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Review

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Endocrine and reproductive manifestations of sarcoidosis

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Introduction

Sarcoidosis is a multisystem protean disorder, characterized histologically by the presence of non-caseating epithelioid-cell granulomas in affected tissues. The aetiology of sarcoidosis remains unclear, although it is recognized as a disease of activated T lymphocytes. Sarcoidosis has an uneven distribution world-wide, with high prevalence rates in European countries such as Sweden and Denmark, compared to China or Japan. There is also geographical or community clustering of the disease. In the UK, for example, where the prevalence rate is 20 per 100 000,[1] the incidence increases from north to south, offering support for the idea that a transmissible agent may play a part in the aetiology of the condition. Interestingly, the incidence and clinical course of sarcoidosis varies in different racial groups living in the same geographical area. There is a 10-fold higher annual incidence in West Indian and Asian immigrants living in London than in the indigenous White population. Furthermore, in West Indian and Asian patients, full recovery appears less likely, and there is an increased incidence of extrathoracic disease.[2]

Onset is most commonly between the ages of 20 and 40 years, although sarcoidosis is occasionally reported in childhood and in the elderly. Although remarkably transient in some individuals, sarcoidosis may run a chronic course for others. There is a diverse range of possible presentations, with respiratory, ophthalmological and dermatological complications, for example. In this article, we outline the endocrine and reproductive manifestations of sarcoidosis.

Vitamin D and calcium metabolism

The association between sarcoidosis and hypercalcaemia is seen in 5–10% of cases. Hypercalcaemia is usually transient in subacute sarcoidosis, but may fluctuate in chronic sarcoidosis, depending on disease activity.[3] The underlying mechanism is thought to involve high circulating concentrations of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2$-D_3], produced by extrarenal 1α-hydroxylation of vitamin D in alveolar macrophages and sarcoid granulomas.[4] Production of $1,25(OH)_2$-D_3 by alveolar macrophages is stimulated in a dose-response fashion by γ-interferon,[5] and it is possible that the increased $1,25(OH)_2$-D_3 production is a compensatory mechanism mounted by the immune system to inhibit the inflammatory process. Granulomatous production of parathyroid-hormone related protein (PTH-rP) may also play a role in abnormal calcium metabolism,[4] where tissue necrosis factor-alpha (TNF-α) and interleukin-6, produced by macrophages, increase PTH-rP gene expression.[4] PTH-rP, the usual aetiological agent of humoral hypercalcaemia of malignancy, was reported in one series to be present in 85% of biopsies of granulomatous tissue from patients with sarcoidosis.[6]

The important targets of $1,25(OH)_2$-D_3 are the intestinal epithelium and bone, where the hormone acts to increase intestinal calcium and phosphate absorption, increase osteoclastic recruitment and bone resorption, and modulate an increase in osteoblastic bone formation.[7] Although hypercalcaemia has long been recognized as a complication of sarcoidosis, the presence of hypercalciuria is

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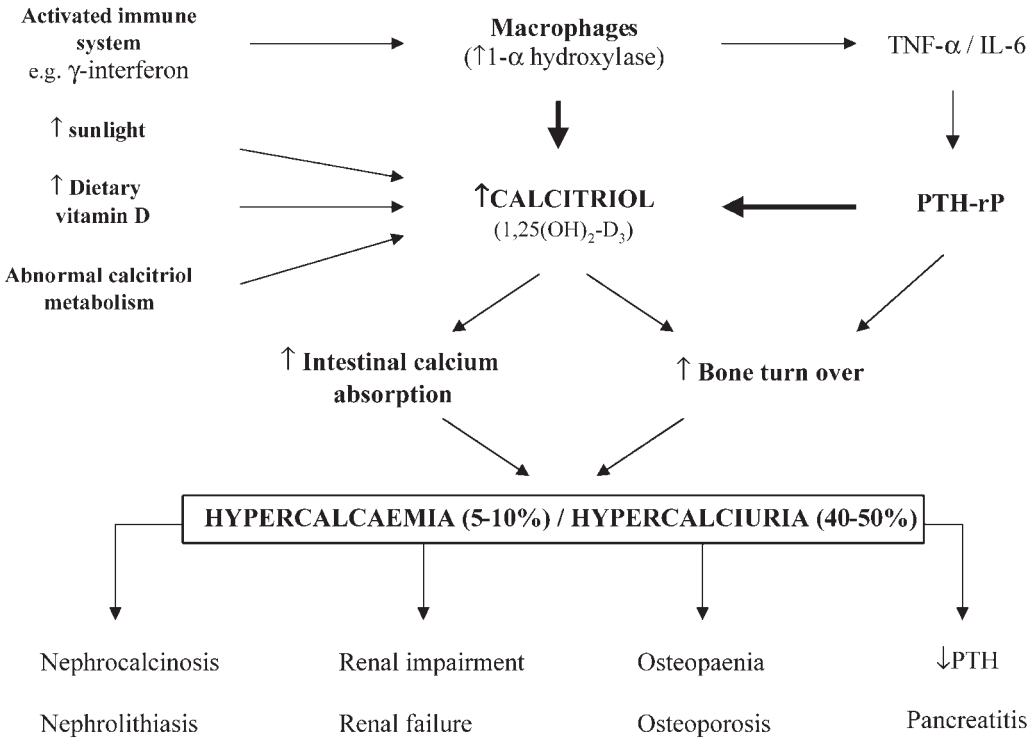

