LITERATURE REVIEW

Farmer's Lung Disease

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ABSTRACT

Occupational lung disease is a lung disease or disorder that occurs due to the inhalation of dangerous particles, mist, vapors, or gases while a person is working. The materials accumulate in the respiratory tract or lungs. The type of lung disease that occurs depends on the size and type of the inhaled material. Substances that cause occupational lung disease are toxic materials called noksa. Noksa is a substance that can cause damage to the anatomical structure of body organs and cause respiratory tract function disorders. The lung disease that many farmers experience is often called farmer's lung disease (FLD). FLD is part of hypersensitivity pneumonitis (HP). HP, also known as extrinsic allergic alveolitis, is a group of lung diseases caused by the inhalation of various antigenic organic materials. The most common cause is exposure to agricultural biological dust derived from straw, mold spores, or other dust. HP can be a secondary reaction due to repeated and prolonged inhalation of specific antigens in sensitive individuals. Diagnosis of FLD is often inaccurate. Many of these cases are diagnosed as idiopathic interstitial lung disease. A complete anamnesis should be performed, especially regarding the history of exposure to moldy hay, previous work, and domestic animals, to determine the existence of a history of exposure to the antigen and to confirm the diagnosis.

INTRODUCTION

The agricultural sector in Indonesia is an essential aspect of the country's economy because agriculture in terms of production is the second most influential sector after the manufacturing industry. Based on the data from International Labor Organization (ILO), around 1.3 million people worldwide work in agriculture, nearly 60% are in developing countries. Most agricultural workers are found in Asia, accounting for more than 40% of the world's farming population. Central Statistics Agency stated that the number of people working in Indonesia in the first quarter of 2018 was 127.07 million people. The agricultural sector has the most significant percentage at 28.79% or 35.7 million people.[1,2]

Based on the data obtained from data and information center of Ministry of Health Republic of Indonesia, occupational lung disease or disorders caused by dust from the processing and storage of agricultural products are estimated to be quite a lot in 2014, namely 40,694 people who experience lung disease due to work.[3]

Occupational lung disease is a lung disease or disorder that occurs due to the inhalation of dangerous particles, mist, vapors, or gases while a person is working. The materials accumulate in the respiratory tract or lungs. The type of lung disease that occurs depends on the size and type of the inhaled material. Substances that cause occupational lung disease are toxic materials called noksa. Some types of particles that can cause lung disease include organic dust particles (vegetable matter, animal cotton dust, grain dust, wood dust), inorganic dust (mining, metal industry, ceramics, silica, asbestos), and irritant gases (petroleum, ammonia, CO_2, NO_2).[4,5]

The lung disease that many farmers experience is often called farmer's lung disease (FLD). The most common cause is the result of exposure to agricultural biological dust derived from straw, mold spores, or other dust.[5]

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Definition

FLD is a part of hypersensitivity pneumonitis (HP) which is mainly caused by inhalation of biological dust from straw, moldy spores, or dust from other agricultural products. This often occurs in the storage of straw or grain and the storage of agricultural products with high humidity levels. FLD was first described by Campbell in 1932.[6]

HP, also known as extrinsic allergic alveolitis, is a group of lung diseases caused by inhalation exposure to various kinds of organisms which are antigens.[7] HP can be a secondary reaction due to repeated and prolonged inhalation of a specific antigen in sensitive individuals. More than 200 antigens have been identified as causative agents for HP.[8]

Epidemiology

The epidemiology of FLD cannot be known with certainty and varies from country to country. This is due to several obstacles, including difficult diagnosis, non-standard classification, geographical variations, and weather in different countries. In a study in the United States, it was found that 30 per 100,000 working people suffer from interstitial lung disease and 2% of these incidents were HP. Wisconsin studied 1,400 individuals and estimated the prevalence for hypersensitivity pneumonitis to be 4.2%. Data in Europe, the prevalence of patients who experienced HP was 4 -15%.[9–11]

