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The alveolitis of hypersensitivity pneumonitis

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ABSTRACT: In the pathogenesis of hypersensitivity pneumonitis (HP) several immune mechanisms are involved. The initial phase, 4–48 h after antigen inhalation, appears to be immune complex mediated and is characterized by an early increase in bronchoalveolar lavage (BAL) neutrophils and the histopathologic features of oedema, neutrophil infiltration of the alveolar wall, and vasculitis. After 12 h to several days, the immune response possibly shifts to a cell-mediated reaction, and the alveolitis consists of cytotoxic effector cells as well as suppressor cells which may be required to modulate the B cell response of antibody production by plasma cells. In this phase, lymphocytes of the OKT8 positive phenotype, natural killer cells, and occasionally a few plasma cells are increased in BAL fluid. The characteristic histopathologic finding is a mononuclear infiltrate consisting of lymphocytes, plasma cells, and foamy histiocytes. After weeks to months, a delayed type hypersensitivity reaction may lead to a slight predominance of OKT4 positive cells in BAL fluid and to granuloma formation. Finally, after months to years, repeated immune-mediated injury to the alveolar wall with release of proteolytic enzymes and fibroblast growth factors may result in pulmonary fibrosis and end stage lung with concomitant increase in BAL neutrophils as in other fibrotic diseases.
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In contrast to sarcoidosis, a multisystemic disease of unknown origin, hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is a disease of well known aetiology. It results from immune reactions located predominantly in the alveolar air exchange portion of the lung and is initiated by repeated exposure to specific extrinsic antigens in individuals with an acquired abnormal sensitivity or heightened reactivity to the inciting agent. Such agents may be airborne and then reach the alveoli by inhalation (organic dust diseases, *e.g.* farmer's lung, bird fancier's lung), or may enter the alveolocapillary unit by the blood stream (*e.g.* drug reactions).

In the pathogenesis of this disorder, several types of immune reactions can be observed [24, 42, 48, 55] (table I). The following is a review of mainly clinical studies of immunological mechanisms in HP with a focus on new insights obtained by bronchoalveolar lavage.

Immune mechanisms

Initially, HP would appear to be an example of an immune complex mediated tissue injury. Antigen is deposited in the lung and circulating precipitating antibodies are present in the blood [10, 39]. Immunofluorescent studies sometimes reveal antigen, antibody and complement components in the lung tissue [60]. Such immune complex mediated reactions are usually characterized by complement deposition and ultimately by infiltration of polymorphonuclear leucocytes into tissues. However, the presence of complement components in lung biopsy as well as lowered serum complement levels are not a general feature of this disease [4, 6] and the polymorphonuclears are not the predominant cells in the tissue reaction found at lung biopsy [4, 41]. Vasculitis, another feature of immune complex mediated tissue injury is not usually observed in this disease [4, 41].

Instead, the disease is usually histopathologically manifested by a patchy mononuclear infiltrate consisting primarily of lymphocytes along with plasma cells and histiocytes with foamy cytoplasm present in the alveolar septa [4, 10, 41]. Granulomas are present in two-thirds of the specimens [41]. These features would be consistent with a cell-mediated immune response, and not with an immune complex mediated reaction (Arthus reaction).

On the other hand, in acute cases early after challenge, vasculitis can be found [5, 27] and there is one report of a decline in the level of serum complement after provocation test [8].

Early neutrophil alveolitis after antigen inhalation

The application of bronchoalveolar lavage (BAL) has brought immunologic studies closer to the site of inflammatory activity. BAL studies support the idea that the first event after antigen inhalation is an immune complex mediated reaction involving a chemotactic migration of polymorphonuclear leucocytes into the alveoli from the peripheral blood [19, 26, 47, 56, 57, 61]. Neutrophil chemotactic factors (NCF) are present in BAL fluid from patients with HP [61]. The chemotactic activity is significantly higher in patients at an acute stage compared to those

Table I. - Time course of the immune reactions and the features of the alveolitis in hypersensitivity pneumonitis.

Time	Immune reaction	BAL feature	Histopathologic feature
4 to 48 hours	immune complex mediated	neutrophil influx	vasculitis edema neutrophil infiltration
12 hours to several days	cell mediated: - suppression of antibody production - cytotoxic effects	lymphocytes↑ - OKT8 - natural killer plasma cells	mononuclear infiltrate - lymphocytes - plasma cells - foamy histiocytes
weeks to months	cells mediated: - delayed type hypersensitivity	lymphocytes↑ - OKT4 - natural killer	mononuclear infiltrate and granulomas
months to years	repetition of the immune mediated injury to the alveolar wall, fibroblast proliferation	lymphocytes↑ - OKT8 neutrophils↑	fibrosis end stage lung

at a quiescent stage [61]. The true nature of the chemotactic activity is not yet known. Possible sources may be fragments of complement (*e.g.* C5a), the release of LTB_4 from macrophages, or of high molecular weight NCF from mastocytes. Patients with an acute and recent antigen exposure show a higher percentage of neutrophils in BAL fluid than those with remote exposure [19, 47, 56].

