HRCT findings in Pneumocystis jirovecii pneumonia, with special emphasis on immunocompromised non-HIV patients.

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Learning objectives

• to depict HRCT findings in Pneumocystis jirovecii pneumonia (PJP) in immunocompromised patients, focusing on non-HIV adults;
• to review the wide spectrum of both infectious and non infectious PJP differential diagnoses at HRCT.
Background

*Pneumocystis jirovecii* - previously known as *P. carini* - is a fungus found worldwide, transmitted via inhalation and causing infection through adhesion to the surface alveolar epithelium of type 1 pneumocytes (1). A main role of T-cells in regulating the immune response against *Pneumocystis* has been supposed (1); therefore, infection represents a main problem for immunocompromised hosts with isolated or combined T-cell deficiency.

The course of *P. jirovecii* infection was initially documented in HIV-positive patients, among whom the highest prevalence was described. The introduction of prophylaxis resulted in an abrupt decrease of infection, whereas it became a main concern among non-HIV immunocompromised hosts. In particular, attention has been given to patients undergoing chemotherapy for solid and hematologic malignancies (especially if treated with R-CHOP 14, ABVD, and FCR protocols), to allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ recipients (mainly heart and lung), and to those undergoing long-term corticosteroid therapy for connective tissue diseases and vasculitis (2, 4).

Symptoms are non-specific and mainly represented by malaise, dry cough and dyspnoea, occasionally associated with fever; in some cases, the infection may induce an acute respiratory distress syndrome (ARDS). Serum CD4+ T-cell count is usually < 200/µL and, in most cases, an increase in serum lactate dehydrogenase (LDH) is documented. Non-HIV patients are at higher risk for rapid course of infection; not properly and readily treated pneumonia induces a mortality of approximately 100% (1).

Chemoprophylaxis has therefore been extended to non-HIV patients, albeit without well-established protocols. The strongest recommendation concerns patients undergoing HSCT, particularly if allogeneic, and solid organ recipients: the administration of chemoprophylaxis for at least 6 months after transplantation has induced a dramatic drop in PJP incidence (about 1% among solid organ recipients in the United States) (1). Trimetoprim-sulfamethoxazole (TMP-SMX) is the standard chemoprophylaxis regimen, with atovaquone and pentamidine as alternative drugs in case of documented hypersensitivity reactions to TMP-SMX or severe renal function impairment (1, 2).

The diagnosis of *P. jirovecii* infection remains a clue for clinicians and an elective field of microbiologists, since the demonstration of labile microorganisms in broncho-alveolar lavage (BAL) or on histologic specimen is still required. In non-HIV patients diagnosis is particularly challenging since infection is mostly associated with low burden of organisms (3).

The role of serum #D-glucane has recently been highlighted, stating its high sensitivity and positive predictive value for *P. jirovecii* infections. Nevertheless, appropriate clinical setting must be taken into account since elevated serum #D-glucane may also be related to other invasive fungal infections (5).
Several studies have investigated the role of High-resolution Computed Tomography (HRCT) in both supporting clinicians in the diagnosis and assessing the severity of infection and its prognosis (6, 7).
Findings and procedure details

I. HRCT findings in PJP

We retrospectively reviewed thirteen PJP cases of immunocompromised, mainly non-HIV patients that underwent HRCT in our institution between 2014 and 2017 because of clinical symptoms (mainly dyspnoea). For all patients, data about serum blood tests, cytofluorimetry, serum LDH and C-reactive protein (CRP), BAL, bronchoscopy, and treatment were collected. In all patients diagnosis was obtained by mean of BAL and/or histologic specimens.

PJP shows a variety of different presentations at HRCT. In non-HIV patients diffuse ground-glass opacity is the main feature, usually involving the upper lobes and sparing the subpleural regions [Fig. 1 on page 9, Fig. 2 on page 9]. Atypical distribution has also been reported (3, 8, 9) [Fig. 3 on page 10]. As described before, these findings are associated with a spectrum of symptoms varying from dry cough with mild dyspnoea to severe ARDS [Fig. 4 on page 11]. When pure ground-glass opacities are present, rapid and complete disappearance of findings can be achieved in the great majority of patients [Fig. 5 on page 12, Fig. 6 on page 13].