Etiology

The causes of FLD can be found in several places. The antigen characteristics that cause FLD have a small particle size, solubility, particle properties, and the ability to generate specific and nonspecific immune responses. The particle size that can cause the disease is 3µm because it can directly enter the terminal bronchioles and alveoli.[12,13] Bacteria and fungi are groups which cause the most FLD (Table 1).[14]

Table 1. Etiology of FLD

Category of Antigen	Specific Antigen	Source	Type of Disease
Bacteria	*Saccharopolyspora rectivirgula* *Thermoactinomyces vulgaris*	Moldy hay, rice seeds	FLD
Fungi	*Aspergillus sp.*	Moldy hay, rice seeds	- FLD - Mushro worker'

Pathophysiology & Pathogenesis

FLD occurs due to hypersensitivity or allergic reactions to organic antigens or chemicals which have low molecular weight and attacks vulnerable groups of people. FLD has nothing to do with increased immunoglobulin E (IgE) and eosinophils. This is not a disease of atopy. The interaction between antibody antigens in FLD causes type III (reactions immune complex hypersensitivity) and IV (delayed-type hypersensitivity).[15]

Certain host characteristics can determine susceptibility to develop FLD. FLD is more common in older men. Although this may depend on differences in exposure levels in people, it can increase in people who smoke because it can reduce IgG responses to inhaled antigens and affect cytokine production and alter the function of macrophages. Environmental risk factors include antigen load, duration of exposure, use of protective equipment, and type of work. The interesting thing about HP mechanism is there are only a few individuals who develop this disease. There are two hypotheses that can explain this. The first hypothesis states that genetic susceptibility or pre-existing environmental factors can increase the risk of developing HP after antigen exposure, and the second hypothesis is a defense mechanism against antigen exposure (Figure 1).[6,7]

Tumor necrosis factor polymorphisms are alpha (TNFa)-associated with inflammatory responses and crystallizable fragments (Fe). The symptoms occur in people with repeated exposure to antigens, thus the immune system becomes sensitized. Expressed normal T cell and Sermsted (RANTES), which is a chemotactic factor, will attract neutrophils to the alveoli, forming immune complexes and activate complement which causes neutrophil alveolitis within the first 4-12 hours after antigen exposure (acute). In subacute and chronic forms of HP, HP is triggered by T lymphocytes via a Th1 immune response which is responsible for lymphocyte alveolitis and granuloma formation. Genetic or environmental trigger factors lead to the development of an immune overreaction resulting in an apparent inflammatory reaction in the lungs. Humoral, cellular, and cytokine immune responses all cause progressive inflammation resulting in granulomatous formation in the lung parenchyma. Granulomatous inflammation requires the expression of Th1 cytokines, including TNF-α, IL-12, and IFN-γ. Continuous exposure to antigens will activate neutrophils and fibroblasts, resulting in collagen deposition and fibrosis.[6,7,15]

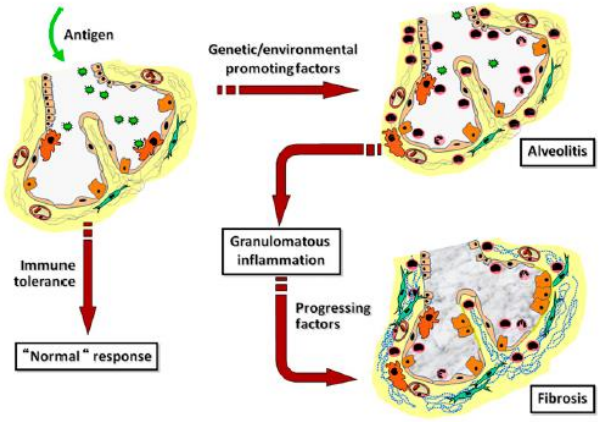

Figure 1. Reaction of aveoli to antigens

Diagnosis

Diagnosis of FLD is often inaccurate. Many of these cases are diagnosed as idiopathic interstitial lung disease. A complete anamnesis should be performed, especially regarding the history of exposure to moldy hay, previous work, and domestic animals, to determine the existence of a history of exposure to the antigen.[11,12,16]

