CHAPTER 15

Rare manifestations of sarcoidosis

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Sarcoidosis may be associated with granulomatous inflammation in any part of the body, usually in more than one area [1]. Rare manifestations of sarcoidosis include unusual patterns of organ involvement, or are the result of granulomatous inflammation developing in unusual locations for sarcoidosis. In other rare cases, sarcoidosis is associated with a second disorder. Although the frequency of individual rare manifestations is by definition low, together they represent a major cause of morbidity and mortality related to sarcoidosis [1, 2]. Given the protean manifestations of sarcoidosis and potential involvement of any tissue, a comprehensive compilation of all reported rare manifestations of sarcoidosis is not possible in this monograph. Nonetheless, an approach to patients who may have rare manifestation of sarcoidosis can be constructed. These rare manifestations reflect the known pathophysiology and clinical behaviour of more common and easily recognisable systemic sarcoidosis. Alternative diagnoses must be excluded, particularly when there are deviations from well-established manifestations or an expected clinical course for sarcoidosis. Given their rarity, none of the clinical approaches or treatment recommendations for the conditions discussed below have been subjected to clinical trials, rigorous or otherwise. The author has seen patients with the conditions listed below, and offers an approach based on this experience and selected published literature. Emphasis will be placed on a systematic approach to these rare manifestations, focusing on organ systems that are not covered by other sections of this Monograph.

General considerations

An initial framework for approaching the challenge of diagnosing and treating rare manifestations of sarcoidosis can be formulated based on current knowledge of the disease and the expected clinical behaviour of sarcoidosis. In all cases, granulomatous inflammation from sarcoidosis interferes with local tissue homeostasis and function; thus, organ impairment is dependent on its location. When the clinician is confronted with identifying whether a rare manifestation of sarcoidosis is present in a patient with known sarcoidosis, an internet search of the medical literature is part of a recommended initial approach to establish a possible association. Invariably, the clinician must be prepared to consider competing diagnoses, particularly when a diagnosis of sarcoidosis has not been established. To confirm an association with sarcoidosis or an alternative diagnosis, directed diagnostic evaluations including biopsy, may be needed. In other situations, a trial of corticosteroid (CS) therapy may be indicated to assess whether there is a clinical response consistent with sarcoidosis.

With rare manifestations of sarcoidosis, a leading concern is whether the specific clinical problem is the result of an alternative, nonsarcoidosis pathological process. The following generalisations on the clinical behaviour of sarcoidosis provide a useful

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starting point to assess *a priori* the likelihood of whether a clinical manifestation may be a result of sarcoidosis or due to an alternative process. First, organ involvement usually defines itself early in the disease regardless of whether the organs involved are commonly or rarely found to be involved in sarcoidosis. For example, only 23% of patients in the A Case Control Etiologic Study of Sarcoidosis (ACCESS) study were found to have one or more new organ systems involved with sarcoidosis during a 2-yr follow-up evaluation; the presence of extrapulmonary involvement at presentation was a risk factor for new organ development [3]. Clinical experience suggests new organ involvement is even rarer after >2 yrs of defined disease. The implication of this clinical observation is that new onset organ involvement that develops years after an initial diagnosis of sarcoidosis must be suspected as having an alternative explanation.

Secondly, >90% of patients with sarcoidosis follow one of two mutually exclusive courses, either remission, generally within the first 2–3 yrs, or a chronic progressive course with progressive organ impairment [1]. Remissions, once they occur, rarely recur (exceptions discussed below). Distinct presentations of sarcoidosis are associated with a different likelihood of these two outcomes. For example, Löfgren's syndrome has a remission rate of 70–80%, whereas patients with lupus pernio or fibrocystic pulmonary sarcoidosis rarely undergo remission [1]. For patients with chronic sarcoidosis, the rate of progression varies from individual to individual, as does their response to treatment. Suppression of inflammation by CS therapy or other anti-inflammatory therapies should not be considered remission, but temporary suppression of the inflammation. If the underlying sarcoidosis inflammation has not undergone remission, the inflammation will return upon tapering or discontinuing therapy, with a variable period of temporary quiescence as the inflammation develops to a critical point where organ function is significantly impaired. Rarely, sarcoidosis follows a remitting-relapsing course usually involving the neurological or ocular systems. The implication of these observations is that new onset symptoms that develop after a period of remission, particularly a prolonged one, should not be attributed to sarcoidosis until alternative explanations are reasonably excluded.

Thirdly, CS therapy is almost always successful in suppressing the inflammation in sarcoidosis, at least over the short term. For visceral sarcoidosis (pulmonary, cardiac, hepatosplenic), there is usually a precisely defined threshold dose of CS therapy that is effective, and this threshold dose rarely changes even after decades of chronic disease. Neurological and ocular sarcoidosis may be exceptions to this generalisation, sometimes with lower CS requirements later in the disease. The implication of these clinical observations is that new symptoms that arise in the context of a patient on a previously effective treatment regimen (assuming compliance is not an issue) must be carefully evaluated for alternative explanations rather than attributed to the emergence of a rare manifestation of sarcoidosis. For example, new pulmonary infiltrates in stable, treated sarcoidosis are more likely to have an alternative explanation, such as infection or pulmonary oedema, than acting as a "flare" of pulmonary sarcoidosis. Clinical manifestations that do not respond to typical CS dosing must also be reconsidered for alternative explanations rather than attributed to a rare manifestation of sarcoidosis.

Although exceptions to the generalisations above occur, these guidelines may help the clinician decide how vigorously to pursue alternative explanations for clinical manifestations that are rarely part of the spectrum of sarcoidosis.

Clinical manifestations

Rare manifestations by organ system

Selected rare clinical manifestations are presented below and summarised in table 1.

