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An Overview of Collagen Vascular Disease–Associated Interstitial Lung Disease

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The collagen vascular diseases (CVDs), also called connective tissue disorders (CTDs), encompass a heterogeneous group of autoimmune disorders with protean manifestations. Many of these disorders have a predilection for pulmonary involvement, especially interstitial lung disease (ILD). Approximately 15% of patients presenting for evaluation of ILD have an underlying CVD.[1] The frequency and pattern of ILD vary with the type of underlying CVD.

CVDs most commonly associated with ILD include rheumatoid arthritis (RA), Progressive Systemic Sclerosis/Scleroderma (SSc), Dermatomyositis/Polymyositis (DM/PM), antisynthetase syndrome (AS), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), and Sjögren syndrome (SS).[2,3] The more common patterns of ILD encountered in patients with CVD include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphoid interstitial pneumonia (LIP), and acute interstitial pneumonia (AIP).[3,4]

Early identification of CVD-associated ILD (CVD-ILD) is essential in guiding patient management. Occasionally, symptoms related to ILD are the first clinical manifestations of the underlying CVD, preceding more classic signs and symptoms.[5] Also, pulmonary involvement portends a worse prognosis, especially if there is associated pulmonary hypertension.[6-9] Treatment typically involves immunosuppression. Medications used to treat CVD may result in lung injury, which must be distinguished from ILD related to the underlying disease. The immunosuppressive drugs used to treat CVDs can predispose patients to opportunistic pulmonary infections, which can confound pulmonary findings.[10] Although this article focuses on interstitial patterns of pulmonary involvement, other thoracic manifestations of the CVDs include airway, vascular, myocardial, pericardial, and pleural involvement.[2,3]

Timely imaging can help diagnose CVD and add prognostic information. Serial imaging, in conjunction with pulmonary function tests (PFTs), can be used to follow severity of pulmonary involvement and to guide management. Imaging can also identify extrapulmonary sites of CVD involvement, such as the esophagus in SSc and the glenohumeral joints in RA. Discussion of imaging findings focuses on the high-resolution CT (HRCT) appearance, given its undisputable role in evaluating ILD relative to other thoracic imaging modalities.

HRCT Patterns Commonly Encountered in CVD-ILD

The HRCT findings characteristic of the various patterns of CVD-ILD mirror the findings seen in corresponding idiopathic interstitial pneumonias (IIPs). For example, when CVD-ILD manifests as UIP, NSIP, or OP, the HRCT findings are similar to the findings seen in UIP in the setting of idiopathic pulmonary fibrosis (UIP/IPF), idiopathic NSIP, and cryptogenic organizing pneumonia (COP), respectively.

Findings typical of the UIP pattern include peripheral- and basilar-predominate reticulation, honeycombing, and traction bronchiectasis, often with spatial and temporal heterogeneity. UIP in the setting of CVD tends to have less honeycombing than UIP/IPF, fewer fibroblast foci on histologic analysis, and a somewhat better prognosis.[11]

HRCT findings in NSIP differ in that ground glass, often with subpleural sparing, predominates rather than honeycombing. Although subpleural sparing may be helpful in diagnosing NSIP, it is not a requirement. NSIP tends to be more spatially and temporally homogeneous than UIP. Typically, NSIP first manifests with ground glass in the setting of active inflammation (cellular NSIP), which will either resolve, stabilize, or develop increasing reticulation, traction bronchiectasis, and honeycombing (fibrotic NSIP). Because NSIP is a common histologic pattern in CVD and may precede other clinical manifestations, the presence of NSIP in any new patient should prompt a thorough workup for underlying CVD.[12]

OP typically demonstrates patchy consolidation or ground glass in a subpleural, peribronchial, or bandlike pattern. OP is also associated with the "reverse halo sign," which may be helpful in suggesting the diagnosis.[13] The presence of OP

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superimposed on other patterns of ILD, especially NSIP, is very suggestive of an underlying CVD.[4] LIP is classically associated with SS and typically manifests as ground glass with poorly defined centrilobular nodules and scattered thin-walled cysts on HRCT images.[14] Cysts associated with calcified nodules may represent amyloid deposits.[15]

AIP pattern commonly expresses itself as airspace disease (consolidation and ground glass) that is usually a manifestation of underlying diffuse alveolar damage (DAD), although occasionally OP is seen as well. This pattern usually occurs in the setting of an acute exacerbation of ILD and can occur in nearly every form of CVD-ILD.[16] When an acute exacerbation manifests as DAD, the prognosis is typically poor. AIP usually superimposes on a different underlying pattern of ILD, such as UIP or NSIP, but can occasionally be the initial pulmonary manifestation of CVD.[2]

Rheumatoid Arthritis

RA is the most common CVD affecting 1% of the population; women are affected 3 times as often as men.[17] Although RA typically manifests as an inflammatory arthropathy, extra-articular manifestations are common and include a variety of cutaneous lesions, atherosclerosis, anemia, neuropathy, episcleritis, vasculitis, renal amyloid deposition, and pleural disease.[18] Pulmonary manifestations include nodules, bronchiectasis, bronchiolitis obliterans, and ILD.[3] The lifetime risk of developing RA-ILD is ~8%. The risk of death for patients with RA-ILD is 3 times higher than for patients with RA alone, making RA-ILD an important cause of morbidity and mortality among patients with RA.[19]

