Farmer's Lung

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ABSTRACT

Farmer's lung, a prototype of hypersensitivity pneumonitis is a predominantly interstitial lung disorder caused by intense, often prolonged exposure to inhaled organic antigens. The most common implicated microbes are the thermophilic actinomycetes, which grow on moldy hay. Workers engaged in farming develop this disease on exposure to hay contaminated with the spores of these microorganisms. Both humoral and cell mediated immunity play a role, as evident by the presence of precipitating antibodies to antigens, lymphocyte predominance in bronchial washings and presence of non-caseating granulomas in biopsy specimens. The disease may present in acute, sub-acute or chronic forms with fever, dyspnoea, dry cough or weight loss, depending on the clinical stage. The diagnosis, though mostly clinical, may require radiological, physiological and immunological evaluations for confirmation of definitive diagnosis. The treatment consists of avoidance of antigen; systemic corticosteroids are effective in suppressing the inflammatory response. The prognosis depends on early diagnosis & effective antigen avoidance.

INTRODUCTION

One of the earliest references to respiratory hazards associated with farming was made by Ramazzini [1] in 1700. However, the credit of first describing the disease and also probably coining the word 'Farmer's lung' for the first time goes to Campbell (2) who described a respiratory illness in farmers working with hay in 1932. Dickie and Rankin (3) in 1958 described granulomatous interstitial pneumonitis in farmers. The causative agent, thermophilic actinomycetes were identified by Gregory and lacey in 1963(4). After Campbell's inititial description in 1932, many other types of hypersensitivity pneumonitis were described. Farmer's lung is a type of hypersensitivity pneumonitis caused by inhalation and subsequent sensitization to organic antigens present in damp, moldy hay. The condition is associated with intense, frequent exposure to biologic dusts & causes an immunologically mediated inflammatory disease involving the interstitium.

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MAGNITUDE OF PROBLEM

Epidemiological studies have revealed a prevalence of 3-5% in farmers in agricultural areas in UK & US (5, 6). The incidence is highly variable, depending on various factors like intensity, frequency and duration of exposure; type of farming and climate. An incidence of 8 to 540 cases per 10,000 persons per year for farmers has been reported (7).

Worldwide, cases of farmer's lung are reported to be on a decline (8) due to increased awareness and improving farming practices. However, a study in the Czech Republic between1992-2005 [9] reported Farmer's diseases of the lung as the most frequent [50% of total] occupational hypersensitivity pneumonitis.

In India, in a study carried out in workers engaged in farming in Delhi (10) farmer's lung disease was diagnosed in 2% of patients.

ETIOLOGY

Thermophilic actinomycetes [now classified as bacteria] which grow in hay or other organic matters stored in a damp condition are the most commonly implicated organisms. Two most usual organisms are Micropolyspora faeni [now called

Faeni rectivirgula] and Thermoactinomycetes vulgaris [11]. Besides these, other organisms like Aspergillus species or other fungi like Absidia corymbifera and to a lesser extent, Eurotium amstelodami have been reported as etiologic agents [1s2]. Exposure to large quantities of hay contaminated with the spores of these organisms is the most common source of inhalational exposure in farmers who develop this disease. Most acute cases occur during cold, damp winter months when farmers use stored hay to feed their livestock.

IMMUNOPATHOGENESIS

The exact mechanism is not known. Considerable insight into immunopathogenetic mechanisms has been gained in recent times. As with other hypersensitivity pneumonitis, both cellular & humoral immunity play a role.

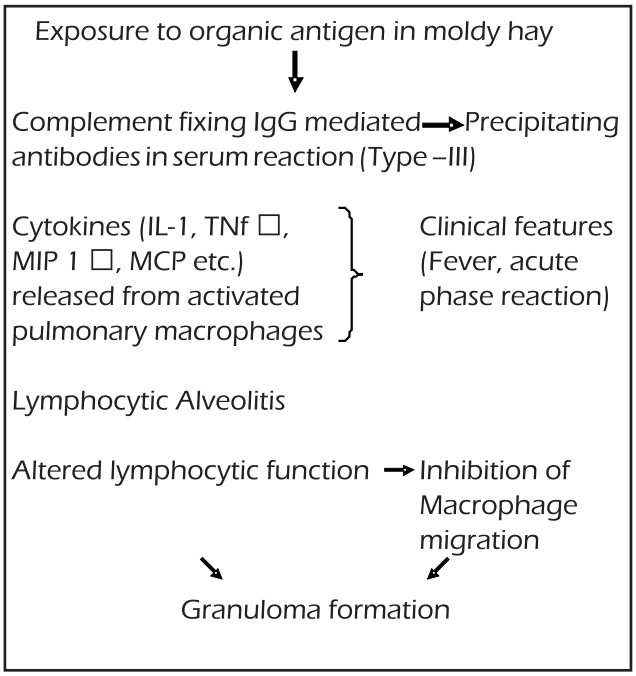
Farmer's lung was initially thought to be an allergic alveolitis caused by a type III, complement fixing immune complex reaction in the lung (12). This conclusion was based on the isolation of precipitating antibodies to inhaled antigen in the blood. But it was observed that these precipitating antibodies (mostly IgG type) were found in many exposed but unaffected farmers, while they were absent in some (13).

