Sarcoidosis: clinical manifestations, staging and therapy (part II)

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Clinical Manifestations

GENERAL FEATURES

In Europe, sarcoidosis is the most frequently observed interstitial lung disease of unknown aetiology. The prevalence rates range between 64 patients per 100,000 population in Sweden and nine patients in Italy, with intermediate numbers observed in Denmark (53 patients), Germany (43 patients), Ireland (40 patients), Norway (27 patients), The Netherlands (22 patients), the U.K. (20 patients), Switzerland (16 patients) and France (10 patients). For the Caucasian population of North America and Afro-Americans, the prevalence is three and 47 per 100,000, respectively (1). Sarcoidosis is a disease with protean manifestations, and although the lung is most frequently involved, the disease can affect any organ of the body. The clinical manifestations are largely non-specific, as are the histological features. Patients with pulmonary sarcoidosis generally present to physicians because of non-specific constitutional complaints (e.g. fever, weight loss, fatigue, anorexia, malaise) and/or symptoms directly related to the chest (e.g. cough, dyspnoea, particularly with exertion, chest pain and, occasionally, haemoptysis). Early in the disease, the physical findings in the chest are usually limited to dry, crackling rales, most commonly heard at the posterior base of the lung.

Although the onset of the disease is usually insidious and discovered in asymptomatic individuals by routine chest X-rays or heralded by constitutional complaints, it will occasionally manifest itself as a medical emergency. Involvement of the eye, the heart, the central nervous system or the development of hypercalcaemia may require immediate action. More than 90% of sarcoid patients will eventually develop pulmonary abnormalities easily recognizable on chest X-ray or tests of pulmonary function (2,3). The chest X-ray is rarely normal; most commonly it reveals bilateral hilar adenopathy and/or diffuse reticulo-nodular infiltrates in the parenchyma. Lung function tests usually reveal a loss in lung volumes (vital capacity and total lung capacity), a reduced diffusing capacity, and a mildly reduced arterial PO₂ that may diminish further with exercise. In general, the ratio of forced expiratory volume in 1 second to vital capacity is normal (4), although sensitive tests reveal airflow limitation (5) and ≈20% of the patients present with unspecific bronchial hyperreactivity (6,7).

DEFINITION

An evaluation of transbronchial or open lung biopsies of patients in the early stage of sarcoidosis gives insight into why the patients suffer from the clinical findings outlined above. The typical findings are those of non-caseating granulomas within the alveolar, bronchial and vascular walls (8-10). These granulomas are diffusely scattered throughout the lung parenchyma. In contrast to the granulomas seen in hypersensitivity pneumonitis, the granulomas of sarcoidosis are well-formed, compact aggregates. They are usually of varying age, ranging from highly cellular lesions to collections with diminishing cellularity, some fibrosis, and progressive hyalinization. Two characteristic zones can be seen in a typical, well-developed sarcoid granuloma: (i) a central zone or follicle which is tightly packed with cells, composed primarily of macrophages, multinucleated giant cells, and epitheloid cells; and (ii) a peripheral zone containing loosely arranged cells like a collar of lymphocytes, monocytes and fibroblasts (Plate 1) (8,11). Although many microscopic features may suggest sarcoidosis, the epitheloid granulomas, especially in their earlier stages, are indistinguishable from those of other idiopathic granulomatous disorders or even granulomatous disorders of known origin, such as berylliosis, tuberculosis or hypersensitivity pneumonitis.

Thus, sarcoidosis is best defined in histopathological terms as 'a disease characterized by the presence in all of several affected organs and tissues of non-caseating epitheloid-cell granulomas, proceeding either to resolution or to conversion into hyaline connective tissue' (8). The clinical diagnosis, however, can only be supported by typical histopathological findings. Pathognomonic criteria or a diagnostic 'gold standard' are absent. Most authorities thus includes several clinical, radiological, immunological and histologic features into their diagnostic criteria since other disease processes can simulate sarcoidosis in many ways. Occasionally, all of these features may suggest the diagnosis of sarcoidosis in patients later proven to have other diseases (12). Therefore, rigorous efforts have to be made to exclude alternative diagnoses, e.g. tuberculosis, lymphoma, berylliosis, etc. (13-18), and patients diagnosed...
more severe the clinical findings at the time of diagnosis and the more organ systems are involved by the disease, the more frequent adverse courses have been observed. Cutaneous sarcoid frequently indicates chronic and disseminated involvement and the prognosis, in general, is poor in patients with advanced skin lesions (21–23).