Pulmonary sarcoidosis. Findings of pulmonary hypertension or cor pulmonale are seen in 1–4% of patients, usually from severe fibrocystic lung disease. Rarely, a granulomatous pulmonary vasculitis is seen that is not explained by the degree of interstitial disease reflected by chest imaging and severely reduced pulmonary function. Dyspnoea out of proportion to the degree of interstitial pulmonary disease should lead to an evaluation for pulmonary hypertension. Limited experience suggests these patients may benefit from drug therapies used for primary pulmonary hypertension [4]. Cardiac sarcoidosis should also be considered as an explanation for unexplained dyspnoea in sarcoidosis [5].

Unusual patterns of pulmonary involvement include the presence of mycetomas, dominant mass-like nodular sarcoidosis or isolated nodules that raise concern of possible malignancy or infection. Lobar atelectasis is very uncommon in sarcoidosis but may be caused by endobronchial nodules or enlarged adjacent lymph nodes. Superior vena cavae syndrome has rarely been documented to be caused by sarcoidosis [6]. Pleural effusions from direct granulomatous involvement of the pleural surface is rare in sarcoidosis and should prompt evaluation to exclude alternative causes, such as infection, malignancy, pulmonary embolism, or causes of transudative effusions [2].

Necrotising sarcoid granulomatosis. Often considered a variant of sarcoidosis, this rare disease is characterised by large, confluent, noncaseating granulomata involving both pulmonary arteries and veins [7]. Systemic vasculitis is not present. Patients may be asymptomatic or have cough, dyspnoea, fever, chest pain, or constitutional symptoms. Chest radiographs typically demonstrate multiple, usually noncavitating, nodules. Pleural disease with pleurisy or pleural effusions occurs in the majority of patients and may be a clue to the diagnosis. Surprisingly, the prognosis is good with spontaneous remission or a rapid response to CS therapy in many patients.

Sarcoidosis of the upper respiratory tract. Sarcoidosis of the upper respiratory tract (SURT) occurs in 5–10% of patients, usually in those with longstanding disease. Severe nasal congestion and chronic sinusitis are typically unresponsive to decongestants and nasal steroids. Rarely, chronic sinusitis or surgical intervention may result in destruction of the nasal septum and a "saddle nose" deformity. Laryngeal sarcoidosis may manifest with hoarseness, stridor and, rarely, as acute respiratory failure secondary to upper airway obstruction. Sleep apnoea has also rarely been directly attributed to SURT rather than a more common association with weight gain from CS therapy [8]. Often SURT is associated with chronic skin lesions, particularly lupus pernio, and joint involvement, which should prompt careful screening for manifestations of SURT [9].

Oropharyngeal manifestations. Although rare, the oral cavity may be involved in sarcoidosis with severe consequences. Tonsillar or pharyngeal involvement (with mass or cartilaginous destruction) often raises a concern of malignancy. Tongue involvement with mass or macroglossia also raises the possibility of malignancy or amyloidosis unless sarcoidosis is apparent elsewhere. Herefordt syndrome, or "uveoparotid fever", is a well known, but uncommon manifestation of acute sarcoidosis characterised by a pattern of fever, parotid and lacrimal gland enlargement, bilateral hilar adenopathy and, often, uveitis and cranial neuropathies.

The Melkersson-Rosenthal syndrome is a rare entity that causes recurrent or progressive orofacial swelling with lip and plicated tongue enlargement; there is frequent salivary gland involvement and cranial neuropathies, particularly VII nerve palsies [10, 11]. Histopathological findings usually reveal sarcoid-like noncaseating epithelioid granulomas. The cause of this orofacial granulomatosis is unknown but conceivably is a variant of Crohn's disease or sarcoidosis. Case reports suggest intralesional or systemic

Table 1. – Rare manifestations of sarcoidosis based on organ systems

Organ system	Rare clinical features (selected)
Pulmonary	Pulmonary vasculitis
	Mycetomas
	Cavitating nodules
	Lobar atelectasis
	Tracheal, bronchial stenosis
	Superior vena cavae syndrome
	Pleural disease
	Pneumothorax
Upper airway	Saddle nose deformity
	Respiratory failure from upper airway obstruction
	Sleep apnoea
Oropharynx	Tonsillar sarcoidosis
	Pharyngeal sarcoidosis
	Periodontal disease
	Tongue mass
Skin	Subcutaneous sarcoidosis
	Ichthyosis
	Alopecia
	Scar granulomas
Ocular	Optic neuritis
	Retinal vasculitis
	Granulomatous orbital inflammation
Hepatic	Massive hepatomegaly
	Jaundice with pruritis
	Cirrhosis with portal hypertension
	Massive splenomegaly
Gastrointestinal	Pancreatic mass
	Gastric involvement
	Small or large intestine involvement
	Appendicitis
Nervous system	Optic chiasma involvement
	Aseptic meningitis
	Cerebritis (white matter involvement)
	Cerebral vascular occlusion
	Encephalitis
	Hypothalamic/pituitary involvement
	Corpus callosum involvement
	Hydrocephalus
	Horner's syndrome, Argyll Robertson or Adie's pupil
	Cerebellar involvement
	Pseudotumour cerebrei
	Brain stem involvement
	Transverse myelitis, intraspinal mass
	Cauda equina or spinal root involvement
	Mononeuritis multiplex
	Peripheral neuropathies
	Small fibre neuropathy (common?)
Cardiac/vascular	Valvular disease
	Pericardial disease
	Ventricular or atrial mass
	Sudden death (not rare?)
Joints/musculoskeletal	Polymyositis
	Bone cysts: long bones, skull, vertebrae
Haematological	Hypogammaglobulinaemia
	Lymphoedema
	Idiopathic thrombocytopenia purpora
Endocrine/exocrine gland	Heerfordt's syndrome
	Hypopituitarism, diabetes insipidus
	Thyroid mass, thyroiditis

Table 1. Continued

Organ system	Rare clinical features (selected)
	Parotid mass
	Lacrimal gland, dacryoadenitis
	Sicca syndrome
Renal/genitourinary	Renal failure
	Uterine mass
	Ovarian involvement
	Menometrorrhagia
	Testicular mass
	Epididymitis
	Intermittent azoospermia

steroids may be helpful in the initial stages. There are scattered reports of other drugs that are occasionally effective, but the disorder is often resistant to medical therapy; surgical cheiloplasty may be attempted to ameliorate disfigurement.

