The Roentgenographic Staging of Sarcoidosis*

Historic and Contemporary Perspectives

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The awareness that sarcoidosis can involve intrathoracic lymph nodes and lung parenchyma in sequential fashion evolved during the first half of this century. This awareness resulted in a roentgenographic staging system that has relevance to the course and prognosis, pulmonary function changes, and the symptom of dyspnea. The following definition or roentgenographic staging is proposed as the simplest, most reproducible system based solely on the roentgenographic appearance, avoiding histopathologic and pathophysiologic inferences. Stage I: bilateral hilar lymphadenopathy; stage II: bilateral hilar lymphadenopathy plus parenchymal infiltration; and stage III: parenchymal infiltration without bilateral hilar lymphadenopathy.

Sarcoidosis emerged into medical consciousness by another name as a dermatologic curiosity in the last half of the 19th century. It was first called Mortimer’s malady, after one of Hutchinson’s early patients.1 Later, Besnier described lupus pernio, a violaceous swelling of the nose, central face, and ears.2 It was Boeck, a Norwegian dermatologist, who first called the granulomatous skin lesion “sarkoid,” because he thought the changes resembled a sarcoma.3 In 1896, Hutchinson, Besnier, and Boeck were participants in a conference at which Hutchinson presented one of his patients.4 Neither Boeck nor Besnier recognized the similarity of the skin lesions in Hutchinson’s patient to those they had previously described. Such were the arcane beginnings in the understanding of sarcoidosis. Boeck in 19055 described a number of patients with skin lesions of “sarkoid,” some of whom had chronic cough, five with documented granulomatous changes in the nasal mucosa. This appears to have been the first published record of involvement of the respiratory tract.

In 1915, Kuznitzky and Bittorf6 published an account of a 27-year-old white male with sarcoidal skin lesions having pulmonary infiltration documented by chest roentgenogram. They called attention to the involvement by sarcoidosis of internal organs in addition to the skin. Some argue it was Schaumann7 who first and most clearly demonstrated the systemic nature of the disease, showing involvement not only of the lung and skin, but also of the bone, liver, lymph nodes, tonsils, marrow, and spleen, even though Kuznitzky and Bittorf preceded him in the literature. By the 1930s, there was a general appreciation that sarcoidosis could involve hilar lymph nodes and lung parenchyma, either together or alone, but the sequence of these changes was not understood. Ustvedt8 was one of the first to claim that bilateral hilar lymphadenopathy represented the earliest change. By 1940, Magnusson9 pointed out that intrathoracic changes were perhaps more constant than any other manifestations, but the primacy of intrathoracic involvement and its characteristic sequential roentgenographic appearance was not yet realized. King10 noted in 1941 that erythema nodosum presented a chest roentgenogram indistinguishable from that of sarcoid disease.

Ultimately, Löfgren,11 after whom Löfgren’s syndrome is named, was to demonstrate bilateral hilar adenopathy as the first roentgenographic change of sarcoidosis and frequently associated with erythema nodosum. It is perhaps due to the large experience afforded him that he was able to ascertain the chronology of development that had eluded recognition by other authors reporting experience with fewer patients. Löfgren observed that patients with bilateral

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hilar adenopathy, particularly if accompanied by erythema nodosum, had a favorable prognosis for spontaneous remission. He further observed, in a small minority of patients, a tendency to develop parenchymal infiltration of the lung, which signified a poorer prognosis for spontaneous remission. Throughout the early period of evolving knowledge on sarcoidosis, it was observed that the disease frequently ran a benign course with spontaneous remission and only infrequently became progressive, chronic, and associated with respiratory impairment. Scadding also recognized bilateral hilar lymphadenopathy as the earliest stage and further classified the parenchymal changes, describing them as mottling, fine reticulations or fibrosis. Nitter appears to have been the first to suggest a staging system designated by Roman numerals I through V. Stage I represented bilateral hilar lymphadenopathy with or without paratracheal lymphadenopathy, but without parenchymal involvement; stage II, bilateral hilar lymphadenopathy with accentuation of parahilar markings, with or without associated paratracheal adenopathy; stage III, diffuse pulmonary nodulation with parenchymal densities varying from 3 to 5 mm in diameter (no mention is made of associated hilar adenopathy); stage IV, disseminated miliary lesions of approximately 1 mm in diameter, simulating those of miliary tuberculosis; and stage V, fibrotic changes involving the lung parenchyma. He noted that patients developing fibrosis demonstrated antecedent parenchymal densities from 3 to 5 mm in diameter (his stage III), whereas those having miliary lesions infrequently developed fibrosis. His study underscored the increasing understanding of sarcoidosis as a disease of variable prognosis and severity, concerning which the appearance of the chest roentgenogram gave important clues. He noted, as had others, that once pulmonary changes had spontaneously resolved, they seldom recurred. By the time of his report, there was a general recognition that sarcoidosis often ran an entirely silent course, which probably accounted for the predominance of serious cases of irreversible pulmonary fibrosis that were reported in many series.