In addition, the diagnosis is performed through laboratory examinations, chest X-rays, and lung function. Diagnosis of HP can use four major criteria approach and at least two minor criteria and there will ne no other lung disease with almost the same picture. This is still a challenge for the medical world because the existing criteria do not have standardized tests and have not been validated, and the level of diagnostic accuracy is unknown. There are several criteria created by Terho, Richerson, Cormier and Lacasse, and Schuyler and Cormier. Below are some of the predefined criteria.[9,17,18]

1. Terho
   Major criteria:
   a. History, physical examination, and pulmonary physiology test indicate interstitial lung disease
   b. HP-compliant chest photo image
   c. There is exposure as a cause
   d. There are antibodies to these antigens
2. Richerson
   Major criteria
   a. History, physical examination, and pulmonary physiology test indicate interstitial lung disease
   b. HP-compliant chest photo image
   c. There is exposure as a cause
   d. There are antibodies to these antigens
3. Cornier and Lacasse
   Major criteria
   a. Exposure according to the disease
   b. There are crackles at the time of inspiration
   c. Lymphocytic alveolitis (on Bronchoalveolar lavage/BAL examination)
   d. Shortness of breathes
   e. Infiltrates on chest X-ray (or High-Resolution Computed Tomography/HRCT)

   Minor criteria
   a. Episodes of fever
   b. Decrease in Diffusing Lung Capacity for Carbonmonoxide (DLCO) value
   c. Precipitation of antibodies to HP antigens
   d. Lung biopsy: Granuloma
   e. Improve by avoiding contact
4. Schuyler and Cormier
   Major criteria
   a. HP-compatible symptoms
   b. Evidence of exposure to antigen-based on history or detection in serum fluids or LAB
   c. Image according to HP on chest X-ray or HRCT
   d. There is lymphocytosis on LAB analysis
   e. HP-compatible histological features
   f. The "Natural challenge" test shows a positive result

   Minor criteria
   a. Rales bibasilar
   b. Decrease in DLCO
   c. Arterial hypoxemia at rest or during activity

Apart from these criteria, there are also those who divide the criteria for FLD or HP according to acute/subacute and chronic conditions (Table 2).[11,16]

Classical Hotel

FLD has several clinical manifestations. In 2016, European Allergy and Clinical Immunology (EAACI) divided the classification of HP into acute, subacute, or chronic conditions.[11,12,16]

Table 2. Diagnostic criteria for FLD or HP

Acute/Subacute	Chronic
- Occupational exposure to antigen sources - Recurrent symptomatic episodes, occurring 4 - 8 hours after exposure - The increased titer of specific IgG antibodies - There are inspiratory crackles on auscultation of the lungs - HRCT picture according to acute/subacute hypersensitivity If none of the criteria above, then one of the criteria below can replace it, namely: - There is lymphocytosis on LAB analysis - Anatomical pathology studies according to acute/subacute circumstances - A positive result on ICT or improvement after avoidance of exposure	- Exposure to antigen sources in the workplace - Increased titer of specific IgG antibodies - There was lymphocytosis on BAL analysis - Decreased DLCO values and/or hypoxemia at rest or exercise - Description of HRCT according to chronic hypersensitivity - Anatomical, pathological examination appropriate to the chronic condition Diagnosis is established if there are four or more of the above criteria.

A. Acute conditions

It occurs about 2 to 9 hours after exposure and improves in 12 to 72 hours without specific therapy. Clinical symptoms that can arise are fever, hypoxemia, gradual onset of weakness, malaise, myalgia, arthralgia, spasms, and cough with phlegm. There are rales at the basal lung on auscultation and cyanosis. On laboratory examination, there is leukocytosis, neutrophilia (which is also found in LAB), and lymphopenia without eosinophilia. On chest X-ray, it will show a picture of acute pulmonary edema. HRCT examination shows patchy or diffuse bilateral ground-glass opacities. These features illustrate the presence of diffuse lymphocytic interstitial pneumonitis. On DLCO examination, an impairment will be found. Most of these symptoms occur at work, and by the time the person leaves work, the acute symptoms will gradually lessen.