Only rough estimates of the mortality of untreated sarcoidosis are available. If untreated, it is associated with a mortality of ~5%. In a recent epidemiological study from Denmark with a median follow-up of 27 years, an excess mortality from sarcoidosis and sarcoidosis-related diseases in patients with advanced radiological findings and deteriorated lung function was perceived in the first 20 years. Although the mortality of the sarcoid cohort was higher than that of the general population, the difference was not statistically significant (23,24). This number may differ in other ethnic groups (25,26) or cohorts with increased frequencies of certain manifestations, such as cutaneous sarcoidosis (27).

PLATE 1. Light photomicrograph of a typical non-caseating granuloma with multinucleated giant cells.

as suffering from sarcoidosis must regularly be subjected to review and further testing (19).

NATURAL COURSE OF THE DISEASE

Most patients with diagnosed sarcoidosis will undergo clinical and radiological resolution of the disease over a period ranging from several months to a few years (20). A few develop a progressive form of the disease which may result in death (21). In those patients undergoing resolution, subsequent biopsy or material examined at necropsy reveal changes ranging from complete resolution with no scarring to focal pulmonary scars without evidence of granuloma formation. The fate of the sarcoid granuloma is morphologically well documented. It may appear fresh for months to years; however, the granuloma ultimately resolves, leaving no morphological changes, or it undergoes an obliterative fibrosis. The fibrosis starts as a rim of collagen around the granuloma and proceeds in a centripetal fashion until the entire structure is replaced by fibrous tissue. The late stage of sarcoidosis is characterized by an extensive, patchy pulmonary fibrosis and a hypertrophy of pulmonary arteries (8,11).

The natural course of sarcoidosis is unpredictable in an individual patient; for example patients with advanced pulmonary infiltrates and splenomegaly may have spontaneous recovery, whereas others with asymptomatic hilar adenopathy may develop severe disease. Extensive clinical and epidemiological studies performed since 1950 emphasize the generally favourable outcome of sarcoidosis. About 70% of the patients presenting with hilar adenopathy alone (i.e. radiographic type I) have spontaneous resolution. In patients presenting with pulmonary infiltrates (types II and III; diffuse parenchymal infiltrates with (type II) or without (type III) hilar adenopathy), this figure is reduced to about 50%. A 40% mortality rate was observed in those who presented with radiographic signs of fibrosis. Generally, the

Staging of Inflammatory Activity

CLINICAL PARAMETERS

For clinical purposes, a staging of the inflammatory activity of the disease is required after establishing diagnosis. Unfortunately, the best approach to this problem has not been determined. However, it is clear that the conventional approaches to staging patients, such as chest X-ray and lung function tests, are neither sensitive to, nor specific for, the inflammatory processes in the lower respiratory tract requiring pharmacological intervention. Thus, while the tests used to periodically evaluate sarcoidosis patients still include chest X-ray and lung function tests, it is now recognized that these tests tell the clinician about the extent of the damage to the lung parenchyma, but not about the activity of the inflammatory processes within the lower respiratory tract. A loss of lung function or a deterioration of X-ray findings over a period of time certainly indicate inflammatory active processes; however, the evidence is indirect and is obtained with considerable delay (2,9).

Computed tomography is capable of revealing indicators of ongoing alveolitis or fibrosis; however, the clinical applicability of this approach remains to be established (28,29).

