Hypersensitivity Pneumonitis: A Plethora of Radiological Findings

Award: Magna Cum Laude
Poster No.: P-0114
Congress: ESTI 2014
Type: Educational Poster
Authors: S. Gupta, J. Brozik, P. Rao, D. Barnes; Leicester/UK
Keywords: Occupational / Environmental hazards, Diagnostic procedure, CT-High Resolution, Thorax
DOI: 10.1594/esti2014/P-0114

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Learning objectives

1. Overview of common clinical manifestations and etiology of hypersensitivity pneumonitis (HP).
2. Illustrate the spectrum of chest radiography and computed tomography (CT) features of hypersensitivity pneumonitis.

Background

The annual incidence of interstitial lung disease has been reported as approximately 30 per 100,000/year with HP accounting for less than 2% of the cases. In the UK, a large general population based study has shown the incidence of HP of approximately 1 per 100,000. Hypersensitivity pneumonitis is a heterogeneous condition, both clinically and radiologically, resulting from the exposure and inhalation of a variety of organic and inorganic compounds. The radiological features are varied and sometimes non-specific, ranging from diffuse alveolar damage to varying patterns of fibrosis, often with overlap between the subacute and chronic findings. Hypersensitivity pneumonitis is recognised as an underdiagnosed condition and early recognition of the disease may help prevent continued antigen exposure to the patient which in turn may halt progression to irreversible fibrosis.

CLINICAL PRESENTATION

Clinical presentation of HP may be acute, subacute or chronic with significant overlap between these presentations. The clinical utility of the various proposed diagnostic criteria is uncertain, largely due to lack of robust validation. Cluster analysis of data from a large prospective multicentre cohort has demonstrated that most of the cases of HP best fit into a two-cluster model. Patients in cluster 1 resembled those suffering from classic acute form of HP and tend to be the ones exposed to thermophilic actinomycete species or fungi (farmer's lung). On the contrary, patients in cluster 2 showed features of classic chronic HP and were individuals with bird antigen exposure (bird fancier's lung). Acute exacerbations of chronic HP has also been described that may occur without further antigen exposure. It is important to distinguish this from recurrent acute HP secondary to continued exposure to the offending antigen.

ETIOLOGY

The vast variety of antigens that are known to cause hypersensitivity pneumonitis fall into three major groups: microbial agents, animal / insect proteins, and low molecular weight
chemicals. HP syndromes are usually named after the occupation associated with the antigen exposure or the antigen that triggers the immune response (Table 1).

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ANTIGEN</th>
<th>ANTIGEN SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microbial agents</strong></td>
<td></td>
<td></td>
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<tr>
<td>Farmer's Lung</td>
<td>Saccharopolyspora rectivirgula</td>
<td>Mouldy hay, silage, grain</td>
</tr>
<tr>
<td>Humidifier / air conditioner lung</td>
<td>Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca</td>
<td>Water reservoirs, contaminated air conditioners</td>
</tr>
<tr>
<td>Malt worker's lung</td>
<td>Aspergillus fumigatus, Aspergillus clavatus</td>
<td>Mouldy barley</td>
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<tr>
<td>Machine worker's lung</td>
<td>Mycobacterium immunogenum, Pseudomonas fluorescens</td>
<td>Aerosolized metalworking fluid</td>
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<tr>
<td><strong>Animal proteins</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bird fancier's disease</td>
<td>Avian droppings, feathers, serum</td>
<td>Pigeons, chickens, parakeets, Budgerigars</td>
</tr>
<tr>
<td>Furrier's lung</td>
<td>Animal Fur proteins</td>
<td>Animal pelts</td>
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<tr>
<td><strong>Insect proteins</strong></td>
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<tr>
<td>Miller's lung</td>
<td>Sitophilus granularis (granary weevil)</td>
<td>Dust-contaminated grain</td>
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<td><strong>Low-molecular weight chemicals</strong></td>
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<tr>
<td>Chemical worker's lung</td>
<td>Trimellitic anhydride (TMA), Methylene diisocyanate (MDI), Naphthylene 1,5 diisocyanate (NDI)</td>
<td>Plastics, rubber manufacturing, Polyurethane foam production</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>6-Mercaptopurine, beta-blockers, Busulphan, cyclophosphamide, Nitrofurantoin, Procarbazine</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Hypersensitivity Pneumonitis Syndromes
The commonest syndromes are farmer’s lung (exposure to Thermophilic actinomycete) and bird fancier’s lung (exposure to a complex mixture of high- and low-molecular-weight proteins from avian serum, faeces and feathers). Other lesser known causes of HP include inhalation of Mycobacterium avium-intercellulare complex organisms (hot tub lung) and drug-induced lung disease.\(^1,8\)

**Imaging findings OR Procedure details**

Imaging findings of HP can be divided into acute, subacute and chronic, which generally correlate with patient's clinical symptoms with overlap of subacute and chronic HP.

