Chest HRCT findings in patients with humoral Primary Immunodeficiencies and recurrent respiratory infections: review of literature and personal experience

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Learning objectives

To describe the broad spectrum of findings on chest High-Resolution Computed Tomography (HRCT) in patients with humoral Primary Immunodeficiencies (hPIPs).
Background

Definition, epidemiology and pathogenesis of hPIDs

Primary Immunodeficiencies (PIDs) are genetically determined conditions characterized by impaired development and/or functioning of the immune system. Although PIDs are caused by genetic defects, only a part of these are diagnosed in childhood, when recurring and unusual infections persist. For the rest, the diagnosis is often late, with more than 40% of cases being diagnosed in adulthood. As reported in the recent literature, PIDs have been divided into nine major subgroups, according to the presence of predominant immunological defect.

Primary predominantly antibody deficiencies, also known as humoral PIDs (hPIDs), are the most common subgroup among PIDs, representing about 50% of diagnoses. The term hPIDs encompasses various disease entities caused by impaired antibody production, related to both, a molecular defect intrinsic to B cells or to a failure of interactions between B and T cells. This condition characteristically leads to recurrent, often severe, upper and lower respiratory tract infections, caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Haemophilus influenzae), and to an increased susceptibility to neoplasms and autoimmune diseases.

The most frequent subtypes of hPIDs and their related clinical features are summarized in figure 1.

Selective IgA deficiency is the most common hPID, affecting approximately 1:700 individuals worldwide, and is often asymptomatic.

Common variable immunodeficiency (CVID), the most common symptomatic condition among hPIDs, is relatively frequent (about 1: 25.000-1.50.000 subjects), from which the adjective "common". CVID affects men and women almost equally. The degree and type of deficiency of serum immunoglobulins, as well as the clinical course vary from patient to patient, hence the attribute "variable". In some patients, there is a decrease in both IgG and IgA, while in others, all three major types of immunoglobulins (IgG, IgA and IgM) are decreased. Defects of T-cells can also be encountered, thus contributing to extremely heterogeneous clinical manifestations. In the majority of cases, the diagnosis is not made until the third or fourth decade of life.

Clinical manifestations

The usual presenting features of hPIDs are recurrent infections involving the ears, nasal sinuses, bronchi (breathing tubes) and lungs (respiratory tract). In case of severe and recurrent lung infections, permanent damage such as bronchiectasies as well as lung fibrosis may develop. The microorganisms that commonly cause these sinopulmonary infections are bacteria (e.g., Haemophilus influenzae, Streptococcus pneumoniae, and
Staphylococcus aureus), that often cause pneumonia also in the general population. Recurrent respiratory infections are the most frequent cause of morbidity and mortality; indeed 67% of patients with CVID present with respiratory manifestations.

Increased risk of cancer in hPIDs is widely reported in the literature, in particular, up to 15% of patients with CVID develop malignancy, mostly affecting the lymphatic system (non-Hodgkin's lymphomas, mainly extranodal and B-cell in origin) or the gastrointestinal tract.

Besides depressed antibody responses and low levels of immunoglobulins, some patients with hPIDs (particularly those with CVID, IgA deficiency, or immunodeficiency with Hyper IgM) may produce autoantibodies directed against body’s own blood cells (e.g., red cells, white cells, or platelets), resulting in autoimmune and rheumatologic disorders.

Patients with CVID are prone to developing a restrictive, non-infectious, interstitial lung disease with granulomatous and lymphoproliferative pattern on biopsy (i.e., lymphoid hyperplasia, follicular bronchiolitis, and lymphocytic interstitial pneumonitis -LIP-), termed Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD). Furthermore, GLILD encompasses a broad spectrum of pulmonary conditions like interstitial pneumonia (with different histological features), and extra-pulmonary conditions like splenomegaly, lymphadenopathy, autoimmune cytopenia, and gastrointestinal and liver diseases, as well as increased risk of developing B-cell lymphomas. The pathogenesis of GLILD has not been fully understood. A definition based on abnormalities on lung imaging (HRCT) together with evidence of granulomatous inflammation elsewhere has been proposed.

