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Editorial

Pulmonary Fibrosis: A Common Cause with Rheumatologists and Physicians

It is highly enigmatic that a 'healing process' should assume a destructive role. But this is exactly what happens in 'Pulmonary Fibrosis' and other similar conditions in the liver or other organs. Fibrosis is the pathological process of healing of a wound following tissue injury and inflammation. It is essentially a process of repair which results in scar formation. Fibrosis is meant to limit the ongoing damage but itself becomes damaging when diffuse and progressive. In the lungs, the process of unchecked fibrosis of normal parenchymal tissue causes progressive loss of function—a cause of respiratory disability, failure and death. Factually, pulmonary fibrosis is the end result of a large number of medical conditions justifying a common cause with physicians in general and rheumatologists in particular.

Diffuse fibrosis of lung parenchyma, commonly referred to as 'diffuse parenchymal lung disease' or 'interstitial lung disease' (ILD) is a syndromic condition secondary to large number of systemic as well as pulmonary conditions.[1,2] Idiopathic pulmonary fibrosis (IPF) in the absence of a known secondary cause is the prototype of ILD which has become an increasingly important condition in view of its progressive and fatal nature. IPF is an aggressive disease with poor outcome akin to that of most forms of cancer. Somewhat similar presentation and progression are also seen in ILDs secondary to rheumatological diseases of autoimmune origin collectively known as connective tissue diseases (CTDs), such as systemic sclerosis (SSc), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD) and others.

There is a fair reason to say that pulmonary physicians should work along with rheumatologists and internists who handle some of these important conditions mentioned in the foregoing paragraph for an efficient management of secondary ILDs. On the other hand, the rheumatologists and internists need to diagnose and manage the potential occurrence of pulmonary fibrosis in these disorders. It is worth mentioning that ILDs in the presence of CTDs has been described in a significantly large number of patient-population. ILD is described in 40% patients with autoimmune myopathies, 30–40% with SSc, 40% with Sjögren's syndrome, 10% of RA and 12% of systemic lupus erythematosus.[3] Others have reported ILDs in almost up to 90% of SSc and up to 68% of RA.[4-6] ILD may sometimes present long before the other manifestations of a yet-to-be diagnosed CTDs.[7]

It is worth mentioning here that some of the most significant advances in pulmonary medicine have been made in the field of pulmonary fibrosis, even though it remains a major challenge for physicians.[8] The scene in this country is similar or worse in view of the restrained resources.[2,9] In the past, treatment of both idiopathic and secondary ILDs involved the use of anti-inflammatory drugs, primarily the corticosteroids. Some of the add-on drugs included immunosuppressives (azathioprine, cyclophosphamide and others), mucolytics and occasionally, anti-fibrotics. Treatment of IPF in particular had been highly unsatisfactory. There has been a tremendous shift in the therapeutic paradigm of idiopathic ILDs, particularly, IPF. Anti-inflammatory drugs were found to be ineffective, in fact harmful in most instances. Several investigators reported that there is no active inflammation in IPF. The disease-pathogenesis largely consists of repetitive cycles of aberrant repair following persistent and/or recurrent injury of the epithelium. It is almost like a neo-proliferative disorder characterised by apoptosis, increased angiogenesis, neo-vascularisation, matrix remodelling, fibroblast activation and dysfunction. On the other hand, ILD associated with a CTD is an inflammatory disease which continues to be treated with anti-inflammatory drugs with fairly good results.

Interstitial fibrosis occurs as the end-result of inflammation which produces clinical, functional and prognostic similarities to primary ILDs. It had been highly debatable whether these patients should be administered anti-fibrotic drugs in addition to treatment with the anti-inflammatory drugs. An early administration of anti-fibrotic drugs should delay its onset and slow down the decline justifying the use. But the drugs do add to the total burden, cost and toxicity of treatment. The benefit was never proven until recently.

The detection of ILD depends upon the enthusiasm with which a physician, most often a rheumatologist in case of CTDs pursues the diagnosis and the methods employed for this purpose. In this regard, the use of high resolution computed tomography scan is a highly sensitive method for early detection. The decision to undertake a particular investigation and the time to do rests with the rheumatologist looking after the patient. It is for this very reason that the British Thoracic Society Guidelines recommend the inclusion of rheumatologists in the multidisciplinary approach for the diagnosis and

management of patients with ILD, and in CTD-ILD.[10] On the other hand, an unrecognised CTD or evidence of autoimmunity may be found in a patient previously diagnosed to suffer from IPF or an idiopathic ILD on a systematic approach to diagnosis and discussion with the rheumatologist.[11]

The need to engage rheumatologists has increased since there is good amount of clinical evidence now to approach the management of CTD associated ILDs with progressive fibrosis on similar lines as IPF. For example, the use of anti-fibrotic drug nintedanib (previously reserved for only IPF) has been now recommended for treatment of other progressive fibrosing interstitial involvement seen in systemic sclerosis.[12,13] The drug has been also found to be useful for progressive fibrosis associated with other CTDs, chronic hypersensitivity pneumonias, sarcoidosis and unclassified idiopathic interstitial pneuomonia.[14,15] Recently, the U.S. Federal Drug Administration (FDA) has also approved the extended indications for the use of anti-fibrotic drugs.[16] The approval was based on a randomised, double-blind, placebo-controlled trial of 576 patients aged 20-79 years with SSc-ILD in whom there was a reduced decline in forced vital capacity with nintedanib than with the use of a placebo. Initial studies have not shown any such benefit with the use of other anti-fibrotic drug.[17]

The pros and cons for and against the use of a particular drug in an individual CTD may change in the near future once the evidence from other trials becomes available. Moreover, new anti-fibrotic drugs which are more effective may also appear on the scene. Nonetheless, there is no doubt that early recognition of a fibrosing ILD in a CTD is important for an early initiation of anti-fibrotic treatment and better prognosis. The use of some of the anti-fibrotic drugs may help to slow down the disease associated decline in lung function and disease progression. It does not stop or reverse the function to its previous levels. An early use is likely to preserve this function before the disease progresses to a significant disability level. While the effect on the mortality remains to be seen in clinical trials, it might also delay the onset of respiratory failure and death. It is, therefore, necessary that a rheumatologist and/or other physicians are on board before deciding the management strategy in a case of CTD associated ILD.

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