Sarcoidosis is a chronic multisystem inflammatory condition, primarily affecting young adults aged between 20 and 40 years.1–3 The hallmark of the disease is non-necrotising granulomata in affected organs, which most commonly include the lung, eyes, and skin. Importantly, sarcoid-related uveitis represents some seven per cent of all uveitis presenting to eye specialists.1

**CASE REPORT**

A 36-year-old Ethiopian woman, who immigrated to Australia in 1999, presented to St Vincent’s Hospital with a six-month history of lethargy and intermittent severe left upper quadrant and epigastric abdominal pain. She reported recent weight loss of about 15 kg. At the time of presentation, she stated that she had already received several months of treatment for anterior uveitis in the left eye only and that the vision remained
significantly reduced. Her last recorded visual acuities (VA) were 6/6 and 6/9 in the right and left eyes, respectively. She was otherwise well. There was no history of fever or night sweats and no respiratory symptoms. Her past medical history included six months of single agent therapy (isoniazid) for latent tuberculosis in 2000.

On examination, she was moderately cachectic (appeared to have lost weight and muscle mass due to disease). The vital signs were unremarkable, the respiratory examination was normal and she was not jaundiced. Her abdomen was soft and non-tender, though palpation revealed moderate hepatosplenomegaly. At presentation, there was no identified palpable lymphadenopathy. The eyes were not examined at this stage.

A chest x-ray (CXR) demonstrated bulky bilateral hilar lymphadenopathy (BHL) (Figure 1). The lung fields were otherwise clear. Follow-up CT scan of the thorax revealed the presence of further lymphadenopathy in the right tracheobronchial angle and sub-carinal locations. This is well appreciated in sagittal reconstruction (Figure 2). There was no interstitial involvement. Abdominal ultrasound demonstrated normal bile duct diameter, thus ruling out the presence of gall-stone disease as an explanation for her abdominal pain. CT scan of the abdomen revealed pathological para-aortic lymph nodes (Figure 3).

Given the patient’s history and radiological findings, the most likely differential diagnoses considered at this time included lymphoma, tuberculosis and sarcoidosis. Full blood examination, serum electrolytes, serum and urinary calcium and quantiferon (interferon response to tuberculous antigens) were all normal. Liver function tests revealed a mildly cholestatic picture, with no elevation of ALT or bilirubin. Serum amylase and lipase levels were normal. β2-microglobulin and LDH levels were slightly elevated, though not to the level often found in lymphoma, leukaemia or myeloma. HBV, HCV, HIV serology was negative. Serum ANA, ANCA, rheumatoid factor and ENA levels were normal.

The patient underwent fibreoptic bronchoscopy that did not demonstrate any endobronchial involvement. Bronchial washings were negative for malignancy and lymphocytosis.

One week after presentation, the patient developed palpable lymphadenopathy in the right supra-clavicular fossa, enabling a minimally invasive biopsy. At biopsy, a large golden yellow node was excised. Histological examination revealed non-necrotising granulomata consistent with sarcoidosis. She was commenced on high dose oral prednisolone (60 mg/d).

Two days after diagnosis and the commencement of treatment, the patient complained of new sudden onset visual disturbance in the right eye. VA in the right eye (6/6 at presentation) had declined to 6/12 (6/7.5 through a pinhole). VA in the left eye was 6/9 with no improvement through a pinhole. Both pupils were fixed and dilated. Eye movements were normal.
Slitlamp examination revealed bilateral posterior synechiae. An iris nodule was present in the right eye. The anterior chambers contained low-grade flare with cells and keratic precipitates were observed in the left eye only. The angles were open and intraocular pressures were normal.

Internal examination revealed vitritis in the right eye in the classical ‘string of pearls’ distribution (Figure 4). There was no retinal involvement and no frank macular oedema. She was commenced on Prednefrin forte and homatropine and continued oral prednisolone.