**Acute HP**

In acute HP the imaging may often be normal\(^9\) or have relatively non-specific findings including ground glass opacity, perihilar consolidation or more rarely more focal areas of consolidation, which generally reflect diffuse alveolar damage. These patients are often treated empirically for infection, exacerbations of asthma or pulmonary oedema without the correct diagnosis ever being known as many will improve when the antigen is removed or steroids are given. The CXR of some patients with acute HP also demonstrate multiple small ill-defined nodular opacities in both lungs with sparing of the apices and bases [Figure 1].
Fig. 1: Acute HP: Chest Radiograph in a 32 year old female patient who kept budgie, presented to the acute admission unit with shortness of breath demonstrates diffuse ground-glass opacities and ill-defined nodules with relative sparing of apices and bases.

**References:** Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK

As the symptoms in acute HP patients resolve rapidly CT is not always performed. However if these acute patients do proceed to CT the findings reflect the CXR findings and include small (1 - 3 mm in diameter), ill-defined soft nodules and ground-glass opacities. The ground-glass opacities may be associated with bilateral diffuse areas of dense air-space consolidation.
Fig. 2: Acute HP: Repeat chest radiograph of the same patient in figure 1 performed 3 months after removal of exposure and prednisolone treatment demonstrates complete resolution of the ground-glass opacities and ill-defined nodules.

References: Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK

Subacute HP

Subacute HP is a progressive, often insidious disease due to prolonged exposure to the incriminating agent / antigen for weeks to months. Due to its gradual non-specific clinical manifestations, patients are generally imaged with CT, although chest radiography
is still often the initial imaging modality. The subacute form may present as a fine nodular or reticulonodular opacities on chest radiograph. The CT demonstrates diffuse soft centrilobular ground-glass nodules (3-5 mm) and ground-glass opacities\(^{11}\) predominantly involving the middle and lower lung zones with striking lobular pattern of mosaic lung attenuation [Figures 3, 4 and 5].

**Fig. 3:** Subacute HP: Axial CT image shows typical ill-defined centrilobular nodules in patient with subacute HP.

**References:** Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK
Fig. 4: Subacute HP: Coronal reconstructed CT image shows typical features of subacute HP with extensive diffuse ground-glass opacities, ill-defined centrilobular nodules and lobular mosaic lung attenuation.

References: Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK
Fig. 5: Subacute HP: Axial CT image of a patient who possessed budgies, shows typical features of subacute HP i.e. diffuse ground-glass opacities, ill-defined centrilobular nodules (blue arrow) and lobular areas of mosaic lung attenuation. References: Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK
Fig. 6: Subacute HP: Repeat CT scan of the same patient in figure 5, performed 3 months after removal of budgies and oral steroid treatment. Axial CT image demonstrates near complete resolution after removal of exposure and prednisolone treatment.

References: Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK

Unlike in sarcoidosis, the fissures and sub pleural regions are typically not involved as the nodules are almost always purely centrilobular. Ground-glass opacities are seen in more than 70% of the patients with subacute HP and are usually bilateral and symmetrical. The centrilobular nodules and ground-glass opacities are not specific to HP and atypical infections, smoking related interstitial lung disease i.e. respiratory bronchiolitis (RB) / respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) may give over lapping appearances. However, the presence of well defined lobular areas of low attenuation with a mosaic pattern, coupled with the other findings is highly suggestive of HP [Table 2].
1) Ground-glass opacities
2) Centrilobular ground-glass nodules
3) Lobular areas of mosaic lung attenuation
4) Headcheese sign: three different densities - normal lung in combination with 1 and 3

* Discriminating features of HP

Table 2: Typical CT features of hypersensitivity pneumonitis

These low attenuation areas, which often conform to the secondary pulmonary lobule are in fact areas of air trapping which are therefore optimally demonstrated on expiratory imaging [Figures 7 and 8].

Fig. 7: Subacute HP: Inspiratory (Figure 7) axial CT image showing ground-glass opacities and lobular areas of mosaic lung attenuation. There is increased conspicuity of the lobular areas of air trapping on expiratory (Figure 8) scan.

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**Fig. 8**: Subacute HP: Inspiratory (Figure 7) axial CT image showing ground-glass opacities and lobular areas of mosaic lung attenuation. There is increased conspicuity of the lobular areas of air trapping on expiratory (Figure 8) scan.

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As a continuum from the above, mosaic low attenuation, ground-glass opacities and normal lung in the same vicinity, give a three attenuation pattern. This has been termed the 'Headcheese sign' [Figure 9], so called due to its resemblance to a meat terrine with a variegated appearance, prepared from pieces of meat from head (and various other parts) usually of a calf or a pig [Figure 10].
Fig. 9: Headcheese sign: Axial CT image demonstrates ‘Headcheese sign’ in patient with subacute hypersensitivity pneumonitis showing combination of three lung attenuations - areas of mosaic lung attenuation (blue arrow), ground-glass opacities (red arrow) and normal lung attenuation (green arrow).

