Sarcoidosis: The disease and its ocular manifestations

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Abstract

Sarcoidosis is a systemic disease that has ocular manifestations. For many patients there is a long course of treatment both topical and systemic. This article describes sarcoidosis both systemic and ocular and some of the treatment modalities used.

Introduction

Sarcoidosis is a condition that has both systemic and ocular manifestations. Due to the nature of the symptoms it can have implications for a patient's quality of life due to the chronicity of the disease (Cox, Brown & Judson, 2004). This paper discussed the general characteristics of sarcoidosis and goes on to consider the ophthalmic manifestations and in particular, uveitis and sarcoidosis

What is Sarcoidosis?

Sarcoidosis is a systemic disease characterised by granulomatous inflammation with the formation of noncaseating granulomas that has both systemic and ocular manifestations.

Granuloma

A granuloma is a term used loosely to refer to mean a small nodule. Pathologically however, a granuloma is an organised (in a tight, ball like formation) collection of macrophages (immune cells). It may also contain lymphocytes, neutrophils, eosinophils, multinucleated giant cells, fibroblasts and collagen. Granulomas form in response to antigens that are resistant to inflammatory cells such as neutrophils and eosinophils. Often, granulomas form in response to an infecting pathogen or other substance foreign to the body. Often though, as in sarcoidosis, the antigen is unknown. Granulomas may have necrosis within them and these usually have an infective cause. If the granuloma appears to be filled with a 'cheese like' substance, this type of necrosis is known as caseation (turning to cheese). Granulomas found in sarcoidosis are non necrotising, non caseating and are often surrounded by bands of fibrosis. They can resolve spontaneously or with scarring, as in pulmonary fibrosis (Adams, 1976, Iannuzzi, Rybicki, Teirstein, 2007).

It can clinically manifest either in isolation or conjointly in any number of organs including lungs, skin, heart, liver, muscles, joints and the eye. It is thought there is some pulmonary involvement in all patients with sarcoidosis with between 25-50% developing ocular symptoms either in isolation or conjointly (Kawagoe and Mizuki,2011). There are also ethnic differences in presentation of sarcoidosis with African Americans more likely to present with Hilar Lymphadenopathy whilst Japanese are more likely to present with ocular sarcoidosis (Margolis and Lowder, 2007).

The cause of sarcoidosis is unknown but airborne particulates, viral or mycobacteria pathogens and occupational exposures have been raised as potential triggers(Margolis & Lowder, 2007). Genetic factors may also contribute to the susceptibility to the development of sarcoidosis due to familial clustering and predominance in some racial groups (Margolis & Lowder, 2007). There is a higher incidence in African Americans than in European and it is less common in Asians.

The disease can present at any age but it is more common between the ages of 20-50 years(Tachibana et al, 2010). . Females have a slightly higher predominance than males (Lodha, Sanchez & Prystowsky).

Sign and symptoms

The symptoms of sarcoidosis are varied and dependent on the primary site of inflammation. Many symptoms though are non specific and can be attributed to other conditions and it is often a process of elimination that leads to diagnosis particularly if no familial links are apparent. Patients can present in a myriad of different ways due to the number of systems that can be affected by the condition. Presenting symptoms may include; encephalopathy, vasculopathy, seizure and ataxia (Phillips & Eggenberger, 2010), myalgia and muscle weakness, or acute arthritis. Other presenting features might be weight loss and fever, pericarditis, heart block, valvular disease and generalised systemic vascularitis, jaundice, ascites and portal hypertension (Abril & Cohen,2003). Alternatively, patients may present with flu like symptoms of fevers, night chills and chronic cough. Many of these signs and symptoms are not always associated with the initial presentation of ocular sarcoidosis.

Systemic sites of Sarcoidosis

Almost all organs in the human body can be affected by sarcoidosis. Respiratory involvement is suspected in up to 90% of patients diagnosed with sarcoidosis (Abril &Cohen, 2003), and is characterised by hilar lymphadenopathy seen on Chest Xray or high resolution CT. Hilar lymphadenopathy may not require treatment if there are no other sites of inflammation identified. The use of steroids to treat respiratory sarcoidosis is the same as treatment for other sites of inflammation so it is often a multi speciality decision to treat (Papadia, Herbort & Mochizuki, 2010).

Neurosarcoidosis has been called the 'great mimicker' as those affected can present with non specific and variable symptoms. However, cranial neuropathy is the most frequent neurological manifestation in approximately 50-70% of patients with neurosarcoidosis. The facial nerve and optic nerve are most commonly affected (Phillips & Eggenberger, 2010).

Cutaneous Sarcoid can manifest itself in different forms. It is often confirmed by biopsy of suspect skin lesions confirming the presence of granulomatous inflammation in the dermis.
Erythema nodosum may be a presenting feature of sarcoidosis but is present with other apparent disease manifestations such as arthritis, oedema and low grade fevers(Lodha, Sanchez & Prystowsky, 2009) .

