Review Article

Jour Cas Stu Cas Rep, 2(1), 2023, 12-17

Journal of Case Studies and Case Reports

Open access peer reviewed international indexed journal Online ISSN: 2583-4428

Content Available at www.saap.org.in

Drug Induced Interstitial Lung Disease: Mechanism and Diagnostic Approach

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Received: 10 Feb 2023 Revised: 26 Feb 2023 Accepted: 19 Mar 2023

Abstract

To achieve remission or stabilize the course of the disease, clinicians may encounter substantial challenges in creating a patient-centered, tailored therapeutic plan and generating a reliable analysis of a particular type of interstitial lung disease (ILD). A precise diagnosis of the specific form of ILD must be made when a patient is evaluated for suspected ILD. Only then can an appropriate organization plan be developed, with the goal of relieving symptoms and restoring or significantly improving quality of life while also providing the patient with useful prognostic information. In order to arrive at a multidisciplinary consensus diagnosis, the results of lung biopsies and lavage are examined. The gold standard for diagnosing interstitial lung disease is a multidisciplinary approach that includes significant aspects of the patient's medical history and physical examination, a blood panel, pulmonary function tests, high resolution computed tomography imaging, and, if necessary, bronchoalveolar lavage. Future management of interstitial lung disease will be influenced by advancements such as the introduction of the disease-modifying anti-fibrotic medicines pirfenidone and nonreading.

Keywords: ILD, Infection, fibrotic pattern, respiratory tract.

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doi: https://doi.org/10.37022/jcscr.v2i1.598

Introduction

The term Interstitial Lung Disease (ILD) characterizes a multitude of pathologies, many, but not all of which mainly affect the pulmonary interstitial. ILD is characterized by inflammation or fibrosis in the interstitial space, which primarily leads to impaired air talk, leading to dyspnoea and, in many cases, respiratory failure to death. Drug-induced interstitial lung disease (DIILD) happens when revelation to a drug causes inflammation and eventually fibrosis of the lung interstitial. DIILD is identified on the basis of medical, physiological and radiological findings consistent with ILD; a time-based relationship between beginning of symptoms and drug exposure; absence of another more likely cause, e.g., infection, pulmonary oedema, radiation-induced lung injury, progression of the fundamental disease; and development upon withdrawal of the suspected causative agent with or without corticosteroid treatment and, in some cases, decline upon re-challenge. Some types of drugs can cause drug-induced interstitial lung disease (DILD). The prevalence of Drug induced lung disease. for each in dividual drug is variable (1).

1. Histology

The histology of interstitial Lung virus (ILD) in common variable immunodeficiency (CVID)is heterogeneous and assorted patterns are frequently observed within a single biopsy, including non-necrotising granulomatous inflammation, lymphoid interstitial pneumonitis, lymphoid hyperplasia, follicular bronchiolitis, establishing pneumonia, and interstitial fibrosis; ILD has to be differentiated a from lymphoma. The histologic findings of pulmonary drug responses are often non-specific and mimic those of other situations, such as idiopathic interstitial pneumonia and collagen vascular disease (2). Almost, all histopathological subtypes of interstitial lung disease may be detected diffuse alveolar injury (DAD), chronic interstitial pneumonia. while some medicines, such as minocycline, methotrexate (MTX), and nitrofurantoin, induce stereotypical

responses in the lungs (EP, acute granulomatous interstitial lung virus, and the cellular kind of non-specific pneumonia respectively), other medicines, such as amiodarone and bleomycin, may be related with additional than one histological pattern (3).

2. Methods

We conducted a systemic review of observational studies in accordance with the preferred reporting items for systemic reviews and meta-analyses consensus guidelines with the aims of:

- ❖ determining the incidence and prevalence of drug induced interstitial lung disease (DIILD),
- ❖ identifying common causative drugs.
- ❖ identifying risk factors for DIILD.
- ❖ Comparing imaging and non-imaging investigations for assessment and diagnosis of DIILD.
- ❖ assessing the prevalence of DILLD subtypes.
- ❖ measuring the impact of glucocorticoid therapy on outcomes.
- ❖ defining the prognosis of DILLD.

