CASE REPORT

Is this still just sarcoidosis, or should we a-DRESS a different diagnosis?

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SUMMARY

An Afro-Caribbean woman presented with worsening breathlessness, weight loss, lethargy and fevers, developing a bilateral florid erythematous rash on her legs. She was recently diagnosed with rheumatoid arthritis and bilateral hilar lymphadenopathy was found on thoracic CT imaging. She was tachycardic and investigations revealed pancytopenia, eosinophilia, raised serum ACE, acute kidney injury and deranged liver function tests. Biopsy of the lymphadenopathy revealed mixed lymphoid cells and liver biopsy revealed extramedullary haematopoiesis, with hypercellular marrow found on bone marrow biopsy. Cardiac MRI was normal, excluding cardiac sarcoid. The patient developed status epilepticus and phenytoin was started. She subsequently developed skin desquamation, in keeping with toxic epidermal necrosis. Skin biopsies revealed atypical granulomas and multinucleated giant cells, which subsequently resolved on steroid treatment. This case highlights an overlap syndrome, with an unclear diagnosis between sarcoidosis, drug reaction or rash with eosinophilia and systemic symptoms and/or hypereosinophilic syndrome and Still's disease. Hence varied serological and clinical features can complicate the distinction between diagnoses.

BACKGROUND

Overlap syndrome is well documented in the medical literature, yet there is a lack of reports to support a diagnosis of overlap syndrome with sarcoidosis. This case is an example of an overlap syndrome with features of connective tissue disease including sarcoidosis, which is further complicated by toxic epidermal necrosis (TEN). The multisystem disease is steroid responsive, and demonstrates how a patient's condition and symptoms may be treated even though a single underlying diagnosis is never reached.

CASE PRESENTATION

A 48-year-old Afro-Caribbean woman presented to her general practitioner with long-standing throat irritation, and a CT of the thorax was performed (figure 1). This revealed bilateral hilar lymphadenopathy, and the patient was therefore referred to respiratory outpatient clinic.

The patient noted a 4-week history of progressive shortness of breath, palpitations and 20 kg unintentional weight loss over this time. In the week preceding her appointment, she had developed fevers and an itchy bilateral florid erythematous rash on her legs. She had one episode of syncope at home, with no epileptic features noted

on questioning. The patient was experiencing palpitations daily, which lasted from a few minutes to hours, and were associated with dizziness and shortness of breath. She stated that a month before her clinic appointment, she was fit and well, and was able to easily walk two miles a day. At presentation in clinic, her exercise tolerance reduced to a few metres.

A diagnosis of rheumatoid arthritis (RA) had been made 6 months previously. The patient had a history of joint pain, stiffness and swelling affecting metacarpophalangeal and proximal interphalangeal joints of both hands for over 6 weeks. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were raised, and the patient tested positive for rheumatoid factor (RF) and anticyclic citrullinated peptide (CCP) antibodies. She was started on methotrexate, sulfasalazine and folic acid. She had no other medical history or medications. She had no known drug allergies. The patient's sister had been diagnosed with systemic lupus erythematosus (SLE) many years previously and was now dialysis dependent. There was no other family history of note.

This patient was born in the UK and had no recent travel history, although she notes that she travels to the Caribbean every 2 years to see family. She had a four pack-year history of smoking cigarettes, and denied recreational drug use or drinking alcohol. There were no occupational exposures noted, as this patient works in administration.

On examination in clinic, the patient appeared unwell. She was tachycardic (heart rate 130 bpm) and tachypnoeic, with no added sounds on auscultation of the chest. Her heart sounds were unremarkable, and there was no evidence of heart failure. There were no palpable lymph nodes and

Figure 1 CT of the thorax. Section from the patient's thorax CT scan for investigation of long-standing throat irritation. Bilateral hilar lymphadenopathy is demonstrated.

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no palpable organomegally on examination. A bilateral extensive vasculitic rash was noted over her anterior shins. A presumptive diagnosis of sarcoidosis was made, and the patient was admitted from clinic for investigation and management of her condition, with a clinical suspicion of cardiac sarcoidosis.

