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Review

Pneumocystis jirovecii pneumonia at chest High-resolution Computed Tomography (HRCT) in non-HIV immunocompromised patients: Spectrum of findings and mimickers

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ABSTRACT

Pneumocystis jirovecii pneumonia (PJP) has emerged as a main issue in non Human Immunodeficiency Virus (HIV) immunocompromised hosts, exposing patients to high mortality rates, especially when the diagnosis is delayed. Since microbiological confirmation is often unfeasible or difficult to obtain, High-resolution Computed Tomography (HRCT) represents a main tool for guiding the diagnosis in the appropriate clinical scenario. Nevertheless, radiologists must be aware that PJP at HRCT is a multifaceted process, with a variety of common and less frequent findings, along with a broad spectrum of infectious (e.g., viral and certain fungal and bacterial pneumonias) and non-infectious (e.g., pulmonary oedema, diffuse alveolar haemorrhage, and drug toxicity) differential diagnoses.

In this review we resume background clinical information on PJP in non-HIV immunocompromised patients, illustrate both typical and less frequent HRCT findings, and present the spectrum of infectious and non-infectious mimickers at HRCT, highlighting the similarities with PJP and providing clues for the differential diagnosis.

1. Introduction

Pneumocystis jirovecii pneumonia (PJP) is a severe pulmonary infection affecting immunocompromised patients, common in subjects with advanced Human Immunodeficiency Virus (HIV) infection [1]. Non-HIV immunocompromised patients can be at risk for PJP, mainly those treated with corticosteroids or having defects in cell-mediated immunity [2]. In these patients, the diagnosis of PJP may be challenging, despite recent advances in diagnostic methods.

High-resolution Computed Tomography (HRCT) is indicated after performing an either negative or inconclusive chest x-ray [3], and can be suggestive of PJP in the appropriate clinical scenario [4].

In this review we provide background clinical information on PJP in non-HIV immunocompromised patients, describe typical and less frequent HRCT findings, and illustrate the spectrum of main infectious and non infectious conditions mimicking PJP at HRCT.

2. Clinical overview

2.1. Definition and epidemiology

First identified in the early 20th century by Chagas [5], Pneumocystis jirovecii – previously known as Pneumocystis carinii – is a fungus [6] transmitted from host to host via inhalation as aerosolized particles [7]. This agent lives almost exclusively in the pulmonary alveoli, causing lung infection through adhesion to the surface alveolar epithelium of type 1 pneumocytes [8]. While Pneumocystis jirovecii is either absent or present at very low levels in healthy people, it is quite

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common in immunocompromised subjects [9]. In the latter group, PJP is a main clinical issue, especially in case of isolated or combined T-cell deficiency, stating the major role of T-cells in regulating the immune response against this agent [10].

PJP was initially documented in HIV-positive patients, often presenting as Acquired Immune Deficiency Syndrome (AIDS) defining illness [11]. Nowadays the prevalence of PJP in HIV-positive patients has significantly decreased, as the effect of chemoprophylaxis and new antiretroviral drugs, while remaining still consistent in non-HIV immunocompromised hosts [2]. In particular, attention has been given to patients undergoing chemotherapy for haematological and solid malignancies, allogeneic haematopoietic 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 [2,4,12]. In those patients, the strongest recommendation for chemoprophylaxis concerns subjects undergoing HSCT, particularly if allogeneic, and solid organ recipients: the administration of trimethoprim-sulfamethoxazole (TMP-SMX) as standard regimen 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) [8]. Nebulised pentamidine is recommended as second-line prophylactic agent when TMP-SMX is contraindicated [12]. Therefore, PJP now occurs mainly in patients who are not receiving adequate prophylaxis.

2.2. Clinical manifestations

PJP presents with non-specific signs and symptoms, such as fever, dry cough, and dyspnoea, occurring in up to 86%, 76%, and 81%, respectively [2]. In some cases, the infection may induce acute respiratory distress syndrome (ARDS), requiring mechanical ventilation [4,13]. Pulmonary auscultation is often equivocal or not significant. Serum CD4+ T-cell count is often < 200/μL [4]. A rapid, non-specific increase in serum lactate dehydrogenase (LDH), marker of lung injury, may be documented, particularly in most severe cases [2].

Non-HIV patients are at higher risk for rapid course of infection than HIV-positive ones, with fewer systemic symptoms [14], and shorter time from clinical onset to diagnosis [15]. The overall mortality is high (31%), up to almost 100% when PJP is not properly and readily treated [8,16].

2.3. Diagnosis and treatment

Since P. jirovecii is difficult to culture, diagnosis usually relies on demonstrating labile microorganisms in respiratory specimens (mainly on bronchoalveolar lavage - BAL) by means of various staining methods (e.g., Gomori's methenamine silver stain) [17] and immunofluorescent assays [12]. Such an identification is particularly challenging in non-HIV immunocompromised patients, since infection is mostly associated with low burden of organisms [18]. To overcome this issue, Pneumocystis-specific polymerase chain reaction (PCR) has recently been proposed as the new test of choice for the diagnosis of PJP, due to its higher sensitivity compared to morphologic methods [19]. Serum β-D-glucan (i.e., a circulating component of the fungal cell wall) assay has been proposed as a rapid and reliable diagnostic tool [20], though other fungal infections may represent a confounder [21]. Tables 1 [22–25] and 2 [26–32] report, respectively, the diagnostic performance of PCR and serum β-D-glucan for detecting Pneumocystis jirovecii in non-HIV immunocompromised patients.

Intravenous administration of TMP-SMX represents first-line therapy for PJP [12,33]. Corticosteroid adjunct in case of moderate-to-severe PJP remains a matter of debate, potentially reducing the duration of mechanical ventilation and Intensive Care Unit admission [2,34].

Table 1
Diagnostic performance of polymerase chain reaction (PCR) for detecting Pneumocystis jirovecii in non-HIV immunocompromised patients with acute lung disease, irrespective of sampling methods and technical details.

Study (first author, year)	Study population	Study design	PJP cases / total patients	Sensitivity (%)	Specificity (%)
Azoulai, 2009 [22]	patients with hematologic or solid organ malignancies, renal transplantation, stem cells transplantation, connective tissue diseases, and other non malignant diseases requiring steroids and/or other immunosuppressive drugs	retrospective	39/448	87	92
Mu, 2011 [23]	Non-HIV immunocompromised patients	retrospective	20/60	100	100
Mühlethaler, 2012 [24]	Patients with autoimmune diseases, solid organ transplantation, hematologic or solid organ malignancies, or other causes of immunosuppression	retrospective	71/242	100	89
Matsumura, 2018 [25]	Patients with autoimmune or inflammatory diseases, solid organ transplantation, hematologic or solid organ malignancies, or with HIV infection[a]	retrospective	39/221	92[b], 95[c]	86[b], 86[c]

PJP: Pneumocystis jirovecii pneumonia.
[a] 7/221 patients were HIV-positive.
[b] GENECUBE assay.
[c] real-time assay.