3.Mechanism involved in DILD

The onset and spread of DILD may be facilitated by a multitude of distinct devices 7. The tissue expression of several forms of lung injury may include the independent or collective activity of both cytotoxic and immunological modes of action 8 (4).

- Cytotoxic pulmonary injury

Cytotoxic pulmonary injury brought on by medication may be caused by a number of mechanisms, such as the production of many cytokines, damage to alveolar patch-up mechanisms, and a reduction in reactive oxygen species in the deactivation of lung metabolites. Numerous delegates might be harmful to the lungs (5).

One common instance of cytotoxic lung harm is chemotherapy lung. During or soon after treatment with chemotherapeutic representatives, such as antibiotics, alkylating drugs, anti-metabolites, nitrosamines (rapamycin analogy), and podophyllotoxins, a severe kind of pulmonary reaction occurs (6).

4. Pathogenesis

The pathophysiology of the progression of fibrotic ILD (PFILD) is attributed to a few mechanisms. Recurrent inflammatory irritation to the epithelium or vascular injury are generally what start the process, causing damage to cells as well as disruption to the healing mechanism. As a result, fibroblasts migrate from the lung epithelium, travel peripherally to the site of damage, and become activated as myofibroblasts (7,8).

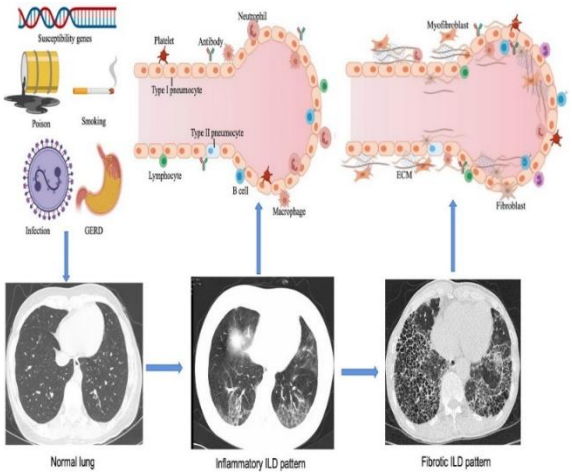


Figure no 1: - Pathogenesis of interstitial lung disease (PILD).

6. Diagnosis

Axial computed tomography (CT) and chest X-ray both show the distinctive appearance of well reticulations and nodular penetrates; in more advanced stages, fibrotic distortion and occasionally the characteristic of a "honeycombing" lung occur. The parameters for characterizing the UIP design, which is the trademark of IPF and indicative of interstitial lung disease, were provided by the American Thoracic Culture/European Breathing Society (9).

Diagnosis of cytotoxic pulmonary injury

Since many anti-neoplastic medicines are routinely given to cancer patients, it can be challenging to determine which drug is the cause of drug-induced pulmonary poisonousness. Unsuitably, at this time, there isn't a single tissue graft or diagnostic test that can conclusively verify a diagnosis of chemotherapy-associated lung virus [10]. Currently, there is no easily accessible or clinically verified analytical test for cytotoxic lung damage that uses in vitro drug task. Many medication responses are thought to be influenced by metabolites of reactive medicines. Analytical assays could be based on variations in the bulk of cells' ability to detoxify medications' response metabolites, which are factors in medicine toxicity reactions (10).