She was reviewed two weeks later, at which time she denied symptoms of abdominal pain or anorexia. Her visual acuity had returned to 6/7.5 in the right eye with some resolution of her anterior uveitis. Further follow-up, one month after discharge, revealed improvement in VA to 6/6 and 6/7.5, with further resolution of her intra-ocular inflammation. At this time, her intraocular pressures had risen to 22 and 26 mmHg and these were treated with aqueous suppressants. At the time of acceptance of this article, the patient continues to be monitored every three months.

DISCUSSION

The prevalence of sarcoidosis has been estimated at 15 per 100,000 population and, in the USA, is three times more prevalent in blacks than whites.5,6 Its aetiology is unknown, though a range of factors including tuberculous infection, beryllium exposure (though rare now) and cold climate have been implicated in the pathogenesis of the condition.2 An immuno-genetic predisposition has been demonstrated through family studies7 and more recent research has found that particular alleles within the major histocompatibility complex (MHC) confer susceptibility to the disease.5,8,9

Pathophysiology

The lung is the most commonly affected organ in sarcoidosis and 90 per cent of cases have changes evident on CXR.10 Approximately 50 per cent of those affected are asymptomatic at the time of diagnosis, having been detected as incidental findings on routine CXR.5,11 When symptomatic, the predominant pulmonary features are of cough, shortness of breath and chest pain. Physical examination of the chest is normal in most cases.

The classification of pulmonary sarcoidosis is performed radiographically6,10 according to the presence of:
Stage I hilar and mediastinal lymphadenopathy
Stage II hilar lymphadenopathy with lung infiltrates
Stage III interstitial infiltrates with shrinking hilar nodes
Stage IV advanced interstitial fibrosis.

The radiographic staging of sarcoidosis correlates well with prognosis11,12 and is used to guide surveillance intervals.11

Non-specific systemic features of sarcoidosis are often present, mimicking those of malignancy and chronic infection. These include anorexia and cachexia, fever, fatigue and weakness. Indeed, non-specific constitutional symptoms may be the only features of sarcoidosis in older patients presenting for the first time.
Extra-pulmonary sarcoidosis can affect a range of organs and homeostatic functions. A brief list is provided in Table 1.

**Ocular involvement in sarcoidosis**
Ocular involvement in sarcoidosis usually presents as decreased VA with haze, floaters, variable pain, photophobia and lacrimation but sarcoidosis can affect the eyes in many ways. We will consider the pathogenesis of such presentations in three sections: anterior segment, posterior segment and the adnexa / extra-ocular structures.

**ANTEOR SEGMENT**
Most commonly, sarcoidosis presents in the anterior segment as a painful unilateral granulomatous uveitis with cells, flare and mutton-fat keratic precipitates. An alternative presentation is that of Löfgren’s syndrome, which describes the condition of bilateral chronic smouldering low-grade granulomatous ocular inflammation in addition to BHL, arthritis, erythema nodosum and constitutional symptoms. Granulomatous iris nodules of the stroma (‘Busacca nodules’) (Figure 5) and of the pupillary margin (‘Koepe nodule’), anterior synechiae, posterior synechiae and ocular hypertension are other frequent findings.

Less commonly, sarcoidosis manifests as conjunctival granulomata and conjunctivitis, keratitis sicca (particularly if lacrimal glands are involved), episcleritis, scleritis and interstitial keratitis. Chronic intraocular inflammation in sarcoidosis can result in cataract formation.

**POSTERIOR SEGMENT**
Approximately one-third of patients with ocular sarcoidosis have posterior segment involvement. It often takes the form of intermediate uveitis (inflammation of the vitreous and peripheral retina) in which white snowball opacities within the vitreous form the classical ‘string of pearls’ (Figure 4) in association with retinal vasculitis and exudates (‘candle-wax dripping’) and phlebitis (‘venous sheathing’). Peripheral neovascularisation with or without haemorrhage is not uncommon. Figure 6 demonstrates a case of severe sarcoid-related posterior uveitis with cystoid macular oedema, haemorrhage and candle-wax dripping.