Chronic cutaneous sarcoidosis. With plaques and subcutaneous nodules affecting the face, particularly around the nose, cheeks and eyes, is termed lupus pernio. Lupus pernio is more common in patients of African descent; it is rare in Caucasians [1]. Less commonly, sarcoidosis may manifest with extensive, deep subcutaneous nodules with oedema, particularly of the lower extremities; the term Darier-Roussy sarcoidosis was earlier used to describe this problem [12]. This sarcoidosis manifestation is often poorly responsive to treatment, though antimalarial drugs, moderate doses of CS, methotrexate or thalidomide may be partially effective.

Granulomatous nodules often develop at sites of previous scars. Rarely, nodules in the skin may develop at sites of tattoos, body piercings or previously punctured sites of the skin or oral mucosa [13]. Other reports document granulomas at sites of silica injections, although the nodules were probably due to sarcoid-like foreign body reaction [14]. More troublesome are reports of sarcoidosis developing in individuals with silicone prostheses [15]. A causal association remains speculative and not supported by larger epidemiological studies, although one report has documented that removal of prostheses was followed by remission of sarcoidosis [16].

Ocular manifestations. Anterior uveitis is the most common eye lesion in sarcoidosis and frequently is the initial presenting manifestation. Rarer ocular manifestations include optic neuritis or retinitis, either of which may present dramatically with blindness (see Chapter 12 of this monograph).

Abdominal manifestations. Hepatic involvement is documented in ~10–20% sarcoidosis patients; rarely granulomatous hepatitis is the sole manifestation of the disease [1, 2]. Active hepatic inflammation may be associated with fever, tender hepatomegaly and pruritus. Granulomatous hepatitis with markedly elevated serum liver function tests *e.g.* >3–5 times normal, usually with an obstructive pattern, may portend a poor prognosis with progressive cirrhosis and portal hypertension if untreated. CS or immunosuppressive therapies are usually effective in preventing progressive hepatic insufficiency in these cases. Methotrexate is usually avoided because of its potential to cause liver toxicity. In rare cases, sarcoidosis may be associated with primary sclerosing cholangitis or primary biliary cirrhosis, diagnosed by the presence of higher titres of specific antimicrosomal or antimitochondrial antibodies. In these instances, the liver disease does not respond to CS therapy.

Abdominal "triad" sarcoidosis. A variant of sarcoidosis, often called abdominal sarcoidosis, manifests with a "triad" of liver, spleen and bone marrow involvement, often

with hypercalcaemia. Although this pattern of involvement may be seen in a patient with multisystem sarcoidosis that includes pulmonary involvement, the greater challenge is for the clinician to recognise this triad syndrome when it is seen without other common manifestations of systemic sarcoidosis. Hepatomegaly, splenomegaly with a moth-eaten radiographic appearance, liver function abnormalities, hypersplenism, abdominal lymphadenopathy, hypercalcaemia and prominent constitutional symptoms are often present. If a diagnosis of systemic sarcoidosis has not been established, usually an intra-abdominal biopsy is needed to exclude malignancy. Granulomas in the liver or bone marrow are nonspecific and should be used to confirm a diagnosis of sarcoidosis only when malignancy or infection are reasonably excluded. If there is associated pulmonary disease or peripheral lymphadenopathy, an intrathoracic or lymph-node biopsy may help confirm a diagnosis of sarcoidosis. Noncaseating granulomas, from a bronchoscopic biopsy, provide confidence in a sarcoidosis diagnosis only when there are no atypical features that favour rigorously excluding malignancy. Abdominal sarcoidosis usually responds to low-to-moderate doses of CS (*e.g.* prednisone 10–20 $mg \cdot day^{-1}$), although side-effects are common and steroid sparing alternatives are often tried.

Symptomatic gastrointestinal involvement in sarcoidosis is unusual. Rarely, direct oesophageal involvement from sarcoidosis may cause dysphagia, but more commonly this symptom is caused by extensive mediastinal lymphadenopathy that impinges on the oesophagus. Gastric sarcoidosis may manifest as dyspepsia or abdominal pain; endoscopic biopsy demonstrates noncaseating granulomas typical of sarcoidosis. The condition usually responds to CS therapy. Alhough autopsy studies show scattered granulomas are often present in the gut in sarcoidosis, clinically symptomatic intestinal sarcoidosis is rare. The presence of a second disorder, such as Crohn's disease, ulcerative colitis or coeliac disease, must be considered in these instances (see later).

Neurosarcoidosis. Neurosarcoidosis can involve any part of the central or peripheral nervous system, together manifesting in ~5–10% of patients with sarcoidosis. Many of its myriad manifestations are rare (discussed in Chapter 11 of this Monograph; table 1).

Cardiac sarcoidosis. Although certain manifestations of cardiac sarcoidosis are rare, the effects may be devastating and should remain high in the differential of patients with a known diagnosis of sarcoidosis (discussed in Chapter 9 of this Monograph; table 1).

Haematological sarcoidosis. Persistent, bulky lymphadenopathy occurs <10% of the time [1, 2]. Splenomegaly, occasionally massive, occurs in <5% of cases and is often associated with hepatomegaly and, occasionally, hypercalcaemia. Nonclonal hypergammaglobulinaemia is present in ≥40–50% of patients. A decrease in the gamma globulin fraction should lead to an evaluation for common variable immunodeficiency (CVID). Pancytopenia may be caused by hypersplenism, or bone marrow infiltration with granulomas. Although peripheral lymphopenia is common, rarely, a profound lymphopenia raises concern of HIV disease. Sarcoidosis is associated with idiopathic thrombocytopenic purpura (ITP) or autoimmune haemolytic anaemia, although this is rare [17]. One report documented the utility of high dose steroids to treat ITP associated with sarcoidosis [18].