Table 2
Diagnostic performance of β-D-glucan for detecting Pneumocystis jirovecii in non-HIV immunocompromised patients, irrespective of sampling protocols and technical details.

Study (first author, year)	Study population	Study design	PJP cases / total patients	Sensitivity (%)	Specificity (%)
Iikuni, 2006 [26]	patients with connective tissue diseases and suspected respiratory infection	retrospective	18/66	78	77
Tasaka, 2007 [27]	patients with hematologic malignancy, collagen vascular disease, interstitial lung disease, organ transplantation, lung cancer and other predisposing conditions[a], having acute lung disease	retrospective	57/295	93	94
Akamatsu, 2007 [28]	living donor liver transplant recipients monitored for invasive fungal infection	prospective	2/180	100	79
Obayashi, 2008 [29]	patients with hematologic or solid organ malignancies, autoimmune diseases, and acquired immunodeficiency syndrome[b], having invasive fungal infection found at autopsy	retrospective	6/104	83	71
Koo, 2009 [30]	cancer patients monitored for invasive fungal infection	retrospective	14/871	93	84
de Boer, 2011 [31]	HIV-negative, adult immunocompromised patients suspected of PJP	prospective	21/31	86	90
Morjaria, 2018 [32]	cancer patients suspected of PJP	retrospective	53/438	70	81

PJP: Pneumocystis jirovecii pneumonia.
[a] 16/295 patients were HIV-positive.
[b] 7/104 patients with acquired immunodeficiency syndrome.

3. Imaging features of PJP

3.1. Role of HRCT

HRCT is the most reliable imaging technique for the detection and differential diagnosis of acute respiratory illness in immunocompromised patients, complementing either negative or inconclusive chest x-ray [3]. HRCT plays also a pivotal role in monitoring the effects of therapy.

Several studies have investigated the role of HRCT in both supporting clinicians in the diagnosis of PJP [4,15,35] and assessing the severity of infection and its prognosis [36,37].

3.2. Typical findings

PJP shows a variety of different presentations at HRCT. In non-HIV patients, extensive ground-glass opacity (GGO) is the main feature, representing alveolitis with accumulation of intra-alveolar fibrin, debris, and organisms [4,15]. Distribution of GGO is usually symmetric, predominant in the perihilar regions and the apices, with peripheral sparing [35] (Fig. 1). A mosaic pattern has been reported in 57% of cases [35] (Fig. 2).

Initiation of specific therapy can induce rapid radiologic improvement on repeated HRCT (median 13 days). On the contrary, ineffective therapy or non-specific treatment are associated with evolution to a mosaic pattern with architectural distortion and increasing density of pulmonary infiltrates [35] (Fig. 3).

Typical sequelae of PJP include architectural distortion (i.e., linear ad irregular opacities, reticulation, and traction bronchiolectasis) in one third of patients, resolving in 74% of cases after a median of 27 days (mean 60, range 11–302 days) [35].

Typical HRCT findings of PJP are resumed in Table 3.

3.3. Atypical and less frequent findings

PJP can present with atypical distribution of GGO in less that 20% of cases, with focal extent or lower lobes predominance [15]. As a consequence of host immune-mediated lung damage, GGO may present in association with consolidations, which are more common and tend to develop more rapidly in non-HIV patients (Fig. 4) [38]. Nodules and/or superimposed septal thickening (i.e., “crazy paving” pattern) (Fig. 5) are other ancillary HRCT findings [39].

Severe forms of PJP may present with ARDS (Fig. 3), being particularly critical in non-HIV patients, with higher rates of failure of non-invasive mechanical ventilation and higher mortality when compared to HIV-positive patients with similar presentation [40].

Pulmonary cysts are very uncommon manifestation in non-HIV patients, reported in 3% of cases (vs. 56% in HIV-positive patients) [15]. Their formation has been attributed to long-standing low-intensity inflammatory process determining tissue destruction [15] (Fig. 6). Occasionally, subsequent pneumothorax or pneumomediastinum may occur [41].

In rare cases, PJP may manifest with solitary or multiple lung nodules of variable size, reflecting granulomatous inflammation (Fig. 7). This pattern as been documented anecdotally in non-HIV patients, in relation to active malignancy, recent corticosteroid use, or immune reconstitution-like syndrome [42]. When nodules are the only manifestation, diagnosis of PJP may be overlooked on both HRCT and BAL, thus requiring careful search for organisms in biopsy specimens [43].

Table 4 resumes atypical and less frequent HRCT findings of PJP.

4. Differential diagnosis

Many different infectious and non-infectious conditions present with an acute mixed-density pattern at HRCT (i.e., areas of GGO and consolidation, in variable proportion), thus potentially mimicking PJP.

