit of a diagnosis, the patient underwent multiple biopsies to assess the nature of her liver and bone lesions.

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### Table 1: Laboratory values*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0 (admission)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count, ×10^9/L</td>
<td>11.3</td>
<td>3.6–9.3</td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>14.8</td>
<td>11.0–15.0</td>
</tr>
<tr>
<td>Platelets, ×10^9/L</td>
<td>383</td>
<td>170–420</td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>59</td>
<td>40–75</td>
</tr>
<tr>
<td>Calcium, adjusted, mmol/L</td>
<td>2.63</td>
<td>2.15–2.58</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>1.6</td>
<td>0.8–1.6</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35</td>
<td>35–48</td>
</tr>
<tr>
<td>Total bilirubin, umol/L</td>
<td>10</td>
<td>7–31</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>77</td>
<td>14–54</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>50</td>
<td>15–41</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>147</td>
<td>38–126</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>58</td>
<td>7–50</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>509</td>
<td>250–580</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>237</td>
<td>36–128</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>41</td>
<td>3–15</td>
</tr>
<tr>
<td>Anti-HAV IgM</td>
<td>Non-reactive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Non-reactive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBC IgM</td>
<td>Non-reactive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs, IU/L</td>
<td>&lt;10</td>
<td></td>
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<tr>
<td>Anti-HBe</td>
<td>Non-reactive</td>
<td></td>
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<tr>
<td>α-fetoprotein, ug/L</td>
<td>1</td>
<td>0–9</td>
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<tr>
<td>CEA, ug/L</td>
<td>2</td>
<td>0–5</td>
</tr>
<tr>
<td>CA 19–9, U/ml</td>
<td>11</td>
<td>0–35</td>
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<tr>
<td>CA125, U/mL</td>
<td>13</td>
<td>0–35</td>
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<tr>
<td>β2-microglobulin, ug/L</td>
<td>2553</td>
<td>0–1900</td>
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<tr>
<td>LDH, U/L</td>
<td>509</td>
<td>250–580</td>
</tr>
<tr>
<td>Peripheral blood film</td>
<td></td>
<td></td>
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<tr>
<td>Majority of the RBCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>appear normochromic and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normocytic, mild neutrophil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild monocytes,</td>
<td></td>
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<tr>
<td>platelets are adequate in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number with some large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>platelets seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloma panel</td>
<td>No paraprotein band seen</td>
<td></td>
</tr>
<tr>
<td>25 (OH) vitamin D, ug/L</td>
<td>&lt;9</td>
<td></td>
</tr>
</tbody>
</table>

*ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HAV, antihumanpesis A virus; anti-HBC, antihumanpesis B core antibody; anti-HBe, antihumanpesis B envelope; anti-HBs, antihumanpesis B surface antibody; AST, aspartate aminotransferase; CA 19–9, cancer antigen 19–9; CA 125, cancer antigen 125; CEA, carcinoembryonic antigen; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyl transpeptidase; HBsAg, Hepatitis B surface antigen; LDH, lactate dehydrogenase; RBC, red blood cell.

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### Table 2: Further blood tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 20 (diagnosis)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin, g/L</td>
<td>24</td>
<td>35–48</td>
</tr>
<tr>
<td>Total bilirubin, umol/L</td>
<td>9</td>
<td>7–31</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>126</td>
<td>14–54</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>48</td>
<td>15–41</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>138</td>
<td>38–126</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>43</td>
<td>3–15</td>
</tr>
<tr>
<td>ACE, U/L</td>
<td>11</td>
<td>8–53</td>
</tr>
<tr>
<td>TB interferon</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>VDRL</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

*ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; TB, tuberculosis; VDRL, venereal disease research laboratory.

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**Figure 1** CT scan of the patient’s thorax, abdomen and pelvis. (A) Paratracheal, prevascular, subcardinal and bilateral hilar lymphadenopathy (measuring up to 1.1 cm in short axis). (B) Multiple hypodensities in both hepatic lobes were seen, with the largest measuring 2.2 cm × 1.7 cm. These did not demonstrate significant arterial enhancement and were inconspicuous in the delayed phase.

**Figure 2** MRI, whole spine. There is heterogeneous abnormal marrow signal demonstrated in the T9 vertebral body as well as a 1.9 cm focal lesion demonstrated in the T12 vertebral body with corresponding abnormal contrast enhancement. No pathological fracture or paraspinal soft tissue mass is demonstrated.
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CT-guided liver biopsy (of lesions adjacent to the right main portal vein as well as the dome) (figure 4A–E)

Of note, there was evidence of coalescing non-caseating granulomata, consistent with granulomatous inflammation. Acid-fast and fungal stains were negative. Unfortunately, no tissue cores were sent for cultures and the patient declined repeat biopsies for this purpose.