Figure 1. Causes and consequences of abnormal calcium homeostasis in sarcoidosis. PTH-rP, parathyroid hormone (PTH) related protein; TNF-α, tissue necrosis factor- α; IL-6, interleukin-6.

three times more common, occurring in approximately 40–50% of patients with sarcoidosis.[7] The mechanism of hypercalciuria is multifactorial, including: (i) increased absorption of calcium with a high urinary calcium/creatinine ratio, associated with elevated serum $1,25(OH)_2$-D_3 levels; (ii) resorption associated with extensive dissemination of sarcoidosis, including bones with high serum angiotensin-converting enzyme levels—osteopenia may occur and hypercalciuria persists on a calcium-poor diet—and (iii) association with osteoclast-activating factor, a bone resorbing substance, produced by activated lymphocytes and mononuclear cells and sarcoid granulomas. Figure 1 illustrates the causes of hypercalcaemia and hypercalciuria in sarcoidosis.

In patients with sarcoidosis, the production of $1,25(OH)_2$-D_3 by granulomas is substrate-dependent. This is supported by the observation that hypercalcaemia in sarcoid patients who live in the northern hemisphere is usually more pronounced in the summer months, due to longer exposure to sunlight which increases the dermal production of vitamin D, in turn leading to increased hepatic production of 25-hydroxyvitamin D by the liver. Compared to normal subjects, the production of $1,25(OH)_2$-D_3 in subjects with sarcoidosis is not regulated by calcium and parathyroid hormone, and may account for the characteristic finding of increased sensitivity to vitamin D in these patients.[8] Of note, even though only around 50% of patients with active sarcoidosis are hypercalciuric, abnormal $1,25(OH)_2$-D_3 metabolism has been described in some who are normocalciuric and normocalcaemic.[9] Furthermore, hypercalcaemia complicating sarcoidosis most often results in suppression of parathyroid function.[10] In contrast, an association with hyperparathyroidism is far less common, only having been reported in 50 cases of sarcoidosis in the past 40 years.[10] Although mechanisms have been suggested to account for this combination of disorders, the frequency is so low that chance association cannot be excluded. However, in patients with clinical evidence of sarcoidosis and steroid-resistant hypercalcaemia, the diagnosis of concomitant primary hyperparathyroidism should be considered.

Abnormal calcium metabolism in sarcoidosis can lead to pancreatitis, nephrocalcinosis, nephrolithiasis, impaired renal function, renal failure and death,[11] highlighting the importance of diagnosing hypercalcaemia and hypercalciuria in these patients (Figure 1). Symptomatic hypercalcaemia presenting with dehydration, nephrogenic diabetes insipidus and altered conscious state is a rare but recognized complication of sarcoidosis. Furthermore, abnormal

calcium metabolism may lead to osteopenia and osteoporosis. In addition to the well-documented increased risk of osteoporosis and fracture posed by corticosteroids[12–14] used in the treatment of sarcoidosis, there is some evidence that subjects with sarcoidosis may have a greater incidence of reduced bone density than the general population prior to commencing treatment.[15] The institution of safe and effective bone protection therapy is necessary in individuals with sarcoidosis, who are often young and require a prolonged course of corticosteroids. Although primary prevention studies suggest that cholecalciferol is not entirely effective in preventing glucocorticoid-induced bone loss,[16] it is well tolerated by patients, and can be used once hypercalcaemia has been excluded. Current available data indicate that bisphosphonates are the most effective agents for the primary and secondary prevention of glucocorticoid-induced osteoporosis.[17,18] It is therefore suggested that the use of bisphosphonates should be limited to patients who have a reduced bone mass before they begin to take corticosteroids, postmenopausal women and those who have shown significant loss of bone mass while receiving suitable hormone replacement (if required) and cholecalciferol.[19] Of the bisphosphonates, alendronate appears to have the most favourable effects[17–19] and has also been successfully used in both men and premenopausal women with sarcoidosis.[20]

Management of abnormal calcium homeostasis includes measurement of serum calcium and albumin in order to estimate the ionized calcium level, 24-h urine collection for calcium excretion and creatinine clearance, and an abdominal ultrasound investigation performed to exclude urolithiasis or nephrocalcinosis. Treatment of the hypercalcaemia and/or hypercalciuria in sarcoidosis (Table 1) is aimed at reducing intestinal calcium absorption and $1,25(OH)_2$-D_3 synthesis. It is accepted practice that all patients be advised to minimize their exposure to sunlight, avoid a diet rich in vitamin D and maintain a fluid intake of > 21/day.[21]

Prednisolone 20–40 mg daily is the drug of choice, because of its effectiveness in rapidly restoring normocalcaemia. Corticosteroids reduce gastrointestinal calcium absorption and inhibit osteoclast function[22,23] because of their effects on the endogenous production of $1,25(OH)_2$-D_3.[7] Corticosteroids are potent inhibitors of 1α-hydroxylase in macrophages,[5] and down-regulate interleukin-2 and γ-interferon,[5] resulting in reduced PTHrP production by macrophages. Prednisolone therapy causes a relatively swift decrease in serum calcium within 2–4 days. A reduction in urinary calcium excretion rate soon follows, within 7–10 days. Once the calcium abnormality is brought under control, prednisolone dosage can be reduced over a period of 4–6 weeks. If hypercalcaemia associated with sarcoidosis fails to resolve on corticosteroid therapy, primary hyperparathyroidism should be excluded.

