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Granulomatous disease: Distinguishing primary antibody disease from sarcoidosis

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Keywords

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Introduction

Common variable immunodeficiency disorders (CVIDs) are the commonest form of symptomatic primary immunodeficiency. We describe four patients who were initially misdiagnosed with sarcoidosis but later found to have CVIDs. Failure to diagnose CVIDs may have serious consequences, as antibody failure may result in recurrent bacterial infections and life-threatening pneumonia with associated bronchiectasis. In addition, conventional immunosuppressive treatment for sarcoidosis may be detrimental in this setting.

The purpose of highlighting this dilemma is to examine the differences in clinical features associated with each disease and to consider how management differs once the diagnosis of antibody deficiency is reached.

Clinical cases

Case 1

A 43 year-old male non-smoker presented with a non-productive cough. Examination revealed cervical lymphadenopathy and parotid enlargement. Chest X-ray (CXR) was normal and lymph node biopsy demonstrated non-caseating granulomata; a diagnosis of sarcoidosis was made. Steroid therapy was not indicated.

Sixteen years later, the patient required three courses of antibiotics for recurrent pneumonia within one year. He had a previous history of recurrent sinusitis and herpes infections occurring after the diagnosis of sarcoid was made.

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Computed Tomography (CT) revealed ground-glass opacification of the lungs with sub-pleural scarring and septal thickening. There was also widespread abdominal lymphadenopathy and splenomegaly. In view of the history of infection, immunoglobulin levels were measured, revealing low concentrations of all three major isotypes (IgG 2.6 g/L [NR 6.0–13.0], IgA 0.15 g/L [NR 0.8–3.0] and IgM 0.3 g/L [NR 0.4–2.5]). A diagnosis of a CVID was made, and immunoglobulin replacement therapy was commenced. He has not had any autoimmune features (Table 1).

Case 2

A 46 year-old lady was diagnosed with sarcoidosis following a six-month history of lethargy, weight loss and anorexia. CXR showed diffuse reticular shadowing and high resolution CT confirmed extensive interstitial thickening with nodules and lymphadenopathy. She also had renal impairment (urea 14.7 mmol/L [NR 2.5–6.7], creatinine 469 µmol/L [70–150]), hypercalcemia (calcium 3.64 mmol/L [2.12–2.62]) and an elevated serum angiotensin converting enzyme (ACE) level (303, NR 8–52). Renal ultrasound demonstrated bilateral hydronephrosis secondary to lymphadenopathy. Biopsy of an axillary lymph node confirmed multiple non-caseating granulomata (Fig. 1). Prednisolone was commenced and bilateral ureteric stents were inserted, with subsequent improvement of renal function. However, the patient subsequently developed Cushingoid features and cataracts, secondary to steroid therapy.

At the time of her diagnosis of sarcoid, total protein was low at 51 g/L (normal range 65–80 g/L); albumin was normal (35 g/L), implying a low globulin fraction. A past history of recurrent otitis media and lower respiratory tract infections predated the diagnosis of sarcoidosis. Of interest, she had been immunized against rubella in her first pregnancy 13 years previously, but had needed re-immunization following the finding that there was no immunity to rubella. There was also a history of hypothyroidism, chronic uveitis and psoriasis. Subsequent measurement of immunoglobulins at the time of her diagnosis of sarcoid revealed a decreased level of IgG<2.0 g/L (6–16) and IgA<0.4 g/L (0.8–2.8) with a normal IgM of 0.7 g/L (0.5–2.0).

The history of recurrent infections with autoimmune diseases suggested a unifying diagnosis of a CVID. This diagnosis was confirmed by low serum immunoglobulin levels and poor specific antibodies. Steroid therapy was gradually discontinued and intravenous immunoglobulin was commenced.

Case 3

A 35 year-old female non-smoker presented with a six-month history of exertional breathlessness, paroxysmal cough, fatigue, weight loss and anorexia. CXR and CT showed widespread nodules throughout both lung fields, with pre-tracheal and hilar lymphadenopathy. Transbronchial biopsy demonstrated non-necrotising epithelioid and giant cell granulomata. Stains for acid-fast bacilli and fungi were negative. A diagnosis of sarcoidosis was made and steroids were commenced. Immunoglobulin levels were not measured at this time.

Past medical history included erythema nodosum (aged 22), immune thrombocytopenic purpura (aged 25) and a severe episode of chicken pox (aged 34).

Despite initial improvement with steroids, the patient continued to experience recurrent bacterial infections of the urinary tract and the upper and lower respiratory tracts, requiring up to 10 courses of antibiotic treatment per year. Immunoglobulin levels were checked and found to be low with IgG<4.4 g/L, IgA<0.9 g/L and IgM<0.3 g/L. Humoral immune responses to Pneumovax® and *Haemophilus influenzae* type b polysaccharide vaccine were absent. A

diagnosis of a CVID was established and immunoglobulin therapy was commenced. Subsequently bronchiectasis was noted on CT scanning.