Bone biopsy of T12 vertebra

No evidence of granulomas or malignancy were found. Bone tissue was sent for mycobacterial, fungal and bacterial stains and cultures, all of which returned negative.

Bone marrow evaluation

Differentials including that of a haematological malignancy were considered and as such bone marrow evaluation was performed and showed no morphological evidence of abnormal cellular infiltrate in the marrow aspirate and trephine biopsy. Cytogenetics showed normal karyotype and there was no flow cytometric evidence of abnormal lymphoid infiltrate.

Cardiac evaluation

Transthoracic echocardiography and 12-lead ECG were normal. No cardiac MRI was planned.

Others

By the time the patient was referred to the rheumatology team, she declined further invasive diagnostic tests as she had by then undergone the above procedures. We had offered her the following:

► Cervical supraclavicular lymph node biopsy and endoscopic evaluation of her gastrointestinal tract
  - A surgical consult was sought to facilitate the biopsy, however as the cervical lymph nodes were deemed to be prominent, but not significantly enlarged both the medical team and patient were advised to monitor the lymphadenopathy first as surgical risk was deemed to outweigh any benefit and limited information yield at present.
  - The patient also declined any endoscopic evaluation as she had no other gastrointestinal symptoms aside from her right upper quadrant pain.

► Bronchoscopy with bronchoalveolar lavage (BAL) and possibly endobronchial ultrasound guided lymph node biopsy of mediastinal lymph nodes (for histology and cultures).

DIFFERENTIAL DIAGNOSIS

The patient is a middle-aged woman with acute-onset polyarthritis and tenosynovitis, acute anterior uveitis, hilar lymphadenopathy, multiple liver hypodensities with underlying granulomatous inflammation and lytic-sclerotic vertebral body lesions.

While there are many ways of approaching the clinical problem, we chose to evaluate the patient based on the differential diagnoses of systemic conditions that may result in widespread granulomatous inflammation. Box 1 illustrates how wide the range of possible differential diagnoses for liver granulomata can be.

In our discussion for the relevant differential diagnoses in this clinical case, we have omitted discussions on drugs and reaction to foreign bodies as the patient had not been exposed to any of the drugs or elements in the past.

INFECTIONS

Mycobacterial infections

Given that mycobacterial infections are endemic in Singapore (with the exception of Mycobacterium leprae), it was important to exclude disseminated mycobacterial infections leading to the patient’s clinical presentation.

We felt that the diagnosis of mycobacterial infections was less likely in the absence of fever and positive supporting investigations, i.e. negative T-spot, absence of acid-fast bacilli on liver and bone biopsies, and negative cultures for mycobacterium from her bone biopsy.

Mycobacterium tuberculosis

Extrapulmonary presentations of Mycobacterium tuberculosis are rare. However, given its prevalence of it in Singapore, it is
undoubtedly a possible differential diagnosis. Liver tuberculosis is a rare presentation of intra-abdominal mycobacterial infections. It is usually found in the context of miliary pulmonary tuberculosis or other infectious foci involving the gastrointestinal tract. The presentation of hepatic tuberculosis may be divided into three types:

- Miliary hepatic tuberculosis, which occurs due to the haematogenous dissemination of infection from a distant site, for example, lung, via the hepatic artery. It is considered the most common type of hepatic tuberculosis.
- Biliary tract tuberculosis, which usually presents with a triad of fever, jaundice and hepatic calcifications. Jaundice in these patients may be due to extrahepatic or infrahepatic strictures, adenopathy and hepatolithiasis.
- Nodular hepatic tuberculosis, which is a localised form of tuberculosis of the liver, that is, tuberculosis. It is a rare entity and was first described by Bristowe in 1838 on post-mortem finding of liver involvement in 12 out of 167 cases of tuberculous ulceration of the intestines.

Diagnosis can be difficult if tuberculosis and tuberculous liver abscesses present as discrete nodules. As the clinical presentation is not specific, a high index of suspicion is needed to reach the diagnosis. Failure to identify this entity may lead to hepatic failure and death. The most common symptoms are right upper quadrant pain, fever, loss of appetite and weight loss. Hepatomegaly may be found with an increase in alkaline phosphatase (ALP) and elevation of transaminases. Anaemia and elevations in ESR are often seen.