Further, the presence of T lymphocytes (CD 8 suppressor more than CD 4 helper) (14) in bronchial washings implicated the cell-mediated immunity. Non-caseating granulomas are found in two thirds of patients (15) suggesting the development of T cell mediated (type IV) delayed type hypersensitivity against the implicated antigens (15).

The precipitating IgG antibodies may play a role in antibody mediated cell cytotoxicity by NK cell or in the antigen - antibody immune reaction (16). Additionally, alternate complement cascade directly activated by the antigens and the inflammatory cytokines I L- & TNF □ produced by the activated pulmonary macrophages participate in the inflammatory cascade (17). Other cytokines secreted by the pulmonary macrophages are IL-8, monocyte chemo attractant protein (MCP-1), macrophage inflammatory protein (MIP) 1 □ & RANTES, which are chemo tactic factors for a variety of cells (17). A defect in the ability of the alveolar macrophages activated by the antigens to suppress the proliferation of lymphocytes is a major factor responsible for lymphocytic alveolitis [18]

The suggested sequence of events is as follows [19].

Why some individuals develop the disease on exposure while others are spared probably depends upon the dose and duration of antigen exposure (20) as well as immunomodulatory effect of smoking.



PARADOX OF CIGARETTE SMOKING

In contrast to other respiratory diseases, farmer's lung is common in non-smokers than smokers [21]. This is probably due to an immunosuppressive effect, primarily on alveolar macrophages which are markedly decreased [22]. There is also decreased release of several cytokines like IL-1, TNF, Interferon, which play a role in the pathogenesis [23].

Paradoxically, when the disease does occur in smokers or ex- smokers, it seems to be more severe and chronic, with a worse survival rate as compared with non- smokers [24].

CLINICAL FEATURES

The clinical features can be categorized into acute, sub acute or chronic forms.

ACUTE FORM

Symptoms occur 4-8 hours after exposure to high doses of microbial spores and resemble an acute viral illness. Patients present with high-grade fever with chills, myalgia, fatigue, dyspnoea and non-productive cough. Examination may reveal end inspiratory crackles, tachypnoea and at times polyphonic wheezes. Recovery usually occurs 24-48 hrs on removal from the environment. Though reversible, severe acute attack may rarely cause respiratory failure or even death. (25)

SUBACUTE FORM

This stage occurs insidiously over weeks to months probably due to low level exposure to the antigen. Patients have progressive dyspnoea & cough. There may be associated fever, anorexia, weight loss, crepitant rales and hypoxemia, especially with exertion.

Symptomatic improvement may occur with further avoidance of antigen exposure.

CHRONIC FORM

Patients present with cough, malaise, weight loss, severe dyspnoea at rest or with exertion. Examination reveals bibasilar rales, weight loss, impaired exercise tolerance. Clubbing is not a feature of farmer's lung and its presence is a strong pointer against it [19]. Since this stage indicates irreversible pulmonary damage due to interstitial fibrosis, avoidance of antigen will not cause complete resolution. In fact, continued exposure portends a poor prognosis.

INVESTIGATIONS

No single test or investigation is diagnostic. Diagnosis is mostly clinical supported by radiological, simple laboratorial and pulmonary function testing.

1. Blood Tests

Presence of precipitating antibodies against the causative antigen indicates exposure but not necessarily the disease, as these are present in a majority of patients with farmer's lung (16). In the acute form patients have a significant blood neutrophilia and lymphopenia (26). Peripheral eosinophilia is characteristically absent (26). In addition, raised levels of acute phase reactants like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) & lactate dehydrogenase (LDH) may be present (27).