The ground was now properly prepared for the important work of Wurm, Reindell, and Heilmeyer, who conclusively demonstrated the merits of a staging system based on the chest roentgenogram that correlated with the course and prognosis of the disease. They divided the disease into three stages—I, II, and III—stage I being bilateral hilar lymphadenopathy without parenchymal involvement, stage II, bilateral hilar lymphadenopathy with involvement of lung parenchyma, and stage III, end-stage with irreversible fibrosis of either a conglomerate or linear, evenly distributed form. It appears from their descriptions that stage III does not involve the presence of detectable bilateral hilar lymphadenopathy on the plain chest roentgenogram. These observations were based on large numbers of patients who were serially followed up, and the sequential evolution from stage I to stage III was convincingly demonstrated.

Following the work of those authors, there emerged the use of some forms of roentgenographic staging in the sarcoidosis literature. Citron designated three phases—1, 2, and 3—phase 1 representing intrathoracic lymph node enlargement, phase 2 pulmonary shadows, and phase 3 pulmonary fibrosis. It may be that the term "fibrosis" is used by some authors in a general sense, merely indicating linear parenchymal shadows and not necessarily implying fibrosis in a pathologic sense. James and Thompson also used Arabic numerals to designate their stages, 1 being bilateral hilar lymphadenopathy, 2 bilateral hilar lymphadenopathy plus parenchymal mottling, and 3 parenchymal mottling without lymph node involvement. This staging system most approximates that which is in common use in the English literature today. Siltzbach showed a clear relationship between roentgenographic stages I, 2, and 3 (similar to that of James and Thompson, using Arabic numerals) and the prognosis of the disease for spontaneous remission. It is apparent, however, that the criteria for staging in the most recent literature varies considerably. Turiaf, for example, used stages I through III, with stage I representing mediastinal lymphadenopathy without parenchymal infiltration, stage II parenchymal infiltration with mediastinal lymphadenopathy, and stage III pulmonary fibrosis (here again, the term fibrosis may be roentgenologic and not pathologic) without mediastinal lymphadenopathy. His colleagues, Chrétien et al., use I through III with subgroups A and B in stage II: stage I represents bilateral hilar lymphadenopathy, stage IIA bilateral hilar lymphadenopathy with pulmonary nodules, stage IIB pulmonary nodules without hilar lymphadenopathy, and stage III fibrosis (here again, "fibrosis" may be roentgenologic and not pathologic). Therefore, there has been a lack of uniformity as to the meaning of the various staging systems, which can prove a source of confusion in interpreting data on prognosis and results of treatment unless one inspects the case data very thoroughly, fitting the patients into the staging system that best fits his prejudice.

Since staging is based on the appearance of the plain chest roentgenogram, it seems reasonable to abide by the limitations of the method, omitting histopathologic and pathophysiologic inferences. Whereas Young et al. and Magnussen et al. and others have demonstrated the presence of granulomas in the parenchyma in stage I, this should not alter the designation of stage I from a purely roentgenographic perspective. Similarly, although conglomerate shadows in association with bullous changes and hard linear shadows reliably indicate
the presence of irreversible fibrosis, one cannot accurately know what is potentially reversible granuloma and what is irreversible fibrosis in the case of evenly distributed reticulonodular pulmonary shadowing. There appear to be three clearly recognizable roentgenographic patterns; enlargement of hilar lymph nodes alone, nodes with parenchymal involvement, or parenchymal involvement without enlargement of hilar lymph nodes. Since these have been shown to evolve sequentially, the designation of stages I, II, and III, otherwise unqualified, seems to be the simplest, most reproducible system based on limitations of the method. I would propose this system as the current universally accepted standard (Fig 1). Stage 0 may be used for those patients having no roentgenographic changes.

