The spectrum of HRCT findings of idiopathic pneumonia syndrome (IPS) in patients who underwent hematopoietic stem cell transplantation (HSCT)

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Idiopathic pneumonia syndrome (IPS) after hematopoietic stem cell transplantation (HSCT) was first introduced by Clark JG, et al. (1), in 1993.

This concept was regarded as non-infectious acute lung injury probably caused by toxicity from the pre-transplantation chemotherapy, total body irradiation (TBI) therapy, and immunological effect including graft-versus-host disease (GVHD) (1).

It is supposed that IPS occurs in approximately 5-25% of allogeneic bone marrow transplantation (BMT) recipients (2).

IPS was defined as “diffuse lung injury occurring after marrow transplant for which an infectious etiology is not identified”. The main pathologic feature of IPS was regarded as diffuse alveolar damage (DAD).

As the following criteria show, the diagnosis of IPS is one of exclusion, especially exclusion of lower respiratory tract infections.

IPS has been firstly limited to DAD as the pathological finding, as shown above, and gradually extended to organizing pneumonia (OP).
Recently, the American Thoracic Society (ATS) updated the concept of IPS and extended the concept to a wider range of “idiopathic syndrome of pneumopathy after HSCT” (3).

Furthermore, ATS has classified IPS into specific entities based in large part on the primary anatomical sites of inflammation and dysfunction; interstitial tissue, vascular tissue, airway tissue, and unclassifiable IPS.
Definition

- An idiopathic syndrome of pneumopathy after HSCT, with evidence of widespread alveolar injury and in which infectious etiologies and cardiac dysfunction, acute renal failure, or iatrogenic fluid overload have been excluded (3).

**DEFINITION OF IDIOPATHIC PNEUMONIA SYNDROME**

I. Evidence of widespread alveolar injury:
   a. Multilobar infiltrates on routine chest radiographs or computed tomography
   b. Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
   c. Evidence of abnormal pulmonary physiology
      1. Increased alveolar to arterial oxygen difference
      2. New or increased restrictive pulmonary function test abnormality

II. Absence of active lower respiratory tract infection based upon:
   a. Bronchoalveolar lavage negative for significant bacterial pathogens including acid-fast bacilli, Nocardia, and Legionella species
   b. Bronchoalveolar lavage negative for pathogenic nonbacterial microorganisms:
      1. Routine culture for viruses and fungi
      2. Shell vial culture for CMV and respiratory RSV
      3. Cytology for CMV inclusions, fungi, and Pneumocystis jirovecii
      4. Direct fluorescence staining with antibodies against CMV, RSV, HSV, VZV, influenza virus, parainfluenza virus, adenovirus, and other organisms
   c. Other organisms/tests to also consider:
      1. Polymerase chain reaction for human metapneumovirus, rhinovirus, coronavirus, and HHV6
      2. Polymerase chain reaction for Chlamydia, Mycoplasma, and Aspergillus species
      3. Serum galactomannan ELISA for Aspergillus species
   d. Transbronchial biopsy if condition of the patient permits

III: Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Cited from the reference (3)
Clinical feature

Causes

- A variety of lung insults, including toxic effects of HSCT conditioning regimens, immunologic cell-mediated injury, inflammatory cytokines, and occult pulmonary infections including CMV and adenovirus.

Incidence, onset and prognosis

- The incidence of IPS in the first 120 days after allogeneic HSCT with myeloablative conditioning is 3 to 15%, and the median time of onset for IPS was initially reported to be 6 to 7 weeks (range, 14-90 days) following allogeneic HSCT, but more recent studies have indicated an earlier median time of onset at 19 days (range, 4-106 days). Mortality rates in allogeneic HSCT recipients range from 60 to 80% (3).

- Concerning IPS after autologous HSCT, most IPS cases are supposed to be diffuse alveolar hemorrhage (DAH), because GVHD and latent CMV infection derived from the graft is uncommon. According to the report of Robbins et al., DAH occurred in 29 out of 141 patients (21%) (4).