Although GLILD occurs more commonly in patients with CVID (in approximately 10-25% of cases), recent studies have shown that similar lung alterations may occur even in other subtypes of PIDs.

Striking lymphadenopathy, usually cervical, mediastinal, or abdominal, and hypersplenism are other common findings in CVID.

**Diagnosis**

Early diagnosis of hPIDs is of paramount importance, in order to reduce morbidity and mortality. Evidence of recurrent infections (and/or infections due to unusual microorganisms) is an important diagnostic clue provided by patient's medical history. In addition, many screening tests, including complete blood count, quantitative serum immunoglobulin levels and measurement of specific antibodies to vaccine can be useful. Recently revised criteria for clinical diagnosis of CVID are illustrated by Ameratunga et al. and ESID.

Thoracic complications, which are found in 60% of patients with hPIDs, and which determine a wide spectrum of radiologic findings, remain the leading causes of morbidity
and mortality. Once the diagnosis of hPIDs is made, it is important to establish baseline pulmonary status: the most effective way is to perform a High-Resolution Computed Tomography (HRCT) scan of the chest.

Chest HRCT is the imaging technique of choice for detection, characterization and quantification of lung complications in patients with hPIDs. HRCT is necessary at the time of diagnosis, as well as for monitoring response to therapy. HRCT is the use of thin-section CT images (0.625-mm to 1.5-mm slice thickness) with a high spatial frequency reconstruction algorithm, to detect and characterize diseases that affect the pulmonary parenchyma and small airways without using IV contrast agents. HRCT is routinely acquired as volumetric single breath-hold dataset, at suspended full inspiration, with patient in the supine position. Additional options, useful in many cases, include obtaining inspiratory prone images to differentiate posterior lung disease from dependent atelectasis and end-expiratory images to evaluate the possible presence of air trapping.

**Treatment**

Immunoglobulin replacement therapy and prophylactic antibiotic therapy demonstrated to be effective in preventing lung infections and indirectly in preventing / slowing structural damage to the airways (such as bronchiectasis). Nevertheless, the progression of lung disease can occur despite adequate replacement therapy and despite the absence of clinically significant infections, suggesting the possibility of existence of additional unknown causative factors.
**Fig. 1:** Clinical features of the most common hPID subtypes.

Fig. 2: Volumetric HRCT protocol performed in our Institution on a 64-slices MDCT scanner (LightSpeed HD Discovery 750, General Electrics, Milwaukee, USA).

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<th>HRCT SPECTRUM OF hPID-related FINDINGS</th>
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**Fig. 3:** HRCT spectrum of chest findings in Patients with hPID

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Findings and procedure details

Between October 2012 and September 2016, 56 patients with clinically and laboratory confirmed diagnosis of hPID, underwent initial (first) chest HRCT in our Institution as routine structured follow-up. 41/56 patients had CVID, 11/56 patients had IgG subclass deficiency, and 3/56 had selective IgA deficiency. All patients reported a long-time history of recurrent respiratory tract infections.

Chest HRCT scans were acquired with a volumetric approach at suspended full inspiration, with patients in the supine position, as reported in figure 2. For 35/56 patients an additional, low-dose end-expiratory scan was acquired.

We describe the most common chest HRCT findings related to hPID, according to our experience and to literature, encompassed in 4 groups as following: a) non-infectious airways disorders# b) infectious airways/parenchymal conditions# c) diffuse parenchymal lung diseases, including Granulomatous and Lymphocytic Lung Disease (GLILD)# d) neoplasms (fig.3). For each mentioned group, the most relevant findings are illustrated and a brief review of the recent literature is reported.

a) Non-infectious airways disorders

Non-infectious disorders, which may affect any bronchial generation, include bronchiectasis (fig. 4 and 5), bronchial wall thickening (fig. 6), mucoid impactions (fig. 7) and air trapping (fig. 8). According to Bierry et al. the frequency of these findings in hPID is between 14% and 60%. Their manifestation is very insidious and often related to chronic structural damage in recurrent respiratory infections.

