Leading Article

Overlap syndromes with sarcoidosis

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Sarcoidosis has been observed in association with various autoimmune disorders, primary biliary cirrhosis, Crohn’s regional enteritis, coeliac disease, amyloidosis and lymphoma, thereby posing the query of whether the relationship is causal or coincidental. These possible overlap syndromes should not, of course, be confused with disorders which may mimic sarcoidosis and so give rise to diagnostic difficulties. Erythema nodosum, uveitis, T and B cell imbalance, and hypergammaglobulinaemia are features of an autoimmune disorder and there is an isolated report of finding specific circulating autoantibodies in sarcoidosis (Favez & Leuenberger, 1975). Overlap syndromes with thyroiditis, Addison’s disease and Sjogren’s syndrome (TASS syndrome) have amplified the possibility that sarcoidosis is an autoimmune phenomenon (Karlish & Macgregor, 1970; Wiesenhutter & Sharma, 1979; Seinfeld & Sharma, 1983) although circulating autoantibodies are not a feature of sarcoidosis (James & Jones Williams, 1985).

Primary biliary cirrhosis

Chronic non-suppurative destructive cholangitis or primary biliary cirrhosis (PBC) is characterized by positive serum mitochondrial antibodies. We have described two middle-aged women with pruritus, liver biopsy findings of PBC, serum mitochondrial antibodies and lung infiltration. Both patients died of liver disease; autopsy studies showed granulomatous lung disease (Stanley et al., 1972). A similar overlap identified four females with hepatic granulomas, positive mitochondrial antibodies and pulmonary disease (Fagan et al., 1983).

The mitochondrial antibody test is the hallmark of PBC for it is positive in 99% of patients but it is always negative in straightforward sarcoidosis. Likewise, the Kveim-Siltzbach skin test is positive in three-quarters of patients with sarcoidosis but it is always negative in primary biliary cirrhosis (James, 1983). These two tests remain most helpful in differentiating the two disorders, but on extremely rare occasions both tests may be positive in the same patient (Karlish et al., 1969; Maddrey, 1983). Such true overlaps are extremely rare and are only acceptable after repeat tests with a different batch of Kveim antigen and after mitochondrial antibody studies have been repeated in another laboratory.

Crohn’s disease

Burrill Crohn and Louis Siltzbach were close colleagues and friends at the Mount Sinai Hospital, New York City, but despite close collaboration they were unable to establish a link between the two chronic granulomatous disorders – regional ileitis and sarcoidosis – which have certain similarities and many differences. We have treated one patient with both disorders – a woman with longstanding Crohn’s regional enteritis complicated eventually by pulmonary sarcoidosis with cavitation and aspergilloma, suggesting profound depression of cellular immunity. There are a few reports of the combination (Morland 1947; Dines et al., 1971; Padilla & Sparberg, 1972). A 32 year old West Indian woman with Crohn’s disease of ileum, oesophagus and buccal mucosa, itself a rare combination, developed transient erythema nodosum and hilar adenopathy during a quiescent phase of Crohn’s disease (Oakley et al., 1983).

Gronhagen-Riska et al. (1983) observed sarcoidosis and Crohn’s disease in the same family. The father had sarcoidosis involving skin, kidneys and spleen. A daughter developed intrathoracic sarcoidosis, a son developed possible renal sarcoidosis with hypercalciuria, and another son developed Crohn’s disease. The father and the three sick children were HLA B8-DR3.

Parotid enlargement

Parotid gland involvement occurs in about 6% and enlarged lacrimals in 3% of patients with sarcoidosis.

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(Greenberg et al., 1964). Sometimes there is confusion between Heerfordt’s, Sjögren’s and Mikulicz’s syndrome but diagnostic difficulty does not signify an overlap syndrome and histology should identify the cause of various oculo-lacrimal-parotid gland syndromes with keratoconjunctivitis sicca. We have followed the course for 25 years of a woman who presented with erythema nodosum and bilateral hilar lymphadenopathy due to sarcoidosis. This subsided but was followed by the gradual development of a Sjögren-like keratoconjunctivitis sicca, Xerostomia and parotid gland enlargement.

Coeliac disease

Douglas et al. (1984) have observed 5 patients with sarcoidosis and coeliac disease, to which may be added another two examples (Simpson, 1984). There has been an interesting follow-up of one of Douglas’ patients (Lowe & Johnston, 1984). For her rhinitis, she was given Dimotapp LA tablets, which contain 3.0 mg of wheat flour per tablet in addition to brompheniramine maleate, phenylephrine hydrochloride and phenylpropanolamine hydrochloride. She promptly had a flare-up of coeliac disease, presumably due to the wheat flour; but also, interestingly, she had a recurrence of erythema nodosum and bilateral hilar lymphadenopathy. This might reasonably suggest a causal relationship between coeliac disease and sarcoidosis in this particular patient. If this is so, then it is an extremely rare association. Or was it just a coincidence?

Amyloidosis

In a 33 year period (1950–83), 52,371 autopsies were performed at the University of Southern California – Los Angeles Medical Center, including 503 with amyloidosis and 116 with sarcoidosis. In seven (1.3%) instances both conditions co-existed; a combination which has rarely been noted in Britain (Swanton et al., 1971) or in the USA (Fresko & Lazarus, 1982). Cole et al. (1985) have described 6 patients with sarcoidosis and lymphadenopathy in whom biopsies showed well-formed epithelioid granulomas in a homogeneous matrix of amyloid, which had initially been regarded as fibrous tissue and subsequent stains revealed amyloid.

The Los Angeles necropsy study also noted the combination of sarcoidosis, amyloidosis and rheumatoid arthritis in three instances. Sarcoidosis and rheumatoid arthritis have similar immunological abnormalities with an OKT4:T8 imbalance, considerable macrophage activity and B cell overactivity. The discordance between cellular and humoral immunity might contribute to the production of clones of amyloid-producing plasma cells.

Neoplasia

Neoplasia may be accompanied by sarcoïd tissue reactions either in the lymph nodes draining carcinomas or intimately admixed in lymphoma. These sarcoïd reactions should not be confused with systemic sarcoidosis and do not, of course, constitute an overlap syndrome. However, on rare occasions, sarcoidosis may precede or follow lymphoma. We have followed two examples. A 30 year old woman with clearcut multisystem sarcoidosis had a splenectomy and the sarcoïd spleen was used to prepare Kveim antigen; 8 years later her sarcoidosis had become quiescent she developed a widespread lymphoma which proved fatal. Another example was of a father and son with sarcoidosis. The son developed and successfully overcame a non-Hodgkin lymphoma but the pulmonary sarcoidosis has persisted. The association was eleven times more frequent than expected in one study (Brincker, 1972; Brincker & Wilbek, 1974) but this was denied by Romer (1980; 1982). Brennan et al. (1983) point out that sarcoidosis precedes lymphoma in most of these true overlap examples, the age of onset of sarcoidosis is relatively late, and Hodgkin’s disease predominates in the lymphoma group.

Conclusion

There should be no shortage of future studies, clinical and epidemiological, to clarify various overlap syndromes with sarcoidosis, for such clues may help to solve the remaining enigma, namely the aetiology of sarcoidosis. But observers need to distinguish true overlap syndromes from diseases that provide diagnostic difficulty; this demands good clinical records, careful observation and well-constructed investigations.

References


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