**Course and Prognosis**

Wurm, Reindell, and Heilmeyer\(^4\) found the best prognosis in patients with stage I disease, an intermediate prognosis in stage II, and the worst in stage III. In the report of Smellie and Hoyle,\(^2\) although they did not use a staging system, one can stage their patients on the basis of the data presented. They observed the natural course of 125 patients for more than two years from the time of discovery. Those presenting with hilar adenopathy alone (stage I) demonstrated spontaneous clearing of the chest x-ray film in 71 percent, and those having pulmonary infiltration (stages II and III) spontaneously cleared in 50 percent. Siltzbach\(^7\) described the outcome of 311 patients, finding 54 percent of patients in stage I completely clearing, with an additional 19 percent demonstrating shrinkage of the hilar lymph nodes. Only 7 percent progressed to stage II. Patients in stage II cleared in 31 percent, but when found in stage III, only 10 percent returned to normal. A worldwide survey involving 11 medical centers and 3,676 patients noted resolution of the chest roentgenogram in 65 percent of patients in stage I, 49 percent in stage II, and 20 percent in stage III.\(^3\)

**Pulmonary Function**

Winterbauer and Hutchinson\(^4\) have summarized the significance of pulmonary function testing in sarcoidosis. They noted that 80 percent of patients without roentgenographic evidence of parenchymal sarcoidosis, ie, stage I, had normal vital capacities, and 70 percent had normal diffusing capacities (Dco). With the advent of parenchymal change (stages II and III), only 35 percent had normal vital capacities and 34 percent normal Dcos. DeRemee and Andersen,\(^5\) reporting on 107 patients, noted that of 21 in stage I, 17 had normal values and four had only mild decreases in Dco. Moreover, none of those patients complained of dyspnea. Of 51 patients in stages II and III, 18 had normal pulmonary function, eight had decreased Dco as the only abnormality, five had pure restrictive disease, and 20 had expiratory slowing (as measured by the maximal mid-expiratory flow rate) plus pulmonary restriction. In this study, the symptom of dyspnea correlated significantly with the finding of expiratory slowing. In addition, those patients with expiratory slowing and dyspnea demonstrated no significant reversibility under the influence of glucocorticoid therapy. Similar findings have been reported by Miller and colleagues.\(^6\)

It appears that roentgenographic staging gives valuable information regarding prognosis, the type and approximate magnitude of pulmonary function change, and the likelihood of dyspnea. In other words, the chest roentgenogram paints the clinical picture of pulmonary sarcoidosis, a major facet of the diagnosis.

**Assessing Inflammatory Activity**

Pulmonary sarcoidosis begins with an alveolitis com-
posed chiefly of thymus-dependent lymphocytes (T cells). These elaborate chemotactic factors which attract monocytes, which ultimately transform into macrophages and epithelioid cells composing the granuloma. The granuloma may resolve either spontaneously or under the influence of glucocorticoids or be transformed into irreversible scar tissue by a process of hyalination and fibrosis. These phases in the pathogenesis occur over variable time frames in each individual patient. Early disease composed chiefly of inflammatory elements should have a better prognosis than late disease characterized largely by fibrosis. Roentgenographic staging allows an inference of early or late disease. That is, stage I, being the earliest, with minimal functional impairment due largely to inflammation, has an excellent prognosis for spontaneous resolution, whereas stage III indicates later disease with greater functional impairment and a larger irreversible fibrotic component, dictating the poorest prognosis. Yet, within stages II and III, complete resolutions are not infrequently observed, occasionally spontaneously, but also under the influence of glucocorticoids. It is apparent that staging has limitations in giving us precise information regarding the relative degrees of potential reversible inflammation (alveolitis and granuloma) and irreversible fibrosis. This consideration is of the utmost importance in evaluating patients for treatment with glucocorticoids and in judging results of such treatment. Though roentgenographic staging is helpful, it is imperfect.

With the advent of bronchoalveolar lavage (BAL) for assessment of cellular fractions, gallium 67 citrate lung scanning, and the determination of serum angiotensin-converting enzyme (SACE), it is now possible to estimate the inflammatory limb of the inflammatory-fibrosis sarcoidosis dichotomy and thereby refine the staging system.