Table 1 Treatment of abnormal calcium homeostasis in sarcoidosis

Non-pharmacological
Avoid diet rich in vitamin-D
Minimize exposure to sunlight
Fluid intake >2 l/day
Pharmacological: Hypercalcaemia/hypercalciuria
Corticosteroids
Ketoconazole
Antimalarials
Chloroquine
Hydroxychloroquine
Methotrexate
Azathioprine
Pharmacological: Osteopaenia/osteoporosis
Bisphosphonates ± Cholecalciferol

Ketoconazole is now considered an appropriate second-line treatment in hypercalcaemic sarcoidosis when oral steroids are ineffective or contraindicated.[19,24] Ketoconazole is an imidazole antifungal agent that inhibits cytochrome P450-linked hydroxylation of $1,25(OH)_2$-D_3. Although the literature supporting the use of ketoconazole in combination with corticosteroids is limited to isolated case reports,[21,25] it has been our experience that the addition of ketoconazole results in the dose of corticosteroids being significantly reduced in all patients and ceased in some. It should be noted that ketoconazole has no role for any other manifestation of sarcoidosis. Chloroquine and hydroxychloroquine also cause inhibition of $25(OH)D_3$-1α-hydroxylase,[26,27] and can be considered for patients who are intolerant of ketoconazole or who develop abnormal liver function tests. Methotrexate and azathioprine are frequently used as adjuvant therapy for sarcoidosis, and help to control hypercalcaemia by reducing the granuloma burden.

Pituitary and hypothalamus

About 5% of patients with sarcoidosis have clinical involvement of the nervous system;[28] however, the incidence of subclinical and undiagnosed neurosarcoidosis (NS) is much higher.[29] Although

its involvement in NS is uncommon, the hypothalamus is the most frequently involved of all the endocrine glands. Sarcoidosis, like other granulomatous diseases, infections, and metastatic tumours, commonly leads to an infiltrative process in the hypothalamo-hypophyseal region,[30] resulting in neuroendocrinological dysfunction,[31] whereas a primary pituitary defect and an empty sella occur rarely.[32] Earlier studies of post-mortem findings in patients with hypopituitarism complicated by sarcoidosis, assumed that pituitary destruction was the cause of hormone loss.[33] However, subsequent reports, demonstrated pituitary responsiveness to synthetic hypothalamic releasing factors in patients with sarcoidosis and hypopituitarism, concluding that hypothalamic insufficiency is the major cause for hypopituitarism in these patients.[34]

Polyuria and polydipsia are common presenting features of hypothalamic involvement, due either to diabetes insipidus or a disordered control of thirst; the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) has also been reported.[35,36] In a study by Stuart *et al.*,[35] polydipsia and polyuria were more often primarily due to thirst dysregulation, with adequate endogenous ADH, than to true diabetes insipidus. There has been a report of chronic hypernatraemia and hypovolaemia in a patient with hypothalamic sarcoidosis who did not complain of thirst.[37] Neuroendocrinological dysfunction also includes hyperprolactinaemia, which normalizes after treatment of sarcoidosis, and is reported to occur in 3–32% of patients;[38] however, other endocrinopathies, including a hypothalamic syndrome, occur in <10% of patients with NS.[39] Table 2 illustrates the clinical features of hypothalamo-pituitary sarcoidosis.

Complete loss of the counter-regulatory response to glucose has been described in hypothalamic sarcoidosis.[40] Given that hypothalamic sarcoidosis can lead to secondary hypothyroidism, hypoadrenalism, and growth hormone insufficiency/deficiency,[41] the counter-regulatory response to hypoglycaemia, namely an increase in catecholamines, glucagon, cortisol and growth hormone, is impaired. The specific region of the hypothalamus responsible for triggering the release of such counter-regulatory hormones during hypoglycaemia has been shown in rat models to be in the ventromedial region.[40] Sarcoid invasion of the satiety centre in the ventral median nucleus of the hypothalamus may also lead to morbid obesity.[42] In addition to the above abnormalities, other manifestations attributed to hypothalamic sarcoidosis include marked somnolence, often preceded or followed by insomnia,[43] extreme variations in body temperature[44] and marked personality changes.[45]

The diagnosis of NS ideally requires evidence of systemic disease, a compatible clinical or neuroradiological picture of sarcoidosis and histological confirmation of non-caseating granulomas.[29] In patients with NS, the chest X-ray is abnormal in only 30% of cases at presentation, whereas >90% of patients with sarcoidosis have an abnormality. The imaging procedure of choice for hypothalamo-pituitary sarcoid is contrast-enhanced magnetic resonance imaging (MRI), which can also be used to follow therapeutic response.[46,47] Cerebrospinal fluid examination, gallium scanning, serum angiotensin converting enzyme (SACE) and CSF angiotensin converting enzyme (CACE) may be of help in supporting the diagnosis, but lack both sensitivity and specificity.[46]

In about 50% of patients with NS, CSF examination reveals characteristic but non-specific abnormalities such as increased protein and a mild pleocytosis, mostly lymphocytes; hypoglycorrhachia is occasionally seen.[48] Normal results of CSF analysis do not exclude hypothalamo-pituitary sarcoidosis. SACE and CACE are helpful in supporting the diagnosis of NS in only a small group of patients. In particular, SACE is often normal in isolated NS; elevation is usually associated with active pulmonary disease. Elevated SACE and CACE, the latter elevated in 50% of patients with NS, reflect an activated disease state, with a sensitivity from 50–86%[49] and 80%,[50] respectively. Elevation of CSF lysozyme and β_2 microglobulin have been reported in some patients with NS,[51] but are less specific than elevation of ACE.[52] Determination of CSF lymphocyte subpopulations (increased T4:T8), oligoclonal bands and IgG index have been used to diagnose and differentiate NS from other diseases, such as multiple sclerosis,