CT appearances of hepatic tuberculosis vary depending on its evolutionary stage (solid, necrotic or fibrous). However, they generally take on the appearance of well-circumscribed lesions with moderate peripheral enhancement. Based on radiological features, the differential diagnosis of the micronodular variant of hepatic tuberculosis includes metastases, lymphoma, leukaemia, sarcoidosis and fungal infection. On the other hand, the macronodular form is seen as large lesions with peripheral rim enhancement and low central attenuation and appears identical to pyogenic abscess, metastases and primary liver tumours. CT appearances of hepatic tuberculosis vary depending on its evolutionary stage (solid, necrotic or fibrous). However, they generally take on the appearance of well-circumscribed lesions with moderate peripheral enhancement. Based on radiological features, the differential diagnosis of the micronodular variant of hepatic tuberculosis includes metastases, lymphoma, leukaemia, sarcoidosis and fungal infection. On the other hand, the macronodular form is seen as large lesions with peripheral rim enhancement and low central attenuation and appears identical to pyogenic abscess, metastases and primary liver tumours.

It is important to be aware of musculoskeletal manifestations of extrapulmonary tuberculosis, that is, tuberculosis septic arthritis and non-suppurative reactive arthritis. The latter is also known as Poncet’s disease.

**Mycobacterium avium complex**

Most cases of disseminated infection due to *Mycobacterium avium* complex (MAC) are described in immunocompromised patients such as those with HIV/AIDS, malignancy and solid organ transplant. It is however possible for MAC to result in disseminated infections in immunocompetent individuals as well.

Manifestation of disseminated MAC (DMAC) infection in immunocompromised individuals has been widely documented: lymphadenopathy, fever, weight loss and night sweats. On the other hand, clinical presentation of DMAC in immunocompetent hosts appears to be limited to localised pulmonary infection in patients with underlying pulmonary conditions. A case series on MAC infections in immunocompetent hosts cited cervical lymphadenopathy as the common presenting feature. There have been case reports of MAC causing hepatic granulomas in immunocompetent individuals.

**Leprosy**

Leprosy is a chronic granulomatous disorder caused by *M. leprae*. It presents as a spectrum of clinical and pathological features:

- Lepromatous leprosy, which may present with multiple lesions, extensive skin and internal organ involvement.
Chronic inflammation with a Acute inflammation.

Tuberculoid leprosy, which is characterised by a single or antosa 6 the clinical phase:

osteomyelitis.15–17 and possibly even suppurative parotitis and granulomatous lung involvement, subcutaneous abscesses, lymphadenitis, and multiorgan involvement. This is then usually followed by during which septicaemia may occur, causing septic shock history of melioidosis is usually characterised by an acute phase

Melioidosis is caused by Burkholderia pseudomallei. The natural component.

predominantly granulomatous picture. Granulomas in melioidosis usually demonstrate a caseous or purulent central necrosis surrounded by epithelioid and giant cells. Fibrosis is observed in lung, lymphoid and bone tissues. Gram-negative bacilli are usually observed.18

Brucellosis
Brucellosis is a systemic granulomatous disorder caused by coccobacilli of the Brucella species. It has been known by various names, including Malta fever, gastric remittent fever and undulant fever.

Humans are accidental hosts and usually acquire the infection through breaches in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal tracts. Ingestion of unpasteurised dairy products remains a common mode of transmission among travellers to endemic areas.20

The clinical manifestations of brucellosis are protean and non-specific: fever or chills, arthralgia or arthritis, anorexia, asthenia, fatigue, weakness, malaise, hepatomegaly and splenomegaly.21 22

Histological findings include that of epithelioid-cell granulomas which may be found in the reticuloendothelial system, lung, brain, bone, joints and soft tissue, and are difficult to distinguish from granulomas due to other causes. Necrotising hepatic granulomas and hepatic microabscesses have been described.23 24

Virus infections
Discrete non-caseating granulomas or fibrin-ring granulomas have been seen in Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections. Likewise, they have also been seen in hepatitis B and hepatitis C infections.25

As the patient’s clinical features were not consistent with EBV and CMV infections, and her serologies for hepatitis B and hepatitis C were negative, these would unlikely be the cause for the patient’s clinical presentation.