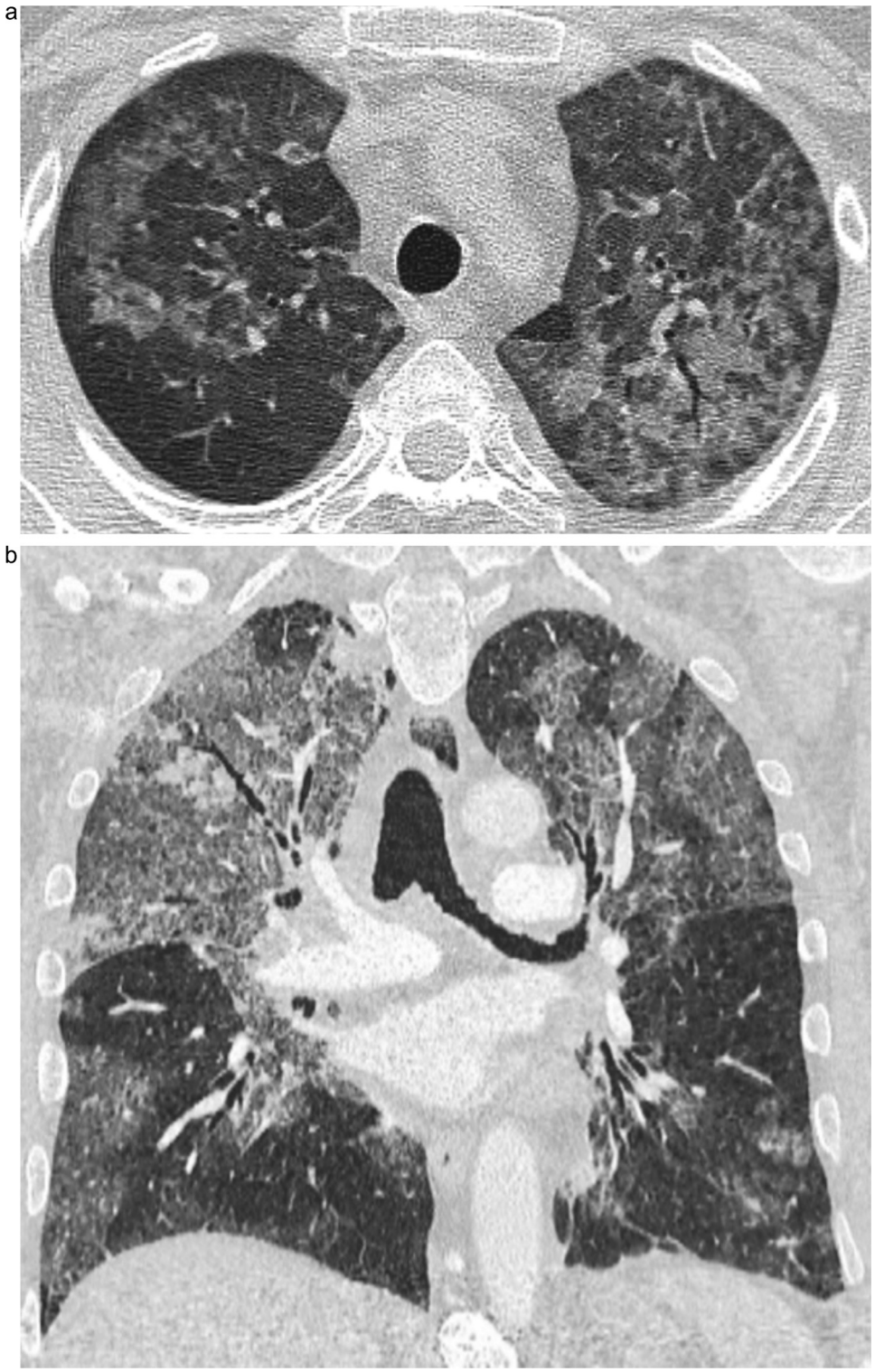

Fig. 1. Typical HRCT findings of Pneumocystis jirovecii pneumonia (PJP).
a: PJP in a 30-yrs-old woman undergoing immunosuppressive therapy after haematopoietic stem cell transplantation for myelodysplastic syndrome. HRCT shows bilateral symmetric ground-glass opacities, sparing the subpleural regions. **b:** PJP in a febrile 67-yrs-old man previously treated for non-Hodgkin lymphoma, with severe hypogammaglobulinemia. HRCT image reformatted on the coronal plane highlights the predominant involvement of the upper lobes.

Viral, fungal, and bacterial agents, as well as pulmonary oedema, diffuse alveolar damage (DAD), diffuse alveolar haemorrhage (DAH), and drug toxicity, should be taken into account in differential diagnosis. Synopses of the most common infectious and non-infectious PJP mimickers are provided in Table 5 and Table 6, respectively.

4.1. Infectious diseases

4.1.1. Viruses

Cytomegalovirus (CMV), Varicella zoster virus (VZV), Respiratory syncytial virus (RSV), Adenovirus, and Herpes simplex virus (HSV) infections may be responsible of pneumonia with acute dyspnoea in

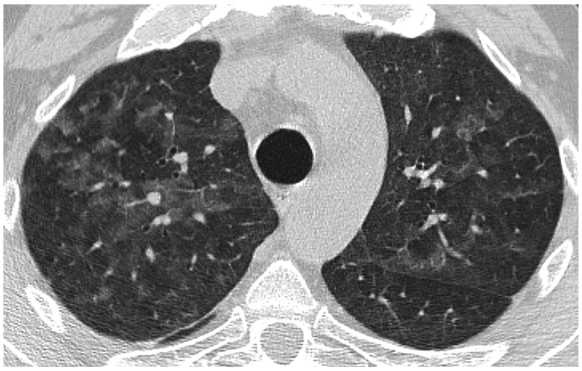

Fig. 2. Pneumocystis jirovecii pneumonia (PJP) presenting with mosaic pattern.
PJP in a 58-yrs-old man undergoing chemotherapy for chronic lymphocytic leukaemia. HRCT reveals bilateral, patchy ground-glass opacities with a mosaic pattern.

immunocompromised hosts. CMV pneumonia is the most frequent viral pneumonia, under the form of both primary infection or reactivation of latent infection following immunosuppression. CMV pneumonia is a major concern in solid organ recipients (mainly after liver and lung transplantation) and in patients treated with allogeneic HSCT for haematological malignancies. Similarly to PJP, the highest risk of infection occurs in the early post-transplantation phase (i.e., between 31 and 100 days after HSCT). T-cell defect and immunosuppressive therapy after HSCT predispose patients to both PJP and CMV pneumonia [44].

Main HRCT findings of CMV pneumonia are focal or diffuse GGO (reflecting DAD), along with consolidation, septal thickening, and small centrilobular or random nodules [45,46]. Differential diagnosis between CMV pneumonia and PJP is considered quite difficult on HRCT (Fig. 8) [44]. Vogel et al. showed that diagnosis of CMV pneumonia may be favoured in case of small centrilobular nodules and unsharp demarcation of GGO, while apical distribution of infiltrates (GGO and consolidation) and mosaic pattern occur more often in PJP [45]. Kunihiro et al. found that GGO was more extensive and mosaic pattern was more frequently observed in PJP than in CMV pneumonia, while nodules (with or without tree-in-bud pattern and halo sign) were more frequent in CMV pneumonia [47].

Detection of CMV DNA in blood and, more specifically, analyses on BAL fluid may be helpful in establishing diagnosis of CMV pneumonia [48].

Noteworthy, CMV infection is a frequent condition in non-HIV immunocompromised patients with PJP, presenting in up to 54% of cases and usually due to reactivation of latent virus [49,50]. Patients treated with T-cell immunosuppressive therapy (i.e., organ transplant recipients) are at higher risk of this co-infection [49,50]. Moreover, as shown in a recent meta-analysis, CMV infection in solid organ recipients significantly increases the risk of PJP, presumably due to its immunomodulatory effect [51]. PJP-CMV co-infection determines more severe lung injury compared to PJP alone, with higher risk of significantly lower PaO2/FiO2 [49], though mortality does not seem to be significantly higher [50]. HRCT findings in PJP-CMV co-infection are heterogeneous, being GGO frequently associated with consolidation and centrilobular nodules. When present, centrilobular nodules should raise the suspicion of co-infection, since they are significantly more common in PJP-CMV co-infection rather than in PJP alone (37% vs. 9%) [49].

