Complicações e Recidiva num Doente com Linfoma do Manto: Um Caso Clínico

Complications and Relapse in a Mantle Cell Lymphoma Patient: A Case Report

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Resumo:

O linfoma do manto, um subtipo de linfoma de células B não-Hodgkin, é uma doença incurável com uma evolução clínica agressiva. Em doentes não elegíveis para transplante, os regimes de quimioterapia prolongam a sobrevida global e livre de progressão da doença, à custa de um aumento do risco de complicações infeciosas.

Os autores descrevem o caso de um homem de 73 anos, previamente diagnosticado com linfoma do manto, sob terapêutica de manutenção com rituximab, que se apresenta com uma série de complicações pulmonares infeciosas e não infeciosas. Um padrão radiológico com infiltrados pulmonares difusos e um nódulo solitário foram a manifestação de múltiplas patologias, e, em última análise, a evidência da progressão do linfoma do manto.

Neste caso, destaca-se que qualquer nova lesão pulmonar, num doente com linfoma ativo ou tratado, deve ser cuidadosamente avaliada para uma possível progressão ou recorrência da doença. Adicionalmente, os autores expõem a gestão complexa de um doente imunocomprometido com sucessivas infeções graves.

Palavras-chave: Linfoma de Célula do Manto; Pneumonia em Organização; Pneumopatias Fúngicas; SARS-CoV-2.

Abstract:

Mantle cell lymphoma, a subtype of B-cell non-Hodgkin lymphoma, is an incurable disease with an aggressive clinical course. In non-transplant eligible patients, chemotherapy regimens extend the overall and progression-free survival, at the expense of an increased risk of infectious complications.

The authors describe the case of a 73-year-old man, previously diagnosed with mantle cell lymphoma, under rituximab maintenance therapy, who presents with a series of infectious and non-infectious pulmonary complications. A radiological pattern of diffuse pulmonary infiltrates and a solitary nodule were the manifestations of multiple conditions, and, ultimately, the evidence for mantle cell lymphoma progression.

In this case, we recall that any new lung lesion in a known or treated case of lymphoma should be carefully evaluated for disease progression or recurrence. We also expose the intricate management of an immunocompromised patient with successive severe infections.

Keywords: Lymphoma, Mantle-Cell; Lung Diseases, Fungal; Organizing Pneumonia; SARS-CoV-2.

Introduction

Mantle cell lymphoma (MCL) is a unique subtype of lymphoma that accounts for approximately 5% of all non-Hodgkin lymphoma (NHL).[1]

The optimal treatment for non-transplant-eligible patients remains unclear, but recent investigation found excellent results with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), followed by rituximab maintenance therapy (RMT), with overall survival of 9.8 years. However, the disease remains uncurable and relapse in the first 24 months after diagnosis predicts an unfavorable prognosis.[2] Importantly, RMT extends the temporal frame with a high risk for infections, particularly in patients who develop hypogammaglobulinemia.[3]

This case report illustrates a series of infectious and non-infectious complications in a patient with mantle cell lymphoma undergoing RMT. The progression of the disease to the lung was confirmed, which has rarely been documented before.

Case Report

A 73-year-old man was diagnosed with stage IV MCL with bone marrow involvement, three years prior to the current presentation. Following six cycles of R-CHOP, a complete response was achieved. RMT was instituted and the eleventh cycle was administered three months before current presentation.