Early in her admission, she was started on bisoprolol, and her tachycardia and palpitations both resolved. However, the patient began to spike temperatures, and subsequent bloods revealed her white cell count (WCC) changed from $6.0 \times 10^9/L$ to over $70 \times 10^9/L$ within a 24 h period. No source of infection was clinically evident. A septic screen consisting of urine dip and analysis, chest radiograph and blood culture was also negative. The patient was started on broad-spectrum antibiotics under the advice of microbiology. Additionally, she was reviewed by rheumatology who stopped her methotrexate and sulfasalazine, and elected to start 60 mg prednisolone. The patient made a clinical improvement with steroids, with her rash and fevers resolving, and her exercise tolerance slowly improving. Her blood markers improved, including a reduction in the WCC and normalisation of her deranged liver function tests.

During her admission, the patient went into status epilepticus, and was therefore started on phenytoin to control her seizures. No focal cause of her seizure activity could be demonstrated on neuroimaging, with a MRI of the brain showing no evidence of encephalitis.

The patient continued to make good clinical progress on prednisolone, and it was felt that she had a multisystem disease process that was responding to the steroids. The medical team was preparing to discharge the patient home with outpatient follow-up, when she developed widespread skin desquamation, which was clinically in keeping with TEN. The patient was admitted to the intensive care unit, and underwent multiple skin biopsies (figures 2 and 3). She was reviewed by dermatology, who suggested that TEN may have developed secondary to phenytoin or as a consequence of the underlying multisystem disease. Furthermore, dermatology advised to stop phenytoin and start Keppra as an alternative antiepileptic.

INVESTIGATIONS

Initial blood investigations revealed a pancytopenia (platelets $88 \times 10^9/L$) with microcytic anaemia (haemoglobin 7.8 g/dL, mean corpuscular volume 75.6 fL), raised eosinophils (eosinophil count $2.1 \times 10^9/L$) and an acute kidney injury (creatinine $157 \mu\text{mol/L}$, urea 23.8 mmol/L). The patient's CRP was also elevated at 68 mg/L. Her liver function tests showed signification derangement with alkaline phosphatase 406 IU/L, alanine aminotransferase 106 IU/L, albumin 17 g/dL and normal bilirubin. Her admission chest radiograph was unremarkable, and an abdominal ultrasound scan showed that both her kidneys and liver were normal with the exception of some incidental haemangiomas noted. The patient's acute renal failure resolved after the administration of intravenous fluids. The lactate dehydrogenase was elevated at 2000 U/L, with vitamin B₁₂ 1 297 pmol/L and serum ferritin 6434 $\mu\text{mol/L}$.

A vasculitic screen was performed, revealing a cytoplasmic antineutrophil cytoplasmic antibodies level that was strongly positive and suggestive of small-vessel vasculitides. RF, CCP and anti-Ro antibodies were also positive. Antidouble-stranded DNA (dsDNA) antibodies, antinuclear antibodies (ANA) and an auto-antibody panel were negative, excluding SLE. The serum ACE level was elevated at 184i U/L, and although this is non-specific, it was felt to support the working diagnosis of sarcoidosis. A virological screen for HIV; hepatitis A, B, C; Epstein-Barr virus and cytomegalovirus was negative.

Cardiac investigations were performed to determine if this patient had cardiac sarcoidosis. An echocardiogram revealed a small pericardial effusion (echofree space in diastole 8 mm) and left ventricular hypertrophy, but no other features suggestive of sarcoidosis. A MRI cardiac scan was normal, and therefore cardiac sarcoidosis was excluded.

The patient underwent a bronchoscopy, during which a biopsy was obtained, revealing normal bronchial mucosa with no granulomas or malignancy demonstrated. A liver biopsy showed extramedullary haematopoiesis. Subsequent bone marrow biopsy revealed a hypercellular marrow without evidence of infiltration by metastatic disease or lymphoma. The

Figure 2 Histology obtained from skin biopsy taken during the acute phase of the desquamating rash. (A) Section demonstrating numerous lymphocytes (labelled L) migrating to the epidermis (labelled Ep) and killing keratinocytes (dead keratinocytes labelled K), in keeping with toxic epidermal necrosis. (B) Section demonstrating a granuloma (labelled G) which is well defined, with multinucleated giant cells (labelled MGC), both features associated with sarcoidosis. (C) Section demonstrating a granuloma (labelled G) that is not typical of either erythema multiforme or sarcoidosis. (D) Section from same biopsy stained with CD8 antibodies showing variable uptake of the stain by cells, suggestive of a diagnosis other than lymphoma.

