Sarcoidosis 2001

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Abstract

In every decade, sarcoidosis makes a chameleon-like change so its profile needs to be updated. It was first recognised as a dermatological curiosity which evolved into a multisystem disorder with bone cysts, uveitis, and intrathoracic involvement. New dimensions were uncovered by biochemistry and immunology, bringing it still nearer the elusive enigma, namely the cause of sarcoidosis. Aetiology includes an understanding of a genetic predisposition and environmental trigger factors. What was left undone in the 20th century will become evident in the 21st century with more sophisticated technology. Likewise, conventional treatments of the past will be superseded by cytokines and other magic bullets of the millennium.

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In Jonathan Hutchinson's day sarcoidosis was a dermatological curiosity which gradually evolved into a multisystem disorder with skin lesions and bone cysts.[1] Still later, the introduction of radiography delineated pulmonary involvement, and thereafter it has been recognised to involve all systems of the body. New dimensions were uncovered by biochemistry and immunology, bringing us still nearer the enigma that continues to elude us—namely, the cause of sarcoidosis.

What was left undone in the 20th century will surely come to light during the 21st century for the will to solve the problem is now harnessed to more sophisticated technology.

Descriptive definition

Sarcoidosis is a multisystem disorder of unknown cause(s) most commonly affecting young adults, and frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. The diagnosis is established most securely when well recognised clinicoradiographical findings are supported by histological evidence of widespread epithelioid granulomas in more than one system. Multisystem sarcoidosis must be differentiated from local sarcoid-tissue reactions. There is imbalance of CDT4:T8 subsets, an influx of Th1 helper cells to sites of activity, hyperactivity of B cells, and circulation of immune complexes. Markers of activity include raised levels of serum angiotensin converting enzyme (SACE), abnormal calcium metabolism, a positive Kveim-Siltzbach skin test, intrathoracic uptake of radioactive gallium, and abnormal fluorescein angiography.

The course and prognosis correlate with the mode of onset. An acute onset usually heralds a self limited course of spontaneous resolution, whereas an insidious onset may be followed by relentless progressive fibrosis. Corticosteroids relieve symptoms, suppress the formation of granulomas (including Kveim-Siltzbach granulomas), and normalise both levels of SACE and the uptake of gallium. A synthesis of clinical features, radiology, histology, biochemical changes, and immunological abnormalities helps to distinguish it from non-specific local sarcoid-tissue reactions.

Genetic and other molecular probes may help to define a sarcoidosis terrain or diathesis and what antigens have a causative role in that susceptible soil.

Immunology

Granulomas form by a stepwise series of events, starting when T helper cells recognise protein peptides presented to them by antigen presenting cells bearing histocompatibility class II molecules. Immunological reactivity or inflammation attract monocyte macrophages which fuse to form multinucleated giant cells and onwards to epithelioid cells. Granuloma formation is aided by a cavalcade of chemotactic factors; Th1 cells induce interleukin (IL)-2, interferon gamma, and tumour necrosis factor (TNF) with the help of IL-12 and costimulator B7. The resulting exuberant granuloma formation is associated with active cell mediated hypersensitivity and tissue destruction. This framework is also remodelled by chemokines, adhesion molecules, matrix receptors of the integrin family, costimulators B7 and CD28, IL-12, and RANTES (regulated on activation normal T cells as secreted).

Bronchoalveolar fluid (BALF) reveals this macrophage class II-CD4Th1 cell synergy with its awesome cytokine cascade. Angiotensin converting enzyme is generated within mature epithelioid granulomas; monocyte chemoattractant protein-1 is detected in macrophages peripheral to the granuloma but not within it. Antigen presenting cells and monocyte chemoattractant protein-1 should not be confused for they act at different stages of granuloma formation. Both reflect early sarcoid activity and are likely to be undetected at the late fibrotic stage. Interferon-inducible protein-10 correlates with activated Th1 cells in BALF.[2–8]

