Sarcoidosis and Lung Cancer: Review

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ABSTRACT

Sarcoidosis is a multisystemic disorder of unknown origin, which is characterized by non-caseating epithelioid cell granulomas with giant cells mainly in the lung. Worldwide, the average incidence is 16 (male) and 19 (female) per 100,000 inhabitants. In some studies, it was described that patients with sarcoidosis have a higher risk of malignancies, especially of lung cancer. The results differ in the available studies. The role of smoking can probably be neglected as far as the development of lung cancer is concerned, because the patients with sarcoidosis are mainly non-smokers. Regarding all of the published clinical studies with totally 22,439 patients with sarcoidosis, a coexistence of sarcoidosis and lung cancer was detected only in 0.7% of the patients. According to the published case reports, mostly squamous lung cell carcinoma was histologically found, followed by adenocarcinoma. These results indicate that the coexistence of sarcoidosis and lung cancer is very rare.

INTRODUCTION

Sarcoidosis is a multisystemic disorder of unknown origin. It mostly occurs at the age between 30 and 40 years. Worldwide, the average incidence rate is 16 for males and 19 for females per 100,000 (1). In Europe, Sweden has the highest overall incidence rate of 24 per 100,000 (2). The lung is the dominant organ of manifestation, but skin, liver, spleen, lymph nodes, salivary glands, eyes, heart, nervous system, muscles and bones may also be involved. The diagnosis is established when clinical and radiographic findings are supported by histological evidence of non-caseating epithelioid cell granulomas. Granulomas of other causes and local sarcoid reactions must be excluded. Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and an increased T-helper cell type-1 immune response at sites of disease. Circulating immune complexes along with B-cell hyperactivity have also been found. The course and prognosis may correlate with the mode of the onset and the extent of the disease. An acute onset with erythema nodosum and asymptomatatic bilateral hilaradenopathy (Löfgren’s syndrome) is characterized by a self-limiting course, whereas an insidious manifestation, especially with multiple extrapulmonary lesions, may be followed by progressive fibrosis of the lungs and other organs.

CLINICAL STUDIES AND CASE REPORTS

In some clinical studies and case reports, it was elucidated that patients with sarcoidosis have an increased risk to develop malignancies of the lung, stomach, colon, liver, kidney, thyroid, testicles, blood and skin (1, 3–14).

The risk of acquiring various malignancies in patients with sarcoidosis is similarly estimated as in patients suffering from diabetes mellitus (15), inflammatory bowel disease (16, 17) or rheumatoid arthritis (18).

The aim of this investigation was to give a survey about the coexistence of sarcoidosis and lung cancer in published clinical studies and case reports.

Brincker (19) evaluated the findings of 2,544 patients with pulmonary sarcoidosis who were collected in a Danish registry during the period from 1962 to 1971 (Table 1). These data showed a 3-fold higher risk for the development of lung cancer. Yamaguchi (20) reported a cohort of 1,411 Japanese sarcoidosis patients during the period 1984–1987. In this study, the sarcoidosis patients had a 3-fold increased risk to die of lung cancer. Seersholm (21) identified a 2-fold increased risk of lung cancer through evaluation of the Danish cancer registry in patients with pulmonary sarcoidosis. However, Romer (22) described no increased risk of lung cancer in 555 patients with sarcoidosis over an observed period of 9–30 years. Lung cancer was diagnosed only in 1 patient, but the calculated statistical expectation was 4.44 lung cancer cases. In a Swedish study, Askling (4) found almost a 2-fold higher risk of lung cancer in 474 patients (Uppsala cohort) with sarcoidosis over a period from 1966 to 1980. In UK, Le Jeune (23) did not observe an increased incidence of lung cancer in sarcoidosis. Boffetta (24) compared to the incidence of cancer among 2,013 White and 3,755 Black male sarcoidosis patients admitted to Veterans hospitals in the United States during the period 1969–1996. The risk of lung cancer was decreased (relative risk 0.60; 95% CI 0.42–0.85).

Ji (1) investigated 10,037 patients with sarcoidosis who were registered in the Swedish hospital discharge register from 1964 to...
lymph nodes are not prognostically different from those patients who do not possess such features (35, 36), but in another study there is evidence that the detection of sarcoid reactions within regional lymph nodes of patients with non-small cell lung carcinoma predicts a lower rate of disease recurrence after surgical resection (39). A similar observation was described in Hodgkin’s disease where the presence of epithelioid granulomas may reflect a favorable prognosis (40, 41).

