SARCOIDOSIS **MEDICAL APPENDIX**

DEFINITION

1. Sarcoidosis is a **multi-system granulomatous disease**. Its cause is unknown, so the definition has to be descriptive. There is more than one accepted definition. A short definition (1985, Scadding and Mitchell) is adequate for most purposes:-

   "A disease characterised by the formation in all of several affected organs or tissues of epithelioid cell tubercles, without caseation though fibrinoid necrosis may be present at the centres of a few, proceeding either to resolution or to conversion into hyaline fibrous tissue".

   A more detailed, internationally accepted definition was formulated in 1991 and is included as an addendum to this Medical Appendix.

CLINICAL MANIFESTATIONS

2. Beginning most often between 20 and 35 years of age but occasionally in childhood or old age, sarcoidosis may involve almost any organ. Both the pattern of presentation and subsequent course can be very varied and milder cases are often asymptomatic, discovered by accident. Symptoms vary from slight to severe, depending on the site and extent of involvement.

3. Sarcoidosis is usually classed as a respiratory disease because pulmonary involvement, even when not predominant, is almost always present and chest symptoms of dyspnoea, wheezing or cough (commonly non-productive) mostly predominate. X-rays reveal hilar gland enlargement in more than 90% of cases.

   3.1 **Acute or subacute onset**, usually in young adults, most often takes a self-limiting course, with spontaneous resolution in about a year. Erythema nodosum (see below) is the most frequent presenting symptom and there is usually bilateral, often symmetrical, enlargement of the hilar lymph nodes, sometimes called Lofgren's syndrome (Stage 1). Paratracheal lymph nodes may also be involved. Pyrexia, general malaise, weight loss and polyarthralgia may be present. Later, other pulmonary changes may be seen on X-ray in addition to the lymph node enlargement (Stage 2).

   3.2 **An insidious onset** of sarcoidosis in middle age is less likely to resolve spontaneously and more liable to cause permanent structural damage with severe organ dysfunction. Chronic pulmonary sarcoidosis (Stage 3) may lead to interstitial fibrosis, pulmonary hypertension and cor pulmonale type heart failure. It can also be complicated by bronchiectasis or cavitation.

4. **Extra-pulmonary manifestations**, with their approximate frequency of occurrence in cases of sarcoidosis in Britain, include:-

4.1 **Skin** (25%) Erythema nodosum (a tender, bluish-pink nodular rash, commonly on the shins) may be associated with sarcoidosis. It is a secondary vasculitic reaction. Cutaneous "sarcoid" (reddish-brown papules), lupus pernio (raised purple plaques usually on the nose and cheeks) and infiltration of scars or tattoos can also occur.

4.2 **Eyes** (20%) Bilateral uveitis (the uveal tract includes the iris, ciliary body and choroid and, by tradition, the retina) which, if untreated, may cause blindness. Conjunctival, lachrymal gland and lid involvement are also common in sarcoidosis.

4.3 **Other lymph nodes** (30%) Mediastinal and peripheral, usually discrete and non-tender.

4.4 **Salivary glands** (4%) Usually parotid gland enlargement.

4.5 **Heart** Although not usually clinically evident, cardiac lesions are found in 15-20% of sarcoidosis cases subjected to autopsy. It can cause sudden death, mostly through arrhythmias. Even among those with ECG changes, only about half have cardiac symptoms.

4.6 **Kidneys** Although some degree of sparse infiltration of the kidneys is usual, symptomatic involvement is not. However, nephrocalcinosis is a late and serious problem in about 1% of cases and can lead to renal failure. Even those patients with normal calcium levels are at risk of renal stone formation.

4.7 **Liver and Spleen** Granulomas occur in both organs, mostly without symptoms or serious dysfunction, although the spleen is enlarged in up to 25% of patients.

4.8 **Nervous system** (7%) Cerebral, meningeal and cranial or peripheral nerve lesions. Neurological sarcoidosis carries a poor prognosis.

4.9 **Musculoskeletal system Bones** (e.g. phalangeal cysts) and **Joints** causing arthritis, which has been reported to occur in 37% of cases of sarcoidosis. The arthritis varies in pattern, is twice as common in women, often with an acute onset and likely to become chronic. Bone changes are particularly common in black patients with chronic skin manifestations. Granulomas in **muscles** are usually asymptomatic but can cause myositis or chronic myopathy. **Gout**, due to overproduction of purines in widespread granulomas, may also complicate sarcoidosis.

4.10 **Endocrines** In a few cases, the posterior pituitary gland is sufficiently affected to cause diabetes insipidus. Other endocrine disturbance is very rare.

5. **Sarcoidosis and reproduction** The disease rarely affects fertility and does not adversely affect the course or outcome of pregnancy. Active sarcoidosis tends to improve with pregnancy and to worsen a few months after delivery.

6. **The Kveim-Siltzbach test** is a minimally invasive supportive test in the diagnosis of sarcoidosis. Although not precise, it particularly useful when biopsy is difficult or negative.

    6.1 The intradermal injection of homogenised human sarcoid tissue extract provokes a delayed, granulomatous, inflammatory reaction, the nature of which is confirmed by skin biopsy, in patients with sarcoidosis. The responsible antigen has not been identified and the basis for this response is uncertain. The test is not universally available.

