Diagnostic algorithm in interstitial lung disease

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Alveolar-interstitial lung disease

- Increased distance diffusion for gas exchange
- Stiffened lung, less compliant
- Ventilation-perfusion mismatch
Interstitial lung disease (ILD)

- Can manifest itself in many ways
- Histological picture can be variable
- Until a few years ago terminology for morphological findings was often confusing
Classification of idiopathic and interstitial lung disease

- Provided a basic distinction in different patterns based on defined criteria
- Aimed at making a clearer distinction between the terminology used for the pathological diagnosis and the clinical diagnosis

Diagnostic problems in interstitial lung disease

- Many diseases share a common histological pattern
- But also: many individual diseases each can manifest themselves in different ways in the lung, each with a different morphological pattern
- Thus: adequate diagnostic procedure: multidisciplinary approach with a merger of clinical- and lung function data, together with radiology and histopathology
- So: when discussing a problematic pathologic diagnosis in ILD, a first step should be to have access to adequate clinical and radiological data
Diagnostic pathology of interstitial lung disease

- For most diagnoses a lung biopsy by an open surgical procedure or video assisted thoracoscopy (VATS) will be needed.

- Limited clinical condition: often hesitation such procedure: lung biopsies may be taken in rather advanced-/ end-stage of disease.

- This may be the first cause of diagnostic problems:
  - Many initially different morphological patterns in interstitial lung disease can progress to a so-called “end-stage lung” (“honeycomb lung”)
  - In a late phase (much fibrosis) several hallmarks of changes related to aetiology, or early, most specific pathogenetic changes will be lost

- Similar difficulty: when only biopsies from most severe areas, instead of at least in addition also biopsies of early and or active areas/ lesions.
Morphologic clues

In some cases specific morphologic clues can aid in further subclassification, and sometimes may lead to a definitive diagnosis

- Microorganisms (bacteria, fungal, other); viral inclusions
- Langerhans histiocytes of pulmonary Langerhans cell histiocytosis (CD1a, S100 positive)
- Malignant cells (often specific morphologic features or localisation, i.e. in lymphatics)
- “Cannibalistic” multinucleated giant cells and multinucleated alveolar lining cells of hard metal (cobalt) pneumoconiosis
- Exogenous material (asbestos bodies, talc, silica, silicates)
- Microliths of pulmonary alveolar microlithiasis
- Multinucleated giant cells or granulomas in sarcoidosis or hypersensitivity pneumonitis
- Eosinophils in pools in eosinophilic pneumonia
- “Holes” and smooth muscle fascicles in lymphangioleiomyomatosis
Diagnostic problems

• Mixed patterns: combining different interstitial changes or combining interstitial and airway pathology; in particular:
  – systemic diseases like collagen-vascular disease (prof. hasleton)
  – side effects of drugs

• At time of diagnosis unknown disease presenting with unusual or non-specific pattern compared to what in general is known or expected from such specific disease entity. Examples:
  – chronic hypersensitivity pneumonitis
  – pulmonary Langerhans’ cell histiocytosis

• Less often observed and therefore unexpected pulmonary complication of:
  – vascular lung disease (prof. Capron)
  – disease of other organ systems (inflammatory bowel disease or neurofibromatosis)

• ILD as a consequence of recurrent subclinical aspirations, usually occur during sleep (gastric herniation, reflux by other causes)
Lung biopsy:
When?

- Timing of the biopsy is critical
- Individualized decision (severity, progression, other clinical parameters)
- But, if a biopsy is indicated:
  - It should be performed early
  - It is to take place before giving any immunosuppressive or immuno-modulating agent
- Late stage biopsy:
  - Often end-stage disease (common final pathways): less or impossible to indicate etiology
  - Difficult to avoid drug-effects
Transbronchial biopsy:

Limited diagnostic possibilities

- Lung transplantation
- Sarcoidosis
- Infections
- Pulmonary Langerhanscell histiocytosis
- Eosinophilic pneumonia
- Lymphangioleiomyomatosis
- (some) malignancies
- Churg-Strauss syndrome/ vasculitis
Lung biopsy: Which?