2. Radiological features

In acute stage, chest radiograph shows bilateral, diffuse micro nodular infiltrate predominantly in lower zone, with sparing of apices [16]. The infiltrates are usually denser towards hila [19]. The changes may disappear with treatment and in between acute episodes the chest X-ray may be normal. High resolution CT (HRCT) demonstrates ground glass opacities due to interstitial infiltration or granuloma or both [16][figure 1][28]

In sub acute stage, reticulonodular appearance with fine linear opacities and small nodules may

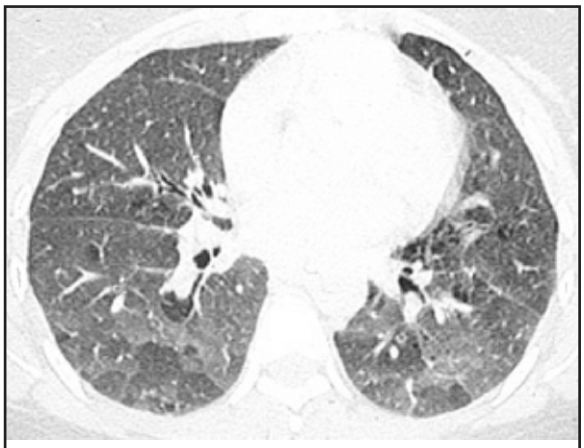


Fig 1. HRCT lungs shows ground glass and mosaic attenuation opacification in the acute phase of hypersensitivity pneumonitis due to moldy hay.

be seen in chest radiograph (16)[figure 2][28].

HRCT in sub acute stage demonstrates centrilobular nodules with larger areas of ground glass opacities, air trapping and mosaic perfusion. The nodules indicate presence of poorly marginated granulomas, air trapping indicates obstructive bronchiolitis while mosaic perfusion indicates re-distribution of blood flow (29)[figure3][28].

In chronic stage, upper and mid - zone fibrotic changes predominate (19) with diffuse

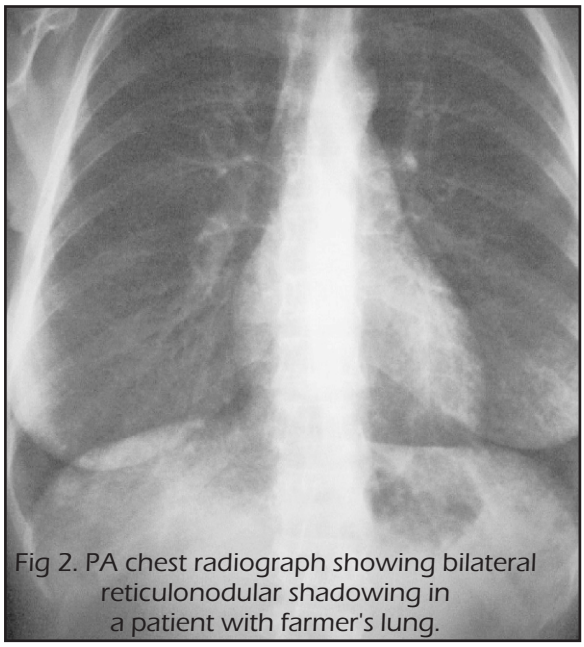


Fig 2. PA chest radiograph showing bilateral reticulonodular shadowing in a patient with farmer's lung.

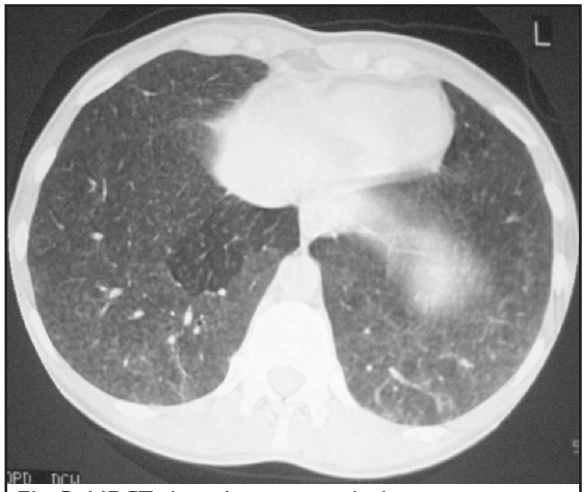


Fig 3. HRCT showing ground glass appearance and reticulonodular opacities in sub acute phase of farmer's lung.

reticulonodular infiltrates, coarse linear opacities, honeycombing & traction bronchiectasis (19,27) often with retraction upwards of pulmonary vessels and well marked emphysema in lower zones (19)[figure 4][280]. Presence of fibrosis in HRCT is associated with reduced survival and may serve as a useful predictor. [30]. HRCT may be helpful in distinguishing farmer's lung from other interstitial fibrosis disease by showing a peribronchiolar or centriacinar distribution of nodular changes (31).