BRONCHOALVEOLAR LAVAGE

Due to the unpredictable course of sarcoidosis, staging parameters of prognostic value are required to enable early therapy in patients with poor prognosis and to avoid unnecessary therapy in those who will have a spontaneous regression of the disease. The percentage of lavage lymphocytes and the CD4/CD8 ratio within these cells have been shown to correlate with the spontaneous course of the disease, at least to some extent. Patients with acute disease and good prognosis have high numbers of lymphocytes with an elevated CD4/CD8 ratio in their lavage, whereas patients with more chronic disease and risk of deterioration exhibit only moderately raised values (30–32). This finding
was reproduced in the author's study population showing only a minor change in BAL cytology in those patients with chronic disease (Fig. 1). Due to the non-parametric distribution of the cells in normal BAL, generally accepted normal values do not exist (33-35). In addition, study populations investigated by different researchers differ in their ethnic composition, leading to a confounding by different clinical presentations (26,27), e.g. more chronic disease in blacks or different immunoresponse genes (25). Both facts may explain why BAL studies reveal so many conflicting results.

The concept of testing functional parameters of lavage cells, i.e. interleukin-2 (IL-2), transforming growth factor β and tumour necrosis factor α (TNFα) release, or of combining these parameters with cytological findings for obtaining prognostic information is currently evaluated in the author’s laboratory (36). Encouraging results indicate that this approach allows the identification of subgroups of patients with good (37) and poor (38) prognosis (see part I of this review, published in this issue of Respiratory Medicine), although similar study designs have thus far failed to do so (39). These approaches exploit the accumulated knowledge of the immunopathogenesis of the disease, but the technical approach is far too complex for an application in every day practice; however, these studies give evidence of prognostic factors in the immunopathogenesis of the disease for which serum markers might be delineated in the future.

SERUM MARKERS

There is easy access to serum, and markers from this body compartment have been used to gauge sarcoidosis for many years. Angiotensin-converting enzyme (ACE) and lysozyme are the oldest serum markers of sarcoidosis (40,41), probing one aspect of the disease's immunopathogenesis, i.e. the granuloma burden. Granuloma is a feature of many chronic interstitial lung diseases, e.g. sarcoidosis, hypersensitivity pneumonitis, berylliosis or histiocytosis X, and are structured masses composed of activated macrophages and their derivates, i.e. epitheloid and giant cells. All these diseases may be associated with elevated serum levels of ACE and lysozyme. In contrast to the foreign body type granuloma, the sarcoid granuloma contains more lymphocytes and, at times, eosinophils, mast cells and fibroblasts. Sequential analysis of the cellular components of these lesions has demonstrated their dynamic nature. An influx, local multiplication and cell death time of immune cells can be observed, most probably governed by inflammatory signals. In immune granulomas, as in sarcoidosis, these signals are likely to be cytokines and cell-cell interactions of lymphocytes, macrophages and their derivates, and fibroblasts (42). The transformation of macrophages to epitheloid cells is associated with the secretion of ACE and lysozyme; however, after stimulation by T-lymphocytes, alveolar macrophages are also known to release these molecules. Although local production by alveolar macrophages could be demonstrated (43,44), these molecules' serum levels mainly indicate the granuloma burden of the total body as demonstrated by morphometry and quantitative mRNA analysis in an animal model of pulmonary granuloma (45) and clinical 67gallium scanning (46). Although ACE and lysozyme are frequently used, there is no correlation between their serum level and response to treatment or prognosis. The initial values do not differ between patients who deteriorate and those who improve (47). Serum levels can, however, be used to monitor therapy (47).

From the concept of the immunopathogenesis of sarcoidosis as described in part I of this review, a number of
serum markers measuring the activation of macrophages, T-lymphocytes and endothelial cells have been delineated.

Neopterin, a small 250 kDa metabolite of the guanosinetriphosphate pathway, is released by activated macrophages and monocytes (48). It gauges the inflammatory activity of these cells rather than their activation in the course of building granulomas. As expected, elevated serum levels were found in sarcoidosis and are used to monitor the activity of cells of the macrophage/monocyte lineage (49-51). Interestingly, a correlation between BAL-cell-released TNFα or IL-6 with serum neopterin could not be observed (52), giving rise to the hypothesis that the elevated neopterin levels are sequelae of cell activation in body compartments other than the alveolar space, such as lymph nodes providing secreted molecules with easy access to the serum.