**Bronchiectasis** is irreversible, localized or diffuse bronchial dilatation, usually resulting from chronic infections, proximal airway obstructions, or congenital bronchial abnormalities. Their HRCT morphology can be cylindrical, cystic or varicose, based on the appearance of the affected bronchi as visualized both on the axial plane and on multiplanar reconstructions (fig.5); in patients with hPID, the most frequent is bronchiectasis with cylindrical morphology, usually affecting middle and lower lobes, bilaterally. Bronchiectasis is regarded as the most frequent HRCT finding in CVID, being reported in 40-95% of cases. On the other hand, bronchiectasis is less frequent in the majority of patients with IgA deficiency, because they produce IgG antibodies, which make them less susceptible to bacterial infections.

**Bronchial wall thickening** is a subjective nonspecific HRCT finding, regarded as a reversible and early sign of acute inflammation. It often accompanies bronchiectasis, indeed similar presentation frequencies are reported in patients with CVID. These findings resemble those observed in patients with chronic obstructive pulmonary disease.
Mucoid impaction also may be present and may mimic findings observed in cystic fibrosis, with tubular or branching opacities appearance on HRCT (fig. 7).

Untreated damage to the airways can result in chronic obstructive pulmonary disease, accompanied by air trapping. On expiratory HRCT scan, air trapping appears as parenchymal areas with less than normal increase in attenuation and lack of volume reduction, with lobular pattern. This finding is reported in 33-43% of patients with CVID. The concomitance of airways disease helps in differential diagnosis between CVID and hypoperfusion consequent to occlusive vascular disorder.

b) Infectious airways/parenchymal conditions

The radiological presentation of infectious conditions of the airways and lung parenchyma is similar to that of immunocompetent patient, although in hPIDs the extension of these conditions can be greater and signs related to old infections (as parenchymal linear and reticular scars, or bronchiectasis) can coexist, in more than 50% of cases (fig. 9). The severity of such alterations correlates with the number of previous infections that occurred over time.

Segmental or lobar parenchymal consolidations (fig.10), or ground-glass opacities, develop due to acute bacterial pneumonia, often associated with hilar and mediastinal adenopathy. Pulmonary consolidations can undergo cavitation, mainly in opportunistic infection (i.e., fungal pneumonia, P. jirovecii pneumonia) and when CD4 deficiency is associated.

HRCT signs of bronchiolar inflammation are tree-in-bud pattern (fig. 11), centrilobular ill-defined nodules, and bronchiolar wall thickening. Bronchial wall thickening and mucoid impactions, when reversible, are regarded to represent signs of acute infection rather than non-infectious conditions.

c) Diffuse parenchymal lung diseases, including Granulomatous and Lymphocytic Lung Disease (GLILD)

In advanced stages of disease, chronic alveolitis and chronic bronchial damage lead to interstitial fibrosis and pulmonary hypertension. HRCT signs of interstitial fibrosis are lung volume reduction, parenchymal linear opacities, architectural distortion, bronchiectasis and traction bronchioloectasis, often with diffuse and bilateral distribution. In patients with pulmonary hypertension HRCT demonstrates an increased calibre of proximal pulmonary arteries or mosaic attenuation pattern. This pattern can be a sign of obstructive airways diseases, occlusive vascular disorders or patchy interstitial diseases. If we identify the presence of low-attenuation area adjacent to small vessels, and there aren’t signs of airways alterations, we can be confidently say that the mosaic attenuation pattern is related to vascular diseases. If this pattern is produced by interstitial lung disease, we
can find areas of higher attenuation (ground glass opacity) that represent the interstitial process and areas of lower attenuation that represent the normal lung.

In our series, most of patients with CVID showed HRCT signs of pulmonary fibrosis, mainly traction bronchiectasis and/or bronchioloelastics, associated with ground-glass areas, parenchymal linear opacities and architectural distortions (fig. 12).