Chronic lymphoedema is a rare manifestation of sarcoidosis, usually due to scarring of intra-abdominal or regional lymphatics of the lower extremities from chronic inflammation. This condition is often associated with considerable morbidity and a generally poor response to medical or surgical intervention; early treatment with effective doses of CS or other anti-inflammatory agents is an unproven, but recommended approach to these patients.

Endocrinelexocrine gland. Hypothalamic/pituitary insufficiency is not an uncommon manifestation of neurosarcoidosis. Pituitary apoplexy or diabetes insipidus are rare, potentially life-threatening manifestations of neurosarcoidosis. Rarely, sarcoidosis can involve the thyroid gland, presenting as a nodule, mass or thyroiditis [19, 20]. Sicca symptoms are not uncommon, caused by inflammation of the salivary and parotid glands. STEUER *et al.* [21] reported a case of sarcoidosis presenting after resection of an adrenocortical adenoma. They speculate that the activity of sarcoidosis was suppressed before surgery by the high circulating cortisol concentrations, and was subsequently unmasked by the adrenalectomy. STEUER *et al*. [21] emphasise that this case illustrates the suppressive rather than curative effects of steroids on sarcoidosis.

Renal disease. Renal insufficiency in sarcoidosis is usually caused by nephrocalcinosis or obstructive uropathy from kidney stones. Rarely, direct granulomatous involvement of the kidneys occurs and is a cause of renal failure. Membranous glomerulonephritis has rarely been associated with sarcoidosis, and tends to be steroid responsive. AA amyloidosis has also been reported in association with sarcoidosis with associated proteinuria [22].

Genitourinary involvement. Sarcoidosis involving the genitourinary tract is rare [1]. In males, sarcoidosis of the reproductive system has been estimated to occur in <0.2% of clinically diagnosed cases and 5% in autopsy studies [23]. Genitourinary manifestations of sarcoidosis include testicular masses and acute epididymo-orchitis with testicular swelling. Biopsy is usually indicated to exclude malignancy in patients with testicular mass regardless of *a prior* diagnosis of sarcoidosis. Occasionally, impotentia has been reported, possibly related to sarcoidosis of the central nervous system or small fibre neuropathy [24, 25].

The effects of genitourinary sarcoidosis on fertility and gonadal function have not been examined in detail. REES *et al.* [26] reported a case of bilateral testicular sarcoidosis with azoospermia and hypogonadism in whom high-dose CS therapy resulted in partial recovery of spermatogenesis and gonadal function. SVETEC *et al.* [27] reported a similar case with epididymal sarcoidosis resulting in secondary infertility. Since sarcoidosis may adversely affect fertility without obvious symptoms, these investigators suggest that patients interested in paternity consider a semen analysis at the time of disease diagnosis.

Sarcoidosis of the genitourinary system is also considered to be rare in females; however, the prevalence of sarcoidosis of the uterus or ovary is unknown since involvement of these organs may be nonsymptomatic and a diagnosis is based on histological examination of removed organs. Uterine or ovarian involvement may cause dysmenorrhoea or manifest as a mass that raises concern for tumours; the latter manifestation mandates a biopsy to exclude primary or metastatic tumours [28]. Involvement of the endometrium is rare and can be found in elderly females with post-menopausal metrorrhagia as a focal disease without any other organs effected [29]. Sarcoidosis involving the vagina or vulva has also been reported [30].

In both males and females, documented bladder involvement is rare [31]; more common is the association of localised or systemic granulomas in association with primary genitourinary malignancies.

Pregnancy and sarcoidosis. Clinical experience suggests pregnancy has little effect on the long-term course of sarcoidosis [1, 32, 33]. Spontaneous improvement in chronic sarcoidosis has been found in some patients during pregnancy and a reduction in CS dosing may be possible during this time. However, in these patients, an exacerbation often follows several months following delivery, consistent with a progression of disease activity, and requires a return to a prior maintenance CS dose. Other than CS, there are no

therapies that are considered safe to use during pregnancy because of the potential for foetal toxicity or teratogenicity.

The reasons for clinical improvement in some patients with sarcoidosis who become pregnant are not known. Conceptually, the improvement during pregnancy is consistent with the known shift in balance of cytokine profiles away from T-helper cell (Th) type 1 reactivity to Th2-type reactivity during normal pregnancy [34]. This premise does not only explain why sarcoidosis patients may improve during pregnancy and worsen after delivery, but also provides an explanation for why patients with asthma, a Th2 dominant disorder, are likely to worsen during pregnancy.

Rare associations with enhanced Th1 immunity

There are several clinically disparate situations associated with enhancement of Th1 immunity that are associated with development or recrudescence of sarcoidosis (table 2). These associations provide additional support to the consensus concept that the pathogenesis of sarcoidosis involves highly polarised Th1 immune responses, presumably to unknown tissue antigens [35]. These dominant Th1 responses are characterised by increased production of interferon (IFN)-γ, interleukin (IL)-12, IL-18, and tumour necrosis factor-α at sites of granulomatous inflammation [36].

T-helper cell type 1 promoting agents. The most clear-cut example of this association is the development of sarcoidosis following the use of therapeutics that are known to enhance Th1 immune responses. For example, administration of IFN-α, IFN-γ and IL-2 biological agents have been associated with onset of new or recrudescent sarcoidosis [37]. IFN-β has also been associated with sarcoidosis when used in multiple sclerosis; for this biological agent, both Th1 and Th2 promoting effects of this drug have been described. Since it is likely that other therapeutics with Th1 promoting effects will be employed in the future, physicians should remain suspicious for sarcoidosis developing in patients being treated with new agents with immunomodulatory effects. Although of unproven benefit, discontinuing the specific therapy should be considered, if possible. If there is a compelling reason for continuing the therapy, the sarcoidosis inflammation generally responds to low dose CS therapy or hydroxychloroquine.