Anergy is an exquisite form of immune apathy due to cytokine dysregulation and signal transduction. With CD28 mediated costimulator there is active T cell proliferation; without it there is ignorance, apathy, and anergy. CD28 and B7 are transmembrane glycoprotein signals on helper T cells and antigen presenting cells respectively. The signals induce the T cell to produce IL-2, which in turn activates the T cell to proliferate and interact with B cells and cytoxic T cells. In due course this costimulation must end and the activated helper T cells are brought under control. This is done by cytotoxic T lymphocyte antigen 4 gene

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Table 1 The chemicals and cytokines which promote and inhibit the road from granuloma to fibrosis (after Elliott, 1999)[13]

Promoted by	*Inhibited by*
Th2 cytokines	Th1 cytokines
Interleukin-1	Interferon gamma
Interleukin-4	Interleukin-12
RANTES	Corticosteroids
Type 1 procollagen	Prostaglandin E
Type 1 collagen	Perfenidone
Fibronectin	Pentoxyfylline
Factors	Thalidomide
Tumour necrosis	Bosentan
Transforming growth-β	Halofuginone
Platelet derived growth	Factor antibody
Endothelin-1	Transforming growth
	Tumour necrosis
	Infliximab
	Entanercept

(CTLA-4) a regulatory molecule on the surface of activated T helper cells.[9 10]

Apoptosis is another mechanism to switch off granulomatous inflammation, achieved via Fas antigen (Fas) and Fas ligand (Fas L). Fas, a cell surface protein that mediates apoptosis is a member of the TNF receptor family. Fas L is expressed in activated T lymphocytes. The Fas/Fas L combination mediates apoptosis of Fas bearing cells, eliminating unwanted inflammatory cells during repair after injury. In this way, apoptosis may be regarded as an useful mechanism resolving granulomatous inflammation and preventing postinflammatory scarring and fibrosis.[11]

Granulomatous inflammation is usually self limiting with spontaneous resolution. It remains a mystery why some patients with sarcoidosis behave in this way whereas in others there is uncontrolled progress to fibrosis. Could one aspect of the puzzle be homoeostasis?

Homoeostasis

Armstrong *et al* have demonstrated an important inter-relationship between TNF-α and TNF soluble receptors in pulmonary sarcoidosis.[12] Alveolar macrophages were cultured in the presence and absence of lipopolysaccharide. There was significant more immunoreactive TNF-α in the BALF than in controls. TNF-α bioactivity was inhibited by increased soluble TNF receptors (TNF-R), particularly in early stage 1 intrathoracic involvement, suggesting a homoeostatic mechanism protecting the lung from excessive TNF production. Indeed, this mechanism may provide one explanation which may prevent subsequent on-going pulmonary fibrosis.

The CD4:CD8 ratio and TNF-α levels in induced sputum correlate with those in BALF and also parallels changes with steroid treatment.[13] The raised CD4:CD8 ratio and increased TNF-α levels in induced sputum in pulmonary sarcoidosis falls towards normal after six months' treatment with oral prednisone. This should prove to be a popular non-invasive method of assessing activity and a monitor of progress with treatment.

The road from granuloma to fibrosis

The most sinister clinical complications or sarcoidosis are the irreversible fibrosis causing glaucoma, cataract, and blindness; nephrocalcinosis; crippling pulmonary failure; hydrocephalus, lupus pernio, and myocardial damage. Indeed, but for fibrosis, sarcoidosis would be clinically insignificant. It is important to explore every antifibrotic avenue of prevention as early as possible in the disorder. The road from granuloma to fibrosis may be accelerated or inhibited by various chemicals and cytokines, and these mechanisms have been expertly discussed in a recent review (table 1).[14] Pirfenidone ameliorates bleomycin fibrosis, inhibits transforming growth factor, and blocks profibrotic cytokines.[15]

Markers of activity

The need for steroid therapy depends whether sarcoidosis is active. Clinical features of activity are erythema nodosum, uveitis, rashes, polyarthralgia, dactylitis, myopathy, neuropathy, lymphadenopathy, parotid and lacrimal gland enlargement, red scars, and cardiac arrhythmia.

It is helpful to complement these clinical features with new techniques. All available data are used to assess activity and serial measurements monitor progress of the disease with treatment (table 2).