Nevertheless, serum or urine neopterin concentrations proved to be very useful clinical parameters to probe the activity of the cells of the monocyte/macrophage lineage in the course of sarcoidosis (49-51, 53).

Activated T cells express an IL 2R, 55 kDa/75 kDa heterodimer on their cell surface and release a soluble form of the 55 kDa chain (sIL-2R) (54,55). sIL-2R can be found in BAL fluid and serum of sarcoidosis patients, and it is released by activated alveolar immune cells (56-59). In addition to lymphocytes, macrophages are capable of expressing IL-2R upon activation, and it has been demonstrated that up to 50% of activated sarcoid alveolar macrophages exhibit increased numbers of IL-2R (60). The relative contribution of lymphocytes and macrophages to the alveolar lining fluid sIL-2R concentration is not known (58, 60). The absence of a correlation between alveolar macrophage TNFα release as marker of cell activation and BAL fluid sIL-2R concentration argues in favour of sIL-2R being a T-lymphocyte marker (61). A major contribution of any BAL cell population to the sIL-2R serum level cannot be expected, as a leakage of the basal membrane or active transport mechanisms allowing a 55 kDa protein to leave the alveolar space has not been observed in sarcoidosis (62).

In agreement with these findings, the sIL-2R serum concentration was found to be independent of alveolar immune cell activation, indicating that these cells are not the predominant contributors to the exaggerated serum levels of sIL-2R (58). The debate about the contribution of IL-2R shedding by peripheral blood monocytes to the serum level has not been settled because quiescent, non-shedding and activated, shedding sarcoid peripheral blood mononuclear cells have been found in clinical investigations with large study populations (58,59,63). Nevertheless, monitoring T-cell activity within sIL-2R serum level reveals an intimate relationship between this parameter and the clinical activity of the disease, providing further evidence for the close linkage between the course of sarcoidosis and the activated state of T-cells (57-60,64). Moreover, those patients without indications for therapy but with high sIL-2R serum levels indicating a T-cell activation in the course of sarcoidosis tend towards a progressing course with subsequent indications for corticoid therapy (36). In some study populations, sIL-2R and ACE serum levels correlate with each other (59,63), but other researchers could not reproduce this finding (57,64), which argues against the hypothesis that sIL-2R is derived from monocytes or alveolar macrophages.

Another marker exclusively expressed and released by T-cells is sCD27, the soluble form of a receptor of the nerve growth factor receptor/tumour necrosis factor receptor gene family (65). sCD27 is shedded after T-cell activation, and the amount of its soluble form is supposed to correlate with the number of activated T-cells. Elevated bronchoalveolar fluid and serum levels have been found in sarcoidosis, and its use as a clinical marker has been suggested (66).

Adenosine deaminase (ADA), an enzyme involved in the purin degradation, is widely distributed in human tissues, and its soluble form gives rise to elevated serum levels. It is related to lymphocytic differentiation and proliferation, showing a significant increase during an immune response. ADA shows high activity in epitheloid granulomas, and its concentration in pleural fluid correlates with T-cell number and markers of their activity (67,68). The latter is one of the reasons why it is considered to be a marker of cell-mediated immunity. Measuring ADA serum levels in sarcoidosis disclosed elevated concentrations in active disease (69,70) and a somewhat higher sensitivity than sIL-2R, ACE or neopterin (71).

Epithelial cells of the lower respiratory tract, especially type II pneumocytes, are integrated into the pulmonary immune response as demonstrated by their constitutive expression of HLA-DR (72) and their expression of adhesion molecules such as CD54 (ICAM-1), CD51 and CD49d (73,74). In parallel with monokine release, an increased expression of adhesion molecules such as CD11/CD18 and intercellular adhesion molecule-1 (ICAM-1) can be observed (75,76). The expression of ICAM-1 has been demonstrated on many cells, including endothelia in sarcoïd tissue, supporting the hypothesis that the ICAM-1/LFA-1 (leukocyte function antigen-I) pathway is involved in the extravasation of leukocytes into sarcoïd lesions (77). ICAM-1 is shedded from the cell surface (sICAM-1) giving rise to elevated concentrations in body fluids (78) segregating with the inflammatory activity of sarcoidosis (79,80).