Case 4

A 19 year-old male presented with weight loss, fatigue, breathlessness, mediastinal lymphadenopathy and hepatosplenomegaly. His past medical history included autoimmune thyrotoxicosis, and recurrent respiratory tract infections in childhood and teenage years. CXR showed reticular shadowing at the left base, and a Kveim test was positive. A diagnosis of sarcoidosis was made. Immunoglobulin levels were not measured at this time.

Six years later, he presented with breathlessness and pleuritic pain, accompanied by a pleural effusion; this was found to be due to bacterial infection. Immunoglobulin levels were measured and revealed a decreased level of IgG < 0.2 g/L and IgA 0.5 g/L with a normal IgM of 0.7 g/L. A diagnosis of a CVID was made and intravenous immunoglobulin was commenced, resulting in resolution of all symptoms and splenomegaly over one year.

Comments from Dr Dilani Arnold, Dr Siraj Misbah and Dr Helen Chapel

We describe four patients who were initially diagnosed with sarcoidosis and managed accordingly, but who were subsequently found to have CVIDs between 3 and 16 years later.

Common variable immunodeficiency disorders (CVIDs) comprise a heterogeneous group of disorders characterized by primary antibody production failure, low serum immunoglobulin levels and susceptibility to recurrent infections [1]. CVIDs account for about 90% of symptomatic antibody deficiencies and may present at any age [2]. The estimated prevalence is 1:10,000 though the true prevalence of CVIDs is likely to be higher, as many cases remain undiagnosed or are misdiagnosed.

The primary abnormality in CVIDs is deficient production of IgG and IgA and may be accompanied by reduced serum IgM concentrations [1]. The inability to make specific antibodies in response to antigens predisposes to bacterial infections, especially with common encapsulated organisms. The most frequent presentation is with recurrent respiratory tract infections (sinusitis, otitis media, bronchitis and pneumonia) [2]. Chronic sepsis of the upper and lower respiratory tracts may lead to chronic otitis media, deafness, bronchiectasis, pulmonary fibrosis and ultimately cor pulmonale. CVIDs may also predispose to gastrointestinal infection and be associated with malabsorption [3]. Approximately 30% of CVID patients have splenomegaly and 12% have arthropathy. About 15% present with or develop autoimmune phenomena such as haemolytic anaemia, immune thrombocytopenia, thyroid disease or gluten-insensitive enteropathy [2], as was apparent in three of our cases.

Some patients with CVIDs exhibit a sarcoid-like presentation comprising breathlessness and persistent cough [4]. Systemic symptoms such as fatigue, weight loss and fever may also occur. As in sarcoid, arthralgia, hepatosplenomegaly and lymphadenopathy are also prominent and clinically, there may be difficulty in distinguishing the two conditions [5,6]. Granulomatous disease can affect the same organs in both diseases. However, in the literature, there do not appear to be any reported cases of granulomatous disease affecting the heart in CVIDs, but cardiac sarcoidosis is reported [7]. The aetiology of granulomata in either situation remains unknown. However, unlike sarcoidosis, a key feature of CVIDs is the prior history of recurrent infections. In our case series, three patients had a history of significant recurrent infection that predated their index presentation (cases 2, 3, and 4).

The early diagnosis of a CVID will facilitate early management and follow up by a specialist familiar with immune deficiencies. The use of intravenous immunoglobulin therapy has been

demonstrated to reduce significantly both the frequency and severity of infection in these patients,[8] so the long-term complications of severe infection and consequent end-organ damage may be averted. Conversely, a misdiagnosis of sarcoidosis in patients with a CVID and the inappropriate use of steroid therapy may result in the long-term complications of steroid therapy (as seen in case 2). Awareness of this presentation of a CVID facilitates early diagnosis and therefore infection prevention with immunoglobulin therapy, obviating structural damage.

Lymphoid interstitial pneumonitis is another unusual but recognized complication of CVIDs. Both CVIDs and sarcoidosis may present with deteriorating lung function, including reduced gas transfer and restrictive changes on pulmonary function testing. Radiological features of both conditions include hilar adenopathy, pulmonary fibrosis, interstitial changes and nodules on CXR and CT [9]. Thus a distinction cannot reliably be made using radiological or functional features alone.

Similarly, the histological appearances of both conditions may be indistinguishable, with the characteristic appearance of non-caseating granulomata. The exact cause of granulomatous disease in patients with CVIDs is yet to be established. However, it has been suggested that elevated levels of TNF may be involved in the development of granulomata in these patients [10].