Sarcoidosis can also result in sight-threatening cystoid macular oedema, multifocal choroiditis and granuloma (Figure 7), which carries a poor visual prognosis, inflammatory optic nerve swelling or frank optic nerve granulomata.
Sarcoidosis

As a disease entity, sarcoidosis spares almost no part of the eye and adnexa. Asymptomatic swelling of the upper lid occurs as a consequence of lacrimal gland involvement. Proptosis may indicate granulomatous extra-ocular muscle involvement or involvement of the globe itself.

Diagnosis

Sarcoidosis should be considered in any young patient presenting with anterior uveitis. The differential diagnoses for anterior uveitis in young people include:

- HLA B27-related disease, the so-called ‘sero-negative spondyloarthropathies’ (that is, ankylosing spondylitis, Reiter’s syndrome, inflammatory bowel disease, psoriatic arthritis)
- systemic inflammatory diseases (that is, sarcoidosis, Behçet’s disease)
- systemic infections such as syphilis (and atypical infections, for example, TB, cryptococcus, fungi)
- neoplasia.

As its features are shared with many conditions and because of its often non-specific presentation, the diagnosis of sarcoidosis can be difficult and is often delayed. In general, patients with dermatological or ocular involvement (except in cases of isolated neuro-ophthalmological disease) are diagnosed relatively late. Patients with posterior or intermediate uveitis, such as described in this case report, are less likely to have HLA B27-related disease, hence other diagnoses should be considered.

The elements of a diagnosis of sarcoidosis are:

- clinical and radiographic findings consistent with the condition
- histological evidence of non-necrotising granulomata
- the exclusion of other conditions with similar features (for example, tuberculosis and histoplasmosis).

In addition to CXR and CT chest (with high resolution cuts), several laboratory tests can add weight to the likelihood of the diagnosis. These are listed in Table 2.

The best confirmatory diagnostic test is histopathological analysis of biopsied tissue. Any accessible lesion can be considered, including granulomata of the lid and orbit, but more commonly lymph nodes, subcutaneous nodules and cutaneous lesions. If there are no easily accessible lesions, trans-bronchial or endoscopic ultrasound-guided fine needle biopsy may be undertaken to avoid a surgical approach. In many patients with mild disease and a typical CXR, histological confirmation is considered unnecessary.

Table 2. Additional investigations for sarcoidosis

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Full blood examination</td>
<td>Anaemia, Leukopenia, eosinophilia, thrombocytopenia, Erythrocyte sedimentation rate elevated</td>
</tr>
<tr>
<td>Serum biochemistry / serology</td>
<td>Hypercalcaemia (and hypercalciuria), Hypergammaglobulinaemia, Alkaline phosphatase elevated, Angiotensin converting enzyme elevated</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>Restrictive lung disease pattern, Gas diffusion decreased</td>
</tr>
<tr>
<td>Broncho-alveolar lavage (BAL) and trans-bronchial biopsy</td>
<td>Lymphocytosis, CD4:CD8 ratio &gt; 4, Confirmatory biopsy</td>
</tr>
<tr>
<td>Gallium-67 lung scan (not routinely used)</td>
<td>Increased uptake corresponding to inflammatory alveolitis</td>
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<tr>
<td>Other imaging</td>
<td>PET or MRI scanning in the diagnosis and staging of sarcoidosis</td>
</tr>
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Management
The natural history of pulmonary sarcoidosis is varied and therefore, unpredictable with a proportion of patients undergoing spontaneous resolution and others progressing to advanced lung fibrosis and death9 (from respiratory failure in one to five per cent11). Chronic progressive disease occurs in about one-third of cases, featuring a relapsing-remitting course in which spontaneous resolution is frequent.12 As a rule, nearly all cases of Stage I disease but almost none of those with Stage IV disease resolve within two years.11 Adverse prognostic features include cardiac involvement, chronic hypercalcaemia, chronic uveitis, pulmonary fibrosis and neurological disease.10–12