Table 2 Clinical features of hypothalamo-pituitary sarcoid

Morbid obesity
Dysregulation of body temperature
Insomnia
Personality change
SIADH
Diabetes insipidus
Hyperprolactinaemia
Hypothyroidism
Hypoadrenalism
Growth hormone deficiency
Impaired counter-regulatory response to hypoglycaemia

SIADH, syndrome of inappropriate secretion of anti-diuretic hormone.

but lack specificity.[53] If the diagnosis remains in doubt, biopsy of the lesion is indicated to establish the diagnosis.[46] It is important to realize that pituitary sarcoid may mimic pituitary tumours[34] and can present with classical bitemporal hemianopia and other field defects which may respond well to high-dose immunosuppressive therapy. Table 3 illustrates the possible investigations and treatment modalities of hypothalamo-pituitary sarcoidosis.

If the diagnosis is certain, corticosteroids remain the mainstay of treatment of NS. Corticosteroids effectively suppress the elevated CD4-CD8 (T4-T8) lymphocyte ratio, decrease interleukin-2 production, and inhibit collagen synthesis, all of which occur at the sites of active disease.[54] Treatment is usually prolonged, exposing the patient to significant steroid-related side-effects. Those unresponsive, or who have a primary contraindication to corticosteroid therapy, often require higher doses, either orally or using pulsed methylprednisolone. In these patients adjuvant or alternative treatment with radiotherapy and/or immunosuppressive agents may be necessary. Azathioprine, cyclosporin, chloroquine and cyclophosphamide have all been tried, with variable success.[55–57] There are very few data on the efficacy of immunomodulatory therapy in NS, and no prospective data are available. Certain authors recommend methotrexate[58] or hydroxychloroquine[59] as first-line steroid-sparing agents, whilst others opt for cyclosporine and azathioprine.[54]

Table 3 Investigation and treatment of Hypothalamo-pituitary sarcoid (HPS)

Investigations that may help in the diagnosis of HPS
Serum and CSF ACE
CSF
Increased protein
Lymphocytosis/lymphocyte subpopulations
Hypoglycorrhachia
↑ lysozyme and β_2 microglobulin
Contrast-enhanced MRI ± gallium scanning
Biopsy of lesion
Treatment of HPS
Corticosteroids
Antimalarials
Hydroxychloroquine
Chloroquine
Other immunosuppressive agents
Azathioprine
Cyclosporin
Cyclophosphamide
Methotrexate
Radiotherapy

CSF, cerebrospinal fluid; ACE, anglotensin converting enzyme; MRI, magnetic resonance imaging.

Thyroid

Sarcoid granuloma in the thyroid was first described in 1938.[60] The thyroid is an uncommon site of the disease, with clinically evident involvement of the thyroid gland infrequently reported in the literature, although its incidence was approximately 4% in some autopsy series.[61,62] Middle-aged women are most frequently affected, and in most cases peripheral or intrathoracic lymphadenopathy is observed.

Hypothyroidism has been noted in patients with sarcoidosis.[63] Hypothyroidism, caused through extensive infiltration by epithelioid granulomas, may be present for some time before the diagnosis of sarcoidosis is made, as illustrated by Brun *et al.*,[64] where the patient was hypothyroid for 3 years before the diagnosis of sarcoidosis was made. There may be (symmetrical or asymmetrical) painless thyroid enlargement with or without fixation to deep tissues of the neck. The association of hyperthyroidism and sarcoidosis has also been described.[63] This observation was made in patients undergoing thyroidectomy for hyperthyroidism, and at autopsy in patients who had previously had surgery for hyperthyroidism. There is no evidence or reason to suggest that sarcoidosis of the thyroid gland predisposes to hyperthyroidism. Unilateral or bilateral proptosis, as seen in patients with hyperthyroidism/Graves disease, may occur in patients with sarcoidosis who do not have endocrine exophthalmos; retro-orbital infiltration by sarcoid tissue being the probable pathogenesis. Other associations of sarcoid and the thyroid include goitre, sarcoid thyroiditis, Hashimotos thyroiditis, de Quervains thyroiditis, painful thyroid enlargement, Hurthle cell hyperplasia[62] and thyroid carcinoma.[65] Diagnosis and therapeutic management prove difficult when thyroid carcinoma and sarcoidosis co-exist.

The relationship between the presence of sarcoid granulomas in the thyroid gland and clinical thyroid disease is not known, and a cause-effect relationship has not been established. Scadding[66] stated that sarcoidosis rarely, if ever results in the functional derangement of the thyroid, while Karlish and MacGregor[67] reported a prevalence of overt thyroid disease in sarcoidosis in 3.6%, with the majority being autoimmune in aetiology. A study by Papadopoulos *et al.*,[68] reported an overall frequency of thyroid autoimmunity of 17% with a 10% frequency of clinical autoimmune thyroid disease, the latter with a histological/cytological appearance of the thyroid, pointing to a genuine autoimmune process rather than to sarcoid dissemination.

