Collagen vascular or connective tissue disorders are a group of autoimmune diseases in which antibodies attack the body’s own organs and systems. Among the many targets of these auto-antibodies is connective tissue, which is the supporting structure for all of the body’s cells.

An important component of connective tissue is the protein, collagen. Abnormalities in blood vessel structure and function are also typical, accounting for the term “collagen vascular diseases,” which is often used interchangeably with connective tissue disorders. These disorders typically feature inflammation and scarring in several organs and tissues. The joints are frequently involved, particularly in the most common of these conditions, rheumatoid arthritis. Thus, rheumatology is the primary medical subspecialty involved in the diagnosis and care of these patients. Lung involvement may complicate the course of most of these conditions and sometimes can dominate the clinical picture.

**Whom does it affect?**

*Epidemiology, prevalence, economic burden, and vulnerable populations*

Some connective tissue disorders, notably rheumatoid arthritis and Sjögren’s syndrome, are quite common, whereas scleroderma (systemic sclerosis) and
lupus (systemic lupus erythematosus) have an intermediate prevalence. All tend to strike mostly young and middle-aged women. They are more common in African Americans, in whom the severity of disease and, in particular, lung involvement is also higher. In the case of scleroderma, an especially vulnerable population is the Choctaw Native Americans in Oklahoma, in whom the prevalence is 469 per 100,000 (1).

The frequency and type of lung involvement in connective tissue disorders varies based on the underlying disease. Of all the connective tissue disorders, scleroderma is most likely to affect the lungs. Pulmonary fibrosis, also known as interstitial lung disease, which results in progressive scarring of the lungs, occurs in over two thirds of scleroderma patients (2). The most serious pulmonary complication of the connective tissue disorders is the involvement of the blood vessels in the lungs, which causes decreased oxygen uptake and pulmonary arterial hypertension (elevated blood pressure in the arteries of the lungs). This occurs in 10 to 15 percent of patients with scleroderma and in up to 5 percent of patients with the other conditions (2).

In lupus, pleurisy (inflammation of the lining around the lung) occurs in over one third of patients, often with pleural effusion (build-up of fluid around the

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Demographics</th>
<th>Most frequent manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>0.3–2.1 percent of population</td>
<td>Female to male ratio: 3 to 1; peak onset at age 35–50 years</td>
<td>Potentially disabling arthritis; increased risk of cardiovascular disease</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus (Lupus)</td>
<td>15–50/100,000</td>
<td>90% are females of child-bearing age; higher prevalence in African Americans</td>
<td>Fatigue, body aches, skin rash, neurologic complaints; effects on kidney, lung, heart</td>
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<tr>
<td>Scleroderma (Systemic Sclerosis)</td>
<td>19–75/100,000</td>
<td>Female to male ratio: 3:1; peak onset in 3rd–5th decades; more frequent in African Americans, Hispanics, and American Indians</td>
<td>Skin thickening; effects on vascular system, lung, kidney, gastrointestinal tract, heart</td>
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<td>Sjögren’s Syndrome</td>
<td>0.5–1 percent</td>
<td>Predominantly middle-aged women (female to male ratio: 9 to 1)</td>
<td>Dry eyes and dry mouth; effects on joints</td>
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<tr>
<td>Polymyositis</td>
<td>1/100,000</td>
<td>More common in women; all ages</td>
<td>Muscle weakness; difficulty swallowing; rash around eyes; effects on heart, lung</td>
</tr>
</tbody>
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lung) (3). Acute and potentially life-threatening types of lung involvement, such as alveolar hemorrhage (bleeding into the lung), are also observed in 5 to 15 percent of lupus patients (3). Evidence of narrowing of the bronchi on breathing tests is surprisingly common, observed in about one quarter of patients with rheumatoid arthritis and Sjögren’s syndrome (4). Bronchiolitis (severe obstruction of the small airways) is an infrequent, but potentially devastating, complication of rheumatoid arthritis. Respiratory muscle weakness leading to shallow and difficult breathing can also occur in connective tissue disorders, especially polymyositis, which involves the muscles elsewhere in the body.

Lung infections are common in connective tissue disorders. This association may be related to the immunologic abnormalities accompanying the primary disease, aspiration of stomach or mouth contents into the lungs, or, most importantly, the effects of immunosuppressive agents used to treat these diseases. Recently, the advent of powerful new immunosuppressive agents (tumor necrosis factor blockers) for rheumatoid arthritis has placed renewed focus on the risks associated with immunosuppressant therapy. These agents may also increase the rates of tuberculosis and other serious infections (5). In lupus, up to half of all deaths are due to infections.