3. Pulmonary Function

In an acute attack, reductions in volumes and

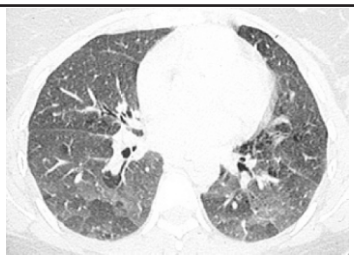


Fig 4. HRCT in a patient with chromic hypersensitivity pneumonitis demonstrates honey combing in the right UL and traction bronchiectasis.

diffusion capacity of carbon monoxide are seen (32) reflecting a filling of the alveolar space with fluid and inflammatory cells. In sub acute and chronic stages, mixed restrictive and obstructive patterns may be seen (16,33). Airflow obstruction may be present due to concomitant asthma (16) or non-specific airway hyper reactivity due to bronchiolitis (34).

4. BAL

In acute stage, neutrophilia followed by lymphocytosis (> 60% of total white cell) is found (16). Preponderance of CD 8 + T cells (14] leads to decrease in the ratio of CD 4/CD 8 +to less than one. Increased specific Ig G, Ig M, and Ig A antibodies may be found in the BAL fluid (35).

5. Lung Biopsy

It should be done when the cause is not clear. In acute stage, bronchiolitis with a neutrophilic infiltrate may be seen (16). Sub acute stage is characterized by diffuse lymphocytic infiltration in the interstitium, non- caseating granulomas and bronchiolitis (16)[figure 5)[28].

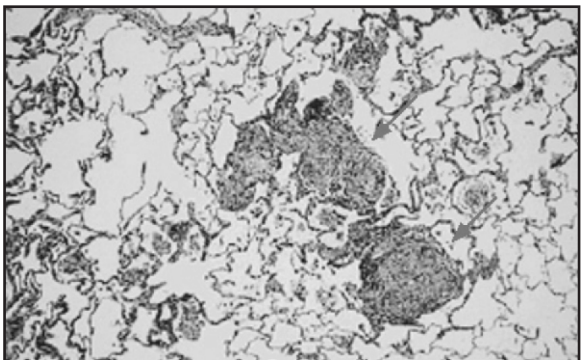


Fig 5. Light microscopy showing mononuclear infiltration & non-caseating granulomas. This finding is usually seen in acute phase, but may also appear in sub acute & chronic phases.

In chronic disease, the granulomatous changes may disappear (19) with interstitial fibrosis and interstitial lymphocytic infiltration (16,19)[figure6][28]. However, these pathologic findings are not pathognomonic.

6.Skin hypersensitivity tests

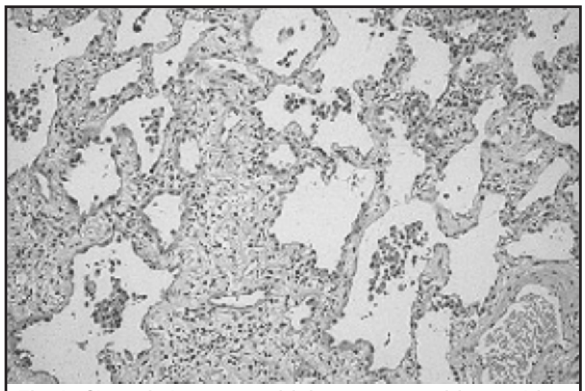


Fig 6. Chronic hypersensitivity pneumonitis resulting in interstitial inflammation associated with fibrosis

The usefulness of these 'challenge' tests is limited. These can be carried out by exposing the subject to the antigen in a normal way (e.g. farmers exposed to moldy hay) or may be carried out under supervision in a hospitalized subject (19). Small dose of the antigen is administered by nebuliser and response is measured in terms of white cell count, temperature and lung function tests [19].

In most cases, clinical history, examination, chest radiography, pulmonary function testing & simple laboratory tests may be sufficient for the diagnosis. However, specific diagnostic criteria have been recommended for the diagnosis of hypersensitivity pneumonitis. Six clinical predictors of hypersensitivity pneumonitis are exposure to offending antigen, positive precipitating antibody to the antigen, recurrent episodes, respiratory crackles, symptoms occurring 4-8 hours after exposure and weight loss (36). When these predictors are present, the probability of diagnosis is at least 98.