Although some evidence exists that sICAM-1 is shedded by immune cells (79,81), the origin of the circulating sICAM-1 in sarcoidosis is not known, as immune cell markers do not correlate with sICAM-1 serum levels (79,80). Thus, it has to be assumed that both epithelial and immune cells contribute to the observed serum sICAM-1 (80), which impedes its clinical use. Furthermore, elevated sICAM-1 levels have not been found in sarcoïdosis patients by all researchers (81,82), casting some doubt on the sensitivity of this marker.

There is multiple histological and immunological evidence of the involvement of pneumocytes II (alveolar epithelial cells type II) in the immunopathogenesis of sarcoidosis (83,84). These cells seem to be capable of promoting (72,85) and dampening (86,87) immunological reactions in the lower respiratory tract, and are integrated into the immunological cytokine network of the lung (85,88,89). The immunopathogenetical phenomena observed in pneumocytes and the basal membrane cause only few alterations in serum parameters. KL-6, a mucinous, high molecular weight glycoprotein, expressed on type II pneumocytes, is found elevated in the serum of patients.
inflammation is particularly disabling or when disfiguring central nervous system, eyes, hypercalcaemia), or when the granulomas cause dysfunction in vital organs (e.g. heart, pulmonary fibrosis). Therefore, early markers of fibrosis are identified, as other sources besides pneumocytes have been shown to predict fibrosis conclusively. They may instead be regarded as indicators of fibroblast activation and extracellular matrix remodelling in the course of inflammation and granuloma formation (95). Thus, the clinical corner stones for the identification of patients at risk for fibrosis remain investigations such as testing of lung function, pulmonary compliance, CO diffusion and chest X-rays.

## Treatment

The aetiology of sarcoidosis remains unknown and therefore no specific treatment is possible. Fortunately, many patients will not require treatment because the symptoms are not disabling and frequently remit spontaneously. Prompt initiation of corticosteroid therapy, however, is indicated when granulomas cause dysfunction in vital organs (e.g. heart, central nervous system, eyes, hypercalcaemia), or when the inflammation is particularly disabling or when disfiguring skin lesions emerge. While there is general agreement that corticosteroids should be administered to patients with extrapulmonary manifestations (96,97), the use of anti-inflammatory drugs in those with involvement of the respiratory system has, until recently, been under debate (98,99). A major obstacle in effectively treating pulmonary sarcoidosis is the inability to predict reliably which patients will recover and which will deteriorate.

Judging by radiographical typing, corticosteroid therapy does not unequivocally change the long-term outcome of the disease (21,22,28,100). However, as mentioned above, radiography might not be the appropriate method for evaluating therapeutic effects, because it indicates organ damage and not inflammatory activity. In a prospective study by Hunningenhake et al., only sarcoidosis patients with evidence of recent deterioration of lung function or severe extrapulmonary disease were treated with corticosteroids. Finding the indication for therapy on the basis of these clinical criteria, it was demonstrated that treatment prevented deterioration or induced improvement of lung function (20). Thus, the ongoing inflammatory processes causing deterioration of lung function can be obstructed, and further deterioration can be prevented.

To achieve a selective delivery of the drug into the compartment most frequently involved and to reduce side-effects, inhalation has been proposed as an alternative way of administering corticosteroids. Only a few studies have explored the role of inhaled corticosteroids in the management of sarcoidosis, and ambiguous results have been obtained. Patients with mandatory indications for corticosteroids cannot be included in these studies, which makes it difficult to judge the efficacy of this therapeutic approach in study populations with only relative indications for therapy (101,102). The use of inhalative budenoside has been suggested for maintaining remission or for preventing further deterioration (101), but this interpretation of the study is under debate (103). Another study using a similar approach failed to demonstrate that the progression of sarcoidosis can be stopped by inhaled budenoside (102), leading to the conclusion that this therapeutic strategy requires further evaluation.