Other possible infectious causes
The patient was on low dose of oral methotrexate (10 mg per week) and was otherwise immunocompetent (HIV screen was negative). She had no other obvious risk factors (including exposure via travel, hobby, pets, occupation) for developing disseminated fungal, parasitic and opportunistic infections, and as such the likelihood of her having had any of the following infections would have been unlikely. It is also useful to note that she had no eosinophilia, which is often present in fungal and parasitic infections.

Histoplasmosis and other fungal infections
Fungal infections are common causes of granulomas and can present as localised or systemic illnesses.

Most histoplasma infections are asymptomatic or self-limiting. Rarely, acute infections result in severe and progressive dissemination. Histoplasmosis may produce clinical disease resembling tuberculosis with features of fever, breathlessness, cough, weight loss, asthenia and joint pain.26 27

Histoplasma infections in immunocompetent hosts may result in epithelioid-cell granulomas in the lung that undergo coagulative necrosis. It may be differentiated from tuberculosis and sarcoidosis on identification of thin-walled yeast forms on fungal stains of histology samples.

Toxoplasmosis
Acquired toxoplasmosis in immunocompetent individuals are generally asymptomatic or associated with a flu-like illness and lymphadenopathy. Disseminated toxoplasmosis usually affects immunocompromised individuals either from acute exposure

Bacterial infections
It was felt unlikely that the patient had a bacterial infection as the underlying cause of her clinical presentation as the patient did not present with any fever or features of septicaemia often present in bacterial infections. Furthermore, she had no occupational, travel and exposure history which would have predisposed her to melioidosis and brucellosis.

Melioidosis
Melioidosis is caused by Burkholderia pseudomallei. The natural history of melioidosis is usually characterised by an acute phase during which septicamia may occur, causing septic shock and multiorgan involvement. This is then usually followed by a chronic suppurrative phase during which patients develop lung involvement, subcutaneous abscesses, lymphadenitis, and possibly even suppurative parotitis and granulomatous osteomyelitis.14–17

Histological findings of melioidosis vary widely, depending on the clinical phase:

Acute inflammation.

Chronic inflammation with a focal granulomatous component.

A predominantly granulomatous picture.

Granulomas in melioidosis usually demonstrate a caseous or purulent central necrosis surrounded by epithelioid and giant cells. Fibrosis is observed in lung, lymphoid and bone tissues. Gram-negative bacilli are usually observed.18

Figure 5 CT of the patient’s liver. Previous liver hypodensities seen at the time of diagnosis were no longer demonstrated on the repeat scan.

Usually lesions are diffusely infiltrated with numerous leprotic bacilli.

Tuberculoid leprosy, which is characterised by a single or few skin lesions and involvement of the nerve at the site of the lesions. Skin biopsies of patients with tuberculoid leprosy demonstrate well-defined giant cell granuloma with or without caseous necrosis and dermal nerve destruction. Leprotic bacilli are usually scanty.

The diagnosis of leprosy is made based on clinical and histological findings. It may be difficult to differentiate tuberculoid leprosy from other infectious and non-infectious granulomas, such as those of syphilis and sarcoidosis, in view of the paucity of leprotic bacilli.14

Learning from errors
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Acute inflammation.

Chronic inflammation with a focal granulomatous component.

A predominantly granulomatous picture.

Histological findings of melioidosis vary widely, depending on the clinical phase:
Systemic vasculitides such as (but not limited to) granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), polyarteritis nodosa and giant cell arteritis. Likewise chronic inflammation of the blood vessels due to systemic lupus erythematosus and rheumatoid arthritis may also result in granuloma formation (rare).

The following are the reasons as to why the above conditions are thought to be less likely:

► The patient’s symptoms were largely non-specific at the point of admission with no previous history pointing towards ‘typical’ features of the autoimmune disorders (table 3).

► At the time of rheumatology review as inpatient, the patient had been off methotrexate for about 3 weeks. There had been no evidence of a flare-up of her arthritis and uveitis despite absence of immunosuppression. This is not in keeping with the natural history of systemic vasculitides and connective tissue disorder, especially if the granulomatous inflammation in the liver developed while the patient was on immunosuppression.

► There was no evidence of vasculitis on imaging and liver biopsy, that is, no fibrinoid necrosis of the arterioles were seen, and no eosinophilic granulomas.

While forme fruste manifestations of the above conditions is always a possibility and absence of vasculitis on biopsy could be attributed to sampling errors, we felt that the constellation of clinical symptoms was not in keeping with the above conditions and hence elected against performing autoantibodies in this patient.