- The entities included in IPS are diverse and shown in the following table.
### Categorization of IPS

**TABLE 2. CATEGORIZATION OF THE CLINICAL SPECTRUM OF LUNG INJURY FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION**

Clinical Spectrum of Disease as Categorized by Presumed Site of Primary Tissue Injury

<table>
<thead>
<tr>
<th>Pulmonary Parenchyma</th>
<th>Vascular Endothelium</th>
<th>Airway Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute interstitial pneumonitis (AIP)*</td>
<td>Peri-engraftment respiratory distress syndrome (PERDS)*</td>
<td>Cryptogenic organizing pneumonia (COP)/Bronchiolitis obliterans organizing pneumonia (BOOP)*</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (ARDS)*</td>
<td>Noncardiogenic capillary leak syndrome (CLS)*</td>
<td>Bronchiolitis obliterans syndrome (BOS)*</td>
</tr>
<tr>
<td>BCNU pneumonitis</td>
<td>Diffuse alveolar hemorrhage (DAH)*</td>
<td></td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>Pulmonary veno-occlusive disease (PVOD)</td>
<td></td>
</tr>
<tr>
<td>Delayed pulmonary toxicity syndrome (DPTS)*</td>
<td>Transfusion-related acute lung injury (TRALI)</td>
<td></td>
</tr>
<tr>
<td>Post-transplant lymphoproliferative disease (PTLD)</td>
<td>Pulmonary cytolytic thrombi (PCT)</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic pneumonia (EP)</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis (PAP)</td>
<td>Pulmonary thromboembolus (PTE)</td>
<td></td>
</tr>
</tbody>
</table>

* Conditions routinely included under the classification of idiopathic pneumonia syndrome (IPS).

Cited from the reference (3)
In early reports, IPS was restricted to this entity, the pathological findings of which were shown as "interstitial pneumonia and diffuse alveolar damage (DAD)."

According to the report of 50 autopsied cases by Poychowdhury et al., 18 cases with DAD also showed diffuse alveolar hemorrhage (DAH) as an accompanied finding, which may suggest that DAD and DAH belong to the same category (5).

**Radiologic findings**

**Radiography**
- Nonspecific
- Diffuse GGO in the bilateral lung field similar to that of DAH or pulmonary edema.

**HRCT**
- GGO and air-space consolidation
- Distribution: in the bilateral lung with a basilar or dorsal predominance (6).
A 54-year-old female patient with multiple myeloma. HRCT images show extensive GGO with intralobular reticulation (crazy-paving pattern) in the bilateral lung. Airspace consolidation is also seen in the dependent lung regions.
A 62-year-old male patient with leukemia.
HRCT images show extensive GGO and airspace consolidation, within which well-defined "spared lobules" are also seen.
Noncardiogenic capillary leak syndrome (CLS)
= Engraftment syndrome
= Peri-engraftment respiratory distress syndrome (PERDS)

- CLS occurs most frequently after autologous HSCT in 7-11% of recipients, however, it sometimes occurs after allogeneic HSCT (7).
- It occurs around 7 days after HSCT at the time of neutrophil engraftment and associated with the overproduction of pro-inflammatory cytokines.
- It shows capillary leak that results in interstitial pulmonary edema.
- According to Capizzi, the mortality rate was not so high (4/19) and patients usually responded to steroid if treated in the early stage (8).

<Radiologic findings>
Radiography
- Similar to those of interstitial pulmonary edema

HRCT
- Bilateral GGO or airspace consolidation distributed predominantly in the hilar or peribronchial regions.
- Smooth thickening of interlobular septa (ILS) is also common (6, 7, 9).
A 52-year-old female patient with leukemia. HRCT images show smooth thickening of interlobular septa (IALS) distributed extensively in the bilateral lung. Right pleural effusion can be seen.
Noncardiogenic capillary leak syndrome (CLS)

A 42-year-old female patient with leukemia. HRCT images show thickening of ILS and GGO in the bilateral lung. Note that hazy centrilobular opacities are also seen in the right middle lobe.
Diffuse alveolar hemorrhage (DAH)

- DAH predominantly occurs in autologous HSCT recipients (20%) more than in allogeneic HSCT recipients (10%).
- Since DAH often occurs at the time of granulocyte recovery, neutrophil infiltration into the lungs has been implicated as one of the pathogenesis of DAH.
- It typically occurs in the first month after HSCT.
- Hemoptysis occurs only in half of patients.
- The accurate diagnosis usually needs bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB) or surgical lung biopsy.
- DAH is usually associated with a high mortality rate, which has been reported as approximately 70-100%.

