Thoracic Surgical Procedures in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is associated with a variety of pleuropulmonary manifestations, some of which require surgical intervention. We investigated the spectrum of indications and results, as well as outcome associated with thoracic surgical procedures in rheumatoid patients.

Methods. Identification and retrospective review of medical records of 100 patients with RA at a tertiary-referral medical center undergoing thoracic surgical procedures over a 24-year period from January 1, 1976, to December 31, 1999.

Results. Sixty-four patients underwent surgical lung biopsy for localized lung lesions, 57 of which were nodules or masses; 24 lesions proved to be malignant. Surgical lung biopsy was undertaken in 40 patients for diffuse interstitial lung disease, 4 cases of which were found to be infectious. Five other patients underwent surgery for pleural disease, 3 of which proved to be benign pleuritis.

Conclusion. Patients with rheumatoid disease undergo thoracic surgical procedures for a variety of indications, including benign and malignant localized lesions and pleural disease as well as diffuse parenchymal lung disease. The overall in-hospital mortality rate was low. However, the subgroup with diffuse interstitial lung disease was found to have a 20% in-hospital death rate following surgical lung biopsy. (J Rheumatol 2004;31:2136–41)

Key Indexing Terms:
THORACIC SURGERY
LUNG DISEASES
RHEUMATOID ARTHRITIS
PLEURAL DISEASES

Rheumatoid arthritis (RA) is a systemic autoimmune process classically characterized by erosive synovitis that is chronic and progressive. It is often associated with numerous extraarticular manifestations, including those of the respiratory system[1-6]. Respiratory manifestations may involve the parenchyma, pleura, conducting airways, pulmonary vasculature, and/or chest wall. In addition, adverse reactions to antirheumatoid drugs may also threaten the respiratory system.

In clinical practice, in the absence of pathologic analysis, these respiratory findings are often attributed to the underlying RA, even though the signs and symptoms are usually nonspecific. Lack of published data on the subject precludes firm establishment of cause and effect. Moreover, some manifestations, such as nodular lesions, frequently necessitate further evaluation to exclude other processes, particularly malignancy. Optimal management of these patients is often controversial. In some instances, histologic analysis may be utilized to more definitively determine etiology and aid in directing treatment, if available.

We performed a retrospective analysis of patients with RA who underwent general thoracic surgical procedures at a large tertiary care medical facility. We wished to determine the spectrum of indications for thoracic surgical intervention, quantify patient outcome postoperatively, and identify the pathological processes encountered.

MATERIALS AND METHODS

From January 1, 1976, to December 31, 1999, a total of 22,276 patients with RA[7] were evaluated at the Mayo Clinic, Rochester, Minnesota. One hundred nine patients (0.5% of total patients with RA; 61 men and 48 women, median age 63 yrs, range 35 to 82), identified by a computer-assisted search of medical records, underwent thoracic surgical procedures (video-assisted thoracoscopic surgery or thoracotomy). Data were abstracted from medical records and included age at the time of surgery, sex, RA manifestations, respiratory symptoms and duration, physical signs, comorbid medical conditions, chest radiographic and computed tomographic (CT) results, indications for surgery, surgical findings, biopsy and culture results, treatment, complications, and outcome.

This study was approved by the institutional review board of Mayo Clinic Rochester.

RESULTS

All 109 patients with RA and undergoing thoracic surgery presented with localized or diffuse pleuropulmonary findings noted on plain radiography and/or CT of the chest. Thoracic surgical procedures were performed to further evaluate and manage intrathoracic abnormalities. Fifty-two

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patients (47.7%) had undergone bronchoscopy before surgery. Seven of these bronchoscopic procedures yielded specimens that were diagnostic of or suspicious for malignancy, but the remainder were nondiagnostic. In addition, 3 other patients had undergone transthoracic needle aspiration biopsy of focal lesions, and all revealed malignancy.

Surgical resection of a localized lesion was performed on 64 of the 109 patients (58.7%). Fifty-seven (89.1%) of these cases represented nodular or mass lesions, 13 patients (22.8%) exhibited multiple nodules, and the remainder (77.2%) had a solitary nodule or mass. The remaining 7 localized lesions were focal pulmonary infiltrates in 6 patients and lobar atelectasis in one (Table 1).