### Table 3: Clinical features of some select autoimmune disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Classical clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Granulomatosis with polyangiitis</strong>&lt;sup&gt;81,82&lt;/sup&gt;</td>
<td><em>► Commonly occurs in older adults</em>&lt;br&gt; <em>► Prodromal: fever, malaise, anorexia, weight loss</em>&lt;br&gt; <em>► Recurrent sinusitis, epistaxis, scleitis (more common than uveitis), orbitis media, polychondritis, oral and/or nasal ulcers, cough, haemoptysis, abnormal chest radiograph (nodules, fixed infiltrates, cavities), abnormal urinary sediment (microscopic haematuria), leucocytoclastic angitis, conjunctivitis, corneal ulcerations, scleitis, optic neuropathy, retinal vasculitis, and uveitis, inflammatory pseudotumours, arthritis, granulomatous inflammation on biopsy of an artery or perivascular area Uncommon presentations involve the gastrointestinal tract, heart, lower genitourinary tract (including ureters and prostate), parotid glands, thyroid, liver or breast</em></td>
</tr>
<tr>
<td><strong>Eosinophilic granulomatosis with polyangiitis</strong>&lt;sup&gt;83,84&lt;/sup&gt;</td>
<td><em>► Prodomal phase: adult-onset (20s—30s) of atopic disease, allergic rhinitis, asthma</em>&lt;br&gt; <em>► Eosinophilic phase: peripheral blood eosinophilia and eosinophilic infiltration of multiple organs, especially the lung and gastrointestinal tract. Pulmonary opacities, asthma and peripheral eosinophilia are present in about 40% of patients</em>&lt;br&gt; <em>► Vasculitic phase: systemic vasculitis of small and medium vessels, associated with vascular and extravascular granulomatosis. The vasculitis phase is often heralded by constitutional symptoms and signs</em></td>
</tr>
<tr>
<td><strong>Polyarteritis nodosa</strong>&lt;sup&gt;85&lt;/sup&gt;</td>
<td><em>► Affects middle-aged or older adults, with male predominance</em>&lt;br&gt; <em>► Though most cases are idiopathic, there are associations with hepatitis B and hepatitis C</em>&lt;br&gt; <em>► The cardinal features of classic polyarteritis nodosa include renal infarcts, renal artery stenosis and visceral microaneurysms</em>&lt;br&gt; <em>► Clinical presentations: constitutional symptoms, mononeuritis multiplex, arthralgia/myalgia, livedo reticularis, purpura and cutaneous ulcers, new-onset hypertension, lung infiltrates (rare), stroke, limb claudication or ischaemia</em></td>
</tr>
<tr>
<td><strong>Giant cell arteritis/temporal arteritis</strong></td>
<td><em>► Older adults</em>&lt;br&gt; <em>► Often presents with constitutional symptoms</em>&lt;br&gt; <em>► Clinical manifestations: anaemia, thrombocytosis, fever, jaw claudication, scalp tenderness, amaurosis fugax, arthritis, aortitis, stroke</em></td>
</tr>
<tr>
<td><strong>Systemic lupus erythematosus</strong></td>
<td><em>► Usually affects ladies of reproductive age</em>&lt;br&gt; <em>► May affect any organ system</em>&lt;br&gt; <em>► Photosensitivity, alopecia, recurrent oral ulcers, arthralgia/arthritis, tenosynovitis, cytopenia, sicca, serositis, myalgia/myositis, microscopic haematuria, proteinuria, oedema, cutaneous lupus</em>&lt;br&gt; <em>► May present with lupus hepatitis and lymphadenopathy</em></td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td><em>► Symmetrical erosive polyarthritis predominantly affecting the small joints of hands and feet</em>&lt;br&gt; <em>► May be complicated by extra-articular manifestations (oculač, vasculitis)</em></td>
</tr>
</tbody>
</table>
abdominal pain, mucoid or bloody diarrhoea, oral ulcers, abdominal masses and enterocutaneous fistulas. Those afflicted with Crohn’s disease may also develop uveitis and enteropathic arthritis.

Histological findings from random biopsies of the alimentary tract in Crohn’s disease demonstrate transmural inflammation consisting of chronic inflammatory cells with lymphoid aggregates as well as non-caseating sarcoid-like granulomas in diseased and unaffected tissue. Such inflammatory changes may also be seen in the lung and other organs such as the liver. It is however unclear whether such changes are due to the condition itself, an associated primary sclerosing cholangitis or an adverse drug reaction.