HRCT signs of organizing pneumonia (OP) may manifest most frequently as a result of recurrent infections. OP is a non-specific pattern of lung response to various insults that is reversible after corticosteroid therapy. On HRCT it manifests as airspace consolidation, typically subpleural and basal and sometimes bronchocentric; other imaging signs of OP can be areas of ground-glass opacity, tree-in-bud pattern, and nodular opacities.

HRCT pattern of LIP is characterized by ground-glass opacity as dominant abnormality; thin-walled perivascular cysts, lung nodules, interlobular septal and bronchovascular thickening, and widespread consolidation may also occur.

The term GLILD refers to the presence of lung granulomatous disease or lymphoproliferative disorders (such as lymphoid interstitial pneumonia), which can coexist in the same patient. In 75% of patients with CVID and GLILD pulmonary alterations can occur. Sarcoid-like non-caseating granulomas are the dominant abnormalities on HRCT; their radiologic appearance is comparable to sarcoidosis, characterized by well-defined nodules with peri-lymphatic distribution, associated to pulmonary fibrosis. In GLILD, ground-glass nodules associated with interlobular septa thickening and parenchymal consolidation with basal involvement (vs. predominant upper lobes distribution of sarcoidosis) have been all described as typical HRCT findings. In our series, 5 patients with ascertained CVID showed HRCT signs suspicious for GLILD (fig. 13-14). Histological confirmations was obtained in 3 cases (fig. 13). HRCT showed coexistence of cylindrical bronchiectasis (with mucoid impaction in some cases), ground-glass opacities, interlobular septa thickening, and areas of parenchymal consolidation (Fig. 14). Findings were bilateral, mainly localized in the right middle lobe, lingula and basal segments of lower lobes. Furthermore, in all these patients high density centrilobular micronodules with subpleural distribution were depicted (fig. 13-14). Response to monoclonal antibodies therapy and superimposed respiratory infections determine the variable appearance and extension of these findings over time, mainly regarding pulmonary nodules and consolidations.

In our experience and also according to the literature, mediastinal adenopathy is a frequently associated finding.

d) Thoracic neoplasms

CVID patients are prone to develop lymphoproliferative diseases, particularly non-Hodgkin's lymphoma, with a lifetime incidence up to 8%; it typically appears on HRCT as an anterior mediastinal mass. Patients with hPIDs may manifest with diffuse, nonspecific,
mediastinal and/or axillary lymphadenopathies, which are difficult to differentiate from malignant disease or sarcoidosis. According to our experience, 10% of patients showed axillary and/or mediastinal adenopathies (fig. 15). HRCT findings of pulmonary lymphoma are multiple, bilateral and bronchocentric areas of consolidation or nodules: since appearance can resemble benign conditions (i.e. GLILD), histopathological characterization may be needed. In our study cohort no patient was diagnosed with lymphoma.

Coexistence of thymoma and hPIDs is defined as Good Syndrome. This condition has a poor prognosis, and should always be suspected in patients with hPID with evidence of an anterior mediastinal mass on CT. In our series one female patient with known diagnosis of CVID manifested thymoma (fig. 16).
**Fig. 5:** Bronchiectasis in a 27-year-old woman with CVID. HRCT 6 mm thick minimum Intensity Projection (minIP) slab image reformatted on the sagittal plane shows cylindrical bronchiectasis in the left lower lobe (white arrow).

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Fig. 6: Bronchial wall thickening in 27-year-old woman with CVID (a) and in a 53-year-old woman with selective IgG1 deficit (b). (a) HRCT image reformatted on the para-axial plane shows bronchial wall thickening associated to cylindrical bronchiectasis in the right middle lobe (white arrow). (b) HRCT 6 mm thick minimum Intensity Projection (minIP) slab image reformatted on the sagittal plane depicts well widespread bronchial wall thickening of peri-hilar bronchi in the left upper and lower lobes.

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Fig. 7: Mucoid impaction in 34-year-old man with CVID. HRCT image of the right lung reformatted on the sagittal plane shows an extensive mucous impaction in the lower lobe (red arrow). Widespread bronchiectasis, bronchial wall thickening and diffuse peribronchial ground-glass opacities are also present (white arrow). Hemophilus influenzae was isolated following bronchoalveolar lavage.