Common variable immunodeficiency. There is a well-established association of sarcoidosis with CVID [38, 39]. Although fundamentally a disorder of antibody (B-cell) production, CVID is heterogeneous in its pathogenesis with associated T-cell defects in ~50% of patients [39]. Due to cross-regulation of Th1 and Th2 responses, it is likely that a subset of patients with CVID are characterised by deficient Th2 (antibody-promoting) responses that results in dysregulated, enhanced Th1 immune responses, perhaps a necessary prelude to the development of sarcoidosis in these patients. Poorly formed granulomas in response to infections occur in CVID, particularly the lung, and must be distinguished from the development of systemic sarcoidosis. Systemic sarcoidosis may develop in ~10% of patients with known CVID [38] or, rarely, CVID may be discovered following a diagnosis of sarcoidosis. In children, a diagnosis of CVID usually precedes

Table 2. – T-helper cell type 1 promoting conditions associated with sarcoidosis

Therapy with IFN-α, IL-2, IFN-γ, IFN-β
Common variable immunodeficiency
Immune reconstitution in HIV patients undergoing HAART therapy
Various collagen vascular disorders

IFN: interferon; IL: interleukin; HAART: highly active antiretroviral therapy.

development of sarcoidosis. Sarcoidosis in these children frequently manifests with abdominal involvement with hepatosplenic enlargement or progressive pulmonary infiltrates; the latter require exclusion of infection before a sarcoidosis diagnosis is made. Since sarcoidosis in children is rare, a diagnosis of sarcoidosis in this age group mandates an evaluation to exclude CVID. Since CVID occurs at any age, a high index of suspicion must be maintained for possible CVID in adults with sarcoidosis. Recurrent sinopulmonary infections or a decreased gamma globulin fraction in patients with sarcoidosis may be clues to the diagnosis. Recently, BATES *et al.* [40] described a subset of patients with CVID and granulomatous-lymphocytic interstitial lung disease with histological changes of lymphocytic interstitial pneumonia (LIP), lymphoid hyperplasia or follicular bronchiolitis in association with granulomatous inflammation. This subgroup of patients had a significantly worse prognosis, with a poor response to CS therapy and evolution to lymphoproliferative disease in 31% of patients. This author speculates that this cohort is a distinct subgroup of CVID patients separate from those CVID patients with systemic noncaseating granulomas typical of sarcoidosis and without dominant features of LIP, follicular bronchiolitis or nonspecific interstitial pneumonia.

In all cases, gamma globulin replacement is indicated to reduce the risk of infections and prevent its consequences, such as bronchiectasis and pulmonary fibrosis. In the present author's experience, low-dose CS therapy (prednisone ≤ 10 mg·day^{-1} or equivalent alternate day therapy) or occasionally, hydroxychloroquine alone, is sufficient to treat those patients with CVID and typical sarcoidosis-type systemic inflammation. The treatment of the subset of CVID patients with granulomatous-lymphocytic lung disease is not clear given their poor response to CS and the need to try to avoid immunosuppressive agents because of the underlying immunodeficiency.

Immune reconstitution in HIV patients. A third clinical situation in which sarcoidosis develops in the context of imbalanced immunity involves HIV patients with immune reconstitution following highly active antiretroviral therapy (HAART) [41]. Although it is often difficult to be confident that granulomatous inflammation in the lungs of HIV individuals is not infectious in nature, sarcoidosis associated with HAART has been associated with skin and pulmonary involvement typical for sarcoidosis. CS have been reported to be beneficial in treating sarcoidosis in this clinical situation. In the present author's experience, the combination of hydroxychloroquine plus inhaled steroids for pulmonary involvement has been effective in preventing progressive pulmonary function impairment or skin disease and avoiding the necessity of oral CS therapy in some of these patients. Perhaps success of this minimal treatment regimen is a reflection of the tenuous nature of the enhanced Th1 immune reconstitution found in these individuals.

Rare associations with autoimmune and other chronic inflammatory diseases

Sarcoidosis is rarely associated with a second, distinct autoimmune disease (table 3). The frequency of an individual developing both sarcoidosis and a second autoimmune disorder appears to be higher than by chance alone, supporting a causal association [1, 42]. Conceptually, many of these autoimmune diseases are associated with dysregulated Th1 immunity that would explain at least one common pathogenetic pathway shared between them. Given the considerable overlap in the systemic manifestations of sarcoidosis and many autoimmune disorders, the second disorder may be difficult to diagnose. In general, clues to the presence of an associated autoimmune disease are found by either clinical manifestations that are outside the spectrum of known sarcoidosis, or an unexpected clinical course or response to therapy (from either a sarcoidosis or autoimmune perspective). An example of the former situation is the

Table 3. – Rare associations of sarcoidosis with other systemic and organ-specific diseases

Organ system	Clinical disorder
Pulmonary	Scleroderma
Oropharyngeal	Melkersson-Rosenthal syndrome
Skin	Pyoderma gangrenosum
	Scleroderma
	Porphyria cutanea tarda
	Vitiligo
Ocular	Idiopathic granulomatous orbital inflammation?
Abdominal	Primary sclerosing cholangitis
	Primary biliary cirrhosis
	Coeliac disease
	Crohn's disease
	Ulcerative colitis
Neurological	Progressive multifocal leukoencephalopathy
Joint/musculoskeletal	Rheumatoid arthritis
	Lupus erythematosis
	Scleroderma
	Mixed connective tissue disease and overlap syndromes
	Marfan
Haematological	Common variable immunodeficiency
	HIV with immune reconstitution
	Autoimmune haemolytic anaemia
	Thrombocytopenia
Exocrine gland	Sjögren's syndrome
	Hashimoto thyroiditis
Renal	Membranoproliferative glomerulitis
	Amyloidosis
Systemic diseases	Autoimmune diseases
	Vasculitis
	Granulomatous vasculitis overlap with sarcoidosis
Malignancy	Lymphoma
	GU cancers: renal, testicular, bladder, ovarian, prostate
	Myeloproliferative disorders
	Thyroid cancer