Connective tissue disorders exact a large economic burden on society. A common measure that integrates mortality and disability and can be thought of as a year of “healthy life” is Disability Adjusted Life Years (DALY). In a recent analysis, rheumatoid arthritis accounted for 98 DALY lost per 100,000 population in the United States, accounting for nearly 1 percent of all DALY lost (6). Direct healthcare costs have been estimated to be about $10,000 annually per patient (in 2006 dollars), plus a similar amount in lost productivity or indirect costs. Annual medical expenditures for lupus patients were over $12,000 (in 2005 dollars) per patient, greater than those for healthy control subjects; in patients with lupus and kidney involvement, costs were nearly four times greater than those for healthy control subjects (7). For scleroderma, a recent Canadian study estimated total annual costs (direct and indirect) at over $18,000 (2007 Canadian dollars; about $17,990 U.S. dollars) per patient (8). The relative contribution of lung involvement versus that of other organs to the overall economic burden, morbidity, and mortality of connective tissue disorders is variable and difficult to ascertain, but significant lung disease clearly has a substantial impact.
What we are learning about the disease

Pathophysiology, causes: genetic, environment, microbes

The causes of connective tissue disorders are unknown, but intense research efforts are beginning to shed light on the mechanisms of tissue injury.

In rheumatoid arthritis, an infectious agent is suspected, but conclusive evidence has yet to emerge. Nonetheless, considerable progress has been made in delineating the cellular and molecular pathways involved in the joint and cartilage destruction of the disease, leading to the successful development of biologic agents that antagonize tumor necrosis factor, a key mediator of tissue damage.

In lupus, an interaction between susceptibility genes and environmental factors is believed to cause the disease. Hyperactivity of the immune system is a prominent feature, and variations in several genes that control the immune
response increase the risk of lupus. The circulating auto-antibodies associated with lupus appear to be important in the disease process. They aggregate in specific tissues, induce inflammation and injury, and alter connective tissue

Case Study

A 46-year-old Caucasian woman and mother of two children with a long-standing history of scleroderma was referred to a pulmonologist for activity-related shortness of breath occurring for the past year. Pulmonary fibrosis was noted on her chest radiograph, accompanied by a reduction in the lung capacity on pulmonary function tests. The scarring was treated with immunosuppressive medications for one year, and supplemental oxygen was started. Her symptoms and lung function tests improved, but 16 months later, her breathing became more labored, and she was hospitalized. An ultrasound of the heart (echocardiogram) demonstrated enlargement of the right side of the heart, with elevation on the estimated pulmonary artery pressure. Pulmonary hypertension was confirmed by right heart catheterization, and she was enrolled in a clinical research study of sildenafil, a drug that “relaxes” blood vessels and has been subsequently approved for treating pulmonary hypertension. With this treatment, she experienced a significant reduction in pulmonary artery pressure accompanied by an improvement in exercise capacity.

However, her condition gradually deteriorated with worsening pulmonary hypertension, despite the addition of a continuous intravenous medication, treprostinil. Lung transplantation was considered, but the procedure was considered too risky, given the extent of skin and esophageal disease. Her breathing continued to become more labored, with decreasing oxygen levels, until she died at age 50.

Comment

This case highlights the clinical challenges of lung involvement in scleroderma, which is the leading cause of death in this condition (2). Treatment options are limited and associated with potentially serious side effects. Moreover, the benefits of therapy are often small, and as this case illustrates, short-lived. Despite the availability of treatment, pulmonary hypertension associated with scleroderma carries a worse prognosis compared with other types of pulmonary hypertension, especially when accompanied by concomitant interstitial lung disease (9).
cells. A similar inflammatory reaction is seen in Sjögren’s syndrome and polymyositis, targeting the salivary glands and muscles, respectively.

Injury to the endothelium (blood vessel cells) is believed to be the initiating pathologic event of scleroderma. This injury, perhaps mediated by immune cells or a viral infection, initiates a cascade of events resulting in narrowing of the small blood vessels, insufficient blood flow, and subsequent scarring. The fibrosis, or scarring, is marked by excessive and seemingly disorganized collagen deposition. Environmental exposures that have been associated with a small minority of cases of scleroderma include silica dust from coal and gold mining, polyvinyl chloride, epoxy resins, and aromatic hydrocarbons.

How is it prevented, treated, and managed?