Two months before presentation he was diagnosed with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pneumonia and hospitalized for two weeks. The Computed tomography (CT) scan revealed extensive bilateral ground-glass

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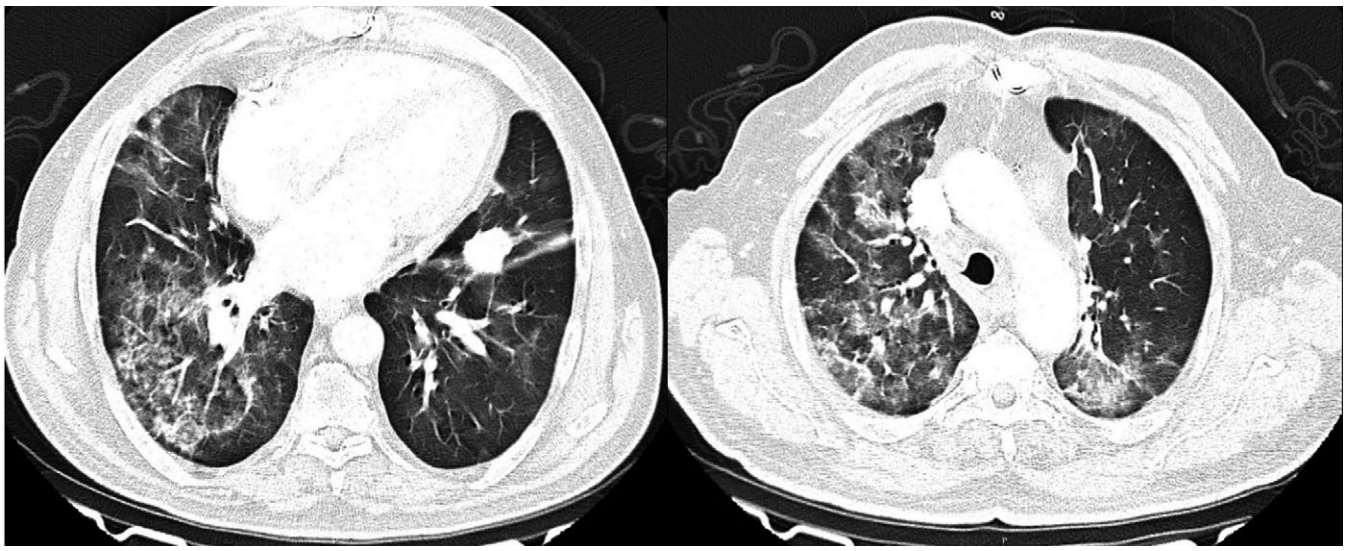

Figure 1: CT-scan of the thorax showing bilateral ground-glass opacities and consolidations extending all lung lobes. A lingular nodule with 29x24 mm causes segmental inferior bronchic narrowing. The patient was diagnosed with SARS-CoV-2 infection and suspected bacterial pneumonia.

opacities, consolidations and a lingular nodule (Fig. 1). Treatment involved intravenous (IV) dexamethasone 6 mg/day and piperacillin-tazobactam 4.5 g/6 hours for suspected concomitant bacterial infection. His condition failed to improve, and a flexible bronchoscopy (FB) was performed. The bronchoalveolar lavage (BAL) isolated a *Magnusiomyces capitatus* and cytology identified fungal hyphae. He tested positive for respiratory syncytial virus (RSV) warranting prescription of oseltamivir. Following a positive evolution, he was discharged home.

Six weeks post-discharge, he presented with asthenia, vespertine fever, dyspnea at rest and dry cough. Physical examination revealed respiratory distress, diffuse crackles on pulmonary auscultation and an oxygen saturation of 99% at room air. Blood tests indicated an elevated C-reactive protein (150 mg/dL) and a slightly increased procalcitonin (0.2 ug/L). CT scan showed new consolidations and ground-glass opacities (Fig. 2), with previous consolidation foci absent, raising suspicion about an organizing pneumonia (OP). The presumed diagnosis of a bacterial pneumonia with risk for multiresistant drug agents superimposed to an OP, prompted the initiation of meropenem 1 g/8 hours and prednisolone 40 mg/day. The patient was admitted to the internal medicine ward.

An extensive array of microbiological tests encompassing aerobic, anaerobic and fungal hemocultures, bacterial and mycobacterial sputum culture, respiratory virus antigen panel, legionella and pneumococcal urinary antigens was conducted. The sputum culture revealed an *Aspergillus fumigatus*, while the remaining tests failed to disclose any significant findings.