4.1.2. Fungal infections other than PJP

Fungi (especially moulds) represent a main cause of lung infection in immunocompromised patients, with Aspergillosis being the most frequent opportunistic fungal pneumonia in allogeneic HSCT and solid organ transplant recipients [44]. Typical HRCT findings of angioinvasive pulmonary aspergillosis include solitary or multiple nodules surrounded by GGO ("halo sign"), and pleura-based, wedge-shaped areas of consolidation, corresponding to haemorrhagic infarcts; the airway-invasive form manifests with signs of bronchopneumonia and bronchiolitis [52]. Nevertheless, less frequent HRCT features include areas of consolidation and/or GGO [53,54], making the differential diagnosis with PJP more difficult (Fig. 9).

The diagnostic work-up of invasive mould infections usually relies on a combination of imaging, microbiological tools (including fungal biomarkers, such as Galactomannan – GM) and histopathology. Tests for GM detection have been validated for use in serum and BAL samples, with sensitivity of 60–80% and 85–90% and specificity of 80–95% and 90–95% in the diagnosis of invasive aspergillosis, respectively [55].

4.1.3. Bacterial infections

Bacterial pneumonia is particularly common in definite subgroups of immunocompromised hosts, especially solid organ recipients. During the perioperative and early post-operative periods, patients are at greater risk for Gram-negative infections (e.g., Pseudomonas aeruginosa, *Klebsiella* spp., and other Enterobacteriaceae) in the form of ventilation-acquired pneumonia.

HRCT findings of bacterial pneumonia in immunocompromised hosts do not differ from immunocompetent patients, including a combination of consolidations, GGO (caused by a partial filling of the alveoli), nodules, and pleural effusion [44]. When distribution of findings is bilateral and GGO predominates, as for classical appearance of Pseudomonas aeruginosa pneumonia [56] or atypical pneumonias (Mycoplasma and Chlamydia), HRCT differential diagnosis with other causative agents may be challenging [57] (Fig. 10).

4.2. Non-infectious conditions

4.2.1. Pulmonary oedema

Causes of pulmonary oedema include heart failure, veno-occlusive disease and fluid overload. Increased hydrostatic pressure in the pulmonary capillaries leads first to interstitial oedema and then to alveolar flooding, with rapid onset, associated to sudden dyspnoea and cough [58]. HRCT shows smooth septal thickening, GGO and consolidations, initially involving the peri-hilar regions, with symmetric and gravitational distribution (Fig. 11). Hydrostatic oedema is the main non-infectious cause of widespread GGO in hospitalized patients [59]. Bilateral pleural effusions and mediastinal findings (i.e., enlarged oedematous lymph nodes, and effacement of fat secondary to extravascular fluid) are frequently associated and help in confirming diagnosis [60].

Another form of iatrogenic pulmonary oedema occurs as a consequence of rapid re-expansion of atelectatic lung, following drainage or evacuation of moderate-to-large amount of pleural disease (e.g., 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 [61]. GGO in the re-expanded lung is the most typical HRCT finding, with diffuse involvement and coexisting consolidation in 45% and 23%, respectively [62]. Contralateral GGO and consolidation may be detected in more than one third of patients [62], thus leading to PJP-like appearance.

4.2.2. Diffuse alveolar damage (DAD)

DAD is a histopathologic pattern of lung injury affecting alveolar components (both pneumocytes and alveolar capillaries), with formation of hyaline membranes, oedema, and eventually fibroplasia [63]. A number of different pathologic conditions can cause DAD in immunocompromised patients, including pneumonia, extrapulmonary sepsis, chemotherapy, HSCT, and transfusion [63]. In all these cases, ARDS is a frequent clinical manifestation. HRCT in the acute phase typically shows heterogeneous foci of GGO and consolidation, usually with air bronchograms. Crazy-paving pattern can be seen as well [64].

