Editorial

Hypersensitivity Pneumonitis
Ignotum per ignotius

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Hypersensitivity pneumonitis (HP), also called *extrinsic allergic alveolitis*, is a complex syndrome of varying intensity, clinical presentation, and natural history, caused by an exaggerated immune response to the inhalation of a large variety of organic particles and chemical products.

The **epidemiology** varies considerably around the world, depending on disease definition, diagnostic methods, type and intensity of exposure, geographical conditions, agricultural and industrial practices, and host risk factors. HP is considered as an orphan disease.

Numerous **inciting agents** have been described including, but not limited to, agricultural dusts, bioaerosols, microorganisms (fungal, bacterial, or protozoal), inorganic chemicals, and ingestion of drugs. Only few exposed individuals develop the disease.

HP can be presented as acute HP, subacute HP, chronic HP, and with acute exacerbations.

ACUTE HP presents 4–8 h after often heavy exposure with fever, malaise, cough, dyspnea and chest tightness (Monday morning fever). The symptoms remit over 24–48 h in the absence of further exposure. **SUBACUTE HP** develops insidiously with lower-level exposure with weight loss, dyspnea, cough and fatigue. In **CHRONIC HP** patients do not give a history of acute symptoms but present with diffuse pulmonary fibrosis which must be distinguished from other conditions, including IPF and fibrotic NSIP. **ACUTE EXACERBATIONS** of chronic HP may occur without further exposure to the offending antigen.

A **two-hit hypothesis** has been suggested for its **pathogenesis**, wherein preexisting genetic susceptibility or environmental factors (i.e., the first hit) increases the risk for the development of HP after antigen exposure (the second hit). Antigen exposure acts as the inducing factor, and genetic or environmental factors act as promoting risk factors. BALF and blood **Treg-cells** from HP patients were totally nonfunctional and unable to suppress proliferation. Low levels of IL-17 were detected in sera and BALF from both normal and asymptomatic individuals, whereas measurable levels were found in patients. Defective Treg-cell function, potentially caused by increased IL-17 production, could account for the exacerbated immune response characteristic of HP.

Cigarette smokers have a lower risk of developing HP than nonsmokers, because of diminished antibody production following exposure to inhaled antigens.

In the acute phase **HRCT** shows mainly ground glass opacities (GGO) while several secondary pulmonary lobules are spared and appear as darker areas in both lower lobes (air trapping). In **subacute HP HRCT** usually shows multiple, so-called acinar nodules, infiltrating the entire lung (Figure 1). In **chronic phase of HP** honeycombing and cylindrical bronchiectasis are present. The major difficulty is differentiating chronic HP from IPF and NSIP. Certain features have been suggested as favoring **HP over IPF or NSIP**: lobular areas with decreased attenuation and vascularity, centrilobular nodules and lack of lower zone predominance of abnormalities (Table 1). However, HRCT features allowed confident distinction of chronic HP from IPF and NSIP only about 50%. HRCT findings may serve as a useful prognostic indicator. **Pathological features** of HP include peribronchiolar mixed inflammatory infiltrate which is usually lymphocyte-dominant. Variable numbers of poorly formed granulomas are characteristic but not necessary to diagnosis. Fibrosis is variable depending on the chronicity of the case.

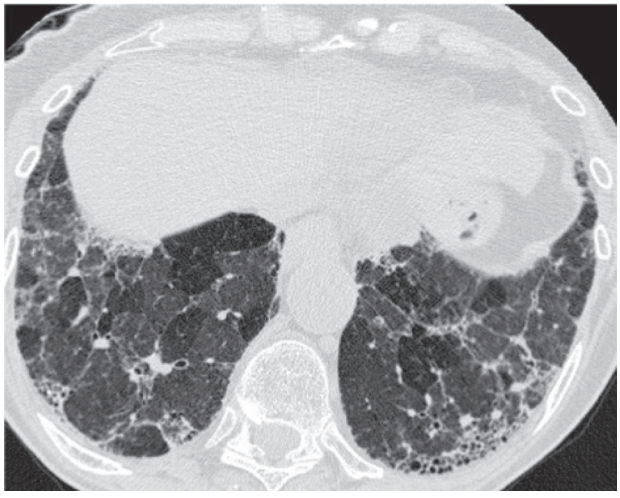

FIGURE 1. A 55-year old farmer with subacute to chronic hypersensitivity pneumonitis. Several secondary pulmonary lobules are spared and appear as darker areas in both lower lobes (air-trapping). Mild reticulation with honeycombing is shown in the left lung base.

TABLE 1. Features suggested as favoring HP over IPF or NSIP

Lobular areas with decreased attenuation and vascularity
Centrilobular nodules
Lack of lower zone predominance of abnormalities.

In patients with clinical and HRCT findings of UIP any one of the following **three criteria** are necessary for diagnosis:

1. Positive bronchial challenge testing (reinforced often with positivity of specific IgG).
2. Specific IgG positivity and surgical lung biopsy (SLB) sample compatible with HP or >20% lymphocytes in BALF (>20% lymphocytes is seen in 85% of patients with chronic HP).
3. Surgical lung biopsy with characteristics of subacute HP.