Malignancy was found in 24 patients (37.5%) with localized lesions (Table 2). Primary bronchogenic carcinoma was present in 20 (12 men, 8 women), consisting of 13 cases of squamous cell carcinoma, 7 cases of adenocarcinoma, and 2 large-cell carcinoma. These lung cancers included 14 with stage I disease, 3 with stage II disease, and 5 with stage III disease. For these, a lobectomy was performed in 19 instances and pneumonectomy in 4 cases (one patient underwent 2 procedures). The sole complication and postoperative death in this group occurred in a 79-year-old man who developed hemothorax and a bronchopleural fistula following a lobectomy. He then underwent completion pneumonectomy, but died of progressive respiratory failure associated with acute respiratory distress syndrome 2 months later. A second primary lung carcinoma subsequently developed in 3 of these patients, 2, 6, and 13 years after initial resection. Notably, all 20 patients with bronchogenic carcinoma were current (6 patients) or previous (14 patients) smokers. All except 2 patients who had bronchogenic carcinomas presented with a solitary nodule or mass; the remaining 2 patients presented with multinodular disease. Radiographically, 19 of the 20 solitary nodules were considered new findings compared with previous radiographs or CT scans. That is, only one patient was observed with serial radiographs prior to surgical intervention. The 4 remaining malignancies were a lymphoma in 2 patients (one of whom had multiple nodules) and a case each of a plasmacytoma and metastatic liposarcoma.

Twenty-three (35.9%) of the localized lesions were found to be granulomas (Figure 1). Although 16 of these were described as caseous, microbiologic proof of infection was documented in only 6. All 6 were fungal infections, including histoplasmosis in 4, and one case each of coccidioidomycosis and cryptococcosis. Four (6.3%) of the localized lesions were diagnosed as rheumatoid nodules, 2 patients presenting with a solitary nodule and 2 with multiple nodules. Thirteen patients had various other findings including intrapulmonary lymph nodes in 3 patients, foreign bodies in 2 patients, nonspecific abscess in 2 patients, nonspecific inflammation in 2 patients, and a broncholith, scar, cyst and bronchiectasis in one patient each.

The indication for surgery was diffuse parenchymal infiltrates on chest radiography in 40 (36.7%) of the 109 patients. Infection was found in 4 patients (10%); nontuberculous mycobacterium was isolated in 2 and *Pneumocystis carinii* and invasive aspergillosis in one each. These 4 patients were all undergoing immunosuppressive therapy that included prednisone. The remaining 36 patients (90%) with diffuse parenchymal infiltrates were found to have a variety of noninfectious acute or chronic interstitial pneumonitis patterns, only 4 of which were thought to be related to antirheumatoid drug therapy (Figure 2).

Pleural disease was the main surgical indication in 5 patients. A sterile pleuritis was found in 3 patients and an empyema in 2.

Postoperatively, 9 in-hospital deaths occurred; 8 of these patients had undergone lung biopsy for diffuse parenchymal lung infiltrates. Causes of death included acute respiratory distress syndrome or diffuse alveolar damage in 5 patients, acute exacerbation of chronic interstitial pneumonia in 3, and organizing pneumonia in one patient. Six of the patients had preoperative pulmonary function test data available and had only mild to moderate impairment of pulmonary function indices.

Table 1. Indications for thoracic surgical procedures.

Diffuse interstitial infiltrates (n = 40)
Pleural disease (n = 5)
Localized parenchymal lesion (n = 64)
Lobar atelectasis (n = 1)
Focal infiltrate (n = 6)
Nodule(s) or Mass(es) (n = 57)
Solitary (n = 44)
Multiple (n = 13)