...answers are realistic to expect:

• Identification of potentially treatable conditions:
  – Infection
  – Alveolar proteinosis
  – Extrinsic allergic alveolitis (hypersensitivity pneumonitis), often avian

• Identification of first manifestation of systemic disease:
  – Immunodeficiency
  – Auto-immune disease

• Important prognostic information
Interpretation lung biopsies

Most prominent location pathology:
- airspace
- interstitium
- mixed

Distribution of the process:
- diffuse
- bilateral/unilateral
- variation in severity

Pattern:
- random
- specific:
  - bronchiolar / bronchocentric
  - associated with lymphatics
  - vascular / arterial
# Diffuse alveolo-interstitial lung disease: Histological patterns and associated clinical syndromes

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Cryptogenic organising pneumonia (Bronchiolitis obliterans organising pneumonia)

Å organising pneumonia op de voorgrond
  • beschadiging of de alveolar capillaire membraan
  • proliferatie of fibroblasten, vooral intra-alveolar
  • alveolar walls zelf in limited mate verdikt met diffuse, limited ontsteking

Å ook beschadiging bronchiolaire epitheel:
  • vorming of intra -bronchial granulatie weefsel
  • op de langere duur fibroblast pluggen.
  • in de chronic fase obliteratie of bronchioli

Å naast de idiopathic vorm talrijke onderliggende oorzaken
Å algemeen goede reactie op therapie m.n. corticosteroïden.
Bronchiolitis obliterans organising pneumonia
Eosinophilic pneumonia

- interstitiallongontsteking gekenmerkt door de aanwezigheid of talrijke eosinophilen in het infiltraat.
  - acute vorm (het syndroom of Loeffler)
    - max. duur 4 weken
    - vaak subklinisch
  - chronic vorm

- beide gevallen:
  - eosinofilie in het bloed
  - op thoraxfoto karakteristieke perifeer gelokaliseerde infiltraten.
  - histologie: gemengdcellig infiltraat met eosinophilicn in het interstitium and ophopingen of eosinophilicn in de alveolar ruimten
Eosinophilic pneumonia

- oorzaak is vaak onduidelijk;
  - sometimes associatie met een parasitaire of mycotische infectie
  - sometimes reactie op sommige medicamenten, zoals nitrofurantoïne, sulfonamiden and penicilline

- prognosis is algemeen goed, sometimes progressie chronic vorm tot longfibrosis met respiratory insufficiëntie.
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Interstitial pneumonia

Acute interstitial pneumonia (AIP)
Usual interstitial pneumonia (UIP)
Desquamative interstitial pneumonia (DIP) / respiratory bronchiolitis interstitial pneumonia (RBILD)
Non-specific interstitial pneumonia (NSIP)

Bekende oorzaken:
- Infectieus of postinfectieus
- Omgevingsfactoren (inhalants)
- Geneesmiddelen

Idiopathisch

Neoplastisch
lymphoproliferatief
Metabool
Other forms idiopathic interstitial pneumonia

(but often etiology known)

- Giant cell interstitial pneumonia
  (most: pneumoconiosis, assoc. with heavy metals)
- Granulomatous interstitial pneumonia.
- Lymphoid interstitial pneumonia
  (often associated with immune deficiencies)
Desquamative interstitial pneumonia (DIP)

- Diffuse alveolar presence of macrophages
- Monotonous, uniform pattern
- Limited thickening alveolar walls
- No alveolar debris/fibrin
Desquamative interstitial pneumonia
Desquamative interstitial pneumonia
Non-specific interstitial pneumonia (NSIP)

- Diffuse
- Uniform in stage of pathologic changes
- Mild inflammatory and fibrotic interstitial changes
- No intra-alveolar exudate

- Better prognosis than UIP
Non-specific interstitial pneumonia
Non-specific interstitial pneumonia
Non-specific interstitial pneumonia,
Fibrotic variant
Acute interstitial pneumonia (AIP) / Diffuse alveolar damage