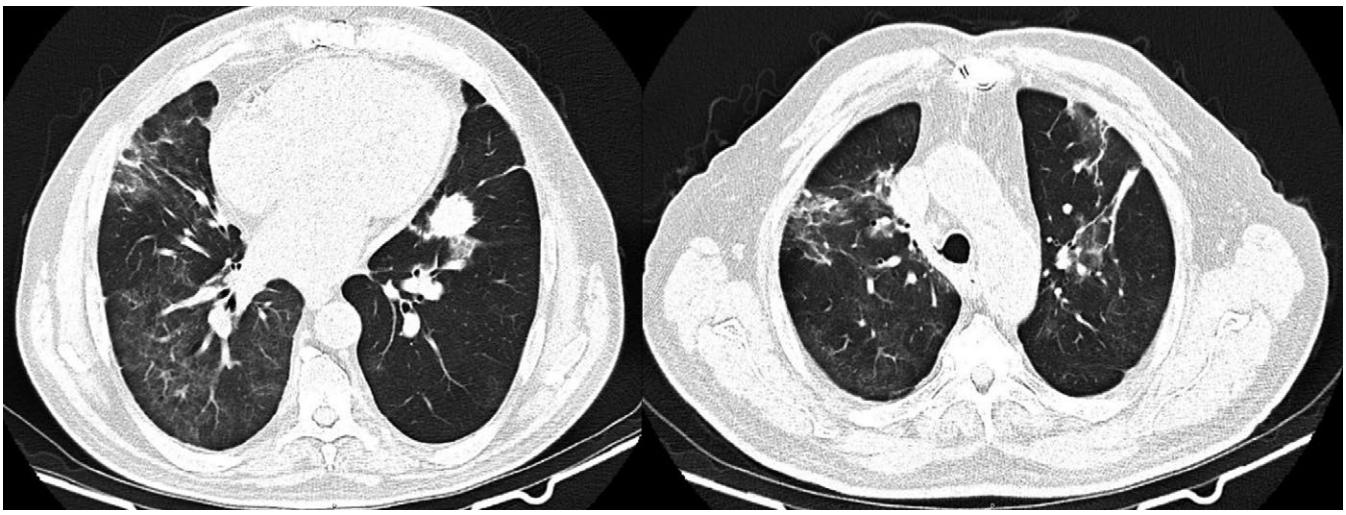

Figure 2: CT-scan of the thorax revealing new parenchymal consolidations and ground-glass opacities with a perilobular distribution. The consolidations previously described disappeared. The patient was diagnosed with bacterial pneumonia superimposed to an organizing pneumonia.