MANAGEMENT

Avoidance of the offending antigen is advisable and preventive measures play a role if it is not possible. Hospitalization with supplemental oxygen and parenteral steroids are indicated in ill patients with abnormalities in lung functions, chest radiograph or hypoxaemia. Corticosteroids should be given for all but mild cases, in a dose of 40 mg/day till adequate clinical improvement occurs [19]. Patients with acute symptoms improve with 1-2 weeks' therapy with oral Prednisolone while sub acute and chronic cases may require 40-80 mg daily with a taper over several months depending upon the response [37]. The obstructive component may respond to short acting bronchodilators and inhaled steroids [16]. Antihistamines and inhaled cromolyn sodium are ineffective. Pentoxifylliine, a non-selective Phosphodiesterase inhibitor, was found to decrease cytokine production from alveolar macrophages in patients with hypersensitivity pneumonitis [38]. Low dose, long term macrolide antibiotics have been demonstrated to be useful in chronic inflammatory respiratory conditions, probably due to their anti-inflammatory action[16].

PREVENTION

Advice regarding prevention of further exposure to antigen is very essential. In many individuals avoidance alone suffices, especially if the disease is diagnosed in early stages. This may involve change of profession or relocation of an employee, which may be cost prohibitive. Hence simple measures like good personal hygiene, good housekeeping including use of industrial vaccume cleaner, proper machinery to contain dust and adequate ventilation may be advised to reduce exposure. Additionally, farmers may have to use properly fitted and maintained respirator protection equipment. Filters in the respirators should be standardized [penetration 1-2 of a standard aerosol] [19] and changed regularly.

PROGNOSIS

If detected and treated in early stages, complete recovery may occur. However patients with chronic disease have permanent sequelae like progressive interstitial fibrosis, emphysema or asthma like symptoms. Steroid therapy causes symptomatic improvement but does not affect the long term prognosis[16].

MEDICOLEGAL ASPECTS

In the UK, all employers, self-employed and employees have certain duties and

responsibilities under the Health and Safety at work etc Act 1974. Under the control of Substances Hazardous to Health Regulations 2002 [COSHH], all employers and self-employed are required to make an assessment of the risk to health from the work activity, to introduce and maintain control measures and inform, instruct and train employees about risks and precautions.

In India, unlike Coal Workers' Pneumoconiosis, which is a notifiable and compensatable disease [Workman's Compensation Act 1923], no such legal provisions exist with farmer's lung.