References: Jan Brozik, Radiologicka klinika, Lekarske fakulty UK a Fakultni nemocnice Hradec Kralove, Czech Republic
Fig. 10: Headcheese sign: The term 'Headcheese sign' is due to the appearance of the lung resembling to a meat terrine. Picture of meat terrine with a variegated appearance, prepared from pieces of meat from head (and various other parts) usually from a calf or a pig.

References: Jan Brozik, Radiologicka klinika, Lekarske fakulty UK a Fakultni nemocnice Hradec Kralove, Czech Republic

The 'Headcheese sign' is classically seen in subacute HP\textsuperscript{15} and, although relatively specific for HP, can occasionally be seen in other conditions including RB-ILD, follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), sarcoid and atypical infections. Thin-walled cysts are very occasionally seen in patients with subacute HP [Figure 11] but are not a distinguishing feature.\textsuperscript{16}
Fig. 11: Subacute HP with a pulmonary cyst: Representative axial CT image in a patient with subacute HP showing multiple centrilobular nodules and a thin-walled cyst in the middle lobe.

References: Jan Brozik, Radiologicka klinika, Lekarske fakulty UK a Fakultni nemocnice Hradec Kralove, Czech Republic

Chronic HP

Chronic HP takes between 4 months and several years to develop and indicates irreversible lung damage and fibrosis. The CXR may shows mid and upper lobe fibrosis in chronic disease with reticular pattern and honeycombing. As with all interstitial lung diseases CT is much more sensitive and specific than CXR and chronic HP is no different. The hallmark CT finding in chronic HP is interstitial fibrosis characterised by reticulations, ground-glass opacities, architectural distortion, volume loss, traction bronchiectasis, bronchiolectasis, and occasional honeycombing [Figures 12, 13, 14 and 15].
Fig. 12: Chronic hypersensitivity pneumonitis: Axial CT images (Figure 12) showing subacute on chronic hypersensitivity pneumonitis with subtle reticulations and lobular areas of mosaic lung attenuation. Repeat CT scan (Figure 13) 5 years later shows progressive fibrosis with architectural distortion, traction bronchiectasis and bilateral lobular areas of mosaic lung attenuation.

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**Fig. 13:** Chronic hypersensitivity pneumonitis: Axial CT images (Figure 12) showing subacute on chronic hypersensitivity pneumonitis with subtle reticulations and lobular areas of mosaic lung attenuation. Repeat CT scan (Figure 13) 5 years later shows progressive fibrosis with architectural distortion, traction bronchiectasis and bilateral lobular areas of mosaic lung attenuation.

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Fig. 14: Chronic hypersensitivity pneumonitis: Representative axial CT image demonstrates honeycombing anteriorly in the upper lobes, minor ground-glass opacities, traction bronchiectasis and architectural distortion. Upper lobe predominance and history of HP / antigen exposure should help differentiate from other fibrotic lung diseases.

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References: Radiology, University Hospitals of Leicester NHS Trust / University of Leicester, Glenfield Hospital - Leicester/UK

The pattern of fibrosis in HP can vary which makes it a diagnostic challenge. The fibrosis can have a predominantly subpleural or peribrochovascular distribution, sparing the lung bases\(^\text{17}\) or can be patchy in distribution. Patients with chronic HP may demonstrate mild honeycombing with a subpleural or peribrochovascular distribution and relative sparing of the lung bases.\(^\text{17}\)

The most important CT features to differentiate subacute / chronic HP from other interstitial lung disease are: lobular areas of decreased attenuation (air trapping on expiratory CT), ill-defined centrilobular nodules, and lack of lower zone predominance of abnormalities.\(^\text{17}\)
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Conclusion

Hypersensitivity pneumonitis is both underdiagnosed and misdiagnosed due to its broad spectrum of clinical, pathological and radiological manifestations. An astute radiologist can often be first person to raise the possibility of the diagnosis of HP leading to other diagnostic tests and search for evidence of antigen exposure. The importance of recognition of CT signs of HP therefore cannot be overemphasised, as this may help prevent irreversible lung damage.

References

8. Travis WD, Colby TV, Koss MN, Rosado-de-Christenson ML, Muller NL, King TE, Jr. Non-neoplastic disorders of the lower respiratory tract: American Registry of Pathology; 2002.


Personal Information

Sumit Gupta MRCP(UK), FRCR, PhD
NIHR Academic Clinical Lecturer / Radiology Speciality Registrar
University of Leicester / University Hospitals of Leicester NHS Trust
Glenfield Hospital
Leicester LE3 9QP
United Kingdom
mail to: drsumitgupta@yahoo.com

Jan Brozik MD
Consultant (Locum) Cardiothoracic Radiologist
University Hospitals of Leicester NHS Trust
Glenfield Hospital, Groby Road, Leicester LE3 9QP
United Kingdom

Praveen Rao MRCP, FRCR
Consultant Cardiothoracic Radiologist
University Hospitals of Leicester NHS Trust