Significant **predictors of HP** are: exposure to a known offending antigen, symptoms 4-8 h after exposure, positive precipitating antibodies, recurrent episodes of symptoms, inspiratory crackles and weight loss.

A diagnostic algorithm is presented in diagram 1.

Serum IgG ab specific to an identified antigen (if known) should be undertaken. The presence of precipitins only indicates exposure and a humoral response (in up to 50% of asymptomatic pigeon breeders and 2–10% of asymptomatic farmers). **Inhalation challenges** may be useful in diagnosing HP to a suspected antigen, but limited to specific research centers.

Idiopathic Interstitial Pneumonias are frequently confused with HP, and vice versa, except when the exposure is readily apparent. Up to **30%** of subjects with histologic HP have no identifiable exposure. In a recent publication (7), 20/46 (43%) of diagnosed as IPF patients had subsequent diagnosis of chronic HP due to occult avian antigen (feather bending).

Antigen avoidance is of critical importance. Usually results in regression of disease and prevents sensitization of other individuals. However, it is not always possible or efficacious. **Glucocorticoids** accelerate initial recovery in severely ill. Prednisone is given in 0.5 to 1 mg/kg of IBW/d (max 60 mg/d), each morning X1-2 wks. and tapered over 2-4 wks. However, long-term outcome appears unchanged. **Inhaled CS** may be effective in treating or preventing recurrence, but not well studied.

There are certain known **prognostic factors**: The duration/intensity of exposure, the histopathologic changes (OP, cellular NSIP vs. fibrotic NSIP or a UIP-like pattern) and the presentation (acute, subacute, or chronic HP). Digital clubbing predicts a worse outcome. Older patients have a less complete recovery. Neither the degree or type of PFTs nor CXR at the time of diagnosis correlate with outcome. HRCT patterns may predict prognosis of chronic HP.

Unmet needs include: Better documentation of incidence and prevalence, Identification of genetic and

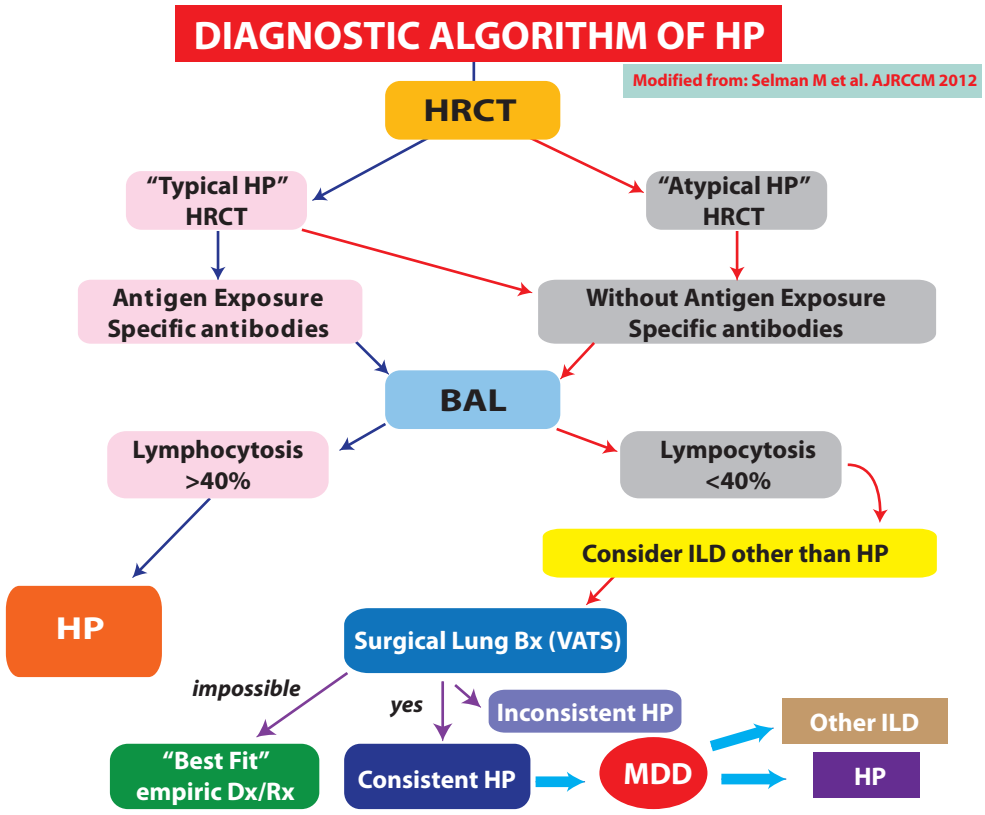

DIAGRAM 1. Diagnostic algorithm of hypersensitivity pneumonitis (modified from ref. 1).

environmental risk factors that affect its occurrence and natural history, Validation of biomarkers of both exposure and disease, Definition of the natural history, Development of a battery of standardized antigens known to cause for diagnosis and investigation of pathogenesis.

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