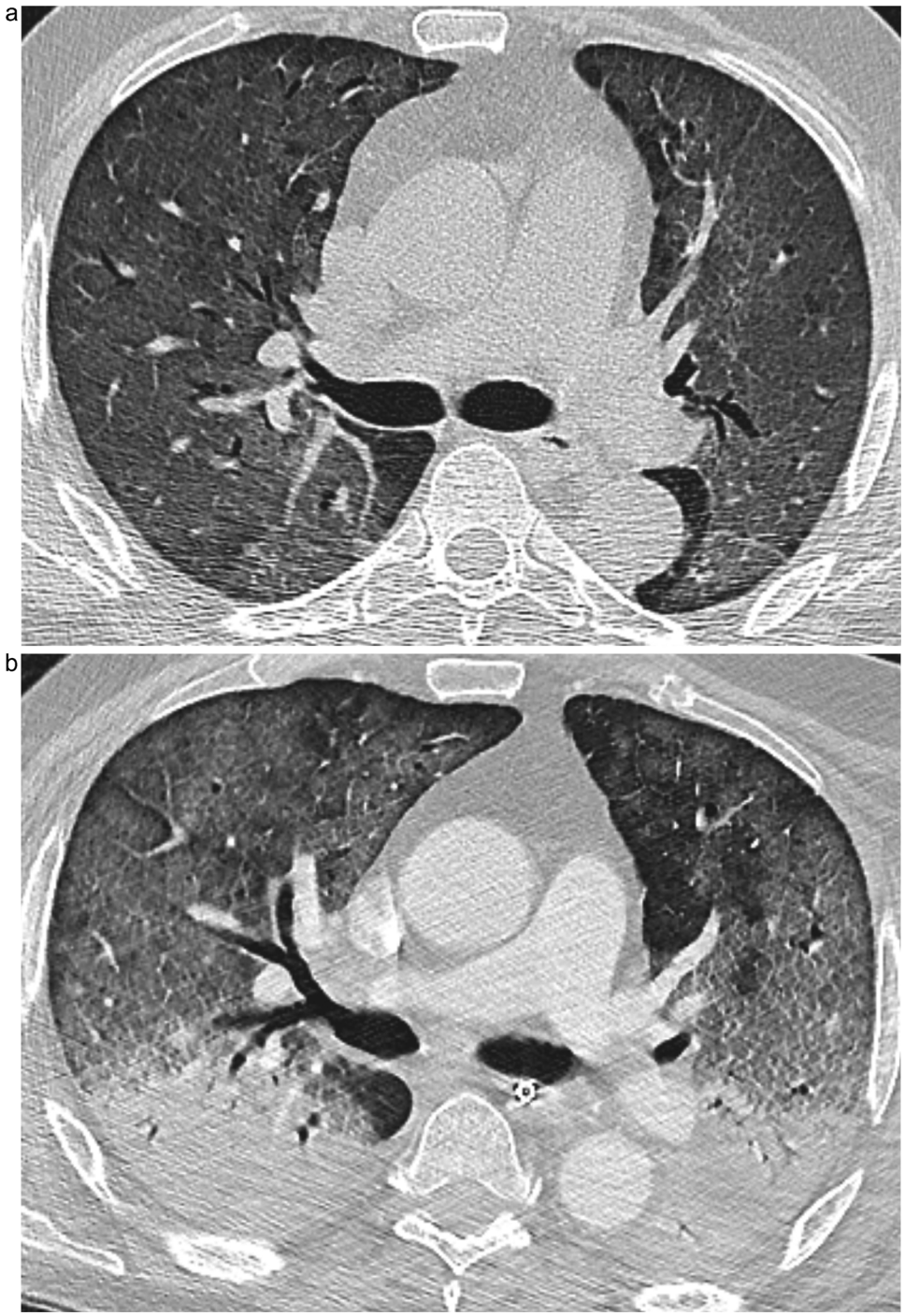

Fig. 3. Pneumocystis jirovecii pneumonia (PJP) evolution after ineffective therapy or non-specific treatment.
PJP in a 70-yrs-old man receiving tacrolimus and mycophenolate after kidney transplantation, with worsening dyspnoea and dry cough. **a:** HRCT performed at the time of hospital admission reveals bilateral, diffuse ground-glass opacities (GGO). **b:** patient developed ARDS two weeks after the clinical onset (despite intravenous administration of trimethoprim-sulfamethoxazole and corticosteroids), with HRCT showing extensive consolidations in the dependent regions of both lungs, along with extensive GGO.

Table 3
Typical HRCT findings in non-HIV patients with Pneumocystis jirovecii pneumonia (Figs. 1,2,3).

Timing	HRCT findings	Distribution
At symptoms onset	GGO	Perihilar, with sparing of lower lung zones and subpleural regions
Evolution in case of ineffective therapy; resolution in weeks-to-months after specific treatment in most of the cases	Mosaic pattern and architectural distortion, with increasing density of infiltrates	Same of the acute phase

GGO: ground-glass opacity.

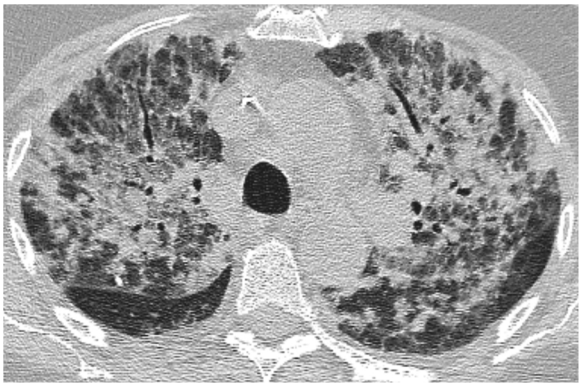

Fig. 4. Atypical HRCT findings of Pneumocystis jirovecii pneumonia (PJP): acute mixed-density pattern.
PJP in a 65-yrs-old woman undergoing chemotherapy for non-Hodgkin lymphoma, developing fever and mild dyspnoea. HRCT performed at the onset of symptoms reveals diffuse ground-glass opacities and consolidations with air bronchogram.

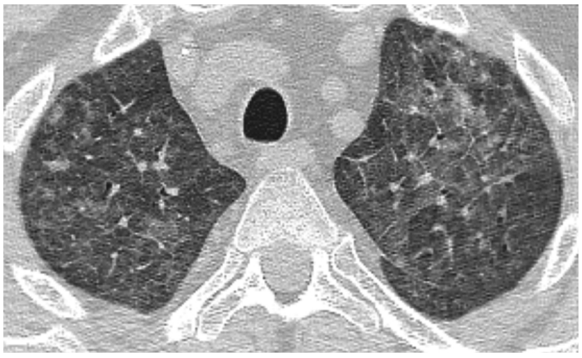

Fig. 5. Atypical HRCT findings of Pneumocystis jirovecii pneumonia (PJP): crazy paving pattern.
PJP in a 46-yrs-old man undergoing chemotherapy for a primary central nervous system lymphoma. HRCT at clinical onset shows diffuse ground glass opacities and small, scattered consolidations, with superimposed smooth thickening of the interlobular septa (i.e., crazy paving pattern).

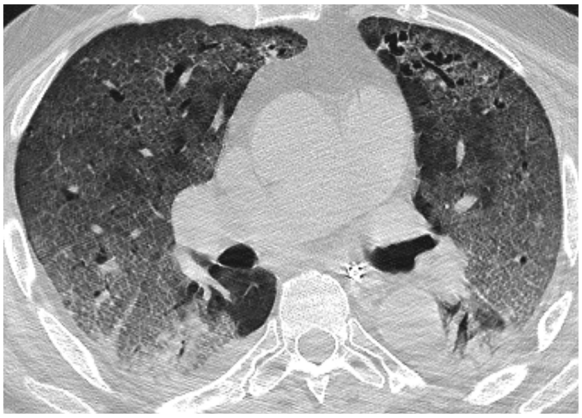

Fig. 6. Atypical HRCT findings of Pneumocystis jirovecii pneumonia (PJP): cysts.
Same patient of Fig. 3. HRCT performed at the time of ARDS highlights small cysts in the anterior subpleural region of the left upper lobe.

When GGO and/or consolidation show diffuse distribution, HRCT appearance overlaps with infections (e.g., PJP and viral pneumonia) and non-infectious conditions (e.g., DAH and pulmonary oedema). The presence of small pleural effusion and a gravitationally dependent

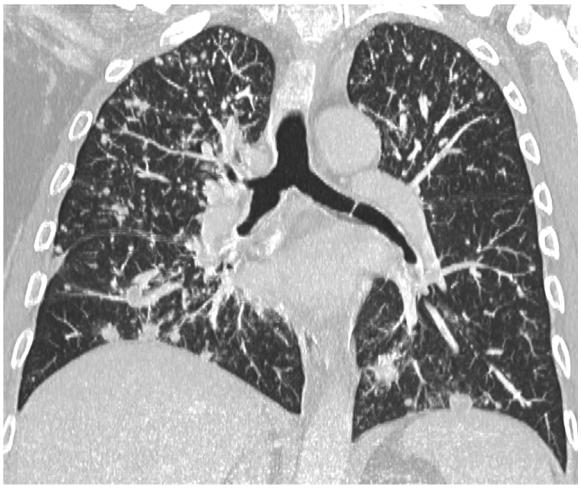

Fig. 7. Atypical HRCT findings of Pneumocystis jirovecii pneumonia (PJP): nodules.
Chronic PJP in a 58-yrs-old man undergoing high-dose corticosteroids and immunosuppressive therapy for systemic vasculitis. HRCT (image reformatted on the coronal plane) performed five months after initiation of specific therapy shows multiple, bilateral, solid nodules, heterogeneous in size. Most findings resolved after one year of therapy, with residual scarring (not shown).

Table 4
Atypical and less frequent HRCT findings in non-HIV patients with Pneumocystis jirovecii pneumonia (Figs. 4–7).