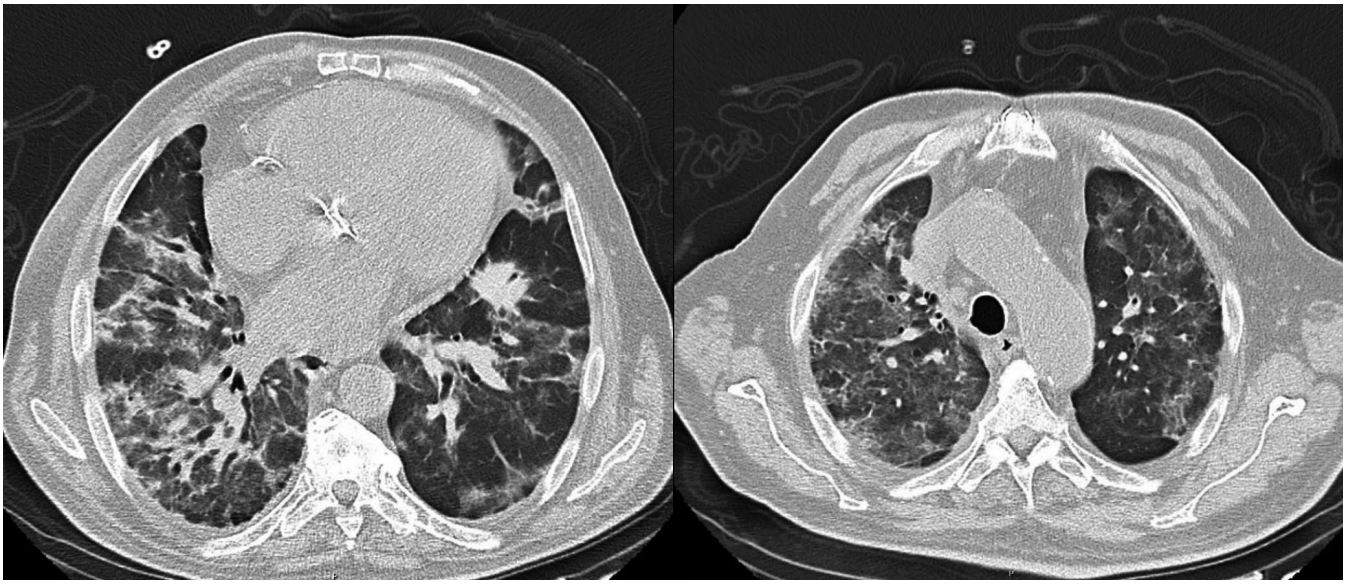

Figure 3: CT-scan of the thorax exposing exacerbated bilateral consolidations, diffuse ground-glass opacities and subpleural reticulation. The lingular nodule has larger dimensions compared with the previous exam (32x26 mm). The patient was diagnosed with SARS-CoV-2 reinfection.

Detection of *Aspergillus fumigatus*, and the previous identification of *Magnusiomyces capitatus*, prompted concerns of invasive fungal infection. Therefore, IV voriconazole 6 mg/kg/12 hours in combination with liposomal amphotericin B 5 mg/kg/12 hours were initiated.

Two weeks post-admission, the fever reappeared, and the respiratory failure persisted. A subsequent FB was conducted, wherein a transbronchial biopsy of the nodule was attempted. BAL isolated a KPC (*Klebsiella pneumonia* carbapenemase) producing *Klebsiella pneumoniae* which prompted the initiation of IV ceftazidime-avibactam 2.5 g/8 hours for nosocomial pneumonia. The lung nodule biopsy was inconclusive.

Two weeks later, the patient's condition deteriorated, and a SARS-CoV-2 infection was identified again. CT-scan showed exacerbated bilateral consolidations, diffuse ground-glass opacities and subpleural reticulation (Fig. 3). The lingular nodule increased in size. As systemic corticosteroid therapy was ongoing, IV remdesivir (loading dose 200 mg, followed by 100 mg/day) was added.

Despite slow clinical recovery, CT-scan showed clear improvement two weeks later (Fig. 4). At this point, a transthoracic