The skeletal system can also be affected. Bone or osseous involvement can be painful but is usually asymptomatic. It causes cystic or destructive lesions mainly

involving the hands and feet and is usually associated with long standing chronic sarcoidosis. The main joints involved are usually the ankles with the next most common the knees, wrists and elbows. Joint involvement can lead to acute arthritis but in chronic sarcoidosis, chronic arthritis is more common (Abril & Cohen, 2004).

Other sites are muscles or myopathy, kidney involvement can cause hypercalcaemia, cardiac symptoms vary from heart block to generalise systemic vascularitis while liver involvement can cause jaundice, ascites and portal hypertension (Abril & Cohen,2004).

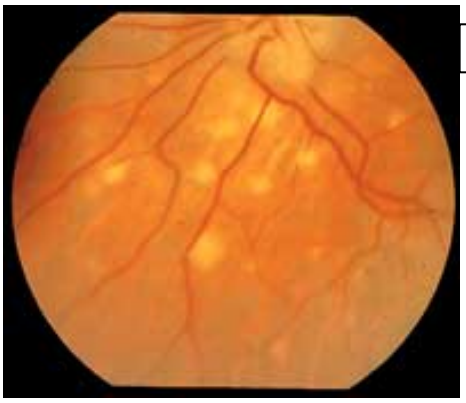
Ocular Sarcoidosis

Estimates of ocular involvement vary between 8-89% (depending on author and ethnicity of the study group as highlighted ealier and by Baughman et al 2001, Nakagawa et al 1978). Sarcoid granulomas can affect any part of the eye and visual system.

Ocular sarcoidosis presents in many guises and generally develops into a chronic condition in many patients resulting in long term attendance at the eye clinic. The most common form of uveitis is a bilateral granulomatous uveitis which is characterised by the presence of ‘mutton fat ‘keratic precipitates (KPs).. There may also be inflammatory nodules (accummulations of inflammatory cells) on the pupillary border (known as Koeppe nodules)_ or on the iris surface (known as Busacca nodules) that are indicative of a granulomatous inflammation (Papadia et al, 2010).

However, other parts of the anterior segment can also be affected with infiltration of the periorbital or lacrimal tissue which may result in keratoconjunctivitis sicca .Granulomas in the angle of the anterior chamber can occur leading to a high intraocular pressure with a small proportion of patients requiring glaucoma drainage surgery.

The posterior segment is also affected with the most common signs being ‘snowballs’, collections of inflammatory cells in the vitreous. There can also be peripheral chorioretinal granulomas as seen below as well as sheathing of the retinal veins and periphebitis. Cystoid macula oedema is also a known complication of sarcoid uveitis. Many of these posterior complications are sight threatening and require urgent treatment (Papadia et al, 2010).



Choroidal Granulomas

Diagnostic tests for Ocular sarcoidosis

A patient presenting to eye clinic with a bilateral uveitis, of unknown cause is always sent for screening tests. These screening tests are a combination of radiographic and blood tests. A chest x-ray is also done to identify the possibility of pulmonary involvement as the presence of bilateral hilar lymphadenopathy is a classic sign of sarcoidosis. Around 90% of patients with sarcoid have hilar lymphadenopathy (Abril& Cohen, 2003). However, if the chest x-ray is normal it may be necessary to do a high resolution CT scan to aid diagnosis due to the high incidence of lung involvement with those diagnosed with the disease (Papadia et al, 2010).

Blood investigations include testing for a rise in Angiotension Converting Enzyme (ACE) and Lysosyme are undertaken as these substances are produced by sarcoid granulomas and therefore aid in the diagnosis of sarcoidosis. However, if a patient is on ACE inhibitors an elevated Lysozyme level may be more diagnostic (Papidia et al, 2010).

Biopsy of granulomas is an ideal way to definitively diagnose sarcoidosis but the site of the sarcoid determines if biopsy is possible or appropriate. The presence of granulomatous inflammation in the biopsy tissue is a positive diagnosis of sarcoidosis (Papadia et al, 2010)

Differential Diagnosis

Uveitis is not solely a disease associated with sarcoidosis and therefore it is essential to exclude other ocular causes and systemic investigations are required to determine a diagnosis of sarcoidosis. Investigations can range from simple blood tests to Magnetic Resonance Imaging (MRI)scans in order to diagnose sarcoidosis.

Tuberculosis is the most important alternative diagnosis to determine. This has become easier now with a blood test 'Quantiferon TB Gold' identifying gamma-interferon release (Papadia et al, 2010).

Vogt-Koyanagi-Harada (VKH) Disease is more common in Asians, Hispanics and Amerindians. Although this can present with granulomatous signs, it can be distinguished from ocular sarcoidosis with the presence of a 'sunset glow' fundus.(Papadia, et al, 2010).

Herpetic uveitis is usually unilateral whereas most sarcoid uveitis is bilateral. The clinical picture is also different especially the presence of iris atrophy demonstrated on slit lamp by transillumination (Papadia et al, 2010).

Other conditions to exclude are Bilateral Fuch's Uveitis, Multiple Sclerosis and Masquerade syndromes.