Ground-glass opacity may present with associated consolidations [Fig. 7 on page 14], nodules [Fig. 8 on page 15] and/or superimposed septal thickening (i.e., “crazy paving” pattern) [Fig. 9 on page 16]. The crazy paving pattern has been associated with a delay in the application of a specific therapy: even if complete radiological resolution is still possible, this condition may require a more invasive treatment including corticosteroids (8).

In rare cases, PJP may manifest with solitary or multiple centrilobular nodules of variable dimensions, reflecting granulomatous inflammation and mimicking lung carcinoma [Fig. 10 on page 17] (3). Pulmonary cysts are another uncommon manifestation. Both nodules and cysts have mainly been described in HIV-positive patients, being extremely rare in other categories of immunocompromised hosts (3).

II. Differential diagnosis

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<th>Non infectious diseases</th>
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<td><strong>Viral infections</strong></td>
<td><strong>Diffuse alveolar haemorrhage (DAH)</strong></td>
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<td><strong>Fungal infections</strong></td>
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<td><strong>Bacterial infections</strong></td>
<td><strong>Diffuse alveolar damage (DAD)</strong></td>
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a) Infectious diseases

- **Viruses**

Cytomegalovirus (CMV), Varicella zoster virus (VZV) and Herpes simplex virus (HSV) infections may be responsible of pneumonia with acute dyspnoea in immunocompromised hosts. CMV pneumonia is the most frequent viral pneumonia, both as primary infection and as reactivation of latent infection following immunosuppression. It is a main concern in solid organ recipients (mainly after liver and lung transplantation, the latter exposing to a long-lasting risk of infection) and in patients treated with allogeneic HSCT for hematologic malignancies, the highest risk of infection occurring during the early post-transplantation period (between 30 and 100 days after HSCT) (4).

The main HRCT finding of CMV pneumonia is focal or diffuse ground glass attenuation areas, often with associated consolidation and septal thickening [Fig. 11 on page 18]. Small nodules, centrilobular in most cases and occasionally showing random distribution, are also common findings (10). A differential diagnosis between CMV and PJP based only on the radiological findings is not always possible, especially in the early phase of disease; knowledge of concurrent PJP chemoprophylaxis is therefore fundamental.

- **Fungal infections other than PJP**

Ground glass attenuation areas may be the expression of many fungal infections, in particular angioinvasive Aspergillosis (invasive pulmonary Aspergillosis, IPA). IPA frequently occurs in patients after allogeneic HSCT and in solid organ recipients in the first six months after transplantation. The most typical findings at HRCT are represented by small centrilobular tree-in-bud nodules, sometimes surrounded by ground glass opacities (the so-called "halo sign"); diffuse ground glass opacities that could be associated with wedge-shaped consolidations may be also commonly detected (11) [Fig. 12 on page 19]. Response to adequate treatment and immune reconstitution in severe immunocompromised patients are associated with cavitation, leading to the characteristic "air crescent sign" (11, 12).

- **Bacterial infections**

Bacterial pneumonia is particularly common in certain subgroups of immunocompromised hosts, first of all solid organ recipients. During the perioperative and early post-operative periods, patients are at greater risk for Gram-negative infections (e.g., Klebsiella spp, Legionella spp. and *P. aeruginosa*) in the form of ventilation-acquired pneumonia (VAP). Beyond six months after transplantation, community acquired pneumonia, mainly caused by Streptococcus spp. and *H. influenzae*, tend to prevail (4).

HRCT findings of bacterial pneumonia in immunocompromised hosts don't differ from what can be observed in immunocompetent patients, and include a combination of
b) Non-infectious conditions

In immunocompromised hosts focal or diffuse ground-glass opacities are mainly infectious in origin. Nevertheless, several non-infectious conditions need to be taken into account, including diffuse alveolar haemorrhage (DAH), pulmonary oedema, diffuse alveolar damage (DAD), and drug toxicity (10).