Table 2 Markers of activity of sarcoidosis

Technique	*Abnormality*	*Reflecting*
Serum angiotensin converting enzyme	Raised	Epithelioid granulomas
Monocyte chemoattractant protein	Raised	Macrophage activity
Interferon inducible protein	Raised	Activated lymphocytes, granulomas, and BAL
Radioactive Ga^{67} and octreotide	Uptake in granulomas	Activated macrophages
Bronchoalveolar lavage (BAL)	Increased CD4:CD8 ratio over 3.5	Sarcoid alveolitis activity
	RANTES	
	Increased TGF-β	
	Imbalance IL-Ira:IL-1β	
Calcium metabolism	Hypercalcaemia	Calcitriol sensitivity by alveolar macrophages
	Hypercalciuria	
Kappa and lambda chain immunoglobulins	Raised	B cell overactivity
Tuberculin skin test	Negative	Cutneous cytokine anergy
		Interleukin-12 neutralised
Kveim-Siltzbach skin test	Positive	Specific for sarcoidosis
		Interaction of CD4T cells and macrophages leading to granuloma
Lung infection spirometry	Impairment	Granuloma load
		Inflammation—fibrosis
Tc-DTPA lung scan	Impaired clearance	Epithelial cell permeability due to inflammation
Fluorescein angiography	Retinal vasculitis with leakage	Indication for steroid therapy and/or laser to overcome leakage
ECG and 24 hour tape	Cardiac arrhythmia	Myocardial sarcoidosis
Magnetic resonance	Abnormal	Mediastinal adenopathy
		Neurosarcoidosis

ECG = electrocardiology, IL = interleukin, TGF = transforming growth factor.

Table 3 Present conventional treatments

Drug	*Routes*	*Remarks*
Corticosteroid	Oral	The first line of treatment.
	Eye drops	Dose may be reduced when given in conjunction with other effective drugs
	Ointment	
	Intravenous	Intravenous pulses for neurosarcoidosis
	Topical	
Non-steroidal anti-inflammatory	Oral	Helpful in acute exudative stage such as erythema nodosum, polyarthralgia, and acute iritis
	Ointment	
	Intravenous	
Methotrexate	Oral once weekly for 9 months	Helpful in controlling chronic skin lesions. May improve vital capacity in chronic pulmonary sarcoidosis
Hydroxychloroquine	Oral thrice weekly for 9 months	Helpful for chronic fibrotic lesions of skin and lung
Immunosuppression	Oral accompanying corticosteroid	Steroid sparing effect making it possible to halve the dose of corticosteroid
Azathioprine		
Cyclophosphamide		
Chlorambucil		
Calcium chelating	Oral until abnormal calcium corrected	Chelate calcium in the gut and prevent its absorption
Effervescent phosphate		Best combined with corticosteroid
Sodium cellulose phosphate		
Potassium p-aminobenzoate	Oral for 9 months	Softens fibrotic skin lesions and keloids
Thalidomide pentoxyfylline	Oral	Inhibitors of tumour necrosis factor may be antifibrotic

Treatment

Conventional treatment of the past comprised steroids followed, if necessary, by methotrexate or hydroxychloroquine (table 3). But this often proved insufficient, and the combined use of all three drugs came into use. This is to be encouraged so that different influences—anti-inflammatory and antifibrotic—are brought into play. Early treatment is the key to the prevention of sinister fibrosis; and hopefully it will make transplantation less necessary.

We must also look beyond our present drugs for additional cytokine therapy for they and their antagonists are the antibiotics and magic bullets of the future (table 4). Nature has herself curbed the overactivity of TNF by producing neutralising TNF-R. It is suggested that this homoeostasis is responsible for the more benign course of early rather than late sarcoidosis. Other TNF blockers include thalidomide and pentoxyfyline. Infliximab is a human-mouse chimeric anti-TNF-α IgG antibody which has been successful in the management of rheumatoid arthritis, Crohn's disease, and psoriasis. Etanercept is a fusion protein made up of two recombinant p75 TNF receptors fused with the Fc portion of the human IgG_1. Infliximab is an antibody against TNF-α whereas etanercept is a receptor for TNF; the former is a human-mouse chimeric product whereas the latter is a fully human protein.