HRCT findings	Distribution
GGO	Focal and/or predominant in lower lung zones
GGO associated with: - consolidations - nodules - septal thickening ("crazy paving" pattern)	Typical distribution; occasionally diffuse
DAD	Diffuse
Nodules or variable size	Multiple, may be solitary
Cysts	Extremely rare; when present are predominant in the upper lobes

GGO: ground-glass opacity.
DAD: diffuse alveolar damage.

gradient with more conspicuous consolidation in the posterior inferior regions of the lungs, may help in supporting diagnosis [64].

Peri-engraftment respiratory distress syndrome (PERDS) is a rare complication of both autologous and allogeneic HSCT, occurring within 5 days of engraftment. PERDS is caused by the release of pro-inflammatory cytokines, and manifests with skin rash, fever, and capillary leak, along with non-infectious pulmonary infiltrates with underlying DAD [65,66]. PERDS is part of the wide spectrum of idiopathic pneumopathies after HSCT which constitute the idiopathic pneumonia syndrome (IPS), a heterogeneous group of conditions in which the presence of DAD is by definition unrelated to infectious aetiologies, cardiac dysfunction, acute renal failure, and iatrogenic fluid overload [65]. HRCT findings of PERDS include bilateral GGO, peri-hilar or peribronchial consolidation, and thickening of the interlobular septa [66] (Fig. 12). When GGO is extensive, the HRCT appearance of PERDS may mimic other conditions presenting with ARDS, including PJP.

4.2.3. Diffuse alveolar haemorrhage (DAH)

DAH is a rare condition occurring in coagulation disorders, collagen-vascular diseases, drugs administration (e.g., bleomycin and citarabine), neoplasms, infections, and allogeneic HSCT as the effect of immune-mediated pulmonary vasculitis [67,68]. DAH complicating

Table 5
Synopsis of the typical HRCT findings of the most common infectious mimickers of Pneumocystis jirovecii pneumonia.

	Typical HRCT findings	Distribution
Viruses		
CMV	Bilateral GGO with unsharp demarcation + consolidations, septal thickening and small, random or centrilobular nodules +/- tree-in-bud and halo sign	Focal or diffuse, frequently involving the lower lobes; sparing of subpleural regions
Fungi		
Aspergillosis	Solitary or multiple nodules +/- halo sign, often with areas of wedge-shaped consolidation and/or GGO	Bilateral > unilateral nodules and GGO; pleural-based consolidation (i.e., haemorrhagic infarcts)
Bacteria		
VAP (Pseudomonas aeruginosa, Klebsiella spp., and other Enterobacteriaceae)	Consolidations, GGO, nodules and pleural effusion	Heterogeneous
Atypical pneumonias (Mycoplasma, Chlamydia)	Predominant GGO	Diffuse, bilateral

CMV: Cytomegalovirus.
GGO: ground-glass opacity.
VAP: ventilation-acquired pneumonia.

Table 6
Synopsis of the typical HRCT findings of the most common non-infectious mimickers of Pneumocystis jirovecii pneumonia.

	Typical HRCT findings	Distribution
Pulmonary oedema	GGO, smooth septal thickening, consolidations, pleural effusion	Bilateral, symmetric and gravitational
DAD	GGO, foci of consolidations with air bronchogram	Diffuse or heterogeneous
DAH	GGO +/- consolidations	Heterogeneous, bilateral, patchy or diffuse, often peri-hilar
Drug toxicity	GGO +/- interlobular septal thickening +/- consolidations	Variable, according to the predominant pattern (DAD, NSIP, OP, HP)

GGO: ground-glass opacity.
DAD: diffuse alveolar damage.
DAH: diffuse alveolar haemorrhage.
NSIP: non-specific interstitial pneumonia.
OP: organizing pneumonia.
HP: hypersensitivity pneumonitis.

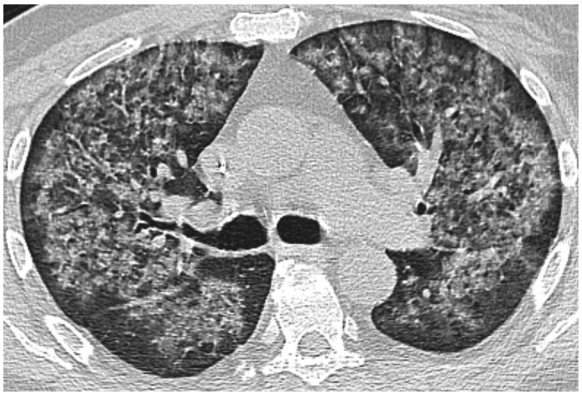

Fig. 8. Cytomegalovirus pneumonia in a 68-yrs-old man with acute myeloid leukaemia.
HRCT shows bilateral, extensive ground-glass opacities, with subpleural sparing.

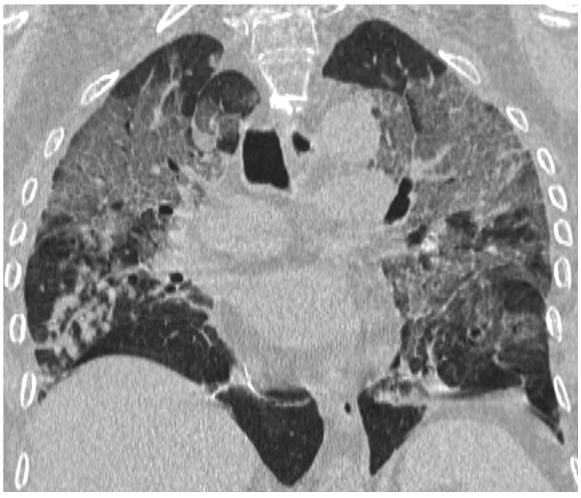

Fig. 9. Invasive aspergillosis in a 67-yrs-old woman previous treated with chemotherapy and radiation therapy for primary glioblastoma.
HRCT image reformatted on the coronal plane reveals bilateral, diffuse ground-glass opacities involving the upper lobes, and centrilobular nodules in the right lower lobe.

HSCT is routinely classified within IPS.

Clinical manifestations include sudden onset of cough, dyspnoea and hypoxemia, haemoptysis (up to 70% of patients), and iron-deficiency anaemia [69]. HRCT findings include bilateral, diffuse or patchy / lobular GGO and consolidations, often with peri-hilar distribution and sparing of the subpleural regions (Fig. 13). In the subacute phase, crazy paving pattern may occur as haemorrhagic material accumulates in the alveoli [70].

4.2.4. Drug toxicity

Sudden dyspnoea in the immunocompromised host may be the expression of drug-induced lung toxicity. HRCT pattern vary, including DAD, non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), and hypersensitivity pneumonitis (HP) [71]. Cleverley et al. showed that GGO is present in the large majority of patients with drug-induced lung disease (85% of total cases in their series), including cases with DAD, NSIP, OP, HP, and pulmonary eosinophilia [72] (Fig. 14).

