Learning objectives

To describe the role of lung HRCT in Common Variable Immunodeficiency (CVID). To summarize HRCT semeiotic in CVID patients with imaging-pathologic correlations.
1. WHAT IS COMMON VARIABLE IMMUNODEFICIENCY?

DEFINITION

Common Variable Immunodeficiency (CVID) is the most frequent primary immunodeficiency, an immune system disorder due to genetic defects, in particular to a deficit in humoral immunity, which leads to low levels of Immunoglobulins (Ig). Many authors underline how it would be more appropriate to refer to this disease as to a syndrome, as it shows an extreme variability with regard both to pathogenetic mechanisms (not completely understood) and clinical presentation[1].

EPIDEMIOLOGY

CVID prevalence and incidence range between 1/50,000 and 1/200,000, and between 1/10,000 and 1/100,000 individuals, respectively[1], [2]. About 30% of patients with a primary immunodeficiency have CVID. Both sexes are affected equally and age at presentation shows a bimodal distribution, as some cases present at late childhood (2nd decade of life) and most cases in young adults (3rd decade of life) or later[1]. Although most cases are sporadic, about 25% of patients show a familiarity for IgA selective abnormalities[2].

PATHOGENESIS

CVID manifestations are based on a defective production of antibodies, particularly due to the inability of B-cells to effectively differentiate into plasmacells (about 50-70% of patients have low levels of memory cells). Many possible responsible mechanisms have been identified, due to impairments both of B-cells and T-cells, the latter involved in maturation and activation of B-cells/plasmacells through mechanisms of cell signalling (e.g., using cytokines). However, at the moment it is possible to identify a genetic abnormality only in 25% of cases (mainly abnormalities involving ICOS- "inducible T-cell costimulator"-, TNF receptor superfamily and CD19)[1]. It is possible that different genetic abnormalities result in different clinical manifestations, and hopefully in the future a better knowledge of pathogenetic mechanisms will enable a better patient management.

CLINICAL PRESENTATION
As a consequence of the above-described immune status, patients are prone to develop infections, particularly caused by capsulated bacteria, such as Haemophilus influenzae and Streptococcus pneumoniae, and by atypical Mycobacteria. Such infections, which are often relapsing, involve mainly upper airways (otitis and sinusitis) and lower airways (pneumonia and bronchitis). Gastro-intestinal infections are also frequent (e.g., Helicobacter pylori gastritis and Giardia lamblia enteritis [2]).

CVID patients have a high incidence of comorbidities. In about 25-50% of cases autoimmune diseases are associated, mainly idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, pernicious anaemia, thyroiditis and enteropathies.

Such predisposal to autoimmune conditions is probably based on defects in mechanisms involved in autoreactivity control during B-cells maturation.

Repeated immune system stimulation caused by infections and abnormal interaction of lymphocytic classes also predispose to granulomatous diseases and lymphoproliferative disorders, ranging from benign forms to lymphomas.

Finally, patients with CVID are at high risk of developing cancer (mainly gastric cancer), probably because of immunodeficiency.

THERAPY

Patients affected by CVID are treated with intravenous administration of immunoglobulines, with the aim to prevent infections; IgGs seem also effective in controlling many associated autoimmune diseases. Airways infections are treated with prompt antibiotic therapy. Finally, respiratory physiotherapy is of paramount importance in these patients [2].

2. LUNG INVOLVEMENT

Lungs are often involved in CVID [3], mainly through two mechanisms:

- Infections (pneumonia, bronchiolitis, bronchitis)
- Granulomatous-lymphoproliferative diseases

Repeated infections yield, as main complications, bronchiectases and pneumatoceles, which favour other infections, which in turn cause further airways damage, in a vicious circle. In most advanced cases bronchiectases and bronchioloectases are responsible of obstructive functional abnormalities (i.e., asthma and BPCO) at spirometry tests [4], and may yield to "air trapping" aspects at imaging. Early detection of such abnormalities is
therefore important, so that appropriate therapies could be timely started (e.g., antibiotics, respiratory physiotherapy, substitutive therapy with Immunoglobulines).