The best evidence for the role of neutrophils in the early phase of HP originates from studies where a BAL was carried out before and after antigen inhalation [26, 47, 57]. 24 [26, 57] or 48 h [47] after antigen challenge there is a significant increase in the percentage of neutrophils. This increase is most pronounced after 24 h. Eight days later, the percentage of neutrophils and lymphocytes does not differ from the initial pre-challenge BAL [26]. These studies demonstrate that there is an immediate and transient neutrophil alveolitis after antigen inhalation in patients with acute HP. The early arrival of neutrophils in the lung following exposure to antigen, and their subsequent replacement by mononuclear cells, has also been shown in an animal model [7].

Lymphocytic alveolitis in the subacute and chronic stages

Several days after inhalative challenge, the local immune response shifts to a cell-mediated reaction, characterized by an accumulation of lymphocytes. This predominant lymphocytic alveolitis as the classical feature of subacute and chronic HP has been demonstrated by many groups [1, 7, 11, 19, 21, 23, 26, 28, 29, 33–35, 43, 47, 53, 56–59, 61]. Average values of lymphocytes are greater in HP (60–70%) than in sarcoidosis (30–50%). A normal lymphocyte percentage in a patient's BAL fluid is not consistent with the diagnosis of symptomatic HP with recent exposure. Many of the lymphocytes are large, atypical forms, with broad cytoplasm and irregular nucleus. In addition to the striking lymphocytosis and a mild increase in neutrophils (average 8–10%), a few plasma cells (0.1–2%) can also be seen in 60% of patients with subacute HP [18] as well as increased percentages of mast cells which exceed 0.5% in 80% of patients [29].

Lymphocyte subpopulations and functions

In contrast to sarcoidosis and berylliosis (diseases with a predominance of OKT4 positive T helper/inducer cells), in HP the OKT8 positive suppressor/cytotoxic phenotype of T cells is increased, which leads to a decrease in the OKT4/OKT8 ratio of BAL cells [1, 18, 20, 33, 53, 61]. In addition, Leu7 positive natural killer cells are significantly increased in the BAL fluid of HP patients *versus* normal nonsmokers and *versus* sarcoidosis patients [1, 18, 20, 53]. As a sign of activation, many T cells in BAL fluid of HP are HLA-DR positive [21].

The phenotypic appearance of T cell subsets is not necessarily correlated with functional properties. In HP, however, a recent study demonstrated that BAL T cells from symptomatic patients display *in vitro* suppressor activity as well as a definite cytotoxic function [53]. BAL T cells from healthy individuals with similar history of exposure showed only suppressor activity.

Evidence of local T cell activation in HP arises not only from increased HLA-DR antigen expression on lung T cells [21] or from cell cycle analysis of BAL cells [11, 35] but also from animal models of HP demonstrating that sensitized lymph node cells release macrophage migration inhibitory factor [32, 49]. In humans, sensitized lymphocytes are present in BAL and produce a factor inhibiting macrophage migration *in vitro* after incubation with pigeon serum or dropping extracts in pigeon breeder's disease [52].

Furthermore, specific proliferative responses of BAL lymphocytes to pigeon antigens consistently occur in patients with pigeon breeder's disease, but less frequently in non-diseased exposed persons [34]. This indicates the presence of specifically activated T cells in the lung parenchyma of diseased subjects.

The role of macrophages

Little is known about the contribution of alveolar macrophages to the alveolitis of HP. In some cases, antigenic and foreign body material is found in macrophages and giant cells of granulomas in the lung [40, 41, 51 and own unpublished observations].

HLA-DR (Class II) antigens, important for effective antigen presentation by macrophages to T cells, are expressed on almost all alveolar macrophages in HP, but there is no difference in normal controls or patients with other interstitial lung diseases [17]. Transferrin (TF) receptors are expressed only during the terminal stage of macrophage differentiation [3] and mediate the uptake of iron which is needed *e.g.* for enhanced cellular metabolism, cell growth, and proliferation. Interestingly, the percentage of alveolar macrophages expressing TF receptors is increased in active sarcoidosis, but is rather decreased in HP [2, 15]. Perhaps TF receptors are down-regulated in HP by cytotoxic lymphocytes including NK cells which are amongst the predominant cells in the alveolitis of this disease. Another explanation could be that TF receptors on macrophages are decreased when phagocytosis of particulate antigen occurs, since in inorganic dust diseases the percentage of TF receptor positive alveolar macrophages is also reduced [16].