Primary biliary cirrhosis and primary sclerosing cholangitis

In the initial stages, patients with chronic biliary diseases are usually symptomatic with a mild derangement in the liver function test often showing elevations in ALP and γ-glutamyl transpeptidase (GGT). Over time the patient develops a predominantly cholestatic picture in transaminitis with associated jaundice, pruritus and clinical features of cirrhosis.

Granuloma formation is reported in 18%–64% of primary biliary cirrhosis cases. The distribution of the granuloma may be portal or lobular, but duct lesions are often seen. Granulomas are also observed in a minority of cases of primary sclerosing cholangitis and are usually well formed, non-necrotising and epithelioid.

Sarcoidosis

Sarcoidosis is a chronic multisystemic disease usually affecting middle-aged adults characterised by non-caseating epithelioid cell granuloma. The lung, lymph nodes, skin, joints, eyes and liver are the most commonly involved organs. The incidence of hepatic granulomata on histology in sarcoidosis is estimated to be 50%–65%. Only 5%–15% of patients have symptomatic hepatic sarcoidosis. The predominant derangement in liver enzyme abnormality is the elevation of ALP and GGT. Serum aminotransferases can be increased to a lesser extent in about 50%–70% of patients. If symptomatic, the most frequent symptoms are that of abdominal pain, pruritus, fever, weight loss and jaundice. A minority of patients progresses to severe cholestatic jaundice, portal hypertension, Budd-Chiari syndrome and cirrhosis.

To date, there is no pathognomonic biomarker to confirm the diagnosis of sarcoidosis. Serum ACE level may be elevated but is normal in approximately 25% of untreated patients. It has limited utility as a diagnostic test due to poor sensitivity and insufficient specificity. Multiple biomarkers are being assessed for their clinical usefulness in making the diagnosis and ascertaining the progression of sarcoidosis. Thus far however it appears that a multiaxial of various biomarkers (such as sIL-2, C-reactive protein (CRP), SAA, chitotriosidase, ACE, γ-globulins, lysozyme, tumour necrosis factor (TNF)-α and CCL18) may be required to achieve the task.

Neoplastic aetiologies

The concept of sarcoid reaction, that is, the formation of epithelioid-cell granulomas in relation to tumour-related tissue reactions is well known. Such reactions may occur in the tumour itself, lymph nodes draining the area housing the malignancy and even in distant tissues.

Sarcoid reactions are seen in predominantly haematological malignancies (both in Hodgkin’s and non-Hodgkin’s disease), though it has also been reported in solid organ tumours such as lung cancer, testicular cancer, uterine cancer and breast cancer.

Sarcoid reactions are driven by B lymphocytes, while these cells do not play a role in sarcoidosis as they are absent in the granulomas of sarcoidosis.

TREATMENT

A working diagnosis of multisystemic sarcoidosis or possible overlap of sarcoidosis with psoriasis was made after considering the following:

- Her initial presentation of acute anterior uveitis, an apparent psoriasiform rash, acute-onset polyarthritis with tenosynovitis without other features of psoriasis (the patient’s back pain did not appear to be inflammatory, no psoriatic nail changes were observed, no history of dactylitis, absence of HLA-B27).
- A positive family history of sarcoidosis in an identical twin.
- Presence of paratracheal, subcarinal and bilateral lymphadenopathy in the absence of respiratory symptoms and lung pathology on CT.
- Multiple liver hypodensities with evidence of non-caseating granuloma on liver biopsy, in the absence of fungal and mycobacterial organisms on special staining of the tissue samples.
- Lytic-sclerotic lesions in T9 and T12 with increased uptake on MRI and bone scan, with no evidence of malignancy on bone biopsy.
- No evidence of haematological malignancy on bone marrow examination.

Learning from errors

To date, there is no pathognomonic biomarker to confirm the diagnosis of sarcoidosis. Serum ACE level may be elevated but is normal in approximately 25% of untreated patients. It has limited utility as a diagnostic test due to poor sensitivity and insufficient specificity. Multiple biomarkers are being assessed for their clinical usefulness in making the diagnosis and ascertaining the progression of sarcoidosis. Thus far however it appears that a multiaxial of various biomarkers (such as sIL-2, C-reactive protein (CRP), SAA, chitotriosidase, ACE, γ-globulins, lysozyme, tumour necrosis factor (TNF)-α and CCL18) may be required to achieve the task.
OUTCOME AND FOLLOW-UP
The patient remained well during her follow-up with us for the following 6 months and improvement was evident in the following domains:
- She had no recurrence of her skin lesions, anterior uveitis and arthritis/tenosynovitis.
- Resolution of cervical and supraclavicular lymphadenopathy.
- Resolution of her right upper quadrant abdominal pain with normalisation of her liver function tests and complete resolution of the previously observed liver hypodensities (figure 5).
- Resolution of her back pain, with stable sclerotic appearance of her T9 and T12 lesions.