Most common lymphoproliferative disorders are follicular hyperplasia (which could have extra-pulmonary localizations, mainly enteric), follicular bronchiolitis, lymphoproliferative interstitial pneumonia (LIP), and lymphomas (ranging from MALTomas to more aggressive forms). They are due to bronchus-associated lymphatic tissue hyperplasia, which in turn is caused by chronic antigenic stimulation and by disorders in the regulation of immune system [5].

Granulomas formation results from T-cells functional anomalies or from imbalance between T-cells and B-cells. Moreover, an association with type 8 Human Herpes Virus (HHV) has been identified, which probably acts overstimulating the immune system. Anyhow, it seems a different disorder than sarcoidosis, although in both cases serum angiotensin-converting enzyme (ACE) levels could be high [1].

Idiopathic pneumonias are also common in CVID patients, particularly organizing pneumonia (but also non specific interstitial pneumonia), again based on abnormal immune system or autoimmune mechanisms.

Lymphoproliferative and granulomatous diseases involving the lung, and idiopathic pneumonia, often coexist in the same patient. This lead to very complex outlines, both at imaging and pathologic analysis, been a precise classification often challenging. Such diseases may also show overlapping features at imaging. Therefore, a unique nosologic entity, namely the "Granulomatous-Lymphocytic Interstitial Lung Disease" (GLILD), has recently been proposed in order to group together granulomatous and lymphoproliferative abnormalities [3].

Generally, lung manifestations of CVID can be divided into two main patterns:

- Airways-based
- Parenchyma-based

The former usually recognizes an infective cause; the latter is generally due to granulomatous-lymphoproliferative diseases or to inflammatory non-infective disorders.

The resulting abnormalities at spirometry tests are different, obstructive pattern prevailing with airways damage and restrictive pattern and deficit in CO₂ diffusion prevailing with parenchymal / interstitial anomalies. The two patterns may coexist in the same patient, although with a variable entity. Therefore, imaging may play a fundamental role in detecting main lung abnormalities and guiding clinical management.
3. IMAGING

Lung imaging, although does not yield fundamental diagnostic criteria, is an essential tool in management of CVID patients, both at the moment of diagnosis and during follow-up. High Resolution Computed Tomography (HRCT) is extremely sensitive in detecting bronchiectases and other complications, as well as on-going infections.

Italian guidelines, for instance, recommend performing a lung CT at the moment of diagnosis and subsequently every 5 years or in presence of clinical indication [2].

According to ACR practice parameters of performance, HRCT entails the use of thin section images (up to 1.5 mm for volumetric scanning) with high frequency reconstruction algorithm, with both volumetric or "step and shoot" technique, the latter both with continuous and discontinuous slices, to assure the best anatomic detail achievable [6]. Contrast media injection is usually not required, considering the predominant involvement of lung parenchyma. The examination is generally performed with patient in supine position, at maximum hold inspiration, to assure good lung expansion. In cases where concerns exist about dorsal involvement, an extra acquisition with patient in prone position is recommended. Examination can be further completed with an expiratory low-dose scan (volumetric or sampling) to assess and quantify the presence of air trapping in case of obstructive abnormalities.

Considering the young age of many CVID patients and the need of repeated examinations in their lifetime, optimization of scan protocol to keep the dose as low as possible is recommended [3]. The fact that CVID patients may also have a higher sensitivity to ionizing radiations than general population makes this technical attention even more important [7].
Findings and procedure details

1. PATIENT POPULATION - preliminary experience

During the period October 2012 - December 2014, we performed at our Institution 35 HRCT in 28 CVID patients. All patients, except one, were asymptomatic for acute airways infections at the moment of the examination. Four patients underwent HRCT follow-up for suspicious lung findings, mainly pulmonary nodules. One patient underwent repeated HRCT in the study period to monitor the effects of therapy on chest GLILD. Fig. 1 and Fig. 2 summarize the main clinical features and HRCT findings of our population.