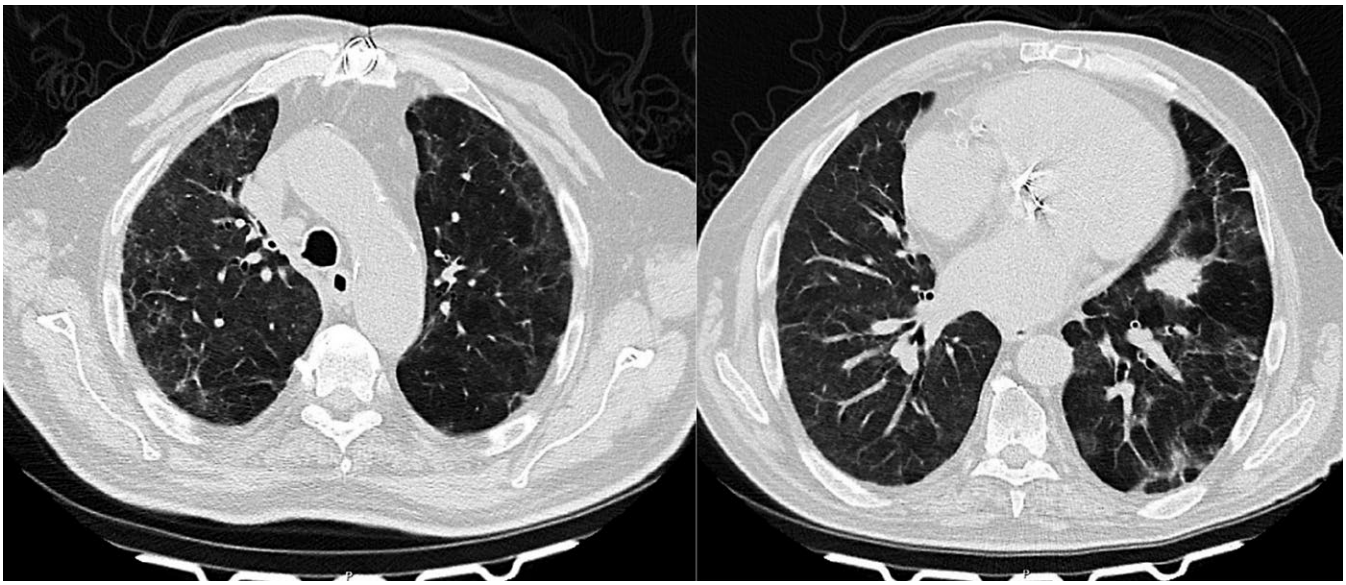

Figure 4: CT-scan of the thorax revealing diffuse ground-glass opacities less intense when compared with previous exam. The lingular nodule remained similar.