GU: genitourinary.

presence of sclerodactyly or sclerodermatous skin changes indicating scleroderma in a patient with sarcoidosis or, conversely, the presence of intrathoracic lymphadenopathy and widespread noncaseating granulomas in the lungs without an infectious aetiology in a patient with known scleroderma. An example of the latter situation is a sarcoidosis patient with a steroid-unresponsive progression of cholestatic jaundice; the presence of antimitochondrial or antimicrosomal antibodies may point to an association with primary biliary cirrhosis or sclerosing cholangitis. Rheumatoid arthritis or lupus erythematosis may be seen with sarcoidosis but require typical clinical manifestations and high titre rheumatoid factor or antinuclear antibody (ANA)s since low titres of rheumatoid factor or ANA are commonly seen in sarcoidosis without clinical features of these autoimmune disorders. One study has found evidence for endocrine autoimmunity in 19% of patients with sarcoidosis [43].

One rare disease association to note is that of sarcoidosis and Crohn's disease or ulcerative colitis [44, 45]. The presence of typical endoscopic findings for these latter disorders usually allows an unequivocal diagnosis in the presence of systemic sarcoidosis. Conversely, although Crohn's disease can be associated with modestly enlarged peripheral or intrathoracic lymphadenopathy and a lymphocytic alveolitis, the presence of extensive pulmonary infiltrates and intrathoracic lymphadenopathy with typical epithelioid granulomas on biopsy provides evidence for systemic sarcoidosis. In the present author's

experience, when sarcoidosis is seen together with Crohn's disease or ulcerative colitis, the two diseases tend to follow independent courses and response to therapy is characteristic for each disorder. The same is also true for autoimmune diseases, such as scleroderma.

Coeliac disease may also be associated with sarcoidosis. Irish investigators found a higher prevalence of coeliac disease in their patients with sarcoidosis, leading them to recommend screening their sarcoidosis population for this disorder [46]. In Sweden, PAPADOPOULOS *et al.* [47] demonstrated gastric autoimmunity and gluten-associated immune reactivity in almost 40% of patients with sarcoidosis with the former being the most frequent gastrointestinal immune manifestation [47]. However, despite this high frequency of humoral autoimmunity, the frequencies of clinical pernicious anaemia or coeliac disease were not increased compared with a control population.

Rare associations with cancer

Noncaseating granulomas may be seen in or nearby tumours and, less frequently, in regional draining lymph nodes. These local sarcoid reactions have been most commonly reported in lymphomas, breast cancer, primary lung cancer, renal cell, ovarian and stomach cancers. Fungal or mycobacterial infection, foreign body or other causes of local granulomas must be excluded. Local sarcoidosis reactions are defined by their limited distribution. Much less commonly, multiorgan granulomas consistent with systemic sarcoidosis develop simultaneously or shortly following the development of cancer or following chemotherapy [48, 49]. The most well-established associations are with lymphoma or testicular cancer. Less commonly, primary lung cancer, uterine, ovarian, breast or liver cancer or myelogenous leukemia is seen with sarcoidosis, though the coexistence of these disorders could be due to chance occurrences. In the situations above, sarcoidosis usually presents with mediastinal or hilar lymphadenopathy or occasionally with pulmonary interstitial nodules or infiltrates. Both the primary malignancy and associated granulomatous nodules from sarcoidosis may demonstrate 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scanning (fig. 1). In these instances, a diagnosis of sarcoidosis is usually established by mediastinal lymph node or open lung biopsy because of the concern of recurrent malignancy (or associated granulomatous infections). In the current author's experience, there is usually little functional lung impairment from pulmonary sarcoidosis in these instances, and treatment is often unnecessary with eventual remission. Although the link between certain cancers, cancer chemotherapy and sarcoidosis remain controversial, it is plausible that the basis for these associations is due to dysregulated Th1/Th2 immunity in these situations. Consistent with this premise, several cases of sarcoidosis and 5q-myelodysplasia have been reported; this chromosomal abnormality results in deletion of several Th2 genes (IL-4, IL-13, CSF2) that probably profoundly affect Th1/Th2 regulation [50].

Rare manifestations from late recurrence of sarcoidosis

A widely held view is that once sarcoidosis undergoes remission, the disease rarely recurs. The exceptions to this "rule" often involve ocular or neurological sarcoidosis, which uncommonly follows a remitting–relapsing course. The present author has seen several cases of late onset neurological involvement, particularly cranial neuropathies that develop suddenly, many years, even decades, following disease remission. Eighth nerve involvement with hearing loss, tinnitus or balance problems may be most common, but other cranial nerves also may be affected. Direct confirmation that the underlying cause is due to sarcoidosis is often lacking because of possible alternatives, such as diabetes or cerebral vascular disease. Nonetheless, some patients respond to CS therapy