Adrenal glands

Involvement of the adrenal glands rarely occurs in sarcoidosis. The functional status of the adrenal gland in patients with sarcoidosis has nearly always been normal when evaluated after stimulation with exogenous ACTH, with the exception of patients with secondary adrenal failure due to hypothalamic-pituitary infiltration by sarcoid granulomas.[41] When there is sarcoid involvement, the adrenal gland is replaced by dense fibrosis, leading to adrenal insufficiency, but patients respond well to glucocorticoid and mineralocorticoid replacement. However, sarcoidosis of the adrenal gland has also been described as leading to an adrenal crisis[67] and death.[69] Both caseating and non-caseating epithelioid granulomas have been reported at autopsy in patients with coexisting sarcoidosis and tuberculosis. Finally, the association between sarcoidosis and Addison's disease is unusual, but when it occurs it is likely to be as a result of autoimmunity.[68]

Pancreas

Sarcoid involvement of the pancreas is extremely rare. In a Japanese review of 663 562 autopsies,[70] 212 cases of sarcoidosis were noted; pancreatic granulomas were found in 2.1% of patients in whom the cause of death was related to sarcoid, and in 1.3% of patients in whom the cause of death was unrelated to sarcoid. Epithelioid granulomas occurring in the pancreas or peripancreatic lymph nodes may produce symptoms related to parenchymal infiltration or common bile duct obstruction. Acute pancreatitis most often occurs in young individuals (18–47 years) and with variable amylase levels at presentation.[71] In some patients there is associated hypercalcaemia, which may also cause pancreatitis. Chronic pancreatitis without a true obstructive pancreatic mass has been reported twice.[71] Isolated sarcoidosis of the pancreas most often presents as a pancreatic head mass, and symptoms include abdominal pain (50%), weight loss (44%) and obstructive jaundice (44%). Given that sarcoidosis of the pancreas is rare, it is important to note that it often mimics pancreatic cancer. In those patients who have a history of sarcoidosis, the diagnosis should be considered, but the possibility of carcinoma of the pancreas must be ruled out.

Noguchi *et al*. reported a patient with pancreatic exocrine deficiency and sarcoidosis.[72] In their report, levels of pancreatic enzymes paralleled changes in the levels in activity of sarcoid lesions in the liver and lungs, as well as the ACE and lysozyme levels; the pancreatic enzymes were reduced by corticosteroid therapy, leading to the conclusion that the pancreatic impairment was due to sarcoidosis. Diabetes mellitus is an unlikely complication of pancreatic sarcoidosis, but is frequently seen in patients as a complication of corticosteroid therapy. Interestingly, necrobiosis lipoidica, a characteristic finding of diabetes mellitus has been reported in patients with sarcoidosis.[63] The significance of this finding, and whether there is a possible cause-effect relationship, has not been determined.

Reproductive system

Male

The frequency of genitourinary sarcoidosis in men is $<0.2\%$ in clinically diagnosed cases, and 5% in autopsy studies.[73] It has been reported to be 10 times more frequent in Black men,[73] in parallel with the increased incidence of sarcoidosis in this group. Sarcoid granulomas have been found in order of decreasing frequency in the epididymis, testis and prostate gland, with only rare involvement of the spermatic cord, scrotum and penis. Initial presentation can include an asymptomatic, painless mass in the scrotum, acute epididymo-orchitis and testicular swelling (Table 4). A hypoechogenic lesion on ultrasound is a recognized feature of testicular sarcoid.[74]

Testicular sarcoidosis as a presenting feature is rare and few reports exist of sarcoid affecting

Table 4 Sarcoidosis of the reproductive system

Male
More frequent in Black men
Asymptomatic mass in scrotum
Acute epididymo-orchitis
Primary testicular failure
Low testosterone
Oligospermia
Infertility
Female
Uterus most commonly affected
Menstrual disturbance
Amenorrhoea
Menorrhagia
Metrorrhagia
Post menopausal bleeding
Erosion of cervix
Granulomatous involvement of
Ovary
Fallopian tubes
Placenta

the body of the testis without concomitant epididymal involvement. The average age of patients with genitourinary sarcoidosis is 31 years, which coincides with the peak occurrence of testicular malignancy, so a high index of suspicion for malignancy must be maintained. The incidence of testicular malignancy is low in the Black population, with only 1.2–3.5% of all testicular tumours found in Black patients. The effect of genitourinary sarcoidosis on fertility has not been studied, but it is reasonable to assume that the fibrosis and occlusion of the ductus epididymis seen in this disease could cause oligospermia and infertility.[75] Leydig cell dysfunction may alter secondary sexual characteristics; however, glucocorticoids are effective in reducing sarcoid-testicular mass and improving gonadal function.

Female

The main significance of sarcoidosis of the genital tract is its differentiation from other lesions, especially tuberculosis. The most common site of involvement of the female reproductive system is the uterus. Sarcoidosis of the uterus is most often diagnosed in the endometrium, because this tissue is amenable to sampling via curettage. In almost all reported cases of uterine sarcoidosis in which the entire uterus was examined after hysterectomy, granulomas were found in the myometrium as well as the endometrium.[76] The frequency with which sarcoidosis is found in the various portions of the uterus appears to reflect sampling bias rather than a true reflection of distribution. Occasionally, when some other pathological process occurring in the cervix serves to focus attention on this tissue, this portion of the uterus is found to be involved. Sarcoidosis cases involving fallopian tubes and the ovary have also been reported.[77]

Clinical manifestations include amenorrhoea, menorrhagia, metrorrhagia, post menopausal bleeding and erosion of the cervix (Table 4). Sarcoidosis of the uterus is usually discovered during the investigation of abnormal uterine bleeding in patients with known sarcoid elsewhere. Involvement of the peritoneum with sarcoid has been reported as causing an elevated CA125 with appearances at operation similar to those of metastatic cancer.[78] Women with uterine sarcoidosis suffer little, if any, detrimental effect with regard to their ability to become pregnant and carry pregnancies to term, and delivery of a healthy baby can occur despite the presence of granulomas in the placenta.[77] Corticosteroids have been used in the treatment of uterine sarcoidosis with improvement in clinical outcome.