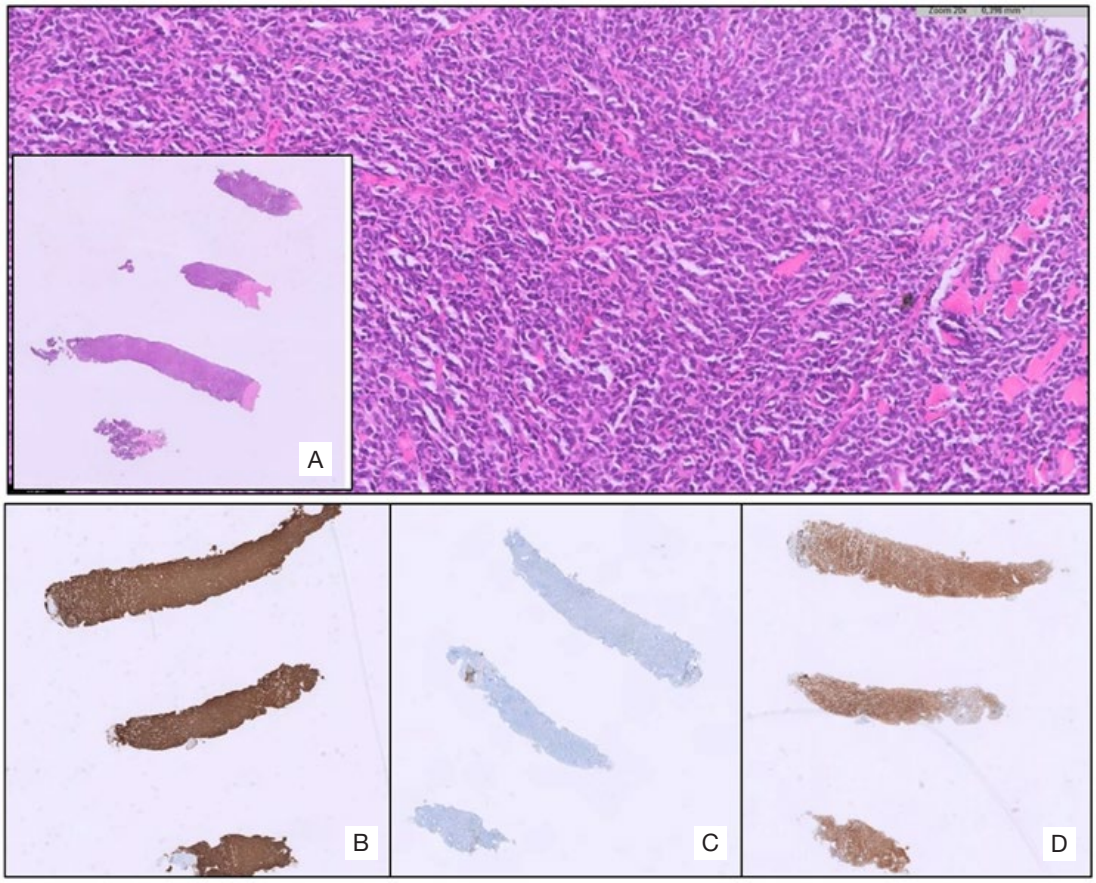

Figure 5: Fragments of needle core biopsy **(A)** showing lung parenchyma infiltrated by small lymphocytes **(B)**, CD20 positive **(C)**, CD3 negative **(D)**, with diffuse expression of cyclin D1 **(E)**. The diagnosis of a mantle cell lymphoma with pulmonary involvement was made.

biopsy was performed. The examination of the tissue sample revealed middle-sized lymphocytes with irregular nuclei and apoptotic bodies. The immunohistochemical staining showed positive results for CD20, cyclin D1, CD43, vimentin, and CD99, with an 80% Mib1/Ki75 proliferative index (Fig. 5). These findings were compatible with MCL.

Concurrently, the patient was diagnosed with herpetic encephalitis, complicated by ischemic central events. He passed away one week after the results of the pulmonary nodule biopsy were made available. The complex clinical course is summarized in Fig. 6.

Discussion

The approach to an immunocompromised patient with pulmonary radiographic abnormalities focuses on extensive exclusion of infection. An initial diagnosis of community acquired pneumonia (CAP) is questioned whenever the clinical resolution is incomplete or delayed in time. Differential diagnoses include opportunistic infectious agents, such as mycobacteria or fungus. However, non-infectious causes, such as neoplasia, drug toxicity, immunologic disorders, heart failure, and pulmonary embolism, should also be considered.

OP is an interstitial lung disease that causes injury to the alveolar wall. The cryptogenic form lacks a specific etiology, whereas the secondary form is associated with conditions such as infections, drug reactions, connective tissue disorders, neoplasms, or aspiration. The clinical presentation is unspecific and similar to that of a CAP. CT-scan typically shows bilateral peripheral consolidations and ground-glass opacities, that are migratory and regress spontaneously. A tissue biopsy is necessary for a definitive diagnosis. Treatment with corticosteroids showed an excellent response.[4] In this case, the diagnosis of an OP was supported by persistent respiratory symptoms, multiple recent infections, as well as pulmonary infiltrates that migrated over time. However, the response to corticosteroids was suboptimal and a solitary nodule is an infrequent presentation. The patient's medical history additionally suggested an OP secondary to a lymphoproliferative disorder.

A rare idiopathic interstitial pneumonia, referred to as acute fibrinous and organizing pneumoniae, was observed in immunocompromised patients undergoing radiotherapy or chemotherapy treatments. The typical radiological appearance are diffuse ground glass opacities and basal consolidations, but a nodular pattern, resembling our case, has also been described.[5]