2. HRCT ACQUISITION PROTOCOLS

In our daily clinical activity, we perform HRCT according to two protocols, based on step-and-shoot continuous acquisition (with heart-gating technique) or on volumetric acquisition. With both of them, patients can be in supine or prone position. The main parameters of the two acquisition protocols are described in Fig. 3 and Fig. 4.

3. HRCT FINDINGS

· AIRWAYS

A common "marker" of CVID is represented by bronchiectases and bronchioloectases, as a result of a repeated damage on airways by recurrent infections. Such findings are becoming however less common, as a consequence of early diagnosis and prompt use of effective treatments [8].

Bronchiectases are defined as bronchi dilatations that result in a ratio between the bronchial lumen and the adjacent lung arterial lumen greater than 1. Other typical signs are the loose of the characteristic distal tapering of the bronchial lumen and the visibility of a bronchial structure within 1 cm from the pleural plane [5, 9]. Usually bronchiectases are cylindrical, with more extensive involvement of lower lobes, middle lobe and lingula, while upper lobes are generally involved only in more advanced cases (Fig. 5, Fig. 6). Often the bronchial lumen shows mucous content.

Other signs of airways damage are:

° thickening of bronchial or bronchiolar wall: it may be defined as a ratio greater than 0.5 between the sum of the thickness of bronchial walls and the diameter of the adjacent pulmonary artery [5]. It may represent an early sign of damage, before that dilatation develops (Fig. 7);
"air trapping" on expirium scans, due to the loss of compliance of the damaged airways;

dystelecctases.

Finally, also "tree-in-bud" nodules (that is to say tiny, branching nodules with a centrolobular/peribronchial distribution), which represent bronchioles whose lumen is filled by non-air content (e.g., mucus, inflammatory cells, fibrosis), are a possible sign of airways involvement, both by infections and non-infectious inflammation, as in Bronchiolitis Obliterans [9] (Fig. 8).

**PARENCHYMA**

Signs of lung parenchyma involvement are:

**CONSOLIDATIONS**: lung parenchyma areas characterized by an increased attenuation [9]; they can have an extremely broad spectrum of appearances, with both solid (obscuring the underlying bronco-vasal structures) and ground-glass attenuation, with irregular or pseudonodular shape. They usually show peribronchial distribution, and internal air bronchogram sign (often due to bronchiectases).

They can represent an acute or recent infective pneumonia, which has therefore to be clinically excluded, or a non-infectious parenchymal inflammation.

For instance, CVID patients often develop organizing pneumonia, likely induced by recurrent infections, bronchiectases and airways chronic obstruction. Typical imaging findings are irregular areas of consolidation, both solid or ground-glass, prevalent at lower lobes, with peribronchial distribution, within which air bronchogram produced by dilated bronchi is visible. Generally such consolidations have a tendency to migrate, also without a specific treatment [3] (Fig. 9, Fig. 10).

Finally, lung primary lymphomas, such as MALTomas, may appear as irregular areas of consolidation.

**NODULES**: they usually show centrolobular/peribronchial distribution. Nodules with a random distribution (i.e., with both centrilobular and subpleural/paraseptal distribution) may be present, reflecting a possible lymphatic spread (Fig. 11, Fig. 12). Nodules can be expression, among others, of:

- lymphoproliferative disorders, such as lymphatic interstitial pneumonia (LIP), where nodules (with random distribution, both centrolobular and subpleural) are associated to ground-glass areas of consolidation, cysts and interstitial thickening [10];
- granulomas, with peribronchial distribution, sometimes large and irregular, with ill-defined borders, both with soft-tissue or ground-glass attenuation. In other cases nodules are tiny and randomly distributed. A lower-lobes predominance is typical [11].

In patients with GLILD, granulomatous and lymphoproliferative abnormalities coexist. In more advanced phases, granulomas may form areas of consolidation, or interstitial thickening can prevail, with presence of pulmonary fibrosis in the most severe cases [4, 8].