Endocrine autoimmunity

Autoimmune disease and sarcoidosis may be related, and the association between sarcoidosis and autoimmune thyroid disease has long been recognized. The frequency and type of endocrine autoimmunity was examined in a series of 89 Swedish patients with sarcoidosis by Papadopoulos *et al*.[68] The study found that 19.2% of the patients with sarcoidosis had clinical or serological evidence of endocrine autoimmunity. Two patients had Addison's disease, both with polyglandular autoimmune syndrome type II; evidence of thyroid autoimmunity was found in 13 patients, eight with clinical autoimmune thyroid disease (two with Graves disease and six with autoimmune thyroiditis), of whom two had PGA syndrome type III, and five with isolated positive thyroid serology; two patients had diabetes mellitus and one had premature ovarian failure. Addison's disease, clinical autoimmune thyroid disease and polyglandular autoimmune syndrome type II were significantly more common compared with the general population. Complex immunological and genetic mechanisms might explain the association of sarcoidosis and autoimmune diseases, and further studies are needed to define the significance of these findings.

Conclusions

Sarcoidosis is a relatively common multisystem disease characterized by epithelioid granulomas. Endocrine gland involvement leads to a diverse range of presentations. Hypercalcaemia and hypercalciuria result primarily from the synthesis of 1,25 hydroxyvitamin-D_3 in sarcoid granulomas. Involvement of the pituitary and hypothalamus can cause diabetes insipidus, SIADH, disordered control of thirst, morbid obesity and impaired secretion of anterior pituitary hormones. Thyroid dysfunction occurs in sarcoidosis and this may be due to an autoimmune process rather than sarcoid dissemination. Testicular sarcoid can present as a painless mass in the scrotum or acute epididymo-orchitis and may cause oligospermia and infertility. Involvement of the female reproductive tract may cause menstrual abnormalities.