- Pathologic changes are uniform
- Sometimes focal hyalin membranes
- Mild alveolitis (lymphocytes, macrophages)
- Thickening of alveolar walls (in particular diffuse proliferation of fibroblasts)
- No obvious collagen fibrosis
Acute interstitial pneumonia
Acute interstitial pneumonia
diffuse fibroblast proliferation and sporadic lymphocytes
Usual interstitial pneumonia (UIP)

- pathologic changes are heterogeneous
- in early stages hyaline membranes
- diffuse alveolitis (lymphocytes, macrophages);
- lymphoid aggregates
- thickening of alveolar walls (increase of fibroblasts, smooth muscle and collagen)
- Fibroblast foci in interstitium in all stages
stage heterogeneity in UIP
Usual interstitial pneumonia: fibroblast focus
“International consensus statement on IPF”

- UIP is essential for diagnosis IPF
  - Idiopathic, progressive, diffuse fibrosing inflammatory process in lung parenchyma
- Open lung biopsy (VATS) recommended in patients with clinical suspicion of IPF, in particular those with atypical clinical or radiologic characteristics
- Most important goal of histopathology is discrimination of UIP and other forms of ILD
Pathologic changes leading to endstage lung fibrosis (honeycomb lung)

- interstitial pneumonia
- diffuse alveolar damage
- anorganic dust exposure
- interstitial granulomatous disease (infections, extrinsic allergic alveolitis, sarcoidosis, berylliosis)
- Langerhans cell histiocytosis
- gastro-esophageal reflux
<table>
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<tr>
<th>Characteristic</th>
<th>UIP</th>
<th>DIP/RBILD</th>
<th>AIP</th>
<th>NSIP</th>
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<tr>
<td>Time course</td>
<td>variable</td>
<td>uniform</td>
<td>uniform</td>
<td>uniform</td>
</tr>
<tr>
<td>Interstitial inflammation</td>
<td>limited</td>
<td>limited</td>
<td>limited</td>
<td>generally prominent</td>
</tr>
<tr>
<td>Collagen fibrosis</td>
<td>irregular</td>
<td>variable, diffuse in DIP; mild in RBILD</td>
<td>no</td>
<td>variable, diffuse</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>fibroblast foci</td>
<td>Geen</td>
<td>diffuse</td>
<td>Rarely; diffuse (rarely fibroblast foci)</td>
</tr>
<tr>
<td>Organising pneumonia</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>rarely, focal</td>
</tr>
<tr>
<td>“honingraatstructuur”</td>
<td>ja</td>
<td>no</td>
<td>no</td>
<td>very rarely</td>
</tr>
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<td>Accumulation intra-alveolar macrophages</td>
<td>rarely, focal</td>
<td>diffuse in DIP; peribronchiolar in RBILD</td>
<td>no</td>
<td>Rarely, irregular</td>
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Open lung biopsy / VATS: Pitfalls

- Inadequate sampling (incl. non-representative biopsy site)
- Mixed etiology:
  - Early age pathology (e.g. BPD) with secondary problems (may be months interval!)
  - Superimposed infections, especially in delayed decision to biopsy
- Post-therapy biopsies
- Overdiagnosis of UIP and DIP (instead of NSIP)

Therefore: multidisciplinary approach! Histopathological diagnosis should be considered together with radiology, clinical information and course
Conclusies

Histopathologisch onderzoek:
in veel gevallen gouden standaard; kan belangrijke bijdrage leveren in aanvulling op klinische gegevens and beeldvormende diagnostiek, relevant voor verdere behandeling and therapie.
Informatie m.b.t. klinisch beloop and radiologische bevindingen essentieel voor optimale diagnose

Belang of beeldvormende diagnostiek:
naast diagnostische bijdrage ook als uitgangspunt voor:
- biopsie of anatomische locatie, representatief voor de afwijking
- locatie alwaar actieve of early fase of het ziekteproces

Tijdstip biopsie is belangrijk:
- indien indicatie than vroeg in het ziekteproces
- geïindividualiseerde multidisciplinaire besluitvorming
Thank you for your attention