    6.2 The test is positive in 85-90% of cases of acute sarcoidosis but only in about 30% of long standing chronic fibrotic disease with lung fibrosis or infiltration. Reactivity wanes as the disease becomes inactive and a negative test does not exclude the diagnosis.

7. **Serum angiotensin-converting enzyme** levels are raised in about 2/3 of patients with sarcoidosis, especially in cases of extensive disease.

8. **Serum globulin** and **specific immunoglobin** are often raised, especially in active sarcoidosis in black patients and more so in females. Circulating **immune complexes** also tend to be raised.

9. **Anomalous immunological reactions** are characteristic of sarcoidosis. A well-recognised example is the reduction of sensitivity to tuberculin. A previously positive tuberculin test may become negative. About 2/3 of sarcoidosis patients do not react to 100 IU of PPD tuberculin, whereas the reactivity to this dose in the healthy population is very much higher. This is an example of depression of cutaneous delayed-type hypersensitivity.

AETIOLOGY

10. The aetiology of sarcoidosis is obscure. The very high frequency of lung and hilar node involvement raises the possibility that there may be an inhaled causative agent. However, extensive research has failed to identify any infective agent, environmental allergy, primary immunological disorder or definite genetic tendency.

11. Some research has suggested the possible involvement of a transmissible agent, perhaps a virus, and instances of clustering have been found. Any such agent would have to be of extremely low infectivity or have an incubation period so long that the contact is unrecognised.

12. Apart from the absence of caseation and tubercle bacilli, the lesions are histologically similar to TB (and studies have demonstrated the presence of mycobacterial DNA) but there is no evidence that the disease is caused by mycobacteria. Sarcoidosis may either follow or precede TB and very rarely they may coincide. The level of immunoglobin IgD is often depressed in sarcoidosis but raised in TB.

13. A variant human herpes virus (HHV-8) DNA has been found in a very high proportion of sarcoid, compared with non-sarcoid tissues, but this does not prove that HHV is a causative agent.

14. An imbalance between subsets of T-lymphocytes and other disturbances of cell-mediated immunity are involved in some way in the pathogenesis of sarcoidosis. The exact relationship is not clear, but the process of granuloma formation seems to involve a reaction between macrophages and T-lymphocytes, triggered by lymphokines. Lymphokines are immune mediators produced by antigen-sensitised T-lymphocytes.

15. There is a link between some manifestations of sarcoidosis and certain HLA patterns. Also, the occasional occurrence of familial sarcoidosis and an apparent excess concordance in identical, compared with non-identical, twins is only slight evidence of a genetic factor in susceptibility. There is not thought to be any strong genetic element determining the disease. However, susceptibility does seem to vary with ethnicity, black races being more susceptible and the disease rare in Arabs, SE Asian Chinese, Inuit (Eskimos) and Amerindians. In London, there is a 10-fold higher annual incidence of carcoidosis in black and Asian immigrants, compared with the indigenous white population.

16. Epidemiology has made little contribution to understanding sarcoidosis. Prevalence varies widely between different populations (e.g. about 27/100,000 in England, 40/ in Ireland and Germany, 64/ in Sweden and only 0.04/ in Spain) but the true frequency is uncertain, as so many cases are asymptomatic.

17. Histological changes resembling those of sarcoidosis are occasionally seen in organs, such as lymph nodes, in cancer or fungal infections. These localised “sarcoid reactions” are not associated with systemic sarcoidosis.

18. Beryllium poisoning by inhalation causes lung disease clinically and pathologically resembling sarcoidosis, usually with a serious outcome similar to stage 3 (see 3.2 above). Exposure to beryllium is now uncommon.

CONCLUSION

19. **Sarcoidosis is a systemic disorder of unknown cause, characterised by its pathological hallmark, the non-caseating granuloma**. It has no proven causal relationship with any external factor. It remits without treatment in about 2/3 of identified cases in white patients and 1/3 of black patients. Otherwise, it may become chronic and involve many organ systems. Although sarcoidosis is fatal in less than 3% of cases, chronic sarcoidosis carries a high rate of morbidity. There is no curative treatment but anti-inflammatory drugs, especially corticosteroids, ameliorate the course of the disease. The progress and eventual outcome appear to be independent of other external factors.

ADDENDUM The 1991 Definition

20. “Sarcoidosis is a multi-system granulomatous disorder of unknown cause(s). It commonly affects young and middle aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. Liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones and other organs may also be involved.

The diagnosis is established when clinico-radiological findings are supported by histological evidence of non-caseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded.

Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and increased helper cell (CD4) / suppressor cell CD8) ratio at the site of involvement. Circulating immune complexes along with the signs of B-cell hyperactivity may also be detectable. Other markers of the disease include elevated levels of serum angiotensin converting enzyme (SACE), increased uptake of radioactive gallium, abnormal calcium metabolism and abnormal fluorescein angiography. The Kveim-Siltzbach test, when appropriate cell suspensions are available, may be of diagnostic help.

The course and prognosis may correlate with the mode of onset and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy heralds a self-limiting course, whereas an insidious onset, especially with multiple extra-pulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs. Corticosteroids relieve symptoms, suppress the formation of granulomas and normalise the SACE levels and the gallium uptake."

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