Sarcoidosis succumbs to antibiotics—implications for autoimmune disease

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Abstract

From time to time there have been reports of autoimmune disease succumbing to tetracycline antibiotics, but many have assumed this was due to coincidence, or to some ill-defined ‘anti-inflammatory property’ of the tetracyclines. But now the inflammation of sarcoidosis has succumbed to antibiotics in two independent studies. This review examines the cell wall deficient (antibiotic resistant) bacteria which have been found in tissue from patients with sarcoidosis. It examines how such bacteria can infect the phagocytes of the immune system, and how they may therefore be responsible for not only sarcoid inflammation, but also for other autoimmune disease. Proof positive of a bacterial pathogenesis for Sarcoidosis includes not only the demonstrated ability of these studies to put the disease into remission, but also the severity of Jarisch-Herxheimer shock resulting from endotoxin release as the microbes are killed. Studies delineating the hormone responsible for phagocyte differentiation in the Th1 immune response, 1,25-dihydroxyvitamin D, are discussed, and its utility as a marker of Th1 immune inflammation is reviewed. Finally, data showing that the behavior of this hormone is also aberrant in rheumatoid arthritis, systemic lupus erythematosus, and Parkinson’s, raise the possibility that these diseases may also have a CWD bacterial pathogenesis.

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1. Sarcoidosis and autoimmune disease

For more than a century, the pathogenesis of sarcoidosis has remained a mystery. Scadding [1] reported that the ‘1949 US NRC Conference on Sarcoid’ identified ‘the plasma globulins’ as often being elevated in sarcoidosis, yet its classification as an autoimmune disease has remained a matter of conjecture. Later definitions tended to portend an antigenic etiology rather than emphasize the autoimmune aspects of the disease. Indeed, the 1999 ATS/ERS/WASOG ‘Statement on Sarcoidosis’ [2] does not even mention the word ‘autoimmune’.

One reason for this confusion is that although sarcoidosis is a systemic inflammatory disease,
diagnosis is most frequently made on the basis of radiographic pulmonary manifestation. However, during the course of a lifetime, sarcoidosis patients present with a variety of maladies. These do not reside uniquely within any one medical specialty. A patient with advanced sarcoid inflammation might present with disease in the lungs, as pulmonary sarcoidosis, in the cardiac muscle as ‘cardiac sarcoidosis’, and in the brain as ‘neurosarcoidosis’. These manifestations have often been viewed, and treated, as different diseases, even though they almost certainly resulted from the same systemic inflammatory process.

Nevertheless, there is currently no doubt that sarcoidosis is a Th1 immune disease [3] and that it shares genetic susceptibility alleles on the HLA-DRB1 gene at loci *1501 with multiple sclerosis (MS) [4] and systemic lupus erythematosus (SLE) [5]. Both of these factors indicate that sarcoidosis has more in common with autoimmune disease than with any antigenic etiology.

2. Occult bacteria in sarcoid tissue

For several decades there have been consistent reports of occult bacteria being found in tissue taken from sarcoidosis patients. Cantwell [6], Mattman [7], Wirostko [8] and Moskovic [9] have all documented the appearance of a special type of tiny microbe, coccoid forms known as cell wall deficient (CWD) bacteria. Cantwell recently summarized the historical perspective in an excellent review ‘Bacteria in sarcoidosis and a rationale for antibiotic therapy in this disease’ [10], which contains numerous color micrographs of these bacterial forms.

Cantwell also reported similar bacteria in tissue from SLE patients [11].

3. Cell wall deficient bacteria

CWD bacteria are resistant to most antibiotics, being pleomorphic forms of active spirochetal and blood-borne species. They proliferate very slowly, and are very difficult to culture. They have adapted to a hostile environment by shedding their cell walls. The pleomorphism from blood-borne to the CWD state can be triggered by antibiotics, but it can also be a protective response to attack by the immune system itself [12]. The bactericidal action of the penicillins is upon the bacterial cell walls, and penicillin-induced morphing of spirochetal bacteria to their CWD form has been observed in-vitro [13].

Some of these CWD bacterial species have adapted to live within the phagocytes of the immune system. The very cells, which are supposed to kill the invading bacteria, actually provide them refuge.

These CWD bacteria are so tiny that 10 (or more) can live in the cytoplasm of the same phagocyte. Wirostko et al. [8], photographed CWD bacteria living within several cells of the immune system: monocytes, lymphocytes and polymorphonuclear leucocytes.

A stunning micrograph from Nilsson et al. [14], shows a (presumed) Rickettsia bacterium replicating within the cytoplasm of a phagocyte from a sarcoidosis patient. Here was evidence that not only could bacteria adapt to live in this harsh environment, but that they could also flourish.

These CWD species have evolved the ultimate survival mechanism. When the harsh environment is removed they are able to morph back into the active blood-borne state [12] and quickly propagate an active blood-borne infection. In the CWD state they are extremely hard to kill, and as they die they dump their toxic load into the cytoplasm of the phagocytes they have infected [15]—the resulting endotoxin creating a Th1 cytokine cascade, which can be life-threatening.