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**Fig. 8:** Air trapping in a 73-year-old woman with selective IgG3 deficit. (a) Inspiratory HRCT image on the axial plane shows bronchiectasis in the lower lobes associated to peri-bronchial consolidations in the right middle lobe and in the lingula. (b) End-expiratory scan at the same level clearly shows air trapping in the lower lobes, more evident on the right side (yellow star).

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Fig. 9: Lung parenchymal scarring in a 48-year-old man with CVID with a long-time history of recurrent respiratory tract infections. HRCT image on the axial plane (a) and HRCT image reformattted on the sagittal plane (b) show linear and reticular parenchymal bands with traction effect on the pleural surfaces associated to mild bronchiecstasis in the upper lobes (black arrows).

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Fig. 10: Infectious pneumonia in a 34-year-old man with CVID. HRCT image on the axial plane shows an extensive consolidation in the right upper lobe. Streptococcus pneumoniae was isolated following bronchoalveolar lavage
Fig. 11: Infectious bronchiolitis in a 44-year-old man with CVID. HRCT 8 mm thick Maximum Intensity Projection (MIP) slab image on the axial plane shows ill-defined tree-in-bud opacities in the lingula. Haemophilus influenzae was isolated following bronchoalveolar lavage.

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Fig. 12: Chronic diffuse lung disease in a 54-year-old woman with CVID. HRCT image on the axial plane shows in the right lower lobe a focal area of ground-glass opacity associated to mild bronchiectasis, parenchymal linear opacities with traction effect on the fissure and architectural distortion.

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**Fig. 13:** GLILD in a 40-year-old woman with CVID. (a) HRCT image reformatted on the sagittal plane clearly shows multiple, small ill-defined, peri-bronchial and bronchocentric nodules in the right lower lobe. (b) HRCT magnification of one of the bronchocentric nodules in the right lower lobe sent for transbronchial biopsy; (c) Photomicrograph (haematoxylin and eosin stain at 20x magnification) of biopsied nodule in fig. b demonstrates a bronchiolar-alveolar parenchyma with a substantial amount of inflammatory cells mainly consisting of lymphocytes in pseudolobular architecture and aggressive features towards the epithelial components. These histological findings are consistent with the diagnosis of granuloma GLILD related.

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Fig. 14: GLILD in a 54-year-old woman with CVID. HRCT image on the axial plane (a) demonstrates patchy areas of peri-bronchial consolidation and ground-glass opacities along with reticulations and mild bronchiectasis. HRCT 6 mm thick minimum Intensity Projection (minIP) slab image reformatted on the sagittal plane of the left lung (b) enhances the presence of the above mentioned findings, in particular bronchiectasis and peri-bronchial consolidations. High density center-lobular nodule is also present in the right lower lobe (black arrow).

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**Fig. 15:** Mediastinal adenopathies in a 54-year-old woman with CVID and GLILD. HRCT image on the axial plane (a) and HRCT image reformatted on the sagittal plane (b) with soft tissue window setting show madiastinal adenopathies (white arrows).

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Fig. 16: Good syndrome in a 68-year-old woman with CVID. HRCT image on the axial plane (a) and HRCT image reformatted on the coronal plane (b) with soft tissue window setting reveal a peripherally calcified oval mass in the anterior mediastinum which was histologically proved to be a thymoma. (c) Magnification of thymectomy shows a perfectly encapsulated lesion with coarse septation and macrocalcification, consisting of a monomorphic spindle cells population. These findings are consistent with thymoma (type A acc. W.H.O 2015; Stage I acc. Masaoka / Koga).

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Conclusion

The knowledge of the pleomorphic spectrum of chest HRCT findings in patients with hPIDs is crucial in differentiating various pathologic lung conditions (i.e., infections and structural airways damage vs. diffuse lung parenchymal disease and suspected neoplasms), which may affect importantly the multidisciplinary management of the patient.
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