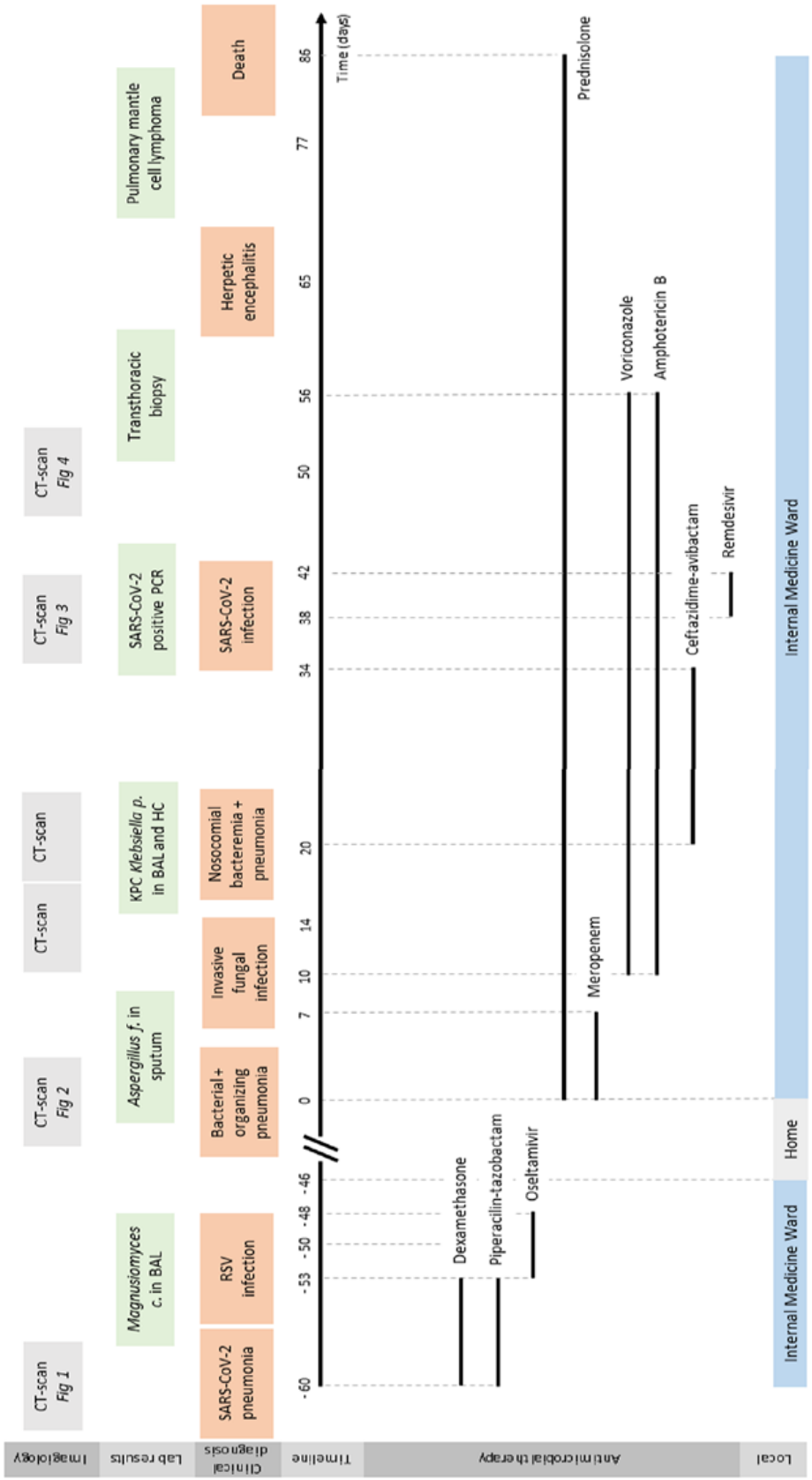

Figure 6: Timeline of the clinical course with information about the local, antimicrobial therapy, clinical diagnosis, laboratory results and imagiology exams.
BAL: bronchoalveolar lavage; CT: computed tomography; HC: hemocultures; Lab: Laboratory; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RSV: respiratory syncytial virus.