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) that has been used in patients with cancer (i.e., renal cell carcinoma, breast cancer, and neuroendocrine tumours) and in kidney

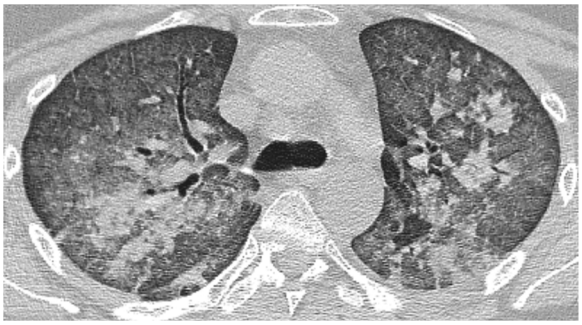

Fig. 10. *Streptococcus mitis* pneumonia in a 36-yrs-old woman with acute myeloid leukaemia, while undergoing conditioning chemotherapy for allogeneic haematopoietic stem cell transplantation (HSCT).
HRCT shows bilateral, diffuse ground-glass opacities and patchy consolidations.

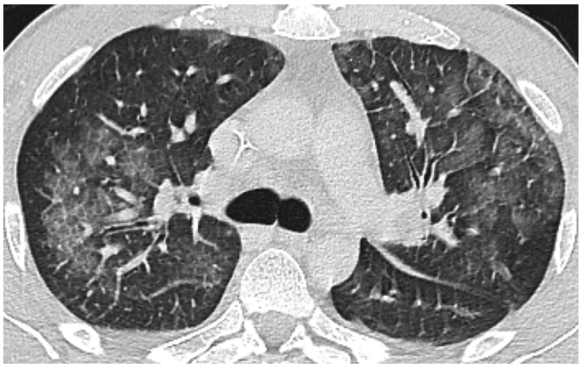

Fig. 11. Pulmonary oedema due to fluid overload in a 37-yrs-old man with chronic myeloid leukaemia in blastic phase.
HRCT shows bilateral, perihilar ground-glass opacities, along with smooth thickening of the interlobular septa and thickening of the left fissure.

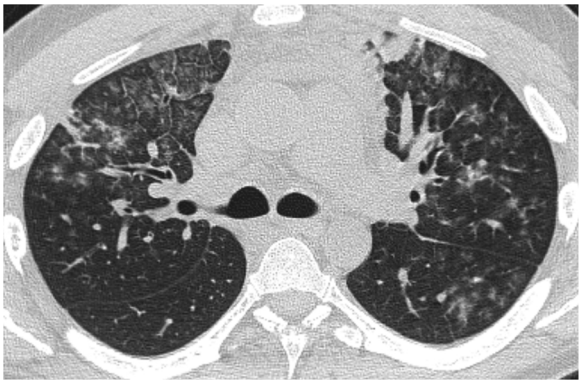

Fig. 12. Peri-engraftment respiratory distress syndrome (PERDS) in a 26-yrs-old man who presented with fever and progressively worsening dyspnoea, shortly after autologous haematopoietic stem cell transplantation (HSCT) for Hodgkin lymphoma.
HRCT shows bilateral ground-glass opacities with lobular distribution, mostly involving the upper lobes, associated with smooth thickening of the interlobular septa.

and heart transplant recipients (to prevent rejection). HRCT patterns include non-specific areas of GGO, multifocal areas of consolidation, patchy distribution of GGO accompanied by interlobular septal thickening, and extensive bilateral GGO or consolidation with traction bronchiectasis [73]. Everolimus administration increases the risk for PJP, thus making differential diagnosis with HRCT potentially challenging (Fig. 15). Serum β-D-glucan measurement and BAL fluid sampling may help in establishing the diagnosis [74].

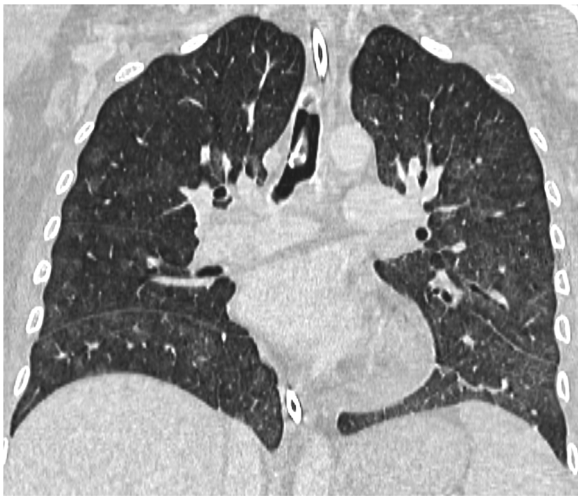

Fig. 13. Diffuse alveolar haemorrhage (DAH) in a 44-yrs-old woman who developed thrombotic thrombocytopenic purpura while undergoing chemotherapy for stage IV breast cancer.
HRCT image reformatted on the coronal plane reveals bilateral, lobular ground-glass opacities, with mosaic pattern.

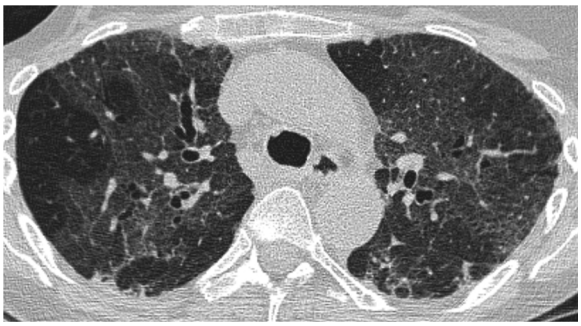

Fig. 14. Bleomycin-related fibrotic organizing pneumonia at early stage in a 59-yrs-old woman with Hodgkin lymphoma, treated with a combination of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD regimen).
HRCT shows bilateral ground-glass opacities-like pattern, associated to subtle signs of architectural distortion in both lungs.

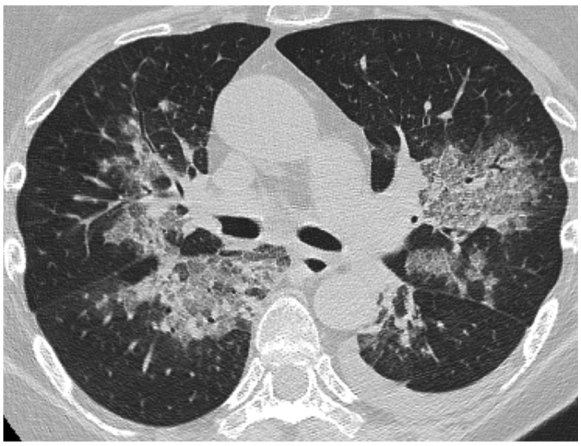

Fig. 15. Organizing pneumonia in a severely dyspnoeic 64-yrs-old woman receiving everolimus for stage IV breast cancer.
HRCT shows bilateral ground-glass opacities and consolidation with peribronchovascular distribution, defining a bronchocentric pattern of organizing pneumonia. The patient experienced rapid clinical improvement after withdrawal of everolimus, with subsequent resolution of HRCT findings (not shown).