Corticosteroids, like cyclosporin A, suppress critical processes in the immunopathogenesis of sarcoidosis, such as

### Table 1. Serum markers for the inflammatory activity of sarcoidosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pathomechanism probed</th>
<th>Clinical usage</th>
<th>Literature (selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme</td>
<td>Granuloma burden, macrophages</td>
<td>Frequent</td>
<td>(43,45,47)</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Granuloma burden, macrophages</td>
<td>Frequent</td>
<td>(41,43)</td>
</tr>
<tr>
<td>Carboxypeptidase N</td>
<td>Granuloma burden, macrophages</td>
<td>Frequent</td>
<td>(41,43)</td>
</tr>
<tr>
<td>Neopterin</td>
<td>Macrophages, monocytes</td>
<td>Limited</td>
<td>(49–51)</td>
</tr>
<tr>
<td>Soluble CD14</td>
<td>Macrophages, monocytes</td>
<td>Under investigation</td>
<td>(51,129)</td>
</tr>
<tr>
<td>Soluble interleukin-2 receptor</td>
<td>T-cells</td>
<td>Limited</td>
<td>(36,57,58,63)</td>
</tr>
<tr>
<td>Soluble CD27</td>
<td>T-cells</td>
<td>Suggested</td>
<td>(66)</td>
</tr>
<tr>
<td>Adenosine deaminase</td>
<td>T-cells</td>
<td>Suggested</td>
<td>(69–71)</td>
</tr>
<tr>
<td>Soluble ICAM-1</td>
<td>Endothelia and immune cells</td>
<td>Suggested</td>
<td>(79–81)</td>
</tr>
<tr>
<td>KL-6</td>
<td>Pneumocytes</td>
<td>Suggested</td>
<td>(90,91)</td>
</tr>
</tbody>
</table>

with active pneumonitis, such as sarcoidosis, cryptogenic fibrosing alveolitis and hypersensitivity pneumonitis (90). Interestingly, these heightened serum levels correlate with alveolitis patterns found by computed tomographic (CT) scan and with a number of cellular parameters of BAL (91). Whether this serum marker is of any clinical value remains to be established, as other sources besides pneumocytes II have been identified (90). The serum markers are summarized in Table 1.

## Fibrosis

The poorest prognosis is found in patients with developing pulmonary fibrosis. Therefore, early markers of fibrosis are in demand to guide therapeutic interventions. In BAL, markers of connective tissue turnover, such as procollagen III peptide, vitronectin, fibronectin and collagenase, can be found (92–95), and much hope has been placed in these phenomena to serve as accurate predictors of fibrosis. Taken together, neither the release of cytokines able to stimulate fibroblast growth nor the increase in indicators of connective tissue turnover have been shown to predict fibrosis conclusively. They may instead be regarded as indicators of fibroblast activation and extracellular matrix remodelling in the course of inflammation and granuloma formation (95). Thus, the clinical corner stones for the identification of patients at risk for fibrosis remain investigations such as testing of lung function, pulmonary compliance, CO diffusion and chest X-rays.
the release of IL-2 by activated alveolar T-lymphocytes (see part I of this review) (101,102), but for cyclosporin A, unequivocal proof of therapeutic effectiveness in pulmonary sarcoidosis has not been obtained (104-106), although a number of case reports demonstrating the benefits of cyclosporin A in corticosteroid-resistant cases have been published (107,108). Most interestingly, these case reports observe both the efficiency and failure of this drug in complicated chronic courses of sarcoidosis with extrapulmonary manifestations such as skin (107) and central nervous system (109,110). Thus, cyclosporin A may serve as a second-line drug with corticoid-sparing capabilities for chronic sarcoidosis, but a commonly agreed definition of its role in the treatment of this disorder has not yet been reached.