Figure 3 Histology section obtained from skin biopsy 14 days after the initial presentation of the widespread desquamating rash. There are less lymphocyte cells found in the epidermis, and no granulomas were found suggesting that the disease process is steroid responsive.

patient underwent an endobronchial ultrasound-guided (EBUS) biopsy of the lymph node identified on the patient's initial thoracic CT scan. The histology demonstrated mixed lymphoid cells, with no granulomas. As multiple biopsies from different sites had failed to demonstrate granulomas, it was therefore felt that sarcoidosis was now an unlikely diagnosis.

After the patient developed skin desquamation, multiple skin biopsies were taken. The first skin biopsy demonstrated a toxic picture, with dead keratinocytes at the top of the epidermis, as seen in erythema multiforme, as well as some features suggestive of TEN (figure 2A). However, this biopsy also revealed multinucleated giant cells suggestive of sarcoidosis and well-formed granulomas (figure 2B), although it also demonstrated granulomatous components that were not typical of sarcoidosis and suggested that there may be another coexisting disease process (figure 2C). Staining of biopsy sections with CD8 antibodies demonstrated variable staining (figure 2D), reducing the likelihood of lymphoma as the underlying disease process. A second skin biopsy taken 12 days later revealed a less florid inflammatory response (figure 3). The epidermis contained a reduced number of lymphocytes and there were no granulomas demonstrated, suggesting that the patient was responding to steroid therapy.

DIFFERENTIAL DIAGNOSIS

The authors concluded that this patient had an overlap syndrome in which a clear diagnosis could not be made despite substantial investigation. The differential diagnosis consists of sarcoidosis, drug reaction or rash with eosinophilia and systemic symptoms (DRESS syndrome), hypereosinophilic syndrome and Still's disease.

TREATMENT

The patient was initially started on 60 mg prednisolone, which was gradually reduced on a slow weaning regimen. She was discharged home on 20 mg prednisolone daily, which was subsequently reduced to 10 mg/day. At this time, the patient remains on steroids, and is taking concurrent bone protection and proton pump inhibitors.

OUTCOME AND FOLLOW-UP

The patient was an inpatient for a total of 60 days, including a 13-day admission on the intensive care unit. She required

extensive nutritional support and input from multiple disciplines including rheumatologists, dermatologists and respiratory physicians. Her skin care required specialist nursing input and extensive management until her rash had healed. Furthermore, after her extensive stay on the intensive care unit, the patient required extended input from physiotherapy and occupational therapy. She was successfully discharged home and her symptoms have remained well controlled on low-dose corticosteroids. The patient has since been weaned off her antiepileptic medication and has remained seizure free. She remains under follow-up of the rheumatology and respiratory teams.

DISCUSSION

Sarcoidosis is a multisystem granulomatous disease of unknown origin and can involve any organ. Diagnosis is established on biopsy, with the identification of non-necrotising granulomas on histology.¹ The incidence of sarcoidosis is 1.0–35.5 in 100 000/year.² It can be difficult to differentiate from other diagnoses as the presenting symptoms and features overlap extensively with other diseases.^{3–4} Sarcoidosis presents with non-specific symptoms including fever, fatigue and weight loss, as well as specific symptoms related to the organ involved.⁵ If treatment is required, extrapulmonary sarcoidosis is generally treated using corticosteroids. Sarcoidosis is a differential diagnosis of bilateral hilar lymphadenopathy,⁶ and in this case, the diagnosis was supported by the initial CT of the chest findings, and the presence of granulomas and multinucleated giant cells on skin biopsy. These granulomas resolved in subsequent biopsies when the patient was on steroid therapy, as would be expected in sarcoidosis. Furthermore, sarcoidosis has been linked to the development of erythema multiforme.⁷ However, there were no granulomas demonstrated on histology obtained from the hilar lymphadenopathy and liver biopsy, which would be expected if sarcoidosis were the underlying pathology.