- **DAH**

DAH is a rare condition due to autoimmune processes inducing pulmonary capillaritis, in some cases related to drugs administration (e.g., bleomycin and citarabine) or to coagulation disorders. Clinically, DAH is characterized by sudden onset of dyspnoea and hypoxemia, with associated haemoptysis (which is absent in up to 30% of cases) and sideropenic anaemia. HRCT findings include ground-glass opacity and consolidations, usually bilateral, diffuse or patchy / lobular, often with peri-hilar distribution with sparing of the subpleural regions [Fig. 14 on page 21]. Crazy paving pattern may also occur (13).

- **Pulmonary oedema**

Increased hydrostatic pressure in the pulmonary capillaries leads first to interstitial oedema and then to alveolar flooding, resulting in smooth septal thickening, ground glass opacities and consolidations at HRCT. These findings initially involve the peri-hilar regions, with symmetric and gravitational distribution; the onset is rapid, in association with sudden dyspnoea and cough [Fig. 15 on page 22]. They can persist on chest x-ray and HRCT for several weeks after the normalization of hydrostatic pressure (14).

Causes of hydrostatic pulmonary oedema include heart failure, veno-occlusive disease and fluid overload, the latter being a possible consequence of supportive care.

A rare form of iatrogenic pulmonary oedema occurs as a consequence of rapid re-expansion of a collapsed lung, following drainage or evacuation of pleural disease (such as pneumothorax, hydrothorax, or haemothorax). It is associated with a wide spectrum of clinical manifestations, from complete absence of symptoms to sudden respiratory failure with tachycardia (15) [Fig. 16 on page 23].

- **DAD**

Alveolar oedema may be the result of a direct damage to the pulmonary epithelium and endothelium, thus increasing permeability in absence of elevated hydrostatic pressure. The histologic abnormalities of DAD progress from an early exudative phase with hyaline
membranes inside the alveolar spaces, through a proliferative phase, to a phase of complete resolution vs. fibrotic degeneration (14).

At HRCT the main finding of DAD is diffuse ground glass opacity, corresponding to the histologic proliferative phase, arising from the peri-hilar regions and displaying a gravitational gradient. In the fibrotic phase, ground glass opacity is more inhomogeneous and accompanied by septal thickening and cystic changes, mainly involving the subpleural regions.

Peri-engraftment respiratory distress syndrome (PERDS) is a rare complication of both autologous and allogeneic HSCT with underlying DAD (16). Its clinical features include skin rash, non-infectious pulmonary infiltrates, fever, diarrhea and capillary leak. Onset of symptoms usually occurs in the peri-engraftment period, within five days after recover of the neutrophil count (17). PERDS often shows a good response to steroid therapy [Fig. 17 on page 24].

- Drug toxicity

Sudden dyspnoea in an immunocompromised host may be the expression of a drug-induced lung toxicity. Findings at HRCT may vary, including non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), an hypersensitivity pneumonia, or a combination of NSIP and OP patterns (18, 19), with diffuse, central ground glass opacities and consolidation that may be virtually indistinguishable from PJP (20).

Drugs that have been related to lung toxicity with diffuse ground glass opacity include inhibitors of mammalian target of rapamycin (mTOR), mainly Sirolimus, but also Everolimus (19, 20) [Fig. 18 on page 25].
Fig. 1: PJP in a 58-year-old male patient undergoing chemotherapy for chronic lymphocytic leukaemia, with sudden onset of dyspnoea and dry cough and not receiving any specific prophylaxis. HRCT image reformatted on the coronal plane shows diffuse ground glass opacities involving the upper lobes and sparing the subpleural regions. Complete resolution of symptoms was obtained after treatment with TMP-SMX.