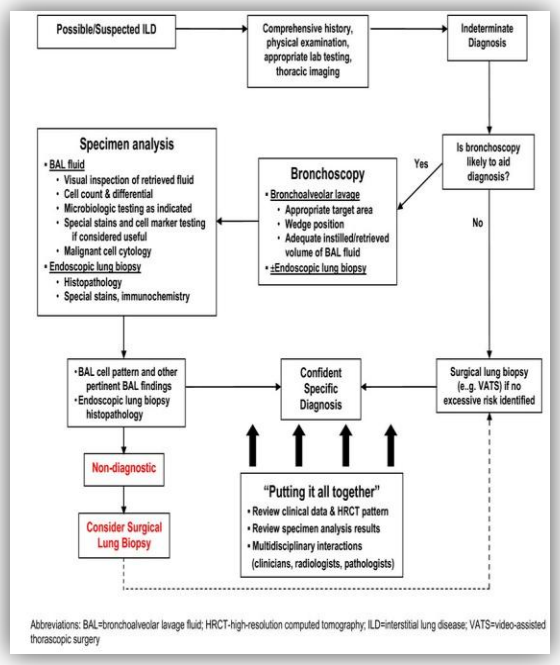


Figure no: 2 Bronchoalveolar lavage fluid (BAL)

➢ Diagnosis of immune mediated DILD

The lungs act as a barrier against viruses by triggering the immune system on a prolonged basis, which leads to effective host defines through inflammation.

This steady, low-level start provides an environment that might support pro-indications and the ensuing responses of the immune system. The most prevalent symptom of minocycline-induced pneumonia (MIP) is EP. Gil et al. found lymphocyte-mediated precise cytotoxicity against minocycline-bearing alveolar macrophages in vitro, suggesting a key involvement for T lymphocytes in the immune response to MIP (11).

7. Classification of interstitial lung disease

❖ Idiopathic pulmonary fibrosis (IPF)

IPF is typically diagnosed in people between the ages of 65 and 70, with an increasing frequency as people age. Male sex, smoking, and wood or metal fume inhalation are risk factors for IPF.

❖ **Non-specific interstitial pneumonia (NSIP)**

Within the group of idiopathic interstitial pneumonias (IIP), NSIP is regarded as a separate entity. Bilateral ground-glass opacities are the most often detected radiological characteristic on HRCT in NSIP. However, this pattern appears not just in idiopathic conditions but also in a number of other contexts, such as medication toxicity and HP, as well as in certain patients who have familial pulmonary fibrosis (12).

❖ **Hypersensitivity pneumonitis (HP)**

This is a multifactorial syndrome with a granulomatous inflammatory pattern that is caused by recurrent exposure to a broad spectrum of putative antigens.

Immune complex formation mediates the non-fibrotic form, while T-lymphocytes are presented with antigens by alveolar and dendritic cells during the fibrotic form (13).

It is impossible to determine the sensitizing antigen in over half of the cases.

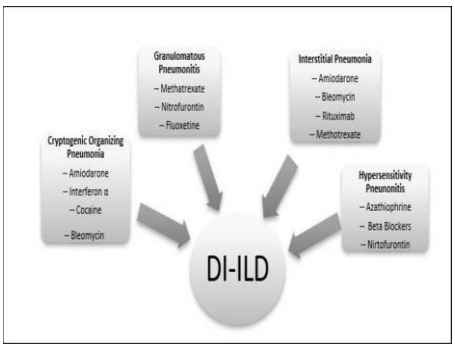


Fig no: -3 Medications of drug induced interstitial lung disease (DIILD)

- Cryptogenic organizing pneumonia: is rare lung condition affecting the small airways bronchioles and alveoli tiny air sacs.
- Granulomatous pneumonitis; this condition causes inflammation in your lungs and other parts of your body.
- Interstitial pneumonia; The interstitial pneumonia are a heterogenous group diffuse parenchymal lung disease characterized by specific clinical, radiologic and pathologic features.
- Hypersensitivity pneumonitis: Hypersensitivity pneumonitis is an immune system disorder in which your lungs become inflamed as an allergic reaction to inhaled microorganisms, plant and animal proteins or chemicals.