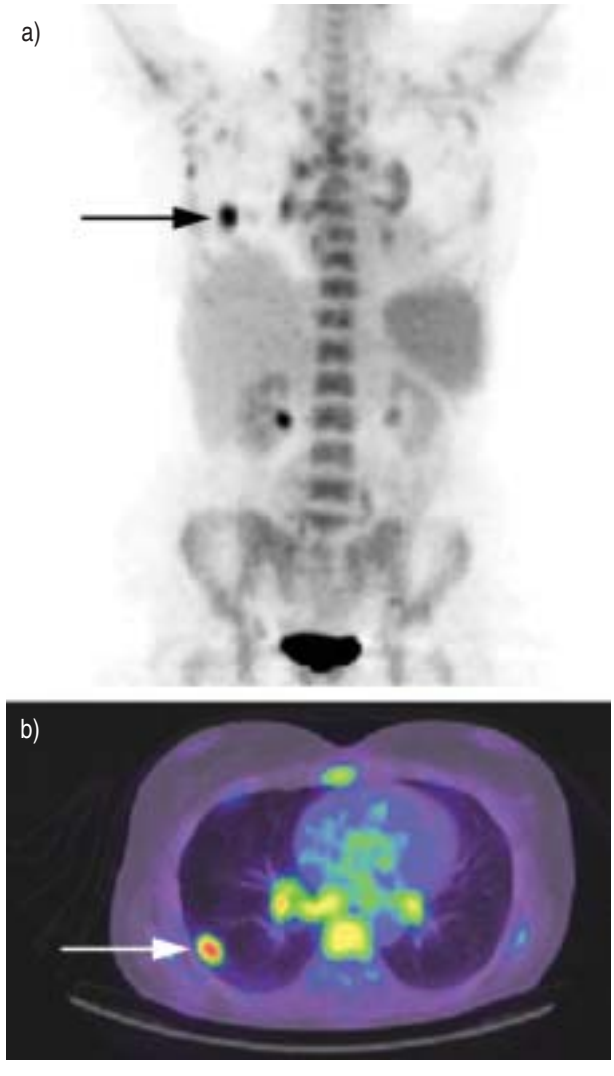

Fig. 1. – a) A three-dimensional reconstruction of a corrected positron emission tomography scan from a patient with a pathologically proven primary lung cancer in the right lower lobe (arrow) and multiple lesions with increased uptake of 18F-2-fluoro-2-deoxglucose from granulomatous lesions consistent with sarcoidosis. b) A high-resolution computed tomography scan of the same patient. This 52-yr-old female was suffering from sarcoidosis-related complaints with fever, weight loss, arthralgias and fatigue for 2 months. The patient had a successful lobectomy; the sarcoidosis was monitored without treatment. Scans appear courtesy of M. Drent (Sarcoidosis Management Centre, University Hospital Maastricht, The Netherlands) and M.J.P.G. van Kroonenburgh (Dept of Nuclear Medicine, University Hospital Maastricht, The Netherlands).

if begun soon after symptom onset, consistent with recurrent sarcoidosis. Recurrent erythema nodosum as part of recurrent Löfgren's syndrome has also been described [51]. Late recrudescence of pulmonary or other visceral involvement from sarcoidosis remain rare and are the topic of few medical reports except when associated with special circumstances, such as following chemotherapy for cancer or the use of Th1 promoting agents. Given the rarity of recurrent sarcoidosis, alternative processes must always be considered before attributing the cause to sarcoidosis.

Approach to diagnosis of rare manifestations

The approach to rare manifestations of sarcoidosis differs depending on whether a diagnosis of systemic sarcoidosis has been established or not. There is no pathognomonic histopathology for sarcoidosis; a diagnosis is based on a compatible clinical picture, histological evidence of noncaseating granulomas and the absence of other known causes of this pathological response [1]. When a clinical manifestation that is rarely associated with sarcoidosis is encountered, patients with a confident diagnosis of systemic sarcoidosis (confirmed by biopsy) may be approached by the following strategy. 1) Evaluate the likelihood that the rare manifestation is a result of sarcoidosis. In this case, a search of the medical literature is often helpful to substantiate a previously documented rare association with sarcoidosis [52]. 2) Assess the risk of waiting for a response to treatment that is indicated based on either systemic sarcoidosis or the specific rare manifestation. If the rare manifestation is known to occur in sarcoidosis, and the risk of missing an alternative diagnosis, such as malignancy or superimposed infection is low, a treatment trial is usually indicated. For example, scattered periventricular enhancing brain lesions on magnetic resonance imaging (MRI) in a patient with a recent diagnosis of systemic sarcoidosis might be treated empirically if cerebral spinal fluid examination reveals no evidence for malignancy or infection. Clinicians must always be willing to re-evaluate for alternative explanations if there is not a prompt response to therapy expected for sarcoidosis. Physicians must maintain a high index of suspicion for nonsarcoidosis diagnoses particularly when new manifestations develop after years of disease, after clinical remission, or in the context of stable treated sarcoidosis.

If a clinical manifestation deviates from that seen in sarcoidosis, or defining an alternative diagnosis cannot be delayed, a more definitive diagnostic approach is indicated. In this situation, directed biopsy of the involved tissue should be considered, even when there is documentation of a prior biopsy that confirmed an original diagnosis of sarcoidosis. For example, the development of an isolated nodular infiltrate or mass in a prior smoker with a history of pulmonary sarcoidosis and a stage I chest radiograph should prompt a recommendation to biopsy to exclude primary lung cancer.

In clinical circumstances in which a diagnosis of systemic sarcoidosis has not been established, a direct diagnostic approach to the rare manifestation must usually be undertaken to exclude competing causes. This situation frequently occurs when evidence for multiorgan involvement is lacking. For example, a meningeal tumour, intraspinal mass, large or asymmetric intrathoracic or abdominal lymphadenopathy warrants direct surgical biopsy to exclude malignancy though sarcoidosis may be in the differential diagnosis. Patients with sarcoidosis in the differential diagnosis should also undergo evaluation for systemic sarcoidosis that may provide a safer biopsy approach, if confirmation of a sarcoidosis diagnosis will obviate the need for a more difficult biopsy procedure. Imaging techniques, such as gallium scan or more recently, FDG-PET scanning, may be helpful in these instances to help define sites of clinically occult inflammation that might provide an alternative diagnostic approach. Laboratory tests are not helpful in confirming a rare manifestation of sarcoidosis but may assist in establishing an alternative diagnosis.

Therapeutic trial

A biopsy to confirm a rare association with sarcoidosis may not be attempted for several reasons: 1) inaccessibility of an involved site; 2) undue morbidity that might be associated with a directed biopsy procedure; or 3) patient refusal. In these situations, a trial of CS should be considered. A treatment trial to assist in the determination of whether a clinical problem is a manifestation of sarcoidosis should use CS as the most reliably effective drug

and the only therapy known to rapidly suppress the granulomatous inflammation. Possibly, infliximab also may affect a rapid response, but experience to date is limited.