B. Subacute conditions

Repeated exposure causes a productive cough, shortness of breath, fatigue, and weight loss. A subacute condition is a form of phenotype which is difficult to identify. In a Lassie study conducted in 2012, 168 patients with HP occurred mostly in the subacute phase. On laboratory examination, lymphocytosis is often found, which is dominated by $CD8^+$ T lymphocytes. HRCT examination shows small nodules of the centers and areas of the lobes that appear dark. This can be caused by cellular bronchiolitis or organizing pneumoniae.

C. Chronic conditions

Chronic conditions can last for months or years. Exposure to low levels over several months will cause progressive shortness of breath with episodes of wheezing, cough with purulent sputum, recurrent low-grade fever, anorexia, weight loss, and occasionally respiratory failure. Chest X-ray shows diffuse interstitial fibrosis. Spirometric examination shows restriction, sometimes accompanied by obstructive abnormalities.

FLD or HP is caused by differences in intensity and duration of exposure. The low intensity of exposure but with longer duration of exposure tends to cause chronic HP, while the high intensity of exposure with short duration tends to cause acute HP.[11,12,16,17]

Medical Examinatio

There is no gold standard for enforcement of FLD or HP. The supporting examinations are needed to enforce HP.

1. Chest X-ray
   Chest X-ray is used primarily to exclude other diseases. Chest X-ray gives an abnormal appearance in 80% of patients, while the rest are normal. Chest radiographs in acute and chronic HP patients differed significantly. The acute radiograph shows a diffuse nodular appearance with scattered shadows or occasional consolidation. This appearance tends to occur in the lower lobe. There may be areas with fibrosis that reflect a previous acute episode. In addition, in chronic conditions, there are widespread reticulonodular infiltrates, fibrosis, and honeycombs appearance. X-ray abnormalities can return to normal if exposure has stopped within a few weeks.[17]
2. HRCT
   The results of a chest CT scan or HRCT are very important in diagnosing HP. In acute conditions, it is often seen as a diffuse infiltrate patch, ground-glass opacity, or consolidation. In subacute conditions, there may be nodular, reticulogranular shadows with ground-glass opacity. In chronic conditions, there is often bronchiectasis traction, thickening of the interlobular septal and lobular reticulation, especially in the peribronchovascular area.[14,18,19]
3. Examination of pulmonary function including DLCO
   Pulmonary function examinations which are performed in serial can help make the diagnosis but are not specific in determining the acute, subacute, and chronic forms. The result may be restriction, obstruction, or mixed abnormalities. The vital lung capacity (CV) and the first second forced expiratory volume (VEP_1) can be normal. In the acute/subacute conditions, there are restrictive symptoms with a normal or increased residual volume. In chronic conditions or residual disease, there are abnormal restriction and obstruction with decreased pulmonary function values.[14,18]
4. BAL
   BAL examination is a standard procedure for diagnosing FLD or HP by checking the fluid obtained from BAL to confirm the presence of microorganisms (bacteria and mycobacterium) and fungi. In alveolitis, lymphocytosis is obtained from BAL examination.[14]
5. Laboratory examination
   On laboratory examination, IgG value is increased and the rheumatoid factor is positive, but the number of eosinophils and IgE in serum is usually normal. In this examination, specific IgG, IgM, and IgA antibodies can be found with specific antigens (precipitation), which, apart from being found from bronchoalveolar rinses, can also be detected in serum.[14]
6. Specific antigen inhalation test
   The provocation test is a method that can help determine the cause, namely by inhaling specific antigens. This test can be performed in 2 ways, naturally by giving repeated exposures, staying in the suspected environment for 72 hours, and in the laboratory by giving inhalation (nebulization) of the suspected antigen extract. Pulmonary physiology examination and blood count are performed 24 hours after the provocation test. Serum specific antibody is a significant predictor of HP (OR: 5.3). The types of antigens available are pigeons, parakeets, dove feathers, *Aspergillus*

sp, *Penicillium*, *Saccharopolyspora rectivingula*, and *Thalassomonas viridans*. The examination of *Trichosporon calcaneum* is already available in developed countries such as Japan. The examination uses the method of immunodiffusion, immunoelectrophoresis, and enzyme-linked immunosorbent assays (ELISA).[14,18]