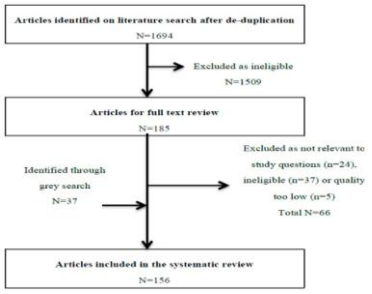


Fig no: 4 The review process from abstract review to final inclusion, in total, these 156 articles report

approximately 6200 patients with conformed or suspected (DIILD.)

We also observed a geographic bias, with almost one-third of the studies coming from Japan (mostly big post-marketing registrations). It has previously been shown that Japanese communities had a higher reported frequency of ILD than those in the west; however, a large portion of this has been thought to be artefactual due to coding and spontaneous reporting procedures, rather than biological reasons (14).

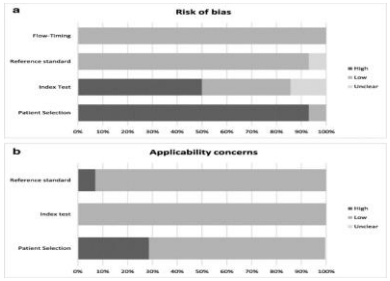


Fig no: -5 Summary of applicability concerns and risk of bias, as assesses using the grading recommendations assessment and development Evidence method.

(a) Risk of bias (b) Applicability concerns.

- Antibiotics

Urinary tract infections are frequently treated and prevented using nitrofurantoin. 16–48% of nitrofurantoin-related adverse events that are documented in registry studies are attributed to DIILD. The percentage of patients who were hospitalized was 75%, whereas the fatality rates for patients suffering from acute lung responses were 0.5% and 8%, respectively. Most cases resolve quickly, and the underlying mechanism is thought to be an acute hypersensitivity reaction. Days after the medication is started, or hours if nitrofurantoin exposure has occurred previously, an acute lung reaction may happen. conducted case-control research contrasting the use of nitrofurantoin with DIILD in relation to other antibiotics (15).

- Amiodarone

Based on registries, amiodarone is one of the most common causes of DIILD, with an incidence of 1.2-8.8% and a mortality of 3-37%. In one study, the median time to death was 17 days, and 37% of patients hospitalized for amiodarone-associated DIILD died within 90 days of admission.

10.Risk Factors for the development of DIILD

Risk factors for DIILD development differ according on the virus, medication, and patient population being treated. Indeed, risk factors have been a common aspect of many drugs.

• Age: For patients receiving treatment with bleomycin gemcitabine, targeted drugs, leflunomide, MTX, amiodarone, and nitrofurantoin, increased age has been found to be a major risk factor for DIILD (16).

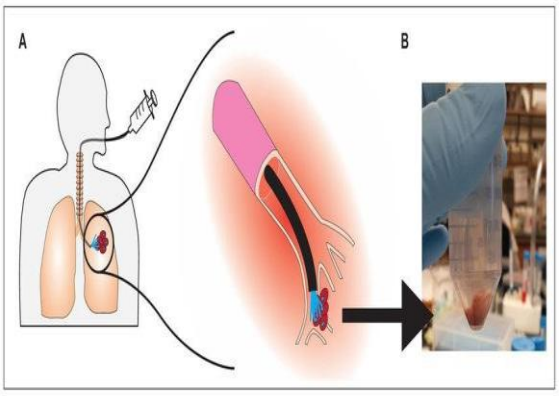
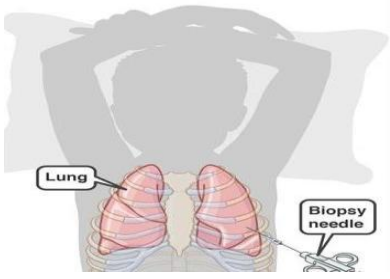


Fig no; 6sampling of broncho alveolar lavage

13. lung biopsy

Few studies have examined the use of lung biopsies, and while nearly all histopathological features have been linked to DIILD, none are DIILD-specific. Although there is little evidence to support the routine use of biopsy in the diagnosis of DIILD, it may be helpful in specific circumstances where there is diagnostic uncertainty or to rule out alternative causes, much as BAL. A lung biopsy is a form of medical operation. The procedure often involves the removal of tissue or growths from the lungs. There are various reasons why a doctor might recommend a lung biopsy. They may choose from several types of biopsies, depending on the type most suitable for the individual (17).