Yeager et al. found no relationship between the percentage of lymphocytes in BAL and any clinical parameter, including the chest roentgenogram, in 14 patients. Stanislas-Leguern et al. found no differences between roentgenographic stages and results for BAL lymphocytes and serum angiotensin-converting enzyme in 70 patients. Crystal and colleagues found no relationship between T cells in the lavage and roentgenographic stages. Rossman et al. studying BAL and SACE in 22 patients found the following: six patients in stage I, one had elevated SACE and three increased BAL lymphocytes. Of 15 patients in stage II, five had elevated SACE and 11 increased BAL lymphocytes. One patient in stage III had normal SACE, but elevated BAL lymphocytes. The authors claimed that BAL was more sensitive in detecting inflammatory activity in sarcoidosis. What is lacking are long-term follow-up data to ascertain if the values for BAL and SACE have any prognostic value. Rohrbach and DeRemee found elevated levels of serum angiotensin-converting enzyme in 67 percent of patients in stage I, 87 percent in stage II, and 95 percent in stage III. Composite data from an international study reported at the Ninth International Conference on Sarcoidosis and Other Granulomatous Diseases showed elevated levels of serum angiotensin-converting enzyme in 56 percent of patients in stage I, 72 percent in stage II, and 56 percent in stage III. Data concerning the relationship of gallium 67 citrate scanning to roentgenographic staging are too few to allow conclusive statements. However, Heshiki et al. found Ga uptake in hilar lymph nodes in 15 of 16 patients in stage I, but no uptake in lung parenchyma. Since gallium citrate has been shown to be taken up by activated monocytes and angiotensin-converting enzyme to be produced by the monocyte line of cells, one would suspect a close relationship of gallium uptake with serum angiotensin-converting enzyme levels. If, indeed, there is no relationship between the various parameters of inflammatory activity—such as the BAL, gallium scanning, or serum angiotensin-converting enzyme—and roentgenographic stage, this fact would suggest that the chest roentgenogram is a more sensitive tool in predicting prognosis. Because spontaneous remission is so frequently observed in stage I, the pulmonary function derangement so minimal, and the patient largely asymptomatic, it is reasonable for the clinician to observe without treatment irrespective of the results of inflammatory parameters. Although Hunninghake et al. have suggested that those patients having high-intensity alveolitis (lymphocyte count of greater than 28 percent on BAL) tend to have more pulmonary function derangement than those having low-intensity alveolitis (fewer than 28 percent lymphocytes), their data must be considered preliminary in that the period of observation has been too short to allow long-term conclusions concerning prognosis. Because of the propensity of sarcoidosis to undergo spontaneous remission, it seems reasonable to assume that degree of inflammatory activity as measured at only one point in time may have little bearing on the ultimate prognosis. Serial measurements of these parameters are needed to determine a trend. More investigations are necessary to correlate course and prognosis and staging with the new tools of BAL, gallium scanning, and serum angiotensin-converting enzyme determinations. It is premature to discard the concept of roentgenographic staging, demonstrated to be helpful in following the course and prognosis.