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Fig. 2: PJP in a 33-year-old male HIV positive patient undergoing discontinuous anti-retroviral therapy and prophylaxis. HRCT image on the axial plane shows diffuse, bilateral ground glass opacities, involving both upper and lower lobes. P. jirovecii oocysts were isolated from BAL.

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Fig. 3: PJP in a 28-year-old female patient presenting to the emergency department for dry cough and worsening dyspnoea, despite three weeks of antimicrobial therapy. HRCT image reformatted on the coronal plane shows bilateral ground-glass opacities, mainly involving the lower lobes and sparing the peri-hilar regions. P. jirovecii oocysts were isolated from BAL. A subsequent diagnosis of HIV infection was made.

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Fig. 4: PJP in a 44-year-old female patient presenting with ARDS five months after allogeneic HSCT for multiple myeloma and undergoing treatment with Tacrolimus and corticosteroids. The patient had always refused to receive specific chemoprophylaxis for PJP because of referred allergy. HRCT image on the axial plane shows bilateral, diffuse ground glass opacities; P. jirovecii oocysts were isolated from BAL.

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Fig. 5: PJP in a 32-year-old female patient undergoing chemotherapy for relapsed acute myeloid leukaemia. HRCT image on the axial plane shows bilateral diffuse ground glass opacities involving both upper and lower lobes; consolidation is also visible in the peri-hilar region of the right middle lobe. Motion artifacts due to the patient's severe tachypnoea are visible.

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Fig. 6: Same patient as figure 5, after two weeks of antimicrobial regimen including TMP-SMX, with significant clinical improvement. HRCT image on the axial plane shows bilateral, patchy, ill-defined residual ground glass opacities.

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Fig. 7: PJP in a 65-year-old female patient who underwent chemotherapy based on R-CHOP regimen for non-Hodgkin lymphoma. Thirteen days after chemotherapy cycle she developed fever and mild dyspnoea. HRCT image on the axial plane shows diffuse ground glass opacities associated with consolidations with air bronchogram, almost exclusively involving the upper lobes.

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Fig. 8: PJP in a 59-year-old female patient undergoing chemotherapy for relapsed multiple myeloma. Transaxial maximum intensity projection (MIP) image shows small centrilobular nodules involving the upper lobes (along with bilateral pleural effusion). *P. jirovecii* oocysts were isolated from BAL.

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Fig. 9: PJP in a 72-year-old woman undergoing high-dose corticosteroid therapy for systemic mastocytosis, who develops sudden fever and dyspnoea. HRCT image reformatted on the coronal plane shows diffuse ground glass opacities with superimposed interlobular septal thickening (crazy-paving pattern), involving the right upper lobe, without sparing of the subpleural regions. Complete regression of symptoms was obtained after antimicrobial treatment with TMP-SMX. HRCT performed four weeks later (not shown) revealed resolution of findings.

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Fig. 10: PJP in a 59-year-old man undergoing high-dose corticosteroid therapy for membranous glomerulonephritis and systemic vasculitis. After the onset of fever and dyspnoea and the evidence of P. jirovecii oocysts from BAL, the patient was given an appropriate antimicrobial regimen based on TMP-SMX, which he took discontinuously. HRCT performed thirty days after the start of treatment shows subpleural consolidation with laminated peripheral calcifications in the right middle lobe, consistent with granulomatous inflammation. Bilateral middle-sized nodules are also visible. Serum #-D-glucane remained elevated, and P. jiroveci oocysts were still found in blood and urine cultures.

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Fig. 11: CMV pneumonia in a 68-year-old man undergoing chemotherapy for acute myeloid leukemia, who suddenly developed respiratory failure. HRCT image reformatted on the coronal plane shows diffuse, ground glass opacities and consolidations involving both upper and lower lobes and sparing the subpleural regions. Elevated serum CMV-DNA levels with normal serum #D-glucane level led to CMV pneumonia diagnosis.