Unfortunately, we are unable to comment on the resolution of her mediastinal lymph nodes as the patient refused to have a repeat CT scan of her thorax due to financial constraints. Furthermore, we cannot comment on her progress after she was lost to follow-up after she emigrated.

DISCUSSION
Sarcoidosis is an infiltrative, inflammatory disorder that may mimic or even occur concomitantly with numerous primary rheumatic diseases (eg, connective tissue disorders such as systemic lupus erythematosus, Sjogren's syndrome, spondylarthritis and vasculitis) and other systemic disorders such as malignancies.

Clinicians may hone in on the diagnosis of sarcoidosis in the setting of 'classical' clinical syndromes, such as Löfgren's syndrome—an acute variant of sarcoidosis classically presenting with erythema nodosum, hilar adenopathy, ankle oligoarthritis and possibly iritis; lupus pernio with acral papulonodules and plaques, upper respiratory tract involvement and lytic bone lesions; Heerfordt's syndrome (a triad of uveitis, cranial nerve palsy and parotid enlargement). Other multisystemic presentations of sarcoidosis requires the vigilance of the managing physicians. On the other hand, extrapulmonary sarcoidosis may pose a diagnostic challenge as there no diagnostic tests specific for sarcoidosis.

A diagnosis of sarcoidosis is usually made by co-relating clinical findings with histological findings of granulomatous inflammation in the absence of alternative diagnoses (such as those discussed in the previous section). This case illustrated this difficulty and also real world challenges such as financial constraints, patients' beliefs and preferences. We had to forego some of the investigations which would have given us additional information to support a diagnosis:
- Lymph node biopsies of the cervical supraclavicular lymph nodes.
- An excision biopsy of the lymph nodes would have provided us with additional information on whether the granulomatous inflammation is a disseminated process, the presence of malignancies and another substrate for microbiological studies. It would also be interesting to see whether the lymph node biopsy could provide us with insight as to whether the granulomatous inflammation was due to sarcoidosis or a sarcoid-like reaction by looking out for differences postulated in published studies.55 56
- Endoscopic evaluation of the alimentary tract.
- Enlargement of supraclavicular lymph nodes is an indication for endoscopic evaluation of the gastrointestinal tract, even in the absence of symptoms. In the setting of granulomatous inflammation of the liver and polyarthritis with anterior uveitis, it would also be prudent to evaluate for mild or occult inflammatory bowel disease and perform a random biopsy of the upper and lower gastrointestinal tracts to look for features of Crohn's disease.35–37
- Microbiological studies of the liver biopsy.
- While the Zielh-Nielsen stain for acid-fast bacilli and fungal stains demonstrated the absence of mycobacteria and fungal elements, this may be due to a sampling bias and thus, a tissue culture for both types of organisms would have been preferred to exclude these infections.
- Bronchoscopy with BAL and possibly endobronchial ultrasound-guided transbronchial lymph node biopsy and endobronchial biopsies There are several utilities for such investigations:
  - Bronchoscopy would allow for evaluation of endobronchial cancers.
  - BAL has multiple purposes:
    - Microbiological studies to rule out infections.
    - There were conflicting reports about the utility of lymphocyte subset analysis, in particular the CD4/CD8 ratio, in the diagnosis of sarcoidosis.57–60 A meta-analysis on the diagnostic performance of BAL fluid CD4/CD8 ratio for sarcoidosis by Shen et al provides evidence that the determination of the BAL fluid CD4/CD8 ratio can aid in the diagnosis of sarcoidosis in patients with high pretest probability of the disease.61 No standardised cut-off exists, but some studies showed that a CD4/CD8 ratio of ≥3.5 strongly suggests sarcoidosis.62 63 It is important to be aware of factors that may affect the CD4/CD8 ratio such as smoking, advanced age and use of glucocorticoids.51 62
  - Endobronchial ultrasound-guided transbronchial biopsy.
  - The use of endobronchial ultrasound-guided transbronchial needle aspiration has gained favour for the diagnosis of sarcoidosis. Recent meta-analysis reported pooled sensitivity of 84% and specificity of 100%.64–67 The pitfall for this modality is, however, the need for presence of mediastinal lymph nodes.
  - Endobronchial biopsies.
  - The British Thoracic Society Interstitial Lung Disease guideline recognises the utility of endobronchial biopsies as adjunct to transbronchial biopsy in increasing the diagnostic yield in cases with suspected pulmonary sarcoidosis.68
- Repeat thoracic imaging to assess the resolution of her mediastinal lymphadenopathy.