------lung biopsy

Fig no:7 Lung biopsy

16.Idiopathic pulmonary fibrosis

The hallmarks of idiopathic pulmonary fibrosis include an irreversible loss of lung function and increasing dyspnea. The typical interstitial pneumonia histological and/or radiological pattern serves as its definition. Coughing and exertional dyspnea are the usual presenting features, with a slow onset. Reduced lung compliance and gas exchange, loss of alveolar architecture, and altered extracellular matrix replace

healthy lung tissue, ultimately resulting in respiratory failure.

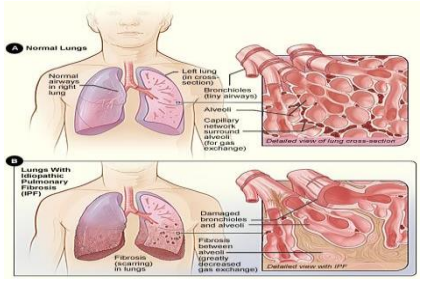


Fig.8.Idiopathic pulmonary fibrosis

17.Treatment

Since ILD-related lung damage is frequently gradual and irreversible, treatment typically focuses on enhancing quality of life, reducing the disease's rate of progression, and using medicine to relieve symptoms.

1. Oxygen treatment
2. Respiratory therapy
3. Symptomatic care
4. Comorbidity treatment may be utilized if necessary. For obstructive sleep apnea, continuous positive airway pressure (CPAP) is used.
5. Surgery.
6. supportive/palliative care.

18.Nintedanib

The intracellular tyrosine kinase inhibitor nintedanib is uttered and acts on multiple tyrosine kinase receptors, such as PDGF, VEGF, and FGF. These receptors are critical for the disruption of the signalling pathway of fibroblast initiation and proliferation. Diarrhoea is the most common adverse effect reported when taking nintedanib. These outcomes led to the acceptance of nintedanib for the treatment of IPF patients, and it was included in the guidelines for this illness.

Conclusion

The complex and varied set of illnesses known as interstitial lung diseases necessitates a comprehensive approach to diagnosis and treatment.

The management of interstitial lung disease will continue to be shaped by developments in anti-fibrotic drugs and innovative pharmacological therapies, such as transbronchial lung biopsies. ILDs continue to fall under the category of orphan illnesses, and they place a growing strain on the healthcare system.

Comorbid condition identification and treatment may also be very beneficial.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