4. Jarisch-Herxheimer shock

We have previously reported [17] that Jarisch-Herxheimer shock (JHS) presents as a worsening of the manifestations of the sarcoidosis disease process itself. As the bacteria are killed there is a massive release of the same cytokines as are gradually released during normal disease activity. Unless the antibiotic dosage is carefully controlled, adverse events may include both life-threatening pulmonary insufficiency and life-threatening cardiac events.

Even though JHS presents a major problem with patient management and antibiotic dosing, its pres-
ence is also proof-positive of a bacterial disease process, and that bacteria are being killed by the antibiotic therapy.

In many ways sarcoidosis is the ideal test-bed to develop antibiotic therapies against these occult bacteria. The JHS symptoms allow therapy to be optimized in ways that would not be possible in inflammatory disease exhibiting a lesser degree of JHS.

5. Minocycline and doxycycline in sarcoidosis

Bachelez et al. [18], described how minocycline effectively treated skin lesions in 10 patients from a cohort of 12. Two patients also exhibited pulmonary manifestations of the disease, and these were also put into remission by a 12-month course of minocycline.

In sarcoidosis the current aim of therapy is ‘to delay the disease progression’. In that context the results achieved by this team were stunning and revolutionary. However, their achievements were marginalized within the sarcoidosis clinical community, which characterized the minocycline treatment as maybe being useful for skin lesions, but overlooked the improvement in pulmonary manifestations.

Further criticism is voiced at the observational nature of the Bachelez study, and its lack of controls. We feel this criticism is totally unwarranted, as clinical trials of sarcoidosis therapies are customarily unblinded, with the ethics of withholding a potentially useful drug from chronically ill patients being traditionally cited as justification for omission of the placebo group.

Unfortunately, Bachelez only used minocycline and doxycycline in their study. There have been persistent reports incorrectly attributing an anti-inflammatory property to these tetracyclines. The resulting confusion about whether the study was killing microbes, or merely administering an anti-inflammatory, also diluted the landmark nature of this study.

6. Antibiotics in sarcoidosis

While discussing the Bachelez study with Cantwell it became clear to us that the CWD bacteria he had seen in the inflamed tissue most probably were the pathologic agent in sarcoidosis. We had previously identified the secosteroid 1,25-dihydroxyvitamin-D (1,25-D) and Angiotensin II as the key hormones driving the systemic inflammatory process [16] and had noted that this biochemistry was consistent with a bacterial pathogenesis, but not with an antigenic etiology.

A study was initiated to try and determine just which antibiotics would be effective against cell-dwelling pathogens, and not just focus on the tetracyclines.

We managed to recruit a larger cohort of 50 sarcoidosis patients for the study described in our JOIMR paper [17]. Our methodology did create some biases, but they turned out to be insignificant when weighed against the almost universal effectiveness of the antibiotic therapy.

JHS was the major problem within our own heterogeneous cohort. Before we developed suitable low-dose antibiotic protocols, we had one patient who needed emergency oxygen, and many patients complaining of worrying cardiac ‘flutters’ and ‘arrhythmia’.

Bachelez also encountered adverse affects (presumably JHS) but took the approach that antibiotic therapy should be selective, with a focus on treating those patients from whom a favorable outcome might be expected.

We took the opposite approach. We tried to fashion a treatment protocol, which would help patients with any degree of disease dysfunction. We took the approach that sarcoidosis had a primary homogenous pathogenesis, and that any patient exhibiting biopsy verified non-caseating granuloma ought to respond to the same therapy. Our results attest to the accuracy of this hypothesis.

7. The secosteroid hormone 1,25-dihydroxyvitamin D

In 1989, Reichel et al. [19] noted that 1,25-dihydroxyvitamin D (1,25-D) appeared to be exhibiting a key immunomodulatory role. This hormone had long been thought to be associated solely with calcium homeostasis in man, but molecular medicine has revealed that it is actually the parathyroid hormone
(PTH), which regulates calcium, not 1,25-D. Although 1,25-D exerts an action upon PTH, it has only a secondary calcemic effect, and this is far less important than the other functions that 1,25-D performs in the body. Casteels et al. confirmed the immunomodulatory role in 1995 [20], as did Lemire in 1998 [21].

By the time that Hewison et al. published ‘Vitamin D as a cytokine and hematopoietic factor’ in 2001 [22], molecular medicine had pretty well determined exactly how this hormone controls the differentiation of hematopoietic mast cells into monocytes, and then catalyzes the differentiation of monocytes into mature macrophages. In other words, molecular science had figured out exactly how this hormone controls the Th1 immune response in man.

Unfortunately, clinical science has been a little slow to respond to this new knowledge. This hormone exists in serum at very low concentrations (typically 75 pmol/l) and it is usually ignored in clinical profiles.

However, Mawer et al. reported that 1,25-D is such a sensitive indicator of the Th1 immune response that it can even be used to determine prognosis in breast cancer [23]. As the level of 1,25-D falls, the level of the body’s ability to mount a Th1 response is also falling, and the prognosis becomes less favorable.