We acknowledge the limitations of the investigations that have been performed, in that there is only limited value of elevations of serum ACE in clinical practice as serum ACE may be elevated in normal subjects and other conditions, including tuberculosis.49


Learning from errors

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Learning from errors

There are several points we wish to highlight with regards to the clinical learning points in this case:

► First, we were unsure whether the patient’s initial presentation of anterior uveitis, polyarthritis and tenosynovitis with psoriasiform rashes was due to psoriasis, or an evolving picture of probable multisystemic sarcoidosis, or whether both conditions coexisted. There was no evidence of enthesitis, dactylitis and psoriatic nail changes, which would have favoured psoriasis. Pictures of the cutaneous lesions and a skin biopsy could have given us more diagnostic clues.

From an immunological standpoint, it is interesting to note that psoriasis and sarcoidosis are both chronic systemic inflammatory disorders driven by type 1 helper T cells (Th1) and type 17 helper T cells (Th17). Given the shared immunological pathways, coexistence of both conditions would be plausible as corroborated by reports and case series of patients with psoriasis and sarcoidosis.66 67-69

► Second, there is a paucity of clinical information on sarcoidosis, despite it being a multisystemic disease that can be debilitating and can result in morbidity if left untreated, that is, liver cirrhosis in patients with hepatic sarcoidosis and20-22 loss of vision in those with sarcoid uveitis.70 This lack of studies is particularly true for non-pulmonary and non-ocular sarcoidosis.

We learnt important points about skeletal involvement of sarcoidosis. It is thought that skeletal involvement occurs in about 1%–13% of patients with sarcoidosis.70 71 Of interest in this case would be large bone lesions and axial skeletal lesions, which tend to become symptomatic. In the vertebral, sarcoidosis may result in widespread vertebral sclerosis or osteolytic lesions with preserved disc spaces. MRI of the affected bone may demonstrate hyperintense lesions on representative sarcoid nodules. The lesions are highly variable with some lesions appearing indistinct while other may be well marginated.72

As there are no specific radiological characteristics for skeletal sarcoidosis, differentials such as multiple myeloma and metastatic disease are often entertained.73 74 Both, bone scintigraphy and FDG-PET/CT can detect skeletal involvement of sarcoidosis, with bone scintigraphy showing increased tracer uptake even before lesions manifest radiographically.74 75

We also learnt that acute tenosynovitis may be a rare presentation of sarcoidosis usually observed in established sarcoidosis and associated with a higher than usual incidence of polyarthritis.66 76 While sarcoid tenosynovitis almost exclusively occurs in the hands,77 there have been reports of ankle tenosynovitis8 8 and Achilles teninits77 in sarcoidosis.

► Lastly, there are, to date, no randomised controlled studies on the treatment of multisystemic sarcoidosis. No doubt, this is likely because sarcoidosis is a rare condition and may be of a self-limiting disease course. Glucocorticoids remain the first-line therapy of choice for the treatment of the myriad of sarcoidosis manifestations,80 sarcoid arthropathy and osseous sarcoidosis. In refractory disease, corticosteroid-sparing immunosuppressants are added. However, the literature on the treatment choice for the treatment of non-ocular, extrapulmonary sarcoidosis, to date, is limited to case reports and case series on the use of azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide and biologics (including rituximab and anti-TNF agents).

The use of anti-TNF agents has been controversial given reports of development of sarcoidosis-like lesions with anti-TNF therapy.82

Learning points

This case illustrated multiple learning points, crucial to rheumatologists and to any other physicians who may encounter similar cases: This case illustrated multiple learning points, crucial to rheumatologists and to any other physicians who may encounter similar cases:

► The importance of good history taking and gathering of relevant clinical information can never be understated.

► Investigation results never replace clinical assessment of the patient, but where investigations, such as histological confirmation, determine the clinical course of action and outcome then appropriate investigations should never be omitted.

► This case also emphasises the need to be vigilant, keep an open mind and not jump to conclusions when making a diagnosis. It is essential to confirm a diagnosis before subjecting patients to treatment decisions and informing them of their prognosis.

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