**Prevention, treatment, staying healthy, prognosis**

Until its causes are positively established, there is no specific preventative strategy for the connective tissue disorders. However, smoking increases the risk of rheumatoid arthritis, and the disease is more severe in smokers, so smoking cessation is an important way to reduce the risk and severity of that disease.

The chronic inflammation in connective tissue disorders is associated with an increased risk of cardiovascular disease events, such as heart attack and stroke. In lupus, the risk of premature cardiovascular disease is increased up to 50-fold, and in rheumatoid arthritis, the risk of death due to a cardiovascular event is increased 50 percent compared with control subjects (10). In this respect, both lupus and rheumatoid arthritis are considered to be independent risk factors for cardiovascular disease, similar to hypertension, diabetes, and smoking. Thus, aggressive prevention of cardiovascular disease should be pursued. Strategies include maintaining a healthy diet, regular exercise, smoking cessation, and careful management of diabetes, high blood pressure, and high cholesterol. Statin drugs, which are used to lower cholesterol, may also have other benefits such as anti-oxidant and anti-inflammatory actions.

The treatment of connective tissue disorders depends on the specific disease, which organs are involved, and how rapidly the disease is progressing. Non-steroidal anti-inflammatory drugs (NSAIDs) are useful for pain, body aches, and fatigue. Anti-malarial drugs can reduce the skin and joint manifestations of lupus. Corticosteroids and other immunosuppressive drugs are useful to control inflammation and can be life-saving for patients with certain acute lung manifestations of
lupus. The U.S. Food and Drug Administration (FDA) has approved several drugs for the treatment of pulmonary hypertension, which is often associated with connective tissue disorders. Unfortunately, scleroderma patients do not appear to benefit from these drugs as much as patients with other forms of pulmonary hypertension.

The prognosis of lung involvement in connective tissue disorders depends on the severity and type of underlying disease. Extensive lung disease, however, carries a 10-year survival rate of only 40 percent (2). The most serious chronic pulmonary manifestation of connective tissue disorders is pulmonary hypertension. Even with therapy, 3-year survival of pulmonary hypertension with scleroderma was only 47 percent in a recent large study from Britain (9).

Are we making a difference?

Research past, present, and future

Past research efforts have characterized the various clinical and pathologic features of respiratory involvement in the connective tissue diseases. With advances in molecular biology techniques, progress is now being made in characterizing the cellular and molecular pathways involved in tissue injury. In addition, associations with certain genetic variants involved in the immune response and the presence of specific auto-antibodies have been linked to these disorders. Understanding the mechanisms by which the different lung manifestations occur and the variations that patients have should identify which molecules are involved in the disease and allow new therapeutic targets to be developed. For example, why do some patients with scleroderma experience no or minimal lung disease, some develop severe interstitial lung disease or pulmonary hypertension, and some develop both?

Large, well-designed clinical trials will continue to be fundamental for bringing new, safe, and effective treatments to clinical practice. The relatively low prevalence of lung disease in connective tissue disorders other than scleroderma makes such trials challenging. Success has been achieved in scleroderma, where a multi-institutional network, the Scleroderma Lung Study, is testing therapies for interstitial lung disease (11). In pulmonary hypertension, after an initial early trial restricted to scleroderma patients (12), subsequent study designs have incorporated connective tissue disorders as a subset within a larger group of subjects without connective tissue disorders. Although this approach has facilitated the approval of
novel agents for these patients, it does not allow us to understand fully the role of these drugs in pulmonary hypertension associated with connective tissue disorders, which may be different from other forms of pulmonary hypertension.

**What we need to cure or eliminate collagen vascular lung disease**

The collagen vascular diseases are almost certainly multi-factorial in origin, and thus, it is unlikely that a single “magic bullet” will be discovered to cure all of them. Continued study of the highly complex immune system and how the body turns against itself in the process of autoimmunity, however, will likely indentify key molecules involved in these processes. The next steps would be to identify ways to bypass or correct the defects and to understand how these factors interact with environmental factors to trigger the diseases and their pulmonary complications. Close collaboration between clinicians and basic scientists will be critical to the success of such efforts. A most important element will be the patients themselves who will take the time and make the effort to participate in the clinical research studies needed to find a cure.
References


Web sites of interest

Arthritis Foundation
www.arthritis.org

Lupus Foundation of America
www.lupus.org

Scleroderma Foundation
www.scleroderma.org

Pulmonary Hypertension Association
www.phassociation.org

Coalition for Pulmonary Fibrosis
www.coalitionforpf.org