Traditionally, the measurement of serum ACE levels had been used in the diagnosis of sarcoidosis. However, this test lacks specificity and elevated levels of ACE are commonly seen in many other conditions, including several unrelated granulomatous diseases such as pulmonary tuberculosis, asbestosis and silicosis as well as sometimes (but not always) granulomatous CVIDs. The elevated serum ACE level in case 2 was used to support the diagnosis of sarcoidosis, resulting in a delay in the diagnosis of a CVID.

Historically, the Kveim test was used in making a definitive diagnosis of sarcoidosis. In case 4, a positive Kveim test was taken to confirm the diagnosis of sarcoid. However, this test is not specific for sarcoidosis and is no longer available in routine clinical practice.

The measurement of serum immunoglobulins is beneficial in distinguishing between sarcoidosis from a CVID, though radiological, histological and biochemical techniques are not necessarily useful. Low immunoglobulin levels are universal in CVIDs but polyclonal hypergammaglobulinaemia is typically found in sarcoidosis. Individuals with CVIDs also lack the ability to produce specific antibodies to the antigens (such as those of pneumococci, haemophilus and tetanus toxoid) and demonstration of failure to produce these antibodies confirms a diagnosis of a CVID.

In conclusion, patients with CVIDs may present with a sarcoid-like syndrome. Although their clinical presentation and histological appearances may be identical, the management of these two conditions is very different. Our cases highlight the diagnostic difficulties inherent in distinguishing between sarcoidosis and a CVID and underline the importance of both a screening history for recurrent infections and the measurement of serum immunoglobulins when faced with a diagnosis of possible sarcoidosis.

Comments from Dr. John Wiggins

Several granulomatous diseases present to chest physicians in a range of guises. By far the commonest in the UK are tuberculosis and sarcoidosis. These diseases are often thought to be easy to distinguish since sarcoidosis includes the well-characterized clinical features of hilar lymphadenopathy, erythema nodosum and uveitis. Looking at these four cases, it is understandable why the initial diagnosis was sarcoidosis, especially as CVIDs are relatively uncommon in respiratory practice and therefore chest physicians may be unaware of these

conditions. The publication of these cases is timely, to remind non-immunologists of the unusual presentation of these patients with treatable immune defects.

In case 1, involvement of the parotid gland, together with lymphadenopathy showing granulomata on biopsy was entirely consistent with sarcoidosis. In this case, recurrence after an interval of 16 years is familiar to chest physicians as a late relapse, although these affect <5% of patients [11]. However, the occurrence of new symptoms at the second presentation may suggest an alternative diagnosis. Measurement of the serum immunoglobulins pointed to the diagnosis of a CVID.

In retrospect in case 2, the early symptoms of recurrent infections may have indicated a diagnosis of a CVID, although the abnormal chest imaging, renal impairment, hypercalcemia and raised ACE are strong pointers to a diagnosis of sarcoidosis. Again sarcoidosis was supported by the result of the lymph node biopsy, and most chest physicians would agree that this presentation warranted oral glucocorticoid therapy. However, serum ACE levels are non-specific and low globulin levels would not occur in sarcoidosis, since these patients present with a polyclonal increase in immunoglobulin levels.

Case 3 is unusual in that this patient had immune thrombocytopenic purpura, an autoimmune disease that can be seen in up to 10% of patients with CVIDs [2]. Failure of sarcoid lesions to respond to oral glucocorticoids is uncommon [11]. Bronchiectasis due to sarcoid-related parenchymal scarring would be unlikely after only six months [11]. Measurement of serum immunoglobulin levels changed the diagnostic emphasis and led to the correct diagnosis.

In case 4, the presentation was again consistent with sarcoidosis from the chest physician's viewpoint, though the presence of autoimmunity as well as recurrent chest infections suggested an alternative diagnosis. In the past the Kveim test was historically valuable as it was non-invasive (compared to an intrathoracic lymph node or liver biopsy that might have been considered in this case) although this was also fairly non-specific. However, new symptoms after a number of years, in particular a pleural effusion, suggested an alternative diagnosis which was confirmed following measurement of immunoglobulin levels.

In summary, all four cases had presentations that were consistent with sarcoidosis; with supporting histology, such a diagnosis could readily be accepted by a chest physician. However, cases 2, 3 and 4 all had a significant history of recurrent infections, which is not typical of sarcoid. Autoimmune diseases were also present in cases 2 and 3, in keeping with CVIDs. In these 4 cases, the diagnosis of a CVID came to light when measurement of serum immunoglobulin levels was carried out. An unusual feature in two of the cases was the long gap (16 years in one case) between the initial diagnosis of sarcoidosis and the appearance of 'new' symptoms. The commonality of clinical features between these two disorders (see Table 1), of which chest physicians may be unaware, raises the possibility that a number of patients with undiagnosed CVIDs may be attending sarcoidosis clinics.