DRESS syndrome is a rare condition in which a drug-induced hypersensitivity reaction occurs, causing an eosinophilia, fever, lymphadenopathy and morbilliform rash.⁸ DRESS syndrome is a multisystem condition that involves most internal organs, most commonly the heart, liver, kidneys, lung involvement with subsequent breathlessness and neurological involvement leading to seizure activity.⁹ The hypersensitivity reaction occurs between 2 and 8 weeks from exposure to the causative agent.¹⁰ A range of pharmaceuticals is associated with DRESS syndrome, including antiepileptics such as carbamazepine, lamotrigine and phenytoin, in addition to allopurinol and sulphonamides, in particular sulfasalazine.¹¹ The treatment for DRESS syndrome is withdrawal of the causing agent and supportive measures. Although the patient's breathlessness, palpitations, liver dysfunction, acute renal failure, fevers and rash could be attributed to either sarcoidosis or DRESS syndrome, the diagnosis of DRESS syndrome was supported by the recent addition of sulfasalazine in the treatment of the patient's RA. In addition, the eosinophilia demonstrated on full blood count and skin biopsy supports this diagnosis.

Hypereosinophilic syndrome is an alternative diagnosis in this case, and is a myeloproliferative disorder with a persistent raised eosinophil count.¹² It is associated with involvement of multiple organs including the heart, lungs, brain and kidneys, without alternative explanation for organ damage.¹³ Classically, the raised eosinophil count needs to present for over 6 months, and secondary causes of hypereosinophilia should be excluded.¹⁴ Given the clinical presentation and history, sarcoidosis and DRESS syndrome are more likely diagnoses. In addition, sarcoidosis is a known cause of eosinophilia and, as such,

hypereosinophilic syndrome cannot be diagnosed according to classical criteria. Furthermore, hypereosinophilic syndrome is associated with intracardiac thrombi and posterior mitral valve thickening,¹⁵ and there was no evidence of these abnormalities on echocardiogram or cardiac MRI. There was also no evidence of splenomegaly on examination or on ultrasound of the patient's abdomen, and the lack of both these findings support an alternative diagnosis.

Adult Still's disease is rare, with an estimated 0.16 of new cases per 100 000 population per year.¹⁶ It is a systemic inflammatory illness that is characterised by high swinging fever, and a pink maculopapular rash with arthritis, myalgia and generalised lymphadenopathy.^{16–17} Hepatosplenomegaly can also occur. Adult-onset Still's disease remains a diagnosis of exclusion.¹⁶ Diagnostic criteria are based on clinical features and not on serological results.^{18–19} In this case, although the patient had a fever, it did not swing, and the rash was noted to be itchy. Both these features point against this diagnosis.

RA is a chronic, systemic, inflammatory disorder of unknown aetiology that primarily involves synovial joints. Systemic symptoms may be present in patients with RA. Up to one-third of patients with polyarthritis have associated myalgia, fatigue, low-grade fever and weight loss. Positive RF and anti-CCP antibodies support a diagnosis of RA, and the latter have much higher specificity (95–98%). Anti-CCP antibodies are known to play an important role in the pathogenesis of sarcoidosis and could be important in revealing the overlap syndromes of sarcoidosis RA.²⁰ ESR and CRP are typically elevated. The blood count is often abnormal in RA where anaemia and thrombocytosis indicate chronic inflammation.

Early RA can be difficult to distinguish from the arthritis of SLE, Sjögren's syndrome, dermatomyositis or overlap syndromes. Yet, in contrast to RA, these disorders are generally characterised by the presence of other systemic features such as rashes and autoantibodies not detected in RA, as seen here. Sarcoid arthropathy, associated with pulmonary disease, can resemble RA, but elevated serum ACE and bilateral hilar lymphadenopathy, as seen in this case, are associated with sarcoid arthropathy, not RA. In total 4 to 38% of patients with sarcoidosis have one or more musculoskeletal manifestations that include arthropathy.²¹

In this patient, it is difficult to establish whether some of the abnormalities identified are related to the patient's pre-existing diagnosis of RA, a new underlying diagnosis, or part of an overlap syndrome. Overlap syndromes are commonly associated with autoimmune rheumatic disease, with up to 25% of patients falling into this category.²²