**CONCLUSION**

Regarding all published studies with 22,439 sarcoidosis patients, only 156 (0.7%) of these patients suffered lung cancer occurred within 10 years after the diagnosis of sarcoidosis in 45 patients.

The published case reports are summarized in Table 2. Yamasawa (26) described 4 cases. In 2 cases, sarcoidosis and lung cancer developed during the same time and could be observed over years. The author speculated that sarcoidosis could be responsible for the uncommon slow progress of lung cancer. Squamous cell carcinoma of the lung was found in 8 patients, followed by adenocarcinoma. Moreover, the coexistence of sarcoidosis and pulmonary carcinoid was described in two case reports (27, 28).

Sakula (29) pointed out three possible interrelationships of sarcoidosis and lung cancer. Lung cancer could develop from the scar tissues of sarcoidosis. Furthermore, it has been discussed that sarcoidosis can be a follow reaction of lung cancer. It is also possible that lung cancer develops regardless of sarcoidosis (30).

In patients with malignancies, sometimes so-called sarcoid-like histological lesions or sarcoid(al) reactions were described (32, 33). These reactions are small accumulations of epithelioid cells in the lymphatic tissue which are associated with tumors, usually cancer. It is assumed that tumor tissue releases a substance that triggers an immunological reaction which configures these sarcoid lesions. As granuloma of sarcoidosis is difficult to distinguish from sarcoid reactions, it is suggested that for the exact diagnosis of sarcoidosis non-caseating granulomas should be histologically proven in two different organs (26).

Laurberg (34) found 20 cases (2.7 %) with sarcoid reactions in the mediastinal lymph nodes of 734 patients with malignant lung tumors. Kamiyoshihara (35) described sarcoid reactions in the regional lymph node or resected lung in 7 patients (2.2%) of a consecutive series of 326 patients with primary lung cancer. Tomimaru (36) detected sarcoid reaction in the regional lymph nodes in 22 patients (1.3%) out of 1,733 lung cancer patients undergoing surgical treatment.

In two case reports, sarcoid-like reactions were found in primary large cell lung cancer and adenocarcinoma of the lung (37, 38). Sarcoid reactions of the regional lymph nodes are not prognostically different from those patients who do not possess such features (35, 36), but in another study there is evidence that the detection of sarcoid reactions within regional lymph nodes of patients with non-small cell lung carcinoma predicts a lower rate of disease recurrence after surgical resection (39). A similar observation was described in Hodgkin’s disease where the presence of epithelioid granulomas may reflect a favorable prognosis (40, 41).

### Table 1. Different studies of coexistence of sarcoidosis and lung cancer (45, 46).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sarcoidosis cases (n)</th>
<th>Lung cancer cases (n)</th>
<th>Percentage (%)</th>
</tr>
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<tbody>
<tr>
<td>Brincker 1974 (19)</td>
<td>2,544</td>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>Yamaguchi 1991 (20)</td>
<td>1,411</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Reich 1995 (47)</td>
<td>243</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Seersholm 1997 (21)</td>
<td>254</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Romer 1998 (22)</td>
<td>555</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Askling 1999 (4)</td>
<td>474</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Le Jeune 2007 (23)</td>
<td>1,153</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Boffetta 2009 (24)</td>
<td>5,768</td>
<td>37</td>
<td>0.6</td>
</tr>
<tr>
<td>Ji 2009 (1)</td>
<td>10,037</td>
<td>91</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>22,439</td>
<td>156</td>
<td>0.7</td>
</tr>
</tbody>
</table>
also from lung cancer (Table 1). In the case reports, the squamous carcinoma type dominated (Table 2). Although the rate of lung cancer is very low, the question of a possible link between sarcoidosis and lung cancer development is often discussed. Statistically, patients with sarcoidosis smoke less than lung cancer patients and smoking in sarcoidosis behaves even inversely (42–44). This relationship between smoking habits and sarcoidosis could explain the low prevalence of lung cancer in patients suffering from sarcoidosis (42). The finding of sarcoid-type histological reactions in lymph nodes or other tissue involved in the spread of lung cancer or other malignancies could be the residual expression of old sarcoidosis which has not been diagnosed previously. On the other hand, it is also possible that the sarcoid-type reactions could be triggered or reactivated by some unknown substances released by the tissue of the tumor. The published clinical results do not explain the low rate of lung cancer in sarcoidosis. Therefore, further research is necessary to elucidate the pathogenic mechanisms of lung cancer development in sarcoidosis.

REFERENCES

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