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EDITORIAL

DPLD- An Alarming Issue for Pulmonologists

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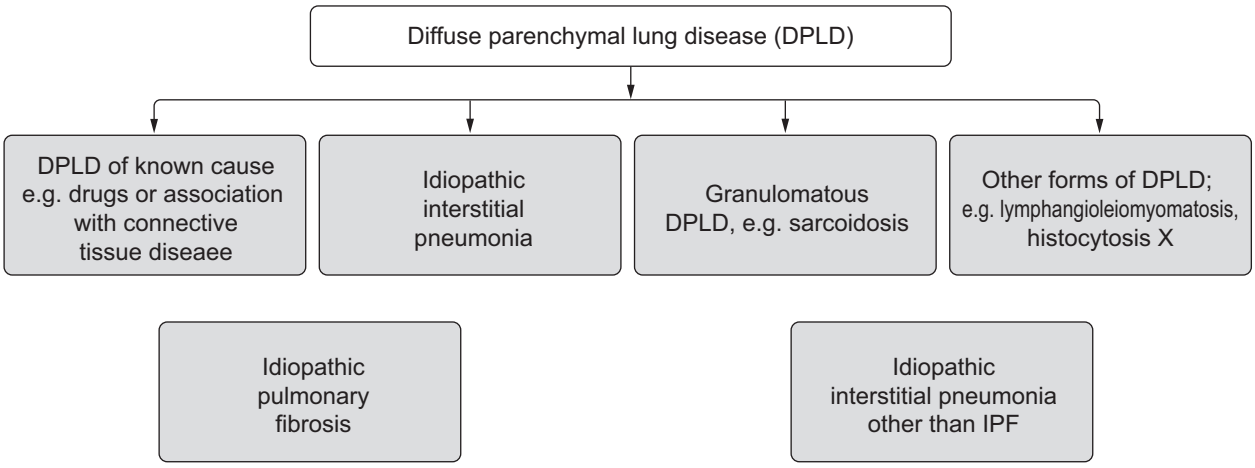
The term DPLD (Diffuse parenchymal lung disease), in general implies the clinical manifestation of inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and alveolar epithelial lining cells.[1]DPLD comprise a broad spectrum of disorders of varying etiology with some similarities in clinical, imaging, physiologic and pathologic features.

There are limited epidemiologic studies describing the global burden and geographic heterogeneity of interstitial lung disease (DPLD) subtypes. Among seventeen methodologically heterogenous studies that examined the incidence, prevalence and relative frequencies of DPLDs, the incidence of DPLD ranged from 1 to 31.5 per 100,000 person-years and prevalence ranged from 6.3 to 71 per 100,000 people. In North America and Europe, idiopathic pulmonary fibrosis and sarcoidosis were the most prevalent DPLDs while the relative frequency of hypersensitivity pneumonitis was higher in Asia, particularly in India (10.7–47.3%) and Pakistan (12.6%). The relative frequency of connective tissue disease DPLD demonstrated the greatest geographic variability, ranging from 7.5% of cases in Belgium to 33.3% of cases in Canada and 34.8% of cases in Saudi Arabia.[2]Studies suggest a prevalence of 81 in 1,00,000 for men compared with 67 in 1,00,000 for women.[3,4]In the United States, the mortality rate from DPLD increased twofold from 1980 to 2014.[5]

Classification of DPLD can be based on several parameters including etiology, clinical features, histopathology, or pattern of radiologic abnormalities. A classification of DPLD based on the presence or absence of an identifiable cause (including underlying systemic disease) is likely the most practical option for clinicians.[1]

The hallmarks of a DPLD are progressive dyspnea and cough, abnormal chest imaging and impairedpulmonary function results.[6,7] The initial evaluation of a patient with suspected DPLD is focused on confirming the presence of DPLD, duration of symptoms and obtaining clues to the underlying cause.[6] This is performed by assessment of demographics and findings gathered from history taking, physical examination, chest imaging and laboratory tests.