Diagnostic criteria for ocular sarcoidois

1. Biopsy supported diagnosis with compatible uveitis – Definite Ocular Sarcoidosis

2. No Biopsy. Bilateral Hilar Lymphadenopathy (BHL) present with compatible uveitis– Presumed Ocular Sarcoidosis

3. No Biopsy, BHL neg. Presence of 3 suggestive intraocular signs and two positive investigational tests. – Probable Ocular Sarcoidosis

4. Biopsy negative. 4 of the suggestive intraocular signs and two positive investigational tests - Possible Ocular Sarcoidosis (Papadia et al, 2010)

Patient example

One patient that I have been involved with had flu like symptoms five months prior to presenting with a bilateral uveitis and on chest X-Ray he definitely had bilateral Hilar lymphadenopathy and therefore pulmonary involvement. Ocular symptoms may occur at different times to respiratory symptoms

These can be generic type symptoms and may only be suspect for sarcoidosis if there are other sites involved or the presence on X ray of bilateral Hilar lymphadenopathy.

It has been interesting to note that many patients presenting with ocular sarcoid have had raised rashes over tattoos that on biopsy are positive for granulomatous inflammation. This is due to the infiltration of sarcoid granulomas in pre existing scar tissue (Lodha et al, 2009).

Treatment

The treatment of ocular sarcoidosis can be long and complicated and often involves administration of long-term steroids. Some of the treatments for ocular sarcoidosis are also used to treat other organ sites of the disease.

Anterior uveitis is treated with topical Pred Forte initially intensively and then are reducing taper which can be a long process. Many patients will have a rebound inflammation when steroids are stopped and therefore a regime must be found where they remain on maintenance topical steroids at the lowest daily rate that controls the inflammation with no rebound of inflammation. Oral prednisone is used for disease not controlled by topical medication or involving posterior segment and this is usually1 mg per kg of body weight initially and then slowly tapered to control the inflammation. However, long term steroid use can lead to ocular side effects such as ocular hypertension requiring an ocular anti-hypertensive and systemic effects such as steroid induced psychosis, sleeplessness, weight gain, moon face and bone density issues. These can be distressing for the patient as the treatment may appear to cause them more problems than the disease and continuing education and support is required by this group of patients

Sometimes it is necessary to look at alternative methods of delivering treatment such as intravitreal or orbital floor Triamcinalone to manage the ocular symptoms, particularly for patients with cystoid macular oedema and vitritis. There is an increased rate of adverse events associated with such treatment such as raised IOP and cataract formation but the systemic complications of long term steroid use are negated. Unfortunately the treatment is short acting and may require repeat injections to manage ongoing symptoms (Sallam, Taylor & Lightman, 2011)

Newer therapies

Cytotoxic Agents

Some of the newer forms of treatment of 'steroid sparing' immunosuppressants as detailed below have been shown to work in ocular sarcoid. These drugs act as adjutants to steroids, suppressing the immune system more effectively than steroids on their own, and the steroid dose can therefore be reduced.

Methotrexate and Azathioprine are second line agents that have been widely used in the treatment in chronic sarcoidosis whilst Cyclophosamide is used in refractory sarcoidois. These are all cytotoxic drugs but are used long term with the aim of significantly reducing the amount of prednisone required and studies show that after 6 months the dosage of prednisone required to control the disease is decreased significantly (Abril & Cohen, 2003).

Mycophenolate mofetil (MMF) is an antiproliferative drug used in immune mediated disorders such as sarcoidosis and has been shown to reduce the severity of the inflammation, the amount of steroids required and the frequency of recurrences with

an improved visual outcome (Jap & Chee, 2008)**.**However these medications a gradual increase in dosage levels until therapeutic levels reached. The patients then require regular liver function and renal function tests to ensure continued safety for use.

Cytokine Modulators

The knowledge that human tumour necrosis factor (TNF) is critical in the genesis and maintenance of granulomatous inflammation and therefore is thought to play a part in the pathogenesis of sarcoidosis has led to the use of new treatments. Infliximab is an monoclonal antibody against TNF. (Baughman & Lower 2007). It may be effective in refractory ocular sarcoid when other treatments have failed (Baughman,2002).

Infliximab is expensive ($NZ1227.00 per dose with minimum of 3 initial doses) and has been funded at our District Health Board in only a few patients per year due to cost. Ocular sarcoid is only one of the forms of uveitis that benefits with Infliximab.

Conclusion

Certainly ocular sarcoid is complicated and requires long term management by consultant ophthalmologists with many patients also seeing other medical specialists with some seen in a combined ophthalmology/immunology clinic.

It is a disease that has long term implications for patients health, their well being and potentially their sight. It is important when a patient presents with a possible sarcoid related uveitis that a systems approach to examination is used to identify potential systemic sites as patients often require care from a multidisciplinary team long term.

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Key Points

- Sarcoidosis has both systemic and ocular manifestations.
- Sarcoidosis can affect the central nervous system, eyes, lungs, skin, lymph gland, heart lungs, kidneys.
- Ocular sarcoid can affect both anterior and posterior segments.
- Treatment of ocular sarcoid can be topical but often systemic is needed to reduce inflammation and risk of permanent visual loss from complications.