Overlap syndrome is a connective tissue autoimmune disease, in which the patient presents with symptoms of more than one disease process.²³ Up to a quarter of patients with connective tissue disease can present with an overlap syndrome, having features of SLE, polymyositis or dermatomyositis, systemic sclerosis with Sjögren's syndrome and RA, evolving either concurrently or consecutively during the disease process.²⁴ Most of these patients do not have a final definitive diagnosis 10 years after symptoms have started to present.²⁵ Cervera *et al*²⁵ have previously described patients with rheumatological disease with systemic symptoms that overlap more than one clinical diagnosis and cannot be definitively defined. Sarcoidosis has previously been documented in association with a variety of autoimmune conditions, which include primary biliary cirrhosis, coeliac disease, amyloidosis, Sjögren's syndrome and Addison's disease.³

This case was also complicated by the possibility that the desquamating rash was TEN caused by the introduction of

phenytoin. This idiosyncratic life-threatening disorder is most commonly drug induced, although infection and transplantation can also precipitate it.^{26–27} Pharmaceutical causes include antibiotics such as sulphonamides, macrolides, penicillins and quinolones, as well as antiepileptic medications including phenobarbital, phenytoin, carbamazepine and lamotrigine.²⁶ Anticonvulsants seem to most commonly precipitate TEN within 2 months of starting the drug, such as in this case. However, this erythematous rash may also have been a manifestation of a multiorgan systemic disease. In this case, sarcoidosis may have been the causative pathological process, with previous cases documenting the presence of skin involvement²⁸ and skin biopsies taken showing some features consistent with this disease. However, sulfasalazine can precipitate DRESS syndrome, and the high eosinophil count and skin biopsy results support this pathological diagnosis.

This case highlights the difficulty of making a clear clinical diagnosis in a patient who is clinically unwell with a multisystem disease process. Our patient presented with varied clinical and serological features that are not within distinct boundaries of a single disease entity, and that fit into more than one diagnosis. In spite of multiple site biopsies, bronchoscopy, EBUS and radiological investigation, we were unable to distinguish between the overlapping conditions in the differential diagnosis, or to reach a single diagnosis. As the patient's condition has remained steroid responsive, we have therefore been able to control the pathology without defining a single diagnosis. As such, we have not further investigated this patient, since the potential risks of subsequent investigations do not outweigh the benefit of having a diagnosis and would not alter this patient's management. This case highlights how a patient's conditions and symptoms may be treated even though the underlying diagnosis remains unclear, although this presents issues with prognosis.

A final diagnosis has not been established. It is difficult to determine whether an overlap syndrome is present with a number of diseases sharing symptoms, or whether two separate diseases are occurring simultaneously. Although this patient's condition is currently well controlled on corticosteroids, it is possible that, in the future, her condition could evolve into a distinct disease process. At the time of her investigation she was

Learning points

- ▶ It is important to recognise the limitations of medical investigations and, when they no longer help, to reach a diagnosis or affect management.
- ▶ The diagnosis of sarcoidosis is established on biopsy, with the identification of non-necrotising granulomas; but it can be difficult to differentiate from other diagnoses as the symptoms and features overlap extensively with other diseases.
- ▶ Eosinophilia is caused by many diseases, including atopy, drug reaction or rash with eosinophilia and systemic symptoms (DRESS) syndrome, small-vessel vasculitides, rheumatoid arthritis, hypereosinophilic syndrome, lymphoma and erythema multiforme.
- ▶ 'DRESS syndrome' is a rare drug hypersensitivity reaction that causes eosinophilia, fever, lymphadenopathy and a morbilliform rash, and involves most internal organs.
- ▶ Overlap syndromes involving sarcoidosis occur, but should be diagnosed only once disorders that mimic sarcoidosis have been excluded.

ANA and anti-dsDNA antibody negative, although given her family history it is possible that her disease could progress into SLE. Overall, it was felt that this case demonstrates an overlap syndrome with an undifferentiated connective tissue disease. Our patient has presented with varied clinical and serological features that are not easily attributed to a single pathological diagnosis. This case highlights the difficulty and, sometimes, impossibility, of reaching a single unifying diagnosis. In such cases, it is therefore important to manage the symptoms of the patient's condition.

Contributors SR collected case information and prepared the initial manuscript, including the literature review. CH edited the manuscript, obtained patient consent and performed a literature review. MS performed the histopathology and provided expertise on this area in preparation of this paper. TCOS oversaw and edited the manuscript.

Competing interests None declared.

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