**Summary and Conclusions**

A large body of literature supports the legitimacy of roentgenographic staging in sarcoidosis. In fact, sarcoidosis is uniquely suited to this concept because of its...
Table 1—Classification of Pulmonary Sarcoidosis Based on Chest Roentgenogram, Pulmonary Function, and Indices of Inflammation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Roentgenographic Appearance</th>
<th>Pulmonary Function</th>
<th>Indices of Inflammation</th>
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<tbody>
<tr>
<td>I A</td>
<td>Characteristic pulmonary nodules, hilar or mediastinal adenopathy</td>
<td>Normal or mildly abnormal</td>
<td>Normal or mildly abnormal</td>
</tr>
<tr>
<td>I B</td>
<td>Asymptomatic or subclinical disease</td>
<td>Normal or mildly abnormal</td>
<td>Normal or mildly abnormal</td>
</tr>
<tr>
<td>I C</td>
<td>Asymptomatic or subclinical disease</td>
<td>Normal or mildly abnormal</td>
<td>Normal or mildly abnormal</td>
</tr>
<tr>
<td>II A</td>
<td>Progressive pulmonary infiltrates, hilar or mediastinal adenopathy</td>
<td>Impaired lung function</td>
<td>Elevated indices of inflammation</td>
</tr>
<tr>
<td>II B</td>
<td>Progressive pulmonary infiltrates, hilar or mediastinal adenopathy</td>
<td>Impaired lung function</td>
<td>Elevated indices of inflammation</td>
</tr>
<tr>
<td>III A</td>
<td>Stationary or improving pulmonary infiltrates, hilar or mediastinal adenopathy</td>
<td>Normal or mildly abnormal</td>
<td>Normal or mildly abnormal</td>
</tr>
<tr>
<td>III B</td>
<td>Stationary or improving pulmonary infiltrates, hilar or mediastinal adenopathy</td>
<td>Normal or mildly abnormal</td>
<td>Normal or mildly abnormal</td>
</tr>
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Key to Symbols:
- I, II, III—Roentgenographic stage
- N—Pulmonary function studies are normal.
- R—Restrictive functional impairment expressed as percentage of predicted total lung capacity
- D—Diffusion capacity expressed in percentage of predicted value
- O—Obstructive ventilatory impairment expressed in percentage of predicted value for FEV1
- B—Bronchoalveolar lavage expressed as percentage of lymphocytes
- G—Ga-67 citrate scan positive or negative
- S—Serum angiotensin converting enzyme expressed as units/ml over upper limit of normal for method

The orderly progression on chest roentgenogram, its variable predilection for spontaneous resolution, the degree of pulmonary function changes, and frequency of dyspnea, all of which have been correlated with the chest roentgenogram findings. Some have questioned the validity of the putative, sequential development, since it is often impossible to find roentgenographic evidence of an antecedent stage. It can be argued that because sarcoidosis is frequently asymptomatic in its onset, it can evolve through the earlier stages before detection. This evolution can be slow or rapid in the individual patient. Certainly, no data have been presented to demonstrate an alternative sequence of development. Young and Magnussen, as previously cited, found interstitial granulomas to be present in stage I, where there is no roentgenographic evidence of parenchymal involvement. This finding has been used to counter Wurm’s argument that the disease begins in hilar lymph nodes and then extends into lung parenchyma, rather than vice versa. Whatever the order of histopathologic change, the validity of the roentgenographic sequence and its clinical correlates are not altered.

One of the most demanding questions is: What is the stimulus or stimuli that initiate and in some cases perpetuate the “sarcoidosis cascade?” By sarcoidosis cascade, I refer to the sequential lymphocytic alveolitis which engenders the granulomatous response that in turn may eventuate in fibrosis. Why is this stimulus so often ephemeral in stage I and often recalcitrant in stages II and III?

By incorporating the newer tests for assessing inflammatory activity with the staging system, one can more clearly depict and classify sarcoidosis. For example, a patient in stage I having normal pulmonary function studies, a low-intensity alveolitis with a lymphocyte fraction of 10 percent, a negative 67Ga scan, and a serum angiotensin-converting enzyme of 40 units/ml (normal 57 units/ml by radiochemical method) could be encoded as depicted in Table 1A. Or a patient in stage II, having a total lung capacity of 50 percent of predicted, a diffusing capacity of 50 percent of predicted, a lavage fraction of 30 percent lymphocytes, a positive gallium scan, and a serum angiotensin-converting enzyme of 80 units/ml could be encoded as in Table 1B. Table 1C depicts the status of a patient in stage III with pulmonary restriction in addition to airways obstruction. The inflammatory indices are essentially normal. By way of this system, one gains an immediate image of the roentgenographic picture, which tacitly transfers information concerning course and prognosis. Annotation of the pulmonary function values indicates the severity of the impairment and serves as baseline for serial comparisons. If obstructive airways disease is present, this would connote an unfavorable prognosis with a likelihood of underlying irreversible fibrosis. The indices of activity complete the picture, again serving as baselines for comparison and allowing an inference concerning potential reversibility.

Although relatively old, the roentgenographic staging is a proven, useful concept in our understanding of sarcoidosis. We should continue to employ it in our investigations of BAL, 67Ga scanning, and determinations of serum angiotensin-converting enzyme. By ignoring staging, investigators will make unnecessary mistakes in the interpretation of newer data. We need something old and something new.

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REFERENCES
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