References

1. Allen JN, Davis WB, Pacht ER. Diagnostic significance of increased bronchoalveolar lavage fluid eosinophils. American Review of Respiratory Disease. 1990 Sep;142(3):642-7.
2. Blum RH, Carter SK, Agre K. A clinical review of bleomycin—a new antineoplastic agent. Cancer. 1973 Apr;31(4):903-14. https://pubmed.ncbi.nlm.nih.gov/4122362/
3. Amulya A, Sirisha V, Rao CB, Chennam JV. CURRENT TRENDS ON ROLE OF NANO PARTICLES ON PULMONARY DISEASES. International Journal of Research in Pharmacy and Chemistry. 2012;2(3):685-703.
4. Cooper Jr JA, White DA, Matthay RA. Drug-induced pulmonary disease: Part 1: Cytotoxic drugs. American Review of Respiratory Disease. 1986 Feb;133(2):321-40. https://pubmed.ncbi.nlm.nih.gov/2869727/
5. Gindi S, Hawisa NT, Baburao C, Khagga M. Role of Ficus bengalensis leaves as a hepatoprotective on rifampicin induced hepatic damage in albino rats. Research Journal of Pharmacology and Pharmacodynamics. 2010;2(6):378-9.
6. Camus P, Fanton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. Respiration. 2004 Aug 13;71(4):301-26. https://pubmed.ncbi.nlm.nih.gov/15316202/
7. Dey B, Hwisa NT, Khalf AM, Mitra A, Katakam P, Rao CB. Pharmaco-epidemiological Studies on Self Medication and Drug Utilization Pattern in Chronic Diseases via Prescription Auditing. International Journal of Scientific Research in Knowledge. 2013 Nov 1;1(11):464. (PDF) Pharmaco-epidemiological Studies on Self Medication and Drug Utilization Pattern in Chronic Diseases via Prescription Auditing (researchgate.net)
8. Li S, Shi J, Tang H. Animal models of drug-induced pulmonary fibrosis: an overview of molecular mechanisms and characteristics. Cell Biology And Toxicology. 2022 Oct;38(5):699-723.
9. Kupferschmid JP, Rosengart TK, McIntosh CL, Leon MB, Clark RE. Amiodarone-induced

complications after cardiac operation for obstructive hypertrophic cardiomyopathy. The Annals of thoracic surgery. 1989 Sep 1;48(3):359-64. *https://pubmed.ncbi.nlm.nih.gov/2774719/*

10. Kumar KR, Nagaraju GV, Subrahmanyam SN, Nagarani K, Shareef S, Tennygilphin M, Namballa M. Assessment on Elements Involving the Academic Performance among Pharmacy Students: A Cross-Sectional Observational Study. Int J Cur Res Rev| Vol. 2021 Dec;13(23):141.
11. Limper AH. Chemotherapy-induced lung disease. Clinics in chest medicine. 2004 Mar 1;25(1):53-64.
12. Logan PM, Primack SL, Staples C, Miller RR, Müller NL. Acute lung disease in the immunocompromised host: diagnostic accuracy of the chest radiograph. Chest. 1995 Nov 1;108(5):1283-7. https://pubmed.ncbi.nlm.nih.gov/7587430/
13. Duran I, Siu LL, Oza AM, Chung TB, Sturgeon J, Townsley CA, Pond GR, Seymour L, Niroumand M. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. European Journal of Cancer. 2006 Aug 1;42(12):1875-80.
14. Meyer KC. Interstitial lung disease in the elderly: pathogenesis, diagnosis and management. Sarcoidosis Vasc Diffuse Lung Dis. 2011 Jul 1;28(1):3-17. https://pubmed.ncbi.nlm.nih.gov/21796886/
15. McFadden RG, Fraher LJ, Thompson JM. Gold-naproxen pneumonitis: a toxic drug interaction?. Chest. 1989 Jul 1;96(1):216-8. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3426467*
16. O'sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Annals of Oncology. 2003 Jan 1;14(1):91-6. https://www.sciencedirect.com/science/article/pii/S0923753419639116
17. Pietra GG. Pathologic mechanisms of drug-induced lung disorders. Journal of thoracic imaging. 1991 Jan 1;6(1):1-7.
18. Ravella S, Angel M, Subramanian H, Thangavel N, Namballa M, Lokesh D, Mishra AK, Nagaraju GV. Navigating the Future of Cancer Diagnosis: A Comprehensive Review of Novel Approaches for Community-Based Treatment. future.;1:6.
19. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. Br Med J (Clin Res Ed). 1982 May 15;284(6327):1440-2.
20. Potente G, Bellelli A, Nardis P. Specific diagnosis by CT and HRCT in six chronic lung diseases. Computerized medical imaging and graphics. 1992 Jul 1;16(4):277-82.