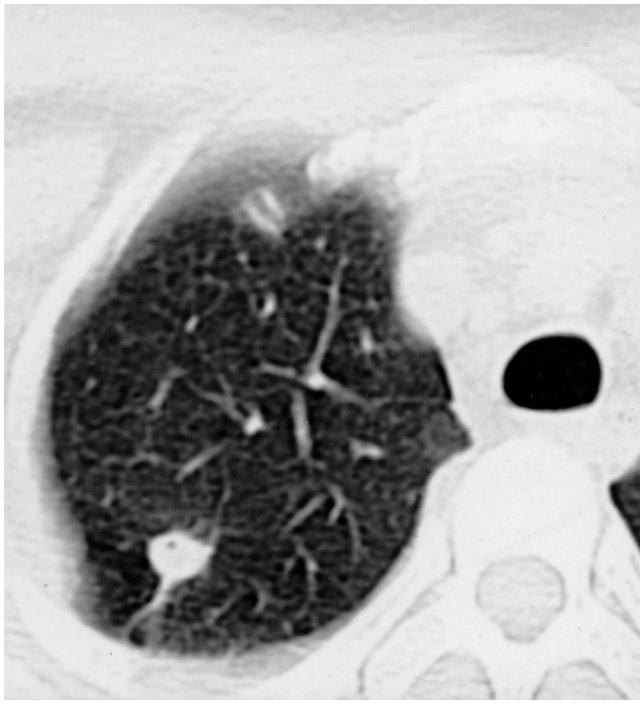
Table 2. Histopathologic diagnoses of localized lesions (n = 64 patients).

Diagnosis	No. of Patients (%)
Malignancy	24 (37.5)
Primary lung cancer	20
Lymphoma	2
Plasmacytoma	1
Metastatic cancer	1
Granuloma	23 (35.9)
Rheumatoid nodules	4 (6.3)
Miscellaneous*	13 (20.3)

* Included intrapulmonary lynph nodes (3), foreign bodies (2), abscess (2), nonspecific interstitial inflammation (2), broncholith (1), scar (1), cyst (1), and bronchiectasis (1).

DISCUSSION

We examined the indications and results of thoracic surgical procedures in all patients with RA seen at our institution. The study was intended to be broad-based in order to



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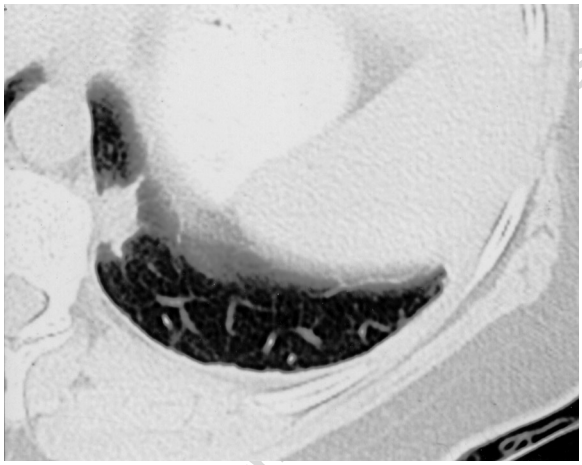

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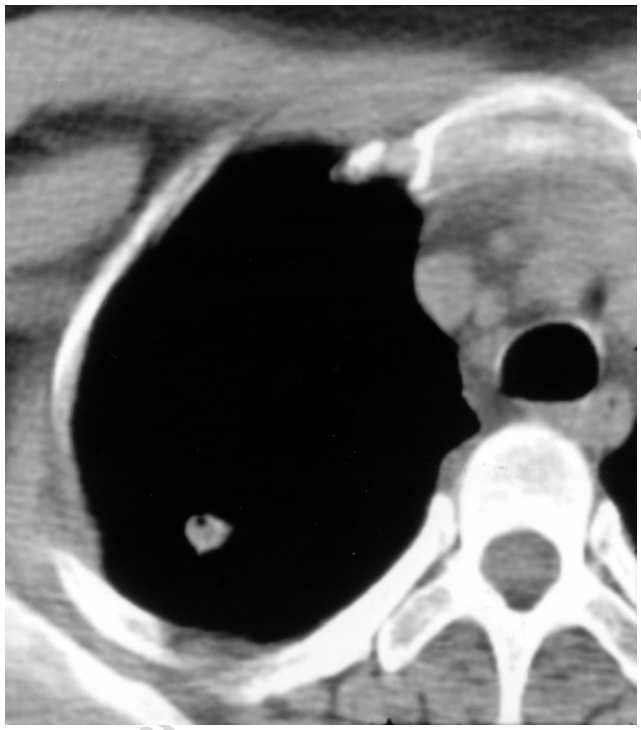