" RETICULAR PATTERN: it points out interstitial involvement, and is usually accompanied by nodules, as in LIP and GLILD. Sometimes only interstitial thickening may be present, with patterns consistent with UIP (usual interstitial pneumonia) or NSIP (non-specific interstitial pneumonia). At last in early phases, lower-lobes distribution is common [4, 8]. Finally, it is worth to say that lung interstitial diseases in CVID patients could be related to coexisting autoimmune diseases, such as systemic lupus erythematosus.

· LYMPHADENOPATHIES

Enlarged mediastinal lymph-nodes are frequent in CVID patients (Fig. 13), particularly when a granulomatous disorder coexists [8, 11]. Usually, after contrast media administration, they do not show hypodense areas, as they do not have colliquated internal regions, but only non-caseous necrosis.

Lymphadenopathies may also be associated with lung parenchymal findings in patients with LIP or organizing pneumonia, although they are not a typical finding of such disorders. Finally, in presence of lymphadenopathies, a lymphoma should be excluded [8].
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<table>
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<tbody>
<tr>
<td>Mean age</td>
<td>50.2 years (18-73)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>8 M / 15 F (28.6% M / 71.4% F)</td>
</tr>
<tr>
<td>Smoke</td>
<td>6 smokers (21.4%)</td>
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<tr>
<td>Coexisting autoimmune diseases</td>
<td>9 patients (32.1%): 2 urticaria; 5 enteropathies; 5 thyroiditis; 1 SLE; 1 Horton arteritis</td>
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<tr>
<td>Neoplasia</td>
<td>5 patients (17.9%): 1 NHL; 1 breast cancer, 1 endometrial cancer, 1 pancreatic neuroendocrin cancer</td>
</tr>
<tr>
<td>Associated lymphoproliferative disorders</td>
<td>2 patients (7.1%): 1 GLILD; 1 follicular lymphatic hyperplasia</td>
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SLE: systemic lupus erythematosus; NHL: non-Hodgkin lymphoma; GLILD: granulomatous-lymphocytic interstitial lung disease

**Figure 1:** main clinical features of our patient population

**Fig. 1:** Figure 1

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<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>NUMBER OF PATIENTS</th>
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<tbody>
<tr>
<td>UNREMARKABLE CT</td>
<td>7 (25%)</td>
</tr>
<tr>
<td><strong>BRONCHIECTASES</strong></td>
<td>11 (39%)</td>
</tr>
<tr>
<td>CONSOLIDATIONS</td>
<td>7 (25%)</td>
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<tr>
<td><strong>NODULES</strong> (including “tree-in-bud” nodules)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>INTERSTITIAL THICKENING</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td>LYMPHOADENOMEGALIES</td>
<td>2 (7%)</td>
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**Figure 2**: main lung HRCT findings in our patient population

**Fig. 2**: Figure 2

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<thead>
<tr>
<th>Scan type</th>
<th>Cardiac Pulse Cine/ Hi-Res</th>
</tr>
</thead>
<tbody>
<tr>
<td>KV</td>
<td>120 (INSPIRATION) - 100 (EXPIRATION)</td>
</tr>
<tr>
<td>mA</td>
<td>300 (INSPIRATION) - 200 in EXPIRATION with manual modulation</td>
</tr>
<tr>
<td>Rotation time (s)</td>
<td>0.35</td>
</tr>
<tr>
<td>Detector covering (mm)</td>
<td>40</td>
</tr>
<tr>
<td>Axial thickness (mm)</td>
<td>0.625</td>
</tr>
<tr>
<td>FOV</td>
<td>Includes both lungs form base to apex</td>
</tr>
<tr>
<td>N.I. (Noise Index)</td>
<td>22.10</td>
</tr>
<tr>
<td>Acquisition modality</td>
<td>patient positioning: supine ± prone; state of respiration: inspiration ± expiration</td>
</tr>
<tr>
<td>WW (H.U.)</td>
<td>1500 (Lung) – 350 (Soft tissues)</td>
</tr>
<tr>
<td>WL (H.U.)</td>
<td>-550 U.H. (Lung) – 50 (Soft tissues)</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>- Axial with lung (slice thickness: 1.25 mm) and soft tissues windowing (5 mm); - Lung coronal MPR</td>
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**Figure 3:** technical parameters of “step-and-shoot”, heart-gated HRCT