7. Lung biopsy
   Transbronchial lung biopsy examination is performed with the aid of bronchoscopy. FLD or HP in acute form can be in the form of neutrophil. Eosinophil infiltration in the alveoli can also describe the presence of luminal and interstitial alveolitis, intra alveolar exudation, bronchiolitis, and non-necrotizing granulomas, which usually occur on the walls of the bronchioles, alveolar ducts, and alveoli. The characteristic feature of granulomas is opacity with a diameter of less than 150 pm (smaller than sarcoidosis). In addition, there is also a dominant infiltration of CD5 T lymphocytes, plasma cells, monocytes, and macrophages in the interstitial area. In FLD or chronic form of HP, there will be inflammation and peribronchiolar fibrosis, bronchiolar smooth muscle hypertrophy, and lymphoid follicular hyperplasia.[14,18]

Management

In FLD or HP, most people can experience recovery on their own, but the recovery takes a relatively long time, even up to several years. Some patients can progress to a more advanced stage, namely until permanent lung damage occurs, which will require long-term treatment. Management of FLD or HP can be:[9,10,17,18,20,21]

1. Avoid exposure to antigens
   Avoidance of antigens is the basis for the management of FLD. This can be performed by improving the process and storage of raw materials which make it easier for bacteria to grow, namely by using disinfectants in contaminated areas, using filters, and improving the air ventilation system by making the warehouse open, or using exhaust fan to circulate air from inside the warehouse to the outside.
2. Use respiratory protective equipment such as a mask or disposable respirator
3. Perform regular health check-ups for workers, especially the lungs, by conducting lung physiology examinations and X-rays
4. Medicamentosa
   Corticosteroids can be given if complaints of breathlessness or other respiratory symptoms are still being felt. This administration is intended to reduce inflammation of the airway and aims to reduce mucus production, which will clog the airways. Corticosteroids can be given by inhalation, mouth, or injection. Corticosteroids can be given in acute and chronic conditions. Oral corticosteroids (prednisone 0.5 - 1 mg / kg body weight) are given every day. Give prednisone or prednisolone with a maximum dose of 40-60 mg/day for 1-2 weeks. Afterwards, the dose should be decreased for 2-4 weeks. Corticosteroid administration is not affected by long-term complaints.[10,18,20]
5. Surgery
   In some chronic progressive conditions characterized by pulmonary fibrosis, lung transplantation may be considered.[10,20,21]

Prognosis

The prognosis of FLD or HP depends on several factors, namely the length of antigen exposure, antigen concentration, host immune response, and the form of clinical manifestations. The non-progressive acute condition has a good prognosis. Poor prognosis occurs in the chronic form characterized by pulmonary parenchymal fibrosis and impaired pulmonary function.[18] In the study of Perez, *et al*., a total of 142 patients with FLD or HP found that the inability to identify the cause was a predictor factor that led to decreased survival rates. The median survival time in patients with HP will decrease from 8.75 years in patients with identifiable substances or substances which act as antigens to 4.88 years in patients who cannot identify the antigen that plays a role.[22,23]

SUMMARY

Indonesia has a very large agricultural sector. There are 35.7 million people who work as farmers from all over Indonesia. Poor storage of agricultural products can cause several lung diseases which affect farmers. One of the diseases that can arise is FLD which is part of HP. This is mostly caused by the inhalation of biological dust from straw, mold spores, or dust from agricultural products. HP is not a disease of atopy. This antibody-antigen interaction causes type III (reactions immune complex hypersensitivity) and IV (delayed-type hypersensitivity). There is no gold standard and validated test for the diagnosis of this disease. HRCT and BAL examinations are highly recommended this time. The best management is to avoid repeated exposure to the source of infection. Corticosteroid treatment can be given in all conditions. History-taking and other tests are essential to reduce mortality in patients suspected of having FLD.

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