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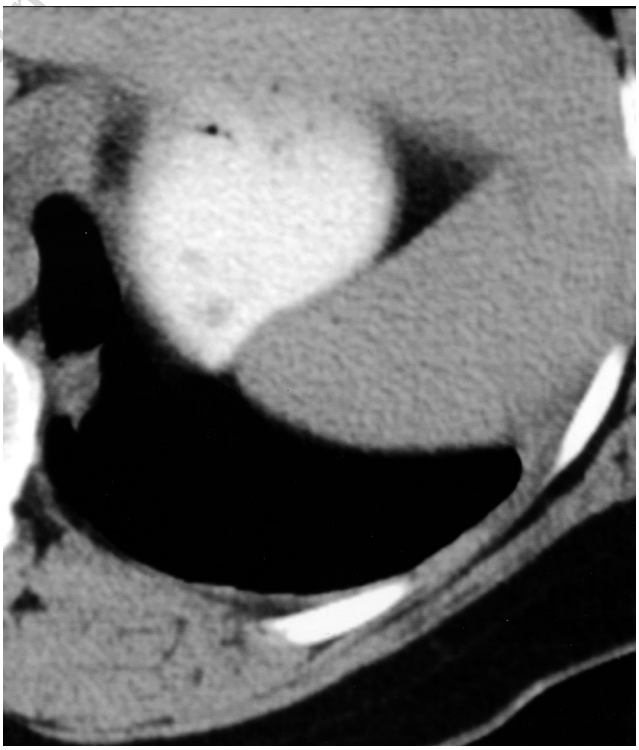

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Figure 1. Multiple pulmonary nodules (A and B) in a 46-year-old female former smoker. Soft tissue windows reveal calcification of the right upper lobe lesion (C), but the uncalcified left lower lobe nodule (D) was excised with video assisted thoracoscopic surgery. Pathologic analysis revealed numerous noncaseating granulomas without evidence of organisms.

include thoracic pathology not necessarily related to underlying rheumatoid disease, e.g., malignancy and infection. The importance of this lies in the controversies surrounding the management of RA patients with lung lesions. That is, when may further evaluation, such as surgical intervention, be indicated? Our survey indicates that patients with RA