Numerous immunosuppressive or immunomodulating drugs, such as azathioprine, chlorambucil, chloroquine, cyclophosphamide, levalmisole and melatonin, have been evaluated with a view to serving as substitutes for corticosteroids, but only ambiguous results have been obtained when used as monotherapeutic agents (96,108,111,112). As for cyclosporin A, the corticoid-sparing effects of these drugs are generally recognized and various combinations of prednisolone and immunosuppressants are used to lower the required dose of corticosteroids in the treatment of chronic sarcoidosis (108,113).

In dermatology, chloroquine and hydroxychloroquine are used to treat non-infectious cutaneous manifestations in a number of diseases, including selected cases of sarcoidosis (114). Local, intraseusal (115) and systemic (116,117) applications are used. In the latter, thorough ophthalmological follow-up examinations are required to check for chloroquine-induced retinopathy, but with this precaution it is considered to be a safe therapy (116).

In sarcoid macrophages, altered vitamin D3 metabolism is observed resulting in increased synthesis of the active vitamin which appears to be involved in the pathogenesis of hypercalcaemia, known to occur in sarcoidosis. In vitro, chloroquine is capable of returning this altered metabolism to its normal state in which the presence of pro-inflammatory cytokines is required to enable macrophages to synthesize vitamin D3 (118). This finding explains the clinical observation that chloroquine or the combination of chloroquine and prednisone are effective measures for the treatment of sarcoid hypercalcaemia (119,120).

Methotrexate has been shown to reduce the inflammatory activity of alveolar macrophages when administered as treatment for sarcoidosis. Radical oxygen intermediates and TNFα release were significantly lower after treatment compared with measurements performed before methotrexate treatment. In addition, under methotrexate, the percentage of BAL lymphocytes declined by about 50% and the CD4/CD8 ratio exhibited a downward trend. Both observations indicate that critical immunopathological mechanisms of alveolar macrophages and lymphocytes are dampened by this drug. In line with this finding, a therapeutic efficiency of methotrexate similar to that of prednisolone was observed (121).

The intracellular mechanisms triggering TNFα gene transcription and action have been elucidated within the last few years, and some drugs originally developed for other indications were found to influence TNFα gene activation or the action of TNFα. It has been demonstrated that pentoxifylline (122) and thalidomide (123) inhibit the synthesis of TNFα and act synergistically with dexamethasone in the human system resulting in a lower TNFα serum level (124-126). These findings led to the hypotheses that both pentoxifylline and thalidomide should be effective drugs in the treatment of pulmonary sarcoidosis. A recent study by Zabel et al. demonstrated in 11 of 18 patients with documented disease progression that pentoxifylline is an effective monotherapeutic agent capable of reversing the loss of pulmonary function (127). In addition, as deduced from in vitro studies, pentoxifylline can be used as a corticosteroid-sparing drug in those patients requiring high-dose prednisone to prevent disease progression (125,127). Carlesimo et al. treated one patient with corticosteroid-resistant, cutaneous sarcoidosis and one patient with contraindications for prednisone with 100 mg thalidomide on alternate days, and observed disease regression with no relapse under maintenance therapy (128).

Thus, the detailed knowledge of the immunopathogenesis of sarcoidosis makes it possible to design studies for finding new therapeutic options, as it has been demonstrated in the cases of methotrexate, pentoxifylline and thalidomide.

Conclusion

Immunological studies have advanced our understanding of the immunopathogenesis of interstitial lung diseases and, in particular, sarcoidosis. Some of the described mechanisms can be clinically applied to detect patients at risk of deterioration or to develop new therapeutic strategies. Using these approaches, methotrexate, pentoxifylline and thalidomide have been identified as drugs effectively suppressing sarcoid inflammation, and soluble IL-2 receptor serum level has been delineated to be a serum marker of sarcoid inflammation. Furthermore, analysing the pulmonary cytokine network in sarcoidosis will yield new staging parameters, possibly supplying prognostic information and guiding therapeutic interventions.

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References

146 TOPICAL REVIEWS