Huang et al. noted that in AIDS the disappearance of 1,25-D is coincident with the disappearance of the body’s ability to react to infection [24]. Further they confirmed that these changes in 1,25-D were not closely coupled to changes in calcium homeostasis.

We reported a study of the levels of this hormone in sarcoidosis [25], and noted that 1,25-D was almost always elevated in this Th1 immune disease. The severity of the systemic inflammation was roughly proportional to the amount of excess 1,25-D being measured by the assay.

The measurement of 1,25-D, and the D-Ratio [25] (a factor representing the energy with which Th1 inflammation generates 1,25-D), can be performed with a draw of just 8 ml of whole blood. We believe this is the single most useful test to assess the status of the immune system of any patient, with or without a formal disease diagnosis.

8. 1,25-D metabolism is aberrant in rheumatoid arthritis, Parkinson’s and SLE

Even though 1,25-D is such a sensitive measure of Th1 immune activity there is very little data available about its behavior in autoimmune diseases other than sarcoidosis.

Mawer et al. [26] documented aberrant 1,25-D metabolism in Rheumatoid Arthritis (RA). They challenged a controlled cohort of 19 RA patients with the precursor, 25-D. Eight of the 19 RA patients generated levels of 1,25-D above the ‘upper limit of normal’. Mawer concluded that the study provided strong evidence for the non-renal synthesis of 1,25-D in patients with RA. This situation exactly parallels the non-renal synthesis of 1,25-D by inflammatory macrophages in sarcoid inflammation.

Sato et al. [27] meticulously collected data on osteopenia in elderly patients with Parkinson’s disease. Their data (Table 2 of [27]) show an inability for the Parkinson’s patients to regulate 1,25-D in response to oral supplementation, with a marked increase in the generation of 1,25-D and/or a corresponding decrease in the value of the observed precursor, 25-D. Using our own nomenclature [25] this is equivalent to saying that the D-Ratio is rising away from the nominal 1.3 of a healthy person [16]. Although this study was not structured to test non-renal synthesis of 1,25-D in elderly Parkinson’s patients, we interpret their data as indicating such an aberrant metabolism exists, indicative of active Th1 inflammation in Parkinson’s.

Similar, but less exhaustive, data have been logged during studies with SLE patients. Huisman et al. [28], and Muller et al. [29], both noting anomalies in the D metabolism associated with SLE.

Since it is our own personal hypothesis that this aberrant D metabolism is associated with one of the primary genetic factors predisposing to autoimmune disease, we note with interest the tantalizing data from Chong et al. [30], who found that patients with active SLE respond differently to exogenous 1,25-D and IL-2 than do controls, or patients with inactive SLE.

9. Future directions

We are currently on the threshold of a revolution in our understanding of autoimmune disease. We are
able to examine similarities between each autoimmune disease by characterizing the genetic haplotypes. We have assays to measure the raw cytokine profiles, and we know enough about the healthy body so that we can accurately elucidate what triggers and sustains both the Th1 and Th2 immune responses.

We now need to explore what happens when the cells of the immune system become host to bacterial and viral parasites. These parasites are capable of activating the immune phagocytes from within, triggering a cytokine cascade without any Lymphocytic intervention. That is the dilemma we have introduced with this review. What happens when the immune system doesn’t operate as it would in a healthy individual? What steps can we take to help it return to normal? With the answers to these questions will come the cure for so much disease.

**References**


**Take-home messages**

- Sarcoid inflammation has now succumbed to antibiotics in two independent trials, demonstrating, ex juvantibus, a primary, homogenous, bacterial pathogenesis.

- Low-dose minocycline is the antibiotic capable of inducing remission in sarcoidosis. A dual regimen of low-dose azithromycin + minocycline is especially effective.

- Jarisch-Herxheimer shock is a major problem. Unless the antibiotic dosage is carefully controlled, adverse events may include both life-threatening pulmonary insufficiency and life-threatening cardiac events.

- The pathogens appear to be multiple species of tiny, slow growing, cell-wall-deficient (CWD) bacteria living within the cytoplasm of phagocytes.

- The secosteroid hormone 1,25-dihydroxyvitamin-D is elevated in patients with Th1 immune inflammation, while the precursor, 25-hydroxyvitamin-D, is depressed.

- 1,25-dihydroxyvitamin-D metabolism is similarly disturbed in (at least) rheumatoid arthritis, SLE, and Parkinson’s, and it is likely that these diseases also have a bacterial Th1 pathogenesis.
IgM anti-oxLDL antibody and carotid artery atherosclerosis

The role of autoantibodies directed against oxidized low-density lipoprotein (oxLDL) in atherosclerosis is not yet understood. In most human studies, elevated levels of anti-oxLDL antibodies predict future cardiovascular events. Karvonen et al. (Circulation 2003;108:2107) report an inverse association between intima-media thickness of the carotid artery and IgM anti-oxLDL in 1,022 middle-aged men. This inverse association remained statistically significant after adjusting for age, gender, LDL cholesterol, CRP and smoking. Several explanations exist for this finding. It is possible that IgM autoantibodies aid in removal of oxLDL, while IgG isotypes do not.