<Radiologic findings>

Radiography
- Non-specific and usually shows diffuse GGO in the central and lower lung zone.

HRCT
- Extensive GGO with or without intralobular reticulation (crazy-paving pattern).
- Centrilobular opacities as perivascular lesions may sometimes be seen in patients with DAH, which will show perivasclar accentuation of hemorrhage (6, 7).
A 37-year-old female patient with leukemia. HRCT image shows bilateral and extensive GGO with subpleural sparing. Note that centrilobular opacities are also seen in the bilateral lung. A combination of GGO and nodules may make it difficult to differentiate DAH from CMV pneumonia. The diagnosis of DAH was confirmed by bronchoalveolar lavage (BAL).
Bronchiolitis obliterans syndrome (BOS)

- Bronchiolitis obliterans (BO) is a chronic inflammatory and fibroproliferative process centered on the terminal and respiratory bronchioles leading to the narrowing of the bronchial lumen by submucosal inflammation or fibrosis.
- It is possible to diagnose bronchiolitis obliterans syndrome (BOS) if pulmonary function testing shows new or progressive obstructive lung defects (10).
  - A 20% decrease in FEV1 and/or a 25% decrease in FEF 25-75 from previous baseline were the proposed criteria.
- The incidence has been reported as between 2% and 14% in allogeneic recipients (11).
- The causes of bronchiolitis obliterans are estimated as viral infections including CMV, autoimmune processes, and injury to the small airways due to GVHD.

<Radiologic findings>

Radiography
- Hyperinflation or a normal finding.

HRCT
- Mosaic pattern of lung attenuation, especially showing a combination of decreased attenuation and decreased vascular caliber, bronchial dilatation.
- The existence of air trapping on expiratory CT (6, 7).
A 44-year-old male patient with leukemia.

A. Inspiratory HRCT image shows minimal existence of mosaic pattern in the bilateral lung areas. Note that minimal bronchial dilatation patterns are seen.

B. Expiratory HRCT image shows a lack of increase in lung attenuation in the large part of the bilateral lower lobes, showing air trapping.
A 30-year-old patient with leukemia.

A. Inspiratory HRCT image shows marked homogenous lung attenuation (mosaic perfusion) in the bilateral lung.

B. Expiratory HRCT image shows evident air trapping in the bilateral lung.
Organizing pneumonia (OP)/BOOP

- Organizing pneumonia (OP) occurs in up to 10% of HSCT recipients (11).
- The risk factors of this entity include allogeneic HSCT and the existence of GVHD.
- OP usually occurs 1 to 13 months after HSCT.
- OP is characterized by edematous granulation tissue polyps within the lumen of alveolar ducts and bronchioles in association with a variable degree of interstitial inflammation and fibrosis.

*Radiologic findings*

Radiography
- Bilateral and peripheral patchy consolidation or GGO.

HRCT
- Airspace consolidation along the bronchovascular bundle or in the subpleural area.
- Although consolidation is more commonly observed and GGO is limited around airspace consolidation in immunocompetent patients, GGO tends to be more frequently and independently observed in immunocompromised patients (6, 7).
Organizing pneumonia (OP)

A 16-year-old male patient with leukemia.

A. HRCT shows extensive GGO and minimal airspace consolidation in the bilateral lung. Note that nodular GGO can also be seen.

B. Pathologic specimen obtained by surgical lung biopsy shows edematous granulation tissue polyps within the alveolar and bronchiolar lumen with minimal thickening of alveolar wall.
A 47-year-old male patient with leukemia.

A. HRCT shows patchy GGO with focal airspace consolidation. Band-like opacities are also seen in the subpleural lung areas. Note that GGO is predominant compared with airspace consolidation.

B-C. Pathologic specimen obtained by surgical lung biopsy shows intraalveolar granulation tissue and minimal thickening of alveolar wall. In another area, concentric narrowing and obstruction of the bronchiolar lumens by submucosal fibrosis are also seen, showing the coexistence of OP and BO.
Transfusion-related acute lung injury (TRALI)

- TRALI is a serious complication of transfusion and few cases with TRALI have been reported after HSCT (12).
- TRALI usually develops within 4 hours of transfusion (12).