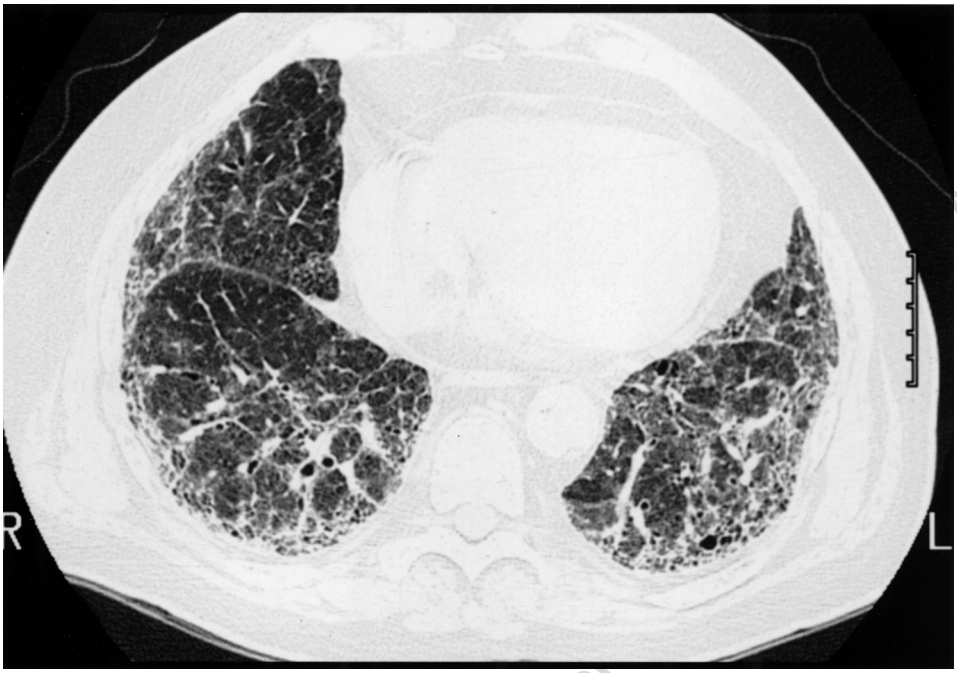

Figure 2. High resolution CT scan of the chest in a 67-year-old man with long-standing RA treated with multiple immunosuppressive medications. Bilateral, predominantly peripheral reticular and ground-glass infiltrates as well as honeycombing are visible. Open-lung biopsy result was consistent with usual interstitial pneumonia. He died at home 2 months later.

undergo thoracic surgical procedures for a variety of indications, including focal lung lesions (many of which were found to be malignant neoplasms), diffuse parenchymal infiltrates, and pleural processes.

Pulmonary manifestations of RA are varied and have been well described[1-6,8-12]. The prevalence of specific manifestations, however, is difficult to estimate due to a number of factors. Published studies are drawn from heterogeneous population groups ranging from autopsy series to a cohort of asymptomatic outpatients. Moreover, varied criteria are utilized to define pulmonary diseases, which are sought using different methods of detection, i.e., radiography, pulmonary function testing, bronchoalveolar lavage, or lung biopsy.

There are a number of diagnostic approaches to lung lesions using tissue samples. There are few published data regarding the use of bronchoscopic or fine-needle aspiration lung biopsy in patients with RA. Filho and colleagues[13] described the use of transthoracic needle aspiration of a lung nodule in a single patient with RA, and noted histologic features to be considered in the diagnosis of a rheumatoid nodule. Popp and colleagues[14] reported the use of bronchoscopy in 46 patients with RA and noted reproducible changes in inflammatory cell counts compared with healthy controls and patients with other connective tissue diseases.

Several studies have focused on analysis of surgical lung biopsy in RA patients[9,10]. The primary objective of these studies was to analyze histopathologic features as well as correlation with chest imaging, pulmonary function testing, and patient outcomes. For example, Yousem and colleagues[8] reported 40 patients with "active pulmonary disease" suspected to be related to underlying RA. This study, and that of Hakala, *et al*[9], showed rheumatoid nodules to be the most frequent lung manifestation of RA. However, both studies also revealed that most patients had more than one histopathologic abnormality that included bronchiolitis obliterans organizing pneumonia (BOOP), other forms of interstitial pneumonias, and lymphoid hyperplasia. Vasculitis, active infection, and pure airway disease (constrictive bronchiolitis) were infrequently encountered. Cervantes-Perez and associates[10] analyzed open lung biopsy specimens from 25 hospitalized RA patients, of whom 11 were asymptomatic. Features of interstitial, vascular, and bronchial involvement were noted in 76% of patients, although the clinical significance of these findings is unclear. Nonetheless, it appears that a significant proportion of patients with pulmonary involvement of RA may be asymptomatic[10,11].

Autopsy data of 81 patients with RA were reported by Suzuki and colleagues, who found 17% of deaths were due to pneumonia and another 9.9% were caused by respiratory failure[12]. Of interest, pulmonary fibrosis was present in 34.6% of all autopsied patients, including 80% of those patients who died from pneumonia[12].

To our knowledge, this is the largest series describing surgical therapy and/or biopsy of pleuropulmonary lesions

in patients with RA. We do not conclude that all lesions encountered were necessarily a result of underlying RA, but believe that important information can be drawn from the data.

In contrast to the case series mentioned above, our study identified only 4 (6.3%) out of 64 patients with localized lesions to have rheumatoid nodules on surgical excision[8,9,15]. This relatively low number may be related, in part, to referral bias at a large tertiary care institution. Malignancy (24 cases) and granulomas (23 cases) were seen more commonly. Notably, the mean age for those patients with lung cancer was 72 years, while the patients with granulomas averaged 56 years of age. Although infection was documented in only 6 cases of granulomas, it is likely that a large proportion of these granulomas was related to previous histoplasmosis, which is endemic to the upper Midwest US where most of our patients reside. Additionally, the relatively low incidence of documented infection is likely related to alternative, nonsurgical methods of detection (sputum culture with or without bronchoscopy).