THERAPY FOR SYSTEMIC DISEASE
Systemic corticosteroids are the mainstay of treatment for sarcoidosis. A recent Cochrane review has determined that patients with Stage II and III disease benefit from a six-to 24-month course of prednisolone but that treatment is not justified in those with Stage I disease.22 The typical starting dose is between 20 and 40 mg/d, which, in those that respond to therapy, can be gradually tapered to the minimally effective dose after two to three months. There is no consensus on the validity of treatment past two years22 and consideration of the significant morbidity associated with chronic steroid use is warranted. Inhaled corticosteroids appear to be ineffective in terms of both disease progression and symptomatic relief.23

Cytotoxic agents, such as methotrexate and azathioprine, can be used as monotherapy or as steroid-sparing agents. They can be used in cases of refractory sarcoidosis or where corticosteroids are contraindicated and have been shown to induce remission in acute exacerbations of chronic sarcoidosis. The anti-malarial agents chloroquine and hydroxychloroquine have been reported to reduce disease activity in severe pulmonary sarcoidosis, although this is not without risk to the eye.24 Reteconazole has been suggested as a steroid-sparing agent in cases of refractory hypercalcaemic sarcoidosis.24

As the cytokine TNF-α is intimately linked to the granuloma formation, a range of immunomodulators, such as infliximab,25 have been trialled for the treatment of sarcoidosis.

THERAPY FOR OCULAR DISEASE
The visual prognosis in ocular sarcoidosis is variable, ranging from transient ocular irritation without impacting vision, through to sight-threatening choroiditis or optic nerve lesions.

Anterior uveitis is best treated aggressively with topical corticosteroids (prednisolone 1%, q1hr to q.i.d.) and topical cycloplegics (for example, homatropine 5%, scopolomine 0.25% or atropine 1%, b.i.d.), usually with good effect. Raised intraocular pressures are usually treated with topical aqueous suppressants (for example, timolol), though raised intraocular pressure in young patients with healthy optic discs is often left untreated as, most commonly, the ocular hypertension subsides comitantly with resolution of the uveitis. Prostaglandin analogues, for example, Latanoprost (Xalatan) 0.005%, and miotics are contraindicated in the treatment of ocular hypertension associated with uveitis due to their pro-inflammatory action.

Significant intermediate or posterior uveitis rarely responds to simple topical therapy. Therefore, systemic corticosteroids (with or without oral non-steroidal anti-inflammatory agents) are indicated for treatment of optic neuritis and intermediate and posterior uveitis, especially if there is dense vitritis, poor vision or cystoid macular oedema.10 In some cases, injected periocular or sub-tenons steroid is used, particularly if there is mild and unilateral posterior uveitis. Where there is severe uveitis and either failure to respond to injected orbital steroids or a contraindication to systemic steroids, intravitreous injections of triamcinolone may be used to improve visual outcome.26,27 As with systemic sarcoidosis, immunosuppressive and anticytokine therapies have been suggested for refractory or sight-threatening disease,28–30 especially when associated with significant systemic disease.

Photocoagulation31 and vitrectomy32 may be used in cases of intermediate and posterior uveitis, where there is retinal neovascularisation and significant vitreous haemorrhage.

CONCLUSION
We present a case of sarcoidosis with Stage I pulmonary involvement, anterior and intermediate uveitis and constitutional symptoms. The unusual feature of the case is the bulky abdominal lymphadenopathy. Confounders in the clinical history include severe and rapid weight loss, abdominal pain (though peritoneal sarcoidosis has been described33) and prior history of tuberculous exposure.

A diagnosis of sarcoidosis was reached following excisional biopsy of a superficial lymph node, following negative bronchoscopy and unremarkable haematological, biochemical and serological work-up.

Ocular involvement in sarcoidosis is common and may be the presenting feature of the disease. Prompt recognition may prevent visual loss and systemic complications.

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