<Radiologic findings>

- Chest radiographic findings include patchy, fluffy infiltration consistent with interstitial pulmonary edema without cardiomegaly.
- There are few reports about HRCT findings.

A 29-year-old female patient with leukemia. HRCT image shows extensive GGO and the smooth thickening of ILS. Bilateral pleural effusions are also seen. This feature is similar to that of CLS.
Eosinophilic pneumonia (EP)

- This entity has rarely been reported as one of chest complications after HSCT. An association with chronic GVHD is assumed (13).
- Clinical and radiologic manifestations are similar to acute or chronic eosinophilic pneumonia which are not associated with HSCT.

A 59-year-old female patient with leukemia.
HRCT images show bilateral patchy GGO and the thickening of ILS. This feature is almost identical to that seen in acute eosinophilic pneumonia.
The radiographic finding of IPS, especially, AIP, CLS, DAH, and TRALI, is non-specific and usually shows diffuse GGO distributed predominantly in the central and lower lung zone. This feature is often indistinguishable from pneumocystis pneumonia (PCP), and cytomegalovirus (CMV) pneumonia, and pulmonary edema.
Pneumocystis jirovecii pneumonia (PCP)

- The incidence of PCP in BMT recipients is reported as less than 10%.
- Characteristic pathologic findings include intraalveolar macrophages or a mixture of inflammatory infiltrates with or without associated hemorrhage.

<Radiologic findings>
- Widespread GGO, which is distributed typically at the perihilar regions with upper lung predominance, is the frequent and characteristic finding.
- Extensive GGO is usually observed with sparing of adjacent secondary pulmonary lobules, which is described as mosaic pattern (6, 14).
- Centrilobular opacities are rarely seen.

A 55-year-old female patient with multiple myeloma. HRCT images show extensive GGO with characteristic mosaic pattern in the bilateral lung. Note that reticular opacities can be seen within GGO (crazy-paving pattern).
Cytomegalovirus pneumonia (CMV pneumonia)

- CMV infection occurs in 70% of recipients, approximately one-third of whom develop CMV pneumonia.
- The pathologic finding is mixed alveolar and interstitial pattern consisting of alveolar macrophages, fibrin, hyaline membranes, proliferating reactive pneumocytes, and hemorrhagic exudates, consistent with DAD and thickening of alveolar wall.

**Radiologic findings**

- Characteristic HRCT findings include patchy or widespread GGO, air-space consolidation, and nodules with centrilobular or randomly distribution (6, 14, 15).

A 48-year-old female patient with leukemia.

HRCT images show numerous nodules with or without halo sign distributed throughout the whole lung superimposed on extensive GGO. Bilateral pleural effusion is also seen.
Pulmonary edema

- Pulmonary edema is one of the earliest complications after HSCT.
- It is sometimes difficult to differentiate this entity from CLS.

**Radiologic findings**

- HRCT findings include enlarged pulmonary vessels, interlobular septal thickening, thickening of bronchial wall, and GGO involving mainly the peribronchovascular, central or dependent lung regions (6, 14).
- Cardiomegaly is usually observed.

An 18-year-old male patient with leukemia. HRCT images show enlargement of pulmonary vessels, ground-glass opacity along the bronchovascular bundles and bilateral pleural effusion. Note that marked interlobular thickening is seen.
Idiopathic pneumonia syndrome (IPS) is an acute lung dysfunction of non-infectious etiology and a severe complication following HSCT.

A couple of decades have passed and the concept of IPS has changed.

In these days, IPS is supposed to include a variety of entities which occurs due to non-infectious causes after HSCT.

Since the therapeutic strategies for IPS are clearly different from those for infectious diseases and therapeutic delay causes poor prognosis of patients, radiologists should know some characteristic HRCT findings of IPS which include a wide spectrum of entities.
References


15. Franquet T, Lee KS, Müller NL. Thin-section CT findings in 32 immunocompromised patients with cytomegalovirus pneumonia who do not have AIDS. AJR 2003; 181: 1059-63.
Thank you for your attention!

Please see the following paper.

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