References

1. Sharma OP. *Sarcoidosis: Clinical Management.* London, Butterworths, 1994:4.
2. Studdy PR. In: Weatherhall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, 3rd edn. Oxford, Oxford Medical Publications: 2820.
3. DeRemee RA, Lufkin EG, *et al*. Serum angiotensin-converting enzyme activity. Its use in the evaluation and management of hypercalcaemia associated with sarcoidosis. *Arch Intern Med* 1985; **145**:677–9.
4. Zeimer HJ, Greenaway TM, Slavin J, *et al*. Parathyroid-hormone-related protein in sarcoidosis. *Am J Pathol* 1998; **152**:17–21.
5. Adams JS, Gacad MA. Characterisation of lα-hydroxylation of vitamin D3 sterols by cultured alveolar macrophages from patients with sarcoidosis. *J Exp Med* 1985; **161**:755–65.
6. Zeimer HJ, Greenaway TM, Slavin J, Hards DK, Zhou H, Doery JC, Hunter AN, Duffield A, Martin TJ, Grill V. Parathyroid-hormone-related protein in sarcoidosis. *Am J Pathol* 1998; **152**:17–21.
7. Sharma OP. Vitamin D, Calcium and Sarcoidosis. *Chest* 1996; **109**:535–9.
8. Bell NH, Gill JR Jr, Bartter FC. On the abnormal calcium absorption in sarcoidosis: Evidence for increased sensitivity to vitamin D. *Am J Med* 1964; **36**:500–13.
9. Basile JN, Liel Y, Shary J, Bell NH. Increased calcium intake does not suppress circulating 1,25-dihydroxyvitamin D in normocalcemic patients with sarcoidosis. *J Clin Invest* 1993; **91**:1396–8.
10. Tomita A. Primary hyperparathyroidism associated with sarcoidosis. *Nippon Ronsho* 1995; **53**:949–52.
11. Sinha RN. Long term management of hypercalcaemia in chronically active sarcoidosis. *J Roy Soc Med* 1997; **90**:156–7.
12. Peel NFA, Moore DJ, Barrington NA, *et al*. Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1995; **54**:801–6.
13. Cooper C, Mitchell M, Wickham C. Rheumatoid arthritis, corticosteroid therapy and the risk of hip fracture. *Ann Rheum Dis* 1995; **54**:49–52.
14. Verstraeten A, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis: effect of low dose corticosteroids. *Ann Rheum Dis* 1986; **45**:852–7.
15. Rizzato G, Montemurro L, Fraioli P. Bone mineral content in sarcoidosis. *Semin Respir Med* 1992; **13**:411–23.
16. Adachi JD, Benson WG, Bianchi F, *et al*. Vitamin D and calcium in the prevention of glucocorticoid induced osteoporosis: a 3 year follow up. *J Rheumatol* 1996; **23**:995–1000.
17. Adachi JD, Benson WG, Brown J, *et al*. Intermittent etidronate therapy to prevent corticosteroid induced osteoporosis. *N Engl J Med* 1997; **337**:382–7.
18. Saag KG, Emkey R, Schnitzer TJ, *et al*. Alendronate for the prevention and treatment of glucocorticoid induced osteoporosis. Glucocorticoid-induced Osteoporosis Intervention Study Group. *New Engl J Med* 1998; **339**:292–9.
19. Conron M, Young C, Beynon HLC. Calcium metabolism in sarcoidosis and it's clinical implications. *Rheumatology* 2000; **39**:707–13.
20. Gonnelli S, Rottoli P, Cepollaro C. Prevention of corticosteroid induced osteoporosis with alendronate in sarcoid patients. *Calcif Tissue Int* 1997; **61**:382–5.
21. Young C, Burrows R, Katz J, Beynon H. Hypercalcaemia in sarcoidosis. *Lancet* 1999; **353**:374.
22. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326**:1196–203.
23. Chesney RW, Rosen JF, Hamstra AJ, Smith C, Mahaffey K, DeLuca HF. Absence of seasonal variation in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer. *J Clin Endocrinol Metab* 1981; **53**:139–42.
24. Bia MJ, Insogna K. Treatment of sarcoidosis-associated hypercalcaemia with ketoconazole. *Am J Kidney Dis* 1991; **18**:702–5.
25. Adams JS, Sharma OP, Diz MM, Endres DB. Ketoconazole decreases the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia. *J Clin Endocrinol Metab* 1990; **70**:1090–5.
26. O'Leary TJ, Jones G, Yip A, Lohnes D, Cohanim M, Yendt ER. The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; **315**:727–30.
27. Barre PE, Gascon-Barre M, Meakins JL, Goltzman D. Hydroxychloroquine treatment of hypercalcemia in a patient with sarcoidosis undergoing hemodialysis. *Am J Med* 1987; **82**:1259–62.
28. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985; **42**:909–17.
29. James DG, Sharma OP. Neurological complications of sarcoidosis. *Proc Roy Soc Med 1967*; **60**:1169–70.
30. Vance ML. Hypopituitarism. *N Engl J Med* 1994; **300**:1651–62.
31. Brust JCM, Rhee RS, Phank CR. Sarcoidosis, galactorrhoea and amenorrhoea: Two autopsy cases, one with Chiari-Frommel syndrome. *Ann Surg* 1977; **2**:130–7.
32. Chiang R, Marshall MC, Rosman PM, Hotson G, Mannheimer E, Wallace EZ. Empty sella turcica in intracranial sarcoidosis. *Arch Neurol* 1984; **41**:662–5.
33. Bleisch VR, Robbins SL. Sarcoid-like granulomata of pituitary gland: cause of pituitary insufficiency. *Arch Intern Med* 1952; **89**:877–92.
34. Stuart C, Neelson F, Lebovitz E. Hypothalamic Insufficiency: The cause of hypopituitarism in sarcoidosis. *Ann Intern Med* 1978; **88**:589–94.
35. Stuart C, Neelon F, Lebovitz H. Disordered Control of Thirst In Hypothalamic-Pituitary Sarcoidosis. *N Engl J Med* 1980; **303**:1078–82.
36. Brunning PF, Koster HG, Hekster REM, Luyendijk W. Sarcoidosis presenting with diabetes insipidus followed up by acute cranial nerve syndrome. *Acta Medica Scandinavia* 1979; **205**:441–4.
37. Luciani JC, Conte-Devolx B, Fourcade JC, Barjon P. Chronic hypernatraemia, hypovolaemia and partial hypopituitarism in sarcoidosis: a case report. *Clin Nephrol* 1980; **13**:242–7.
38. Turkington RW, Macindoe JH. Hyperprolactinaemia in Sarcoidosis. *Ann Intern Med* 1972; **76**:545–9.
39. Jawardi MH, Hanson TJ, Schemmel JE, Beck P, Katz FH. Hypothalamic sarcoidosis and hypopituitarism. *Hormone Res* 1980; **12**:1–9.