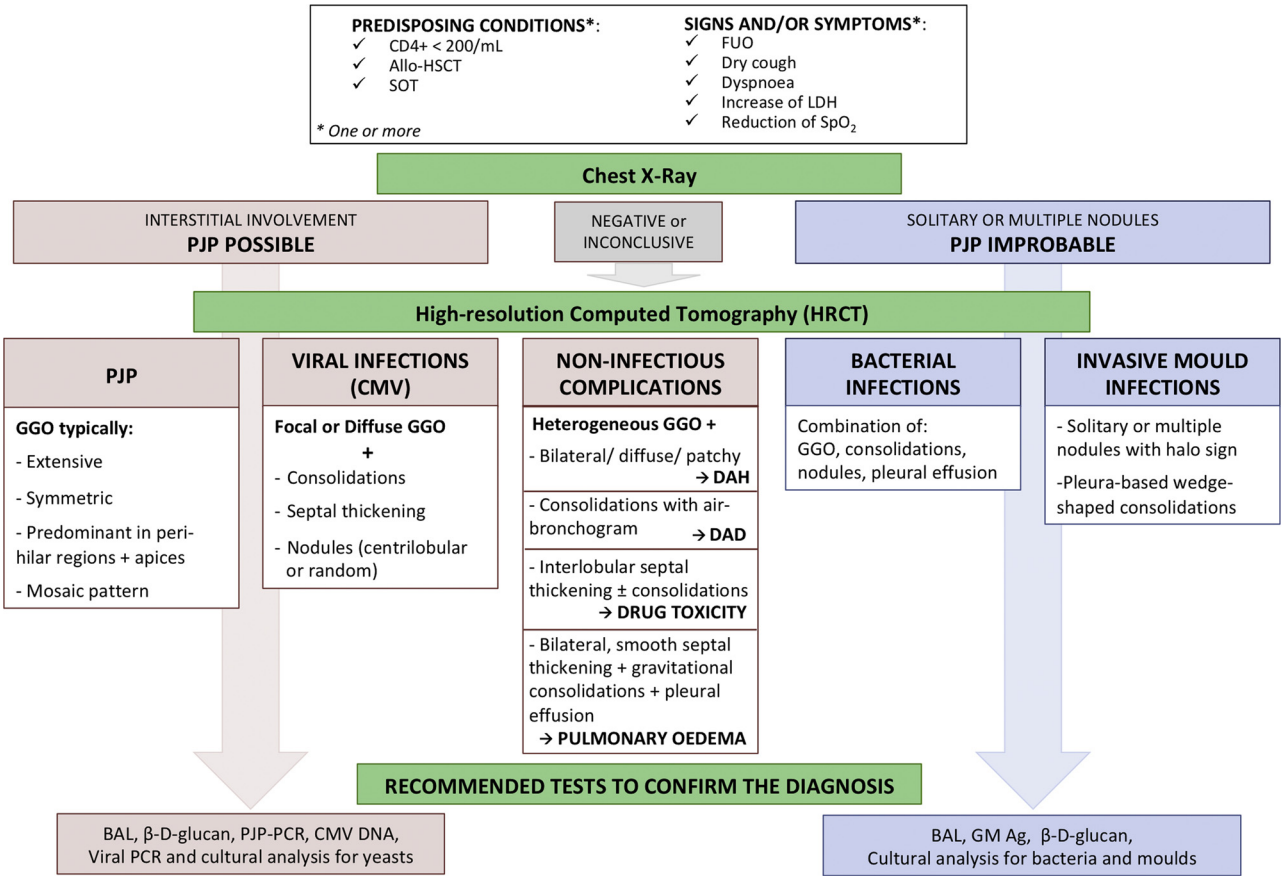

Fig. 16. Decision-tree algorithm combining clinical, laboratory and radiological findings for the evaluation of suspected Pneumocystis jirovecii pneumonia (PJP) in non-HIV immunocompromised patients.
Allo-HSCT: allogeneic hematopoietic stem cell transplantation
SOT: solid organ transplantation
FUO: fever of unknown origin
LDH: lactate dehydrogenase
GGO: ground-glass opacity
DAH: diffuse alveolar haemorrhage
DAD: diffuse alveolar damage
BAL: bronchoalveolar lavage
GM Ag: Galactomannan antigen

Idelalisib is an inhibitor of the B-cell receptor signalling pathway that has been recently approved for the treatment of chronic lymphocytic leukaemia and refractory follicular lymphoma. Cases of idelalisib-related pneumonitis have been reported, showing a diffuse GGO pattern at HRCT that can mimic PJP [75,76].

In order to guide the radiologist through the multifaceted clinical and radiological scenario of PJP and its differential diagnoses, we propose a decision-tree algorithm combining clinical, laboratory and HRCT findings (Fig. 16). Despite the inherent overlap among the described pathologic conditions, we believe that this algorithm could represent a valuable framework for the evaluation of suspected PJP in non-HIV immunocompromised patients.

5. Conclusions

In spite of improvement in outcome due to increasing use of specific chemoprophylaxis, PJP still remains a major complication in immunocompromised non-HIV patients, particularly those with haematological or solid-organ malignancy, and organ transplantation. HRCT findings are multifaceted, varying from the well-documented diffuse central ground glass opacity to more challenging patterns, related to less typical distribution and/or to less frequent features.

When approaching the immunocompromised patient with an acute mixed-density pattern at HRCT, the radiologist should consider the possibility of PJP, and be familiar with the wide spectrum of other infectious and non-infectious differential diagnoses. Clinical information (including causes/type/duration of the underlying immunological defect, clinical symptoms, and possible chemoprophylaxis for PJP) and laboratory findings (including serum LDH, β-D-glucan, CMV DNA, GM, and analyses on BAL fluid) are essential in helping to establish HRCT diagnosis of PJP.

Contribution

Study concepts: L. Cereser.
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Data acquisition: L. Cereser, A. Dallorto.
Quality control of data and algorithms: A. Candoni, S. Volpetti, E. Righi.
Data analysis and interpretation: N.A.
Statistical analysis: N.A.
Manuscript preparation: L. Cereser, A. Dallorto.
Manuscript editing: A. Candoni, S. Volpetti, E. Righi.
Manuscript review: R. Girometti, C. Zuiani.

Ethical approval for research

N.A.

Conflicts of interest

None.

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