Aetiology

The causes of sarcoidosis comprise two interwoven factors, namely the genetic background and the environmental operative target.

The genetic background is often referred to under the terms terrain, diathesis, and constitution. Erythema nodosum is seen most frequently in Irish women, Puerto Ricans reaching New York, and Martiniques migrating to Paris. Sarcoidosis is more common in Afro-Americans and in the West Indies. It is common in the Japanese but infrequent in Chinese, Greeks, and Cypriots. A recessive mode of inheritance is evident in familial sarcoidosis. There is some correlation between genetic predisposition and whether the course of the disease carries a good or poorer prognosis (table 5).[16]

Takemoto *et al* have noted an association between angiotensin II receptor gene polymorphism and SACE activity in patients with sarcoidosis.[17]

It is equally important to investigate triggers which may set in motion the disorder in predisposed individuals. Many different antigens have been suspected including bacteria, fungi, viruses, and chemicals (table 6).[5] Dr C G Teo of the Public Health Laboratory, Colindale has identified human herpes virus 8 genome by the polymerase chain reaction amplification in the blood of 78% of patients with sarcoidosis compared with 7% in controls (personal communication).

Table 4 Site of action of immunosuppression and scope of future therapy

Immunosuppressive drug	*Target*
Corticosteroids	Prevent T cells producing cytokines particularly interleukin-2
Cyclosporin	
Tacrolimus	
Sirolimus (rapamycin)	Blocks intercellular signal transduction by interleukin-2 receptor
Azathioprine	Purine synthesis inhibitors inhibit T cell proliferation
Mycophenolate	
Monoclonal antibodies OKT3	Block T cell receptor
Cytotoxic T lymphocyte	Block costimulatory signal CD28
Antigen-4-gene (CTLA-4)	Prevents graft *v* host disease
	Psoriasis
	Transplantation/Graves' disease
Infliximab	Human mouse chimeric antitumour necrosis factor (TNF) antibody
Etanercept	Human protein of recombinant p75 TNF receptors fused with Fc portion of human IgG_1
Pentoxyfylline/thalidomide	TNF blockade

Table 5 A correlation between genetic predisposition and clinical features (Martinetti et al 1995[16])

HLA class II	*Prognosis*	
	Good	*Chronic*
A1, B8	+	
DR17	+	
DR3	+	
DR14, DR16		+
DR5J		+
DRW52	+	
DQB1 0201	+	
DQB1 0503		+
TNFA2	+	
	Other correlations	
DR3, DR4	Females	
DR5	Males	
B13, B35	Early onset	
A30, B8, DR3, DR4	Late onset	
B27, A2	Pulmonary only	
A1, B8, B27, DR3	Stage I	
B12, DR4	Stage II	
Angiotensin II type receptors (Takemoto *et al* 1998[17])	High activity of SACE	

SACE = serum angiotensin converting enzyme.

Table 6 Suspected causal agents (James and Zumla 1999[5])

Bacteria and related organisms	
Mycobacteria	
Streptococcal cell wall	
Propionibacterium acnes	
Borrelia burgdorferi	
Mycoplasma	
Nocardia	
Virus	*Chemicals*
Epstein-Barr	Beryllium
Herpes	Zirconium
Rubella	Pine pollen
Measles	Peanut dust
Cytomegalo	Clay
Coxsackie B	
Retrovirus	

Is sarcoidosis an autoimmune disorder?

There are several pointers to an autoimmune disorder including erythema nodosum, uveitis, sarcoid thyroiditis, Sjogren's syndrome, hypergammaglobulinaemia, the occasional presence of odd non-specific circulating antibodies, overlap syndromes with recognised autoimmune disorders; and finally an impressive response to corticosteroid therapy. However true sarcoid autoantibodies have not been regularly noted, and sarcoidosis does not share the female preponderance which is a feature of all autoimmune disorders.

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