The aetiology of both diseases is unknown and although the association between the two disorders is documented, the precise relationship remains poorly understood. Both may represent a similar immunopathogenesis in terms of cytokines, such as TNF provoking granulomata, but the underlying cause in each case may be very different.

From the chest physician's viewpoint, perhaps the simplest message is to measure immunoglobulin levels routinely in all patients with features suggesting sarcoidosis. Indeed this inexpensive test may be more useful than many of the 'routine' investigations done in these patients. Furthermore such measurements should be regarded as mandatory in any patient with 'established sarcoidosis' who then developed unexplained infections, autoimmunity or other unusual clinical features.

Comments from Dr Charlotte Cunningham-Rundles

Arnold et al report a group of four patients who had pulmonary and/or lymph node granulomata, and were diagnosed as having sarcoidosis, delaying the discovery of underlying immune deficiency for years. In each case, there were significant clinical indicators indicative of immune deficiency, including significant and recurrent bacterial infections, lack of an expected antibody response, immune thrombocytopenia and a case of chicken pox as an adult. Granulomata in CVIDs occur in lungs, lymph nodes, liver, spleen, bone marrow, brain, skin, kidneys and other organs, in between 8 to 20% of subjects with this immune defect [2]. The cause of this tissue reaction has not been well understood, but is associated with autoimmunity, lung and organ damage and clearly shortened survival [12].

Unfortunately the presence of granulomata, as one of the cardinal manifestations of CVIDs, continues to be unknown to many clinicians and even pulmonologists, although a number of cases and reviews of this association have been published over the years. Standard textbooks of medicine and pulmonary disease and commonly used Web based tools such as Up-to-Date, do not include CVIDs as a diagnostic consideration when granulomata are found on biopsy. Once the diagnosis of sarcoidosis is made, other diagnostic considerations are not likely to be entertained. Fasano et al. [4] noted a delay of 3 to 19 years before CVIDs was diagnosed in such subjects; Mechanic et al. [5] reported a delay of 2 to 17 years, similar to cases 1, 2 and 3 here, each of whom had clinical characteristics of immune deficiency for more than a decade before the CVID was diagnosed. As Arnold et al point out, while the usual diagnostic tests associated with sarcoidosis (hypercalcemia, increased ACE and a positive Kveim test) are not helpful as they may be found in subjects with CVIDs, the presence of low serum immunoglobulin levels and lack of protective antibody rapidly provides the correct diagnosis. When sarcoidosis is diagnosed and steroids given, additional morbidity is likely, as this leads to adverse effects (as in case 2) and further immune suppression. However, after CVIDs are recognized and appropriate therapy with immune globulin initiated, clinical improvement can be expected, as in the cases reported here.

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Figure 1.
Hematoxylin and Eosin stained histological specimen from case 2 demonstrating the presence of granulomata with multinucleated macrophages (giant cells) within an axillary lymph node.

Table 1
Comparison of clinical, radiological, histological and laboratory features in CVIDs and sarcoidosis

Features	Case 1	Case 2	Case 3	Case 4	Sarcoid ^a	CVIDs ^b
<i>Cough</i>	+	–	+	–	60%	90%
<i>Dyspnoea</i>	–	–	+	+	60%	Very rare
<i>Weight loss</i>	–	+	+	+	60%	Uncommon
<i>Fatigue</i>					Common	Common
<i>Splenomegaly on ultrasound</i>	–	–	+	+	15%	30%
<i>Hepatomegaly on ultrasound</i>	–	–	–	+	5%	Low prevalence
<i>Lymphadenopathy</i>	+	+	+	+	90%	
<i>Autoimmune disease</i>	–	Hypothyroidism	Erythema nodosum	ITP	–	
<i>Uveitis</i>	–	+	–	–	65%	Rare
<i>Skin involvement</i>					20–35%	Unusual
<i>Erythema nodosum</i>					10%	–
<i>Recurrent infections</i>	+	+	+	+	–	100%
<i>Radiological features of sarcoid</i>	+	+	+	+	Bilateral hilar lymphadenopathy	Bronchiectasis or normal
<i>Restrictive changes on pulmonary function tests</i>	+	+	+	+	80%	Rare
<i>Granulomata on biopsy</i>	+	+	+	+	100%	Only in granulomatous phenotype
<i>Raised ACE levels</i>					60%	Not done
<i>Serum immunoglobulin levels</i>	+	+	+	+	Polyclonal increase in IgG and IgA	IgG and IgA well below the lower limit of normal
<i>Primary antibody failure</i>	+	+	+	+	–	Demonstrably low specific antibodies

^aData from reference [5].

^bData from reference [10].