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Taking a careful history is of paramount importance in identifying the clinical manifestations. Duration of symptoms, smoking history, review of the past medications, family history of hereditary disorders, occupational history; all are important. Patients often present with cough, which is typically dry and distressing, and breathlessness, which is often insidious in onset but thereafter relentlessly progressive. Physical examination reveals the presence of inspiratory crackles and in many cases digital clubbing develops. The typical radiographic findings include in the earliest stages, ground glass and reticulonodular shadowing, with progression to honeycomb cysts and traction bronchiectasis. Pulmonary function tests typically show a restrictive ventilatory defect in the presence of small lung volumes and reduced gas transfer.[8] If the clinical, imaging and laboratory results are inconclusive, lung histopathology may be needed to reach a specific DPLD diagnosis.[1]

Idiopathic pulmonary fibrosis:

Among DPLDs, there is a subset of disorders referred to as idiopathic interstitial pneumonias (IIP) that comprise a heterogenous group of diffuse parenchymal lung diseases characterized by varying patterns of inflammation and fibrosis.[9,10] IPF (Idiopathic pulmonary fibrosis) is the most common form of IIP accounts for 20-30% of DPLDs.[4,11,12] It is associated with characteristic clinical, radiographic, physiologic and pathologic manifestations but is also a diagnosis of exclusion.The incidence and prevalence of IPF are not fully defined. A systematic review analyzing data from populationbased studies in 1968 to 2012 estimated an incidence range of to 9 cases per 1,00,000 per year for Europe and North America.[13] Both the incidence and prevalence of IPF increase markedly with age, particularly over 75 years[12] and is uncommon before the age of 50 years. There is a strong association with cigarette smoking. IPF is progressive, irreversible and usually fatal, with a portion of these deaths attributed to the phenomenon of 'acute exacerbation."The clinical course of patients with IPF is variable and can display long periods of stability, a steady gradual decline, and/or periods of acute deterioration.[14,15]

Acute exacerbation of IPF is defined as " an acute clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality" The diagnostic criteria include (1) previous or concurrent diagnosis of IPF, (2) acute worsening or development of dyspnea typically less than 1 month of duration, (3) CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern and (4) deterioration not fully explained by cardiac failure or fluid overload.[16]Little is known about the pathogenesis of acute exacerbation of IPF. Along with histopathology of diffuse alveolar damage, there is evidence of loss of alveolar epithelial cell integrity.[17] It has been suggested that acute exacerbation of IPF may represent a response to a clinically occult infection[18,19] but direct evidence of an association with infections is still missing.[20]

Treatment:

DPLD is not a single disease but encompasses many different pathological processes. Hence treatment is different for each disease. If a specific occupational exposure cause is found, the person should avoid that environment. If a drug cause is suspected, that drug should be discontinued.

Many cases due to unknown or connective tissue-based causes are treated with corticosteroids, such as prednisolone.[21] Some people respond to immunosuppressant treatment.

Treatment of IPF: IPF is a progressive and fatal disorder without any spontaneous remission and, until the recent introduction of antifibrotic therapy, no therapy had been shown to be effective.

Era before antifibrotic therapy: Although corticosteroids alone were the mainstay for the treatment of IPF for many years, the response to corticosteroid in IPF has been almost uniformly poor. In addition, significant complications can result from corticosteroid therapy, affecting the quality of life. Because of poor response of IPF to corticosteroids, various immunomodulatory agents were tried but studies on combination therapy (prednisone, azathioprine and N-acetylcystine) was shown to be associated with increased rate of death and hospitalizations compared with placebo.[1]

Current Era: On the basis of accumulating knowledge about the pathogenic mechanisms involved in IPF, newer antifibrotic agents i.e. Pirfenidone and Nintedanib have been developed. Pirfenidone is a novel antifibrotic agent that inhibits

progression of fibrosis in animal models. Nintedanib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor, vascular endothelial growth factor receptors and fibroblast growth factor receptors. Both pirfenidone and nintedanib reduce the rate of FVC decline by approximately 50% over 1 year of treatment in patients with IPF. Pooled data analysis and post adhoc analysis suggest these drugs may improve quality of life, reduce the rate of hospitalizations and acute exacerbations, and prolong survival. Combination therapy with both pirfenidone and nintedanib is being explored. Given the scarcity of donars along with age consideration and comorbidities seen in IPF patients, lung transplantation is indicated only in carefully selected patients with severe lung disorders unresponsive to pharmacological treatment.[1]

Management of acute exacerbation has generally consisted of enhanced immunosuppression with pulse dose of methylprednisolone, sometimes combined with another immunosuppressive agent, such as cyclophosphamide or cyclosporine, but no convincing evidence of benefit has been demonstrated.[1] Management of other comorbidities including Gatroesophageal reflux disease, pulmonary hypertension, sleep-related breathing disorder, lung cancer and other issues must be sorted out.