40. Fery F, Plat L, Van De Bourne P, Cogan E, Mockel J. Impaired Counterregulation of Glucose in a Patient with Hypothalamic Sarcoidosis. *N Engl J Med* 1999; **340**:852–7.
41. Veseky D, Maldonono A, Levey G. Partial Hypopituitarism and Possible Hypothalamic Involvement In Sarcoidosis. *Am J Med* 1977; **62**:425–30.
42. Vesely DL. Hypothalamic sarcoidosis: A new cause of morbid obesity. *South Med J* 1989; **82**:758–61.
43. Colover J. Sarcoidosis with involvement of the nervous system. *Brain* 1948; **71**:451–5.
44. Jefferson M. Sarcoidosis of the nervous system. *Brain* 1957; **80**:540–56.
45. Gjerse A, Kjerulif-Jensen K. Hypothalamic lesion caused by Boek's sarcoid. *J Clin Endocrinol* 1950; **10**:1602–8.
46. Randeva HS, Davison R, Chamoun V, Bouloux PM-G. Isolated neurosarcoidosis—a diagnostic enigma: Case report and discussion. *Endocrine* 2002; **17**:241–7.
47. Sherman JL, Stern BJ. Sarcoidosis of the CNS: comparison of unenhanced and enhanced MRI images. *Am J Radiol* 1990; **155**:1293–301.
48. Gaines JD, Eckman PB, Remington JS. Low CSF glucose level in sarcoidosis involving the central nervous system. *Arch Intern Med* 1970; **125**:333–6.
49. Schultz T, Miller WC, Bedrossian CW. Clinical application of measurement of angiotensin converting enzyme level. *JAMA* 1979; **242**:439–41.
50. Oksanen V, Fyhrquist F, Somer H, Gronhagen-Riska C. Angiotensin converting enzyme in cerebrospinal fluid: a new assay. *Neurology* 1985; **35**:1220–3.
51. Oksanen V, Gronhagen-Riska C, Tikanoja S, Somer H, Fyhrquist F. Cerebrospinal fluid lysozyme and β_2-microglobulin in neurosarcoidosis. *J Neurol Sci* 1986; **73**:79–87.
52. Selroos O, Klockars M. Relation between clinical stage of sarcoidosis and serum values of angiotensin converting enzyme and $beta_2$-microglobulin. *Sarcoidosis* 1987; **4**:13–17.
53. Li CY, Yam LT. Cytologic and immunohistochemical studies of cerebrospinal fluid in meningeal sarcoidosis. *Acta Cytologica* 1992; **36**:963–7.
54. Agbogu BN, Stern BJ, Sewell C, Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. *Arch Neurol* 1995; **52**:875–9.
55. Stem BJ, Schonfeld SA, Sewell C, Krumholz A, Scott P, Belendiuk G. The treatment of neurosarcoidosis with cyclosporine. *Arch Neurol* 1992; **49**:1065–72.
56. Sharma OP. Neurosarcoidosis. A personal perspective based on the study of 37 patients. *Chest* 1997; **112**:220–8.
57. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med* 1997; **157**:1864–8.
58. Lower EE, Baughmann RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155**:846–51.
59. Sharma OP. Effectiveness of Chloroquine and Hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement. *Arch Neurol* 1998; **85**:1248–54.
60. Spencer J, Warren S. Boeck's Sarcoid: Report of a case, with Clinical Diagnosis Confirmed at Autopsy. *Arch Intern Med* 1938; **62**:285–96.
61. Maycock RL, Bertrand P, Morrison CDE. Manifestations of sarcoidosis: analysis of 145 patients with a review of nine series selected from the literature. *Am J Med* 1963; **35**:67–89.
62. Bacci V, Giammarco V, Germani G, Pelosio A, Nardi F. Hurthle Cell Hyperplasia and Sarcoidosis of the Thyroid. *Arch Pathol Lab Med* 1991; **115**:1044–5.
63. Winnacker J, Becker K, Katz S. Endocrine Aspects of Sarcoidosis. *N Engl J Med* 1968; **278**:483–90.
64. Brun J, Mouriquand C, Combey P, *et al*. Thyroidite sclereuse d'origine sarcoidosique avec myxoedeme et fibrose pulmonaire diffuse. *Lyon Med* 1959; **91**:179–88.
65. Middleton WG, de Souza FM, Gardiner GW. Papillary carcinoma of the thyroid associated with sarcoidosis. *J Otolaryngol* 1985; **14**:241–4.
66. Scadding JC. Sarcoidosis with special reference to lung changes. *Br Med J* 1950; 745–53.
67. Karlish AJ, MacGregor GA. Sarcoidosis, thyroiditis and Addisons disease. *Lancet* 1970; **ii**:330–3.
68. Papadopoulos K, Hornblad Y, Liljebladh H, Hallengren B. High Frequency of Endocrine Autoimmunity in Patients with sarcoidosis. *Eur J Endocrinol* 1996; **134**:331–6.
69. Maycock RL, Bertrand P, Morrison CE, *et al*. Manifestations of sarcoidosis: analysis of 145 patients with a review of nine series selected from the literature. *Am J Med* 1963; **35**:67–87.
70. Iwai K, Tachibana T, Hosoda Y, Matsui Y. Sarcoidosis autopsies in Japan: frequency and trend in the last 28 years. *Sarcoidosis* 1988; **5**:60–5.
71. Siavelis H, Herrmann M, Aranha G, Garcia G, Eubanks T, Reyes C. Sarcoidosis and the pancreas. *Surgery* 1999; **125**:456–61.
72. Noguchi H, Hirai K, Sea A, Yoshitake M, Sakai T, Abe H, Hidaka R, Tanikawa K. Sarcoidosis Accompanied by Pancreatic Impairment. *Intern Med* 1993; **32**:15–20.
73. Turk C, Schacht M, Ross L. Diagnosis and Management of Testicular Sarcoidosis. *J Urol* 1986; **135**:380–1.
74. Metcalfe MS, Rees Y, Morgan P, O'Reilly K, Sandu DPS. Sarcoidosis presenting as a testicular mass. *Br J Urol* 1998; **82**:769–70.
75. Cho YS, Park JN, Suh JE, Rhu NS, Cho DI, Kim JW. A case of sarcoidosis accompanied azoospermia. *Tuberculosis Resp Dis* 1991; **38**:179–85.
76. DiCarlo Jr FJ, DiCarlo JP, Robboy SJ, Lyons MM. Sarcoidosis of the uterus. *Arch Path Lab Med* 1989; **113**:941–3.
77. Chalvardjian A. Sarcoidosis of the female genital tract. *Am J Obstet Gynaecol* 1978; **132**:78–80.
78. Trimble EL, Saigo PE, Freeberg GW, Rubin SC, Hoskins WJ. Peritoneal Sarcoidosis and Elevated CA125. *Obstet Gynaecol* 1991; **78**:976–7.