BIBLIOGRAPHY

1. Ramazzini B.1940.De Morbis artificium Berardim. Ramazzini diatribe[Diseases of workers]. The Latin text of 1713 revised with translation and notes by Wilmer Cave Wright. The University of Chicago Press, Chicago, IL.
2. Campbell J M. Acute symptoms following work with hay. Br Med Ind 1946; 3: 64
3. Dickie H, Rankin J. Farmer's lung: an acute granulomatous interstitial pneumonitis occurring in agricultural workers. JAMA 1958; 167:1069-76.
4. Gregory P, Lacey M. Mycological examination of the dust from moldy hay associated with farmer's lung disease. J Gen Microbiol 1963; 30: 75: 88.
5. Morgan DC, Smyth JT et al. Chest symptoms in farming communities with special reference to farmer's lung. Br J Ind Med 1975; 32: 228.
6. Madson D et al. The prevalence of farmer's lung in an agricultural population. Am Rev Respir Dis 1976; 113: 171.
7. Laurianne GW, Eduardo EC. Farmer's lung. Emedicine. Medscape's continually updated clinical reference. Updated 16 April 2009.
8. Arya A, Roychoudhary K, Bredin CP. Farmer's lung is now in decline. Ir Med J. Jul-Aug 2006; 99[7]: 203-5.
9. Fenclova Z et al. Occupational Hypersensitivity Pneumonitis reported the Czech national registry of occupational Diseases in the period the 1992-2005. Ind Health 01 Aug 2009; 47(4): 443-8.
10. Gaur SW, Gangwar M et al. Farmer's Lung disease in north Western India. Indian J Chest Dis Allied Sci 1992; 34:9-56.
11. Duchaine C, Meriaux A, Brochu G, et al. S.rectivirgula from Quebec dairy barns: Application of simplified criteria for identification of an agent responsible for farmer's lung disease. J Med Microbiol 1999; 48[2]: 173-80]
12. Roussel S, Reboux G et al Microbiological evaluation of hay and Relapse fever in patients with farmer's lung. Occup Environ Med. 2004; 61: e 3
13. Burrel R, Rylander R.A. critical review of the role of precipitins in Hypersensitivity Pneumonitis. Eur J Respir Dis. 1981; 62: 332.
14. Costable U, Bross KJ et al. T Lymphocytosis in broncho alveolar lavage fluid of hypersensitivity pneumonitis: changes in profile of T cell subsets during the course of the disease Chest 1984; 130:1046
15. Kumar: Robbins and Cotran Pathologic basis of Disease, Professional Edition, 8th Ed 2009 Saunders.
16. Kurup VP, Zacharisen MC, Fink JN. Hypersensitivity Pneumonitis. The Indian Journal of chest disease and Allied Sciences 2006; Vol 48: 115-128
17. Denis M, Pro-inflammatory cytokines in hypersensitivity Pneumonitis. AM J Respir Crit care Med 1995; 151: 164-9
18. Dakhama A, Israel E, Assayag F, et al. Eur Respir J 1996;9:1456-1462.
19. Seaton A. Crofton and Douglas' respiratory Diseases. Wiley Blackwell; 5th Edition, 1002-1019.
20. Malmberg P, Rask Andersen A, Rosenhall L. Expsosure to microorganism associated with allergic Alveolitis and reactions to mold dust in farmers. Chest1993; 103:1202.
21. Depierre A, Dalphin JC, et al. Epidemiological study of farmer's lung in five districts of the French Doubs province, Thorax 1988; 43[6]: 429-35.
22. Moszczynski P, Zabinski Z, et al. Immunological findings in cigarette smokers. Toxicol Lett 2001; 118[3]: 121-7.
23. Blanchet MR, Israel Assayag E, et al. Inhibitory effect of nicotine on experimental hypersensitivity pneumonitis in vivo and in vitro. Am J Respir Crit Care Med 2004; 169: 903-9
24. Oshtsuka Y, Munakata M, et al. Smoking

promotes insidious and chronic farmer's lung disease deteriorates the clinical outcome. Intern Med 1995; 34[10]: 966-71.

25. Kokkarinen J, Tukianen H, erho Eo. Mortality due to Farmer's lung in Finland. Chest 1994:106:509.
26. Richerson HB, Bernstein IL, Fink JN et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. J Allergy clin Immunol 1989:84:839-44.
27. Mohr LC. Hypersensitivity pneumonitis. Curr opin pulm Med 2004:10:301-11.
28. Khan AN, Ghanem S, et al. Extrinsic Allergic Alveolitis:Multimedia. emedicine. Medscape.com/article/356120-media.
29. Patel RA, Sellami D, Gotway M B et al. Hypersensitivity Pneumonitis:Patterns on high resolution CT. J Comp Assist Tomogr 2000:24:965-70
30. Hanak V, Golbin JM, et al. HRCT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. Chest volume 134, Issue 1 [July 2008]
31. Buschman DL, Gamsu G, Waldron JA, Klein JS, King TE, Chronic hypersensitivity pneumonitis: use of CT in diagnosis. Am J. Roentgenol 1992; 159:957.
32. Rankin J, Kobayashi M, Barbee RA, Dickie HA. Pulmonary antigens. Med Clin North Am 1967; 51:459.
33. Harrison's Principles of Internal Medicine. McGraw Hill. 17th Edition.
34. Selman Lama M. Perez Padilla R. Airflow obstruction and airway lesions in hypersensitivity pneumonitis. Clin Chest Med. 1993:14:600-714.
35. Drent M, van Velzen-Blad H. Diamant M et al. Bronchoalveolar lavage in extrinsic allergic alveolitis: effect of time elapsed since antigen exposure. Eur Resp J 1993; 6:1276-81.
36. Lacasse Y, Selman M, Costbel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 2003:168:952:81.
37. Fink J, Zacharisen M. In Adkinson NF, Yunginer J, Busse W, Bochner B, Holgate S, Simons FE, editors. Middleton's Allergy: Principles and Practice. Philadelphia: Mosbys and Co;2003:pp 1373-90.
38. Tong Z, Chen B, et al. Extrinsic Allergic Alveolitis: inhibitory effect pentoxifylline on cytokine production by alveolar macrophages. Ann Allergy Asthma Immunol 2004;92:234-9.