Despite the advancement of medical science, the longterm survival in IPF is distinctly poor, after diagnosis the median survival is approximately 3 years; with only 20-35% survive up to 5 years.[1]

Using a database from the National Center for Health Statistics, OLSON et al.[22]clearly show for the first time that the mortality rates have increased from 1992 to 2003. Although these data do not confirm that the prevalence is increasing, they do suggest that there have been improvements in reporting and identification of fibrotic lung diseases. But still a vast of majority of patients are remain undiagnosed. Early recognition of symptoms, appropriate diagnosis ang comprehensive care of patients are essential to reduce the current mortality and morbidity resulting from DPLD.

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References:

1. Ryu JH, Selman M, Lee JS, Colby TV, King JR TE.Idiopathic pulmonary fibrosis. In: Broaddus VC, Ernst JD, King Jr TE, Lazarus SC, Sarmiento KF, Schnaap LM, et al, editors. *Murray & Nadel'sTextbook of Respiratory Medicine*. 6th edition. Philadelphia: Elsevier.2016:1118-1144.
2. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in Global Prevalence of Interstitial Lung Disease. Front Med (Lausanne). 2021 Nov 4;8:751181. doi: 10.3389/fmed.2021.751181. PMID: 34805219; PMCID: PMC8599270.
3. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of Interstitial lung diseases. *Am J Respir Crit Care Med*. 1994: 150 (4):967-972.
4. Demedts M, Wells AU, Anto JM, et al. Interstitial lung diseases: an epidemiological overview. *EurRespir J Suppl*. 2001;32:2s-16s.
5. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Trends and patterns of differences in chronic respiratory disease mortality among US countries, 1980-2014. *JAMA*. 2017;318(12):1136-1149.
6. Ryu JH, Daniels CE, Hartman TE, YiES. Diagnosis of Interstitial lung diseases. *MayoClin Proceed*.2007;82(8):976-986.
7. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thorasic Society in Collaboration with the Thorasic Society of Australia and New Zeland and the Irish Thorasic Society. *Thorax*. 2008; 63 suppl 5:v1-58. *Erratum Thorax*. 2008;63(11);1029.
8. Reid PT, Innes JA. Respiratory Medicine. In: Ralston SH, Penman ID, Strachan MWJ, Hobson RP,editors. *Davidson's Principles and Practice of Medicine*. 23rd edition. UK: Elsevier.2018: 605-608.
9. Travis WD, Costabel U, hansell DM, et al. an official American Thorasic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir CritCare Med*. 2013;188(6):733-748.

10. Larsen BT, Colly TV. Update for pathologists on idiopathic interstitial pneumonias. *ArchPathol Lab Med*.2012;136(10):1234-1241.

11. Thomeer MJ, Costabe U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung disease in three European countries. *EurRespir J suppl*.2001:32:114s-8s.

12. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*.2006;174(7):810-816.

13. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *EurRespir J*.2015;46(3):795-806.

14. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005; 142: 963–967.

15. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 16: 636–643.

16. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit CareMed*.2016;194(3):265-275.

17. Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. EurRespir J 2003; 22: 821–826.

18. Hyzy R, Huang S, Myers J, et al. Acute exacerbation of idiopathic pulmonary fibrosis. Chest 2007; 132: 1652–1658. 32.

19. Vannella KM, Moore BB. Viruses as co-factors for the initiation or exacerbation of lung fibrosis. Fibrogenesis Tissue Repair 2008; 1: 2.

20. Tomioka H, Sakurai T, Hashimoto K, et al. Acute exacerbation of idiopathic pulmonary fibrosis: role of Chlamydophila pneumonia infection. Respirology 2007; 12: 700–706.

21. "Interstitial lung disease: Treatments and drugs" Mayo Clinic.com

22. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med* 2007; 176: 277–284.