Anecdotal reports of an association between RA and lung carcinoma have been published, although it is generally believed that the incidence of lung malignancies in this population is no higher than that seen in the general population[16,17]. Isomaki, *et al*, however, reported a higher incidence of lymphoma, leukemia, and myeloma in RA patients compared with controls in the Finnish population[16]. They also found the incidence of lung cancer was increased in men but not in women. More recent data from Europe also report increased risk of lung cancer found in an analysis of hospital-based records of patients with rheumatoid disease[18,19].

Our series identified 20 cases of primary bronchogenic carcinoma, 12 men and 8 women, all of whom were either current or former tobacco smokers. The predominant type appeared to be squamous cell, and 2 men later developed a second primary lung cancer of different histology. In 95% of the cases, patients proceeded directly to surgery, without serial radiographic observation, likely related in part to smoking status, age, and development of a new lesion on chest imaging. Patients appeared to tolerate surgery well, with a single postoperative complication as described above. Two cases showed a background of interstitial fibrosis on histologic examination of the resected lung specimen. It has been suggested that pulmonary fibrosis may present a risk for the development of lung cancer[20,21]. Relationship correlation between cigarette smoking, lung cancer, and RA deserves further investigation, but it appears that nodular lesions in this patient population should be viewed with a higher suspicion of neoplasm.

Pleural involvement is thought to be one of the most common respiratory manifestations of RA, and has been reported in up to 50% of patients[1-6]. It often occurs concurrently with other thoracic manifestations of RA, such as rheumatoid nodules or interstitial parenchymal disease[4]. Although it has been suggested that empyema is more common in patients with RA compared to the general population[2], our study identified only 2 cases, while 3 additional patients with pleural disease proved to have a sterile pleuritis. These apparently small numbers may be partly related to referral bias, but also suggest that many cases of pleural disease in RA are self-limited or responsive to medical therapy.

Roughly one-third of our patients underwent thoracic surgery for evaluation of diffuse interstitial lung infiltrates. Most of these cases represented interstitial pneumonitis and fibrosis attributed to the underlying RA, i.e., "rheumatoid lung." Drugs were implicated as the cause of diffuse lung infiltrates in only 10% of these cases and infectious causes were identified in another 10%. Recent revisions in the classification of idiopathic interstitial pneumonias may have clinical relevance with respect to rheumatoid lung disease[22]. We are currently reexamining these lung biopsy specimens to reflect the most recent accepted classification scheme.

The 20% rate of postoperative mortality in the diffuse lung disease group was unexpectedly high. Most of the lung biopsy specimens revealed diffuse alveolar damage or acute interstitial pneumonia superimposed on chronic interstitial pneumonia. It appeared that many of these patients were experiencing acute exacerbations, with surgical lung biopsy utilized to help exclude treatable conditions such as infection. This risk of postoperative mortality did not appear to correlate with the degree of pulmonary function impairment. Those that died had relatively mild pulmonary dysfunction, while others with more severe impairment survived the postoperative period. As the understanding of the pathophysiology of interstitial lung disease in RA evolves, and improved treatments become available, surgical lung biopsy may become more important in the early management of these patients.

We conclude that patients with RA undergo thoracic surgical procedures for a variety of indications, including focal lung lesions, pleural abnormalities, and diffuse interstitial infiltrates. Focal abnormalities may deserve close attention, as nearly one-third of focal lesions proved to be malignant, and all occurred in patients with history of smoking. Further research is needed to determine the influence, if any, of underlying systemic inflammation on the development and course of lung malignancy. Although pleural involvement is commonly encountered in RA, very few patients require surgical intervention. Operative mortality was relatively low, except in a subset of patients undergoing surgical lung biopsy for evaluation of diffuse lung infiltrates. These deaths appeared to be related to preexisting lung disease and acute exacerbations for which these patients were being evaluated. Further investigation of these issues seems warranted.

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