**Fig. 3:** Figure 3

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<table>
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<tr>
<th>Scan type</th>
<th>Helical full</th>
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<tr>
<td>KV</td>
<td>120</td>
</tr>
<tr>
<td>mA</td>
<td>Automatic modulation (≤240)</td>
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<tr>
<td>Detector covering (mm)</td>
<td>40</td>
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<tr>
<td>Helical thickness (mm)</td>
<td>1.25</td>
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<tr>
<td>FOV</td>
<td>Includes both lungs form base to apex</td>
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<tr>
<td>N.I. (noise index)</td>
<td>18.4</td>
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<tr>
<td>Acquisition modality</td>
<td>patient positioning: supine ± prone; state of respiration: inspiration ± expiration</td>
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<td>WW (H.U.)</td>
<td>1500 (Lung) – 350 (Soft tissues)</td>
</tr>
<tr>
<td>WL (H.U.)</td>
<td>-550 (Lung) – 50 (Soft tissues)</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>- Axial with lung (slice thickness: 1.25 mm) and soft tissues windowing (5 mm); - Lung coronal MPR</td>
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**Figure 4:** technical parameters of helical HRCT

**Fig. 4:** Figure 4

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**Figure 5**: 73 y.o. woman with CVID and history of breast cancer. Bronchiectases in the middle and inferior lobe of the right lung and at lingula and peribronchial consolidation in the right middle lobe are shown.

**Fig. 5**: Figure 5

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**Figure 6:** same patient of Fig. 5. Cystic bronchiectases with bilateral paracardiac distribution are shown.

**Fig. 6:** Figure 6

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**Figure 7**: 38 y.o. woman with GLILD. Bronchial wall thickening, bronchiectases and irregular consolidations at lung bases are shown.

**Fig. 7**: Figure 7

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**Figure 8:** 58 y.o. man with symptomatic CVID for recurrent infections, in substitutive therapy with Ig. “Tree-in-bud” aspects are shown: tiny, branching nodules with peribronchial distribution, suggesting inflammatory process in distal airways.

**Fig. 8:** Figure 8

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**Figure 9**: 50 y.o. woman, with history of lymphoma. Irregular consolidations with peribronchial distribution (some of them with air bronchogram) and migrant (“wax and wane”) behaviour over months.

**Fig. 9**: Figure 9

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Figure 10: 58 y.o. man with CVID in treatment. Irregular areas of consolidation, with peribronchial distribution and ground-glass attenuation are shown.

Fig. 10: Figure 10

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**Figure 11**: 38 y.o. woman with GLILD. Small round nodule with soft-tissue attenuation in the right inferior lobe is depicted.

**Fig. 11**: Figure 11

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**Figure 12:** 60 y.o. woman with CVID and possible GLILD. Diffuse nodules at lung bases, with random distribution, both peribronchial and subpleural. Mild interstitial thickening is also present.

**Fig. 12:** Figure 12

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**Figure 13:** 38 y.o woman with GLILD. Mediastinal lymphadenopathies are shown.

**Fig. 13:** Figure 13

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Conclusion

Lung involvement is a common finding in CVID. HRCT performed at the time of diagnosis is therefore important to assess the degree of pulmonary damage. Imaging at follow-up can also be useful to evaluate the damage evolution and the appearance of complications such as lymphoproliferative and granulomatous disorders.

Several HRCT findings may be present, often of difficult interpretation, due to overlapping and variable patterns. Ongoing infections (pneumonia, bronchiolitis) and lymphoproliferative disorders, including lymphomas, should always be considered in the differential diagnosis. Lung abnormalities may also be related to autoimmune disorders associated to CVID. The knowledge of pathologic mechanisms underlying CVID lung alterations is fundamental to correctly describe and understand HRCT findings.
Personal information

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