RA-ILD is commonly associated with a variety of patterns of ILD. This is in contradistinction to most other CVDs, which primarily manifest with 1 or 2 particular patterns of ILD. The patterns of ILD most commonly associated with RA include UIP (most commonly) (Fig. 1), NSIP (Fig. 2), and occasionally OP. Lee et al[20] found UIP to be the most common histopathologic pattern in patients with RA-ILD (56%), followed by patients with NSIP (33%) and patients with OP (11%). Among IIPs, UIP pattern is associated with a much worse prognosis as compared with other IIPs, such as idiopathic NSIP and cryptogenic OP. Patients with RA-ILD and a UIP pattern on imaging also appear to have a worse prognosis and are less likely to respond to therapy as opposed to patients with RA-ILD with an NSIP or OP pattern or both.[21,22]

Systemic Sclerosis/Scleroderma

SSc is a rare chronic autoimmune disorder, with both limited and diffuse forms that result in fibrosis and deposition of collagen. It may present with a variety of clinical manifestations, including tight thickened skin, joint contractures, pigmentation changes, vascular occlusion resulting in ulcers, Raynaud phenomenon, dilated hypomotile bowel, and renal disease.[23] Pulmonary involvement typically manifests as ILD or pulmonary hypertension or both, which are significant causes of morbidity and mortality.[24] The prevalence of ILD in patients with SSc varies from 25%-90% depending on the subtype of SSc and the methods selected to define ILD.[25]

NSIP is the most common pattern of ILD in SSc, representing approximately 80% of cases (Fig. 3). There are a small but significant number of cases that present with a UIP pattern as well.[26-28] Studies suggest that patients with a UIP pattern in SSc have poorer outcomes as compared with patients with an NSIP pattern.[27,28] Often patients with SSc have a patulous esophagus, which can help suggest the underlying diagnosis (Fig. 3). Bronchiectasis in SSc can be prominent and when out of proportion to the amount of fibrosis, it can be used to help diagnose SSc. Some have postulated that this may be due to a combination of traction bronchiectasis from the ILD and

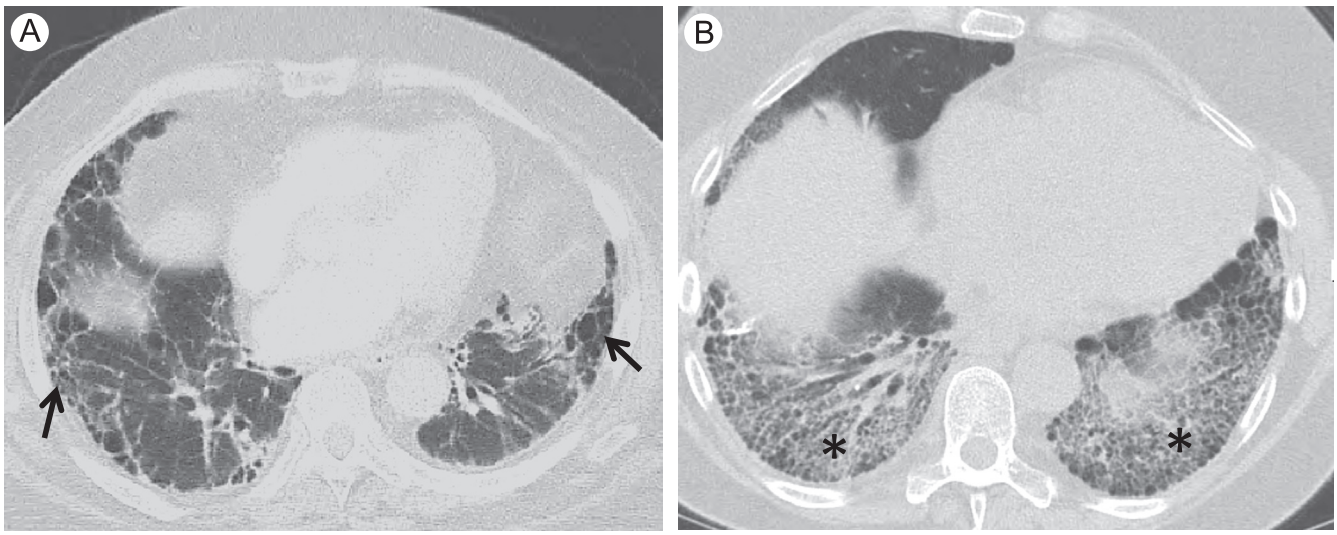

Figure 1 Rheumatoid arthritis. (A) High-resolution CT (HRCT) image from an 81-year-old woman with rheumatoid arthritis (RA) and usual interstitial pneumonia (UIP) on biopsy. Note the peripheral and basilar predomanent honeycombing with irregular septal line thickening, traction bronchiectasis, and a relative paucity of ground glass (arrows). (B) HRCT image from a 65-year-old woman with RA and fibrotic nonspecific interstitial pneumonitis (NSIP) on biopsy. Note that there is less honeycombing and more ground glass (*) as compared with (A).