Few studies have been related to macrophage activation in HP. Increased phagocytic and bactericidal activity of alveolar macrophages occurs in rabbits two and four weeks after sensitization and challenge with M. faeni [54]. Recently, increased phospholipid methylation in alveolar macrophage cell membrane consistent with macrophage activation was found in some patients with HP [37].

Further studies are needed to document the functional status of alveolar macrophages in HP. Unlike sarcoidosis, where many alveolar macrophage- and lung T cell-derived mediators, which modulate macrophage/T-cell interactions, have been extensively studied and found to be released spontaneously or in increased amounts, such data are not available for HP at the present time.

Soluble components of BAL fluid

Consistent with the concept of locally produced antibodies, the concentrations of IgG, IgM and IgA are increased in BAL fluid of patients with HP [14, 38, 43] the IgA levels being higher in BAL fluid than the serum levels [38]. In addition, precipitating antibodies specific to the offending antigens have been found in BAL fluid, as in serum [38, 43]. Abnormal surfactant composition with markedly reduced or absent phosphatidylcholine (PC) levels have been reported in HP [31], but this severe decrease in the major component of the surfactant phospholipids could not be confirmed by other studies where PC levels were found to be normal in HP as well as in sarcoidosis [22, 30, 50].

Evolution of the lymphocytic alveolitis

After removal of patients from exposure, the increase in BAL lymphocytes may persist for years despite clinical recovery [19, 29, 56], whereas mast cells, neutrophils and plasma cells return to normal [19, 29]. The decreased T4/T8 ratio is raised towards normal values [19, 61]. The ratio may even increase to elevated values in some cases for a certain period of time before eventually returning to normal [19]. HLA-DR positive lung T cells normalize within six months after avoidance of further exposure (own unpublished observations).

Subclinical alveolitis in asymptomatic exposed individuals

A BAL lymphocytosis often occurs in asymptomatic apparently healthy farmers [12, 13] and pigeon breeders [33, 34]. This subclinical alveolitis is more frequent in farmers with positive serum precipitins against offending antigens [12]. Follow-up studies for two or three years showed that the BAL lymphocytosis persisted and that no subject developed farmer's lung disease [13]. At present, therefore, a pathologic BAL finding with increased percentages of lymphocytes in exposed but otherwise healthy persons has to be considered as evidence of sensitization, but not of disease, as is true for serum precipitins.

Unresolved questions

It is still not clear why sensitization occurs in some but not all exposed persons and why only some sensitized individuals develop disease. In this context, a recent study looked for the development of interstitial lung disease caused by particulate organic antigens such as ovalbumin and bovine gamma globulin after specific immunization in strains of mice with different genetic backgrounds [46]. The degree of disease as judged by a histomorphologic score was different in some of the different strains suggesting that a variety of immune and non-immune related genes may contribute to individual susceptibility to develop HP. Studies of HLA types in human HP have been contradictory regarding the association of disease with a certain histocompatibility locus [9, 25, 36, 44, 45].

Finally, important questions are: what happens to those with a subclinical alveolitis; how many of them with continued exposure will eventually get chronic disease, and why? Is it solely the culmination of exposure, a decrease in effective host immunity, or the effect of an unrecognised adjuvant?

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RÉSUMÉ: Des mécanismes immunitaires sont incriminés dans la pathogénie des pneumopathies d'hypersensibilité. La phase initiale, 4 à 48 heures après l'inhalation d'antigène, semble être liée à l'apparition de complexes immuns et est caractérisée par une augmentation précoce des neutrophiles dans le lavage alvéolaire et sur le plan histologique par un oedème, une vascularité et une infiltration neutrophilique des parois alvéolaires. Douze heures à quelques jours plus tard la réponse immunitaire se déplace probablement vers un réponse cellulaire, et l'alvéolite consiste en cellules effectrices cytotoxiques et suppressives qui pourraient servir à moduler la production d'anticorps par les lymphocytes B et les plasmatocytes. A ce stade dans le liquide de lavage alvéolaire on trouve des lymphocytes porteurs du phénotype OKT8, des cellules NK (natural killer) et occasionnellement quelques plasmatocytes. Sur le plan histologique on trouve une infiltration par des cellules mononucléées, lymphocytes, plasmatocytes et histiocytes spumeux. Après quelques semaines à quelques mois une réaction de type hypersensibilité retardée peut entraîner une légère prédominance des cellules porteuses du phénotype OKT4 dans le liquide de lavage alvéolaire et la formation de granulomes. Finalement, après des mois ou des années, les agressions répétées de la paroi alvéolaire libérant des enzymes protéolytiques et des facteurs de croissance pour les fibroblastes aboutissent à l'installation d'une fibrose pulmonaire terminale avec une élévation concomittante des neutrophiles dans le lavage comme dans les autres maladies fibrosantes.