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Fig. 12: Aspergillosis in a 67-year-old female patient with severe lymphopenia after receiving chemotherapy and radiation treatment for glioblastoma multiforme. HRCT image on the axial plane shows confluent centrilobular nodules in the right middle lobe, along with bilateral ground glass opacities and consolidations, and right pleural effusion. HRCT performed five days later (not shown) reveal cavitation of the largest nodules in the right middle lobe, with worsening of bilateral ground glass opacities and persistence of consolidations. Elevated galactomannan on serum and BAL and high levels of #D-glucane led to the diagnosis of invasive aspergillosis.

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Fig. 13: Bacterial pneumonia in a 25-year-old male patient undergoing chemotherapy for acute myeloid leukaemia, who developed fever and dyspnoea. HRCT image reformatted on the coronal plane shows peri-hilar ground glass opacities involving the upper lobes, and consolidation with air bronchogram in the right upper lobe. Since blood cultures were persistently negative, an empirical antimicrobial treatment with Meropenem and Tigecycline was administered, with prompt regression of symptoms and disappearance of radiologic findings a few weeks later.

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Fig. 14: DAH in a 44-year-old female patient developing thrombotic thrombocytopenic purpura while undergoing chemotherapy for breast cancer. The patient presented with tachycardia, oxygen desaturation and anaemia. HRCT image on the axial plane shows bilateral, patchy ground glass opacities involving the upper lobes. #D-glucane and tests on BAL were persistently negative, and wide spectrum antimicrobial treatment failed in determining clinical improvement. Patient revealed thrombotic microangiopathy, and underwent several cycles of apheresis, without response. The woman died three weeks later for brain haemorrhage.

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Fig. 15: Pulmonary oedema due to fluid overload in a 44-year-old male patient with dyspnoea and peripheral oedema, while undergoing cytoreductive chemotherapy with Hydroxyurea for acute myeloid leukaemia with hyperleukocytosis. HRCT image on the axial plane shows bilateral ground glass opacities involving the upper lobes and associated with smooth thickening of interlobular septa. Bilateral pleural effusion was also present (not shown).

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Fig. 16: Re-expansion pulmonary oedema in a 63-year-old female patient undergoing chemotherapy for ovarian cancer, with sudden onset of oxygen desaturation and hypotension after thoracic drainage placement for pleural effusion in the right lung. HRCT image on the axial plane shows ground glass opacities associated with smooth septal thickening and consolidations involving the lower and middle right lobes. Atelectasis as a consequence of pleural effusion is visible in the dorsal region of the left lower lobe and lingula. Right pneumothorax is also evident.

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Fig. 17: Peri-engraftment respiratory distress syndrome (PERDS) in a 25-year-old male patient undergoing autologous HSCT for Hodgkin Lymphoma, with fever and malaise beginning two days after the transplantation and progressively worsening. HRCT image on the axial plane shows bilateral ground glass centrilobular opacities, which mainly involve the anterior regions of the upper lobes. Blood cultures and BAL were persistently negative.

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**Fig. 18:** Everolimus induced pulmonary toxicity in a 64-year-old female patient undergoing treatment with Everolimus and Exemestane for breast cancer, with sudden onset of fever, dry cough and dyspnoea, needing non-invasive ventilation. HRCT image on the axial plane shows diffuse ground glass opacities with associated consolidations involving the peri-hilar regions and sparing the subpleural spaces. Left pleural effusion is also present. Cultures from BAL were negative for bacteria and fungi. Since Everolimus was withdrawn, complete regression of symptoms and disappearance of radiologic findings was obtained (in four weeks), without need for antimicrobial treatment.

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Conclusion

HRCT findings of PJP are multifaceted, varying from the well-documented diffuse central ground glass opacity to more challenging patterns, related to concomitant septal thickening and/or consolidations. While approaching the dyspnoeic immunocompromised patient, the radiologist must be familiar with the wide spectrum of both infectious and non-infectious differential diagnoses, and should always be aware of basic clinical information (including specific chemoprophylaxis for PJP and causes/type/duration of immunological defect).
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