The keys to an effective therapeutic trial are the following: determine objective measures by which response will be measured; use an effective dose for the organ/tissue involved; and use an adequate length of time. High doses of corticosteroids may acutely reduce oedema, but the underlying granulomatous inflammation typically takes weeks, even months, for maximal suppression. Thus, a trial of CS should generally continue for $\geq$2–3 months before concluding whether the manifestation is treatment responsive. Depending on the organ/system involved, there is often a minimally effective dose that is required for suppression of the granulomatous inflammation. For example, to assess reversibility in possible cardiac sarcoidosis or pulmonary hypertension from granulomatous pulmonary vascular disease, prednisone 20–30 $mg \cdot day^{-1}$ is usually sufficient for a therapeutic trial dose. Intractable cardiac arrhythmias usually warrant a higher CS dose. Abdominal sarcoidosis typically responds to prednisone 15–20 $mg \cdot day^{-1}$. Higher doses may provide additional confidence in assessing potential responsiveness, but may not be necessary, as long as the length of the trial is adequate. None of these anecdotal observations has been substantiated by clinical trials. Functional response to adequate CS therapy usually undergoes a logarithmic improvement that plateaus in weeks to months, but the final level of improvement will be dependent on the amount of fibrosis or irreversible tissue damage that is present before the trial is started. In patients with extensive fibrosis there may be little functional improvement; response to treatment in these instances may be assessed by stability of disease in patients who previously had documented progressive decline in organ function, *e.g.* as in pulmonary, cardiac or hepatic sarcoidosis.

Treatment

CS are the cornerstone of therapy for rare manifestations of sarcoidosis given their overall reliability in acutely providing symptomatic relief and reversing organ dysfunction in almost all patients with active inflammation. Guidelines for the use and dosing of CS have been largely based on clinical experience with few well-controlled clinical trials, and controversy exists regarding their overall effectiveness in altering the long-term course of the disease. Nonetheless, a consensus view is that these drugs should be used for the initial treatment of serious, organ-threatening or life-threatening manifestations of sarcoidosis, whether the manifestations are rare or common [1]. The antimalarial drugs, hydroxychloroquine and chloroquine, may be useful as first-line drugs for dominant skin, nasal mucosal and sinus sarcoidosis, but have not been consistently effective for pulmonary or systemic disease. Hypercalcaemia, laryngeal, bone and joint involvement have been reported to respond to either hydroxychloroquine or chloroquine. Given the overall safety of these drugs and their lack of immunosuppression, these drugs are frequently tried as steroid-sparing or replacing drugs for nonlife-threatening sarcoidosis. The indications for the use of immunosuppressive therapies and other CS-sparing drugs for more serious manifestations in those with chronic sarcoidosis are discussed elsewhere in this Monograph.

Conclusions

Rare manifestations of sarcoidosis involve unusual patterns of multi-organ involvement or specific organs uncommonly affected in sarcoidosis. These rare

manifestations reflect a pathophysiology and behaviour similar to commonly recognised clinical manifestations of sarcoidosis.

Rare cases of sarcoidosis are associated with Th1 promoting biological agents, common variable immunodeficiency or HIV patients with immune reconstitution, situations that may reflect dysregulated Th1 immunity in sarcoidosis. Sarcoidosis may rarely be associated with a second disorder, such as autoimmune disease or cancer.

A literature search by internet search engines should be utilised to determine whether unexpected manifestations have been previously reported for sarcoidosis. In patients with a confirmed diagnosis of sarcoidosis, a treatment trial for rare manifestations is often justified if the risk of missing an alternative diagnosis is low. If a diagnosis of systemic sarcoidosis has not been established, a directed biopsy approach to the rare manifestation is usually needed to exclude competing causes. Imaging techniques, such as gallium or PET scanning or MRI, may provide evidence for a pathological process but are nonspecific.

A CS trial to treat or confirm a link to sarcoidosis requires an adequate dose and duration to assess responsiveness; re-evaluation for alternative explanations is indicated if there is not a prompt response to therapy expected for sarcoidosis.

Summary

Although most sarcoidosis patients develop manifestations within a clinical framework typical for sarcoidosis, a small number of patients develop unusual manifestations that challenge clinicians to diagnose and establish treatment for these problems. These rare manifestations are usually the result of either an uncommon pattern of systemic involvement or granulomatous inflammation developing in an unusual location for sarcoidosis. Despite being rarely seen, these clinical manifestations reflect the same underlying pathophysiological mechanisms and clinical behaviour common to more easily recognisable systemic sarcoidosis. Similarly, the known T-helper cell type 1 (Th1) polarisation in sarcoidosis provides the clinician with a reminder that Th1-promoting therapeutics, such as interferon-α, common variable immunodeficiency or immune reconstitution in HIV patients, are associated with development of sarcoidosis. Sarcoidosis may also be associated with autoimmune disease or cancer, although this is rare.

An approach to sarcoidosis patients with possible rare manifestations must be individualised according to whether a diagnosis of sarcoidosis has already been established or not. As an initial step, an internet search may substantiate previous experience with similar manifestations. The clinician will often need to: 1) recommend additional diagnostic testing or biopsy, unless there is already biopsy-proven systemic sarcoidosis; and 2) check the rare manifestation is consistent with sarcoidosis and that the chance of an alternative diagnosis is low. In this latter situation, the clinician may recommend a trial of corticosteroid treatment to support an association with sarcoidosis. In patients without a confirmed diagnosis of sarcoidosis, a directed evaluation with biopsy is usually indicated.

In all situations, the clinician must remain vigilant that unusual manifestations of sarcoidosis may, in fact, represent an alternative condition. Although the diagnostic approach to rare manifestations must be individualised, the patient and clinician are usually rewarded by establishing a link to sarcoidosis so that treatment specific to sarcoidosis can be tailored for maximal benefit.

Keywords: Autoimmunity, sarcoidosis, T-helper cell type 1 immunity.

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