The identification of a mold, such as *Aspergillus*, causing invasive fungal disease (IFD), requires microscopic examination, culture of blood or other sterile product, or DNA detection in a tissue. The presence of at least one host factor, a clinical feature, and mycologic evidence is required for probable disease in immunocompromised patients.[6] In our case, the patient had a hematologic malignancy, pulmonary lobar consolidations, and two fungi detected on sputum, BAL, and microscopically, thus satisfying the criteria for IFD. Although the radiological findings could have raised suspicion about an eosinophilic pneumonia associated to aspergillosis, the hemogram and BAL differential cell count failed to confirm eosinophilia.

Magnusiomyces capitatus is an opportunistic pathogen for humans. Microscopically, the organism is a type of yeast capable of producing arthroconidia, hyphae, blastoconidia and pseudohyphae. Reports on systemic infections have primarily emerged from Mediterranean countries, and are linked to hematological malignancies that cause neutropenia.[7,8] The isolation of this yeast in a respiratory specimen of a neutropenic patient with pneumonia is indicative of probable infection. The most effective course of treatment is not yet established. Recent reviews confirm high activity of amphotericin B against this species and highlight a potential role of the new triazoles, particularly voriconazole.[8] Despite the absence of neutropenia, our patient had a hematologic malignancy undergoing RMT, exposure to systemic corticosteroids, a pulmonary nodule consistent with a fungal infection, and isolation in a sterile specimen, which reduces the likelihood of colonization. The initial detection of hyphae in the cytological analysis of BAL can indicate a morphological form of *Magnusiomyces capitatus*, although it is also consistent with the subsequently identified *Aspergillus fumigatus*.

Immunocompromised patients are particularly vulnerable to SARS-CoV-2 infection. An increased risk of hospitalization, intensive care unit admission and death has been consistently reported, even after complete vaccination.[9] The subgroup of patients with hematologic malignancies or on B-cell depleting agents displace an impaired adaptative humoral immunity, with prolonged viral shedding, viral rebound and chronic infection. It is difficult to treat as new viral mutations emerge over time.[10] In this case, the authors question whether the second SARS-CoV-2 infection was a reinfection or an exacerbation of a persistent, untreated, infection. The successive infectious complications, reflecting a severe degree of immunosuppression, seem to support the last hypothesis.

Rituximab rarely causes interstitial lung disease as a side effect, usually presenting as acute or subacute OP about 2 weeks after the last infusion, around the fourth cycle.[11] Our patient presented more than 3 months after receiving rituximab, which would be an atypical chronological course.

Pulmonary involvement in NHL at presentation is infrequent but increases to 24% over the course of the disease.[1] The most common radiological findings are solitary or multiple nodules, mass consolidations, alveolar or interstitial infiltrates, pleural effusions and mediastinal adenopathies.[12]

MCL is characterized by an initiation event of t(11;14)(q13;q32) translocation leading to cell cycle dysregulation and cyclin D1 overexpression. For the majority of patients, MCL is an incurable disease with an aggressive clinical course.[13] Extranodal progression is common, but, unlike other NHL, pulmonary involvement is exceedingly rare.[1] Due to the non-specific radiological features, any new lung lesion in a known or treated case of lymphoma should be carefully evaluated for disease progression or recurrence.[14]

Interestingly, herpetic encephalitis is not more frequent in the immunocompromised population. However, it progresses faster and has higher morbidity and mortality rates.[15]

After a complex series of infectious complications, the progression of mantle cell lymphoma to a rare location was confirmed in the histological sample of the lung nodule. The severe immunosuppression was ultimately attributed to the rituximab therapy, as well as the uncontrolled lymphoproliferative disease. ■

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Declaração de Contribuição

ALV – Desenho do artigo, pesquisa bibliográfica, redação e aprovação da versão final.
LNS – Redação e revisão do artigo.
PCF, RPR – Redação do artigo.
MM, RA – Revisão do artigo.
Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

ALV - Design of the article, bibliographical research, writing and approval of the final version.
LNS - Drafting and revising the article.
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