

Pneumologia

Impact of SARS-CoV-2 on lung cancer patient under immunotherapy

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Abstract

English:

Patients with lung cancer have an increased vulnerability to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection, and the association of the two diseases increases the severity of the infection. We present the case of a patient aged 72 years, a former 30 pack year (PA) smoker with 12 years withdrawal, and unvaccinated anti-SARS-CoV-2, with GOLD 2 COPD, hypertensive, recently diagnosed with left bronchopulmonary neoplasm and under immunotherapy. The patient had a fast-evolving SARS-COVID infection to a critical form, complicated with acute pulmonary embolism, nosocomial fungal infection, myelodysplastic syndrome, moderate multifactorial anaemic syndrome and heart disease. The unfavourable evolution of the patient's condition led to the temporary suspension of oncological treatment throughout the critical period, but without the progression of neoplastic disease. Although bronchopulmonary neoplasm emphasises the severity of SARS-CoV-2 infection, it is not mandatory to develop a harmful oncologic outcome without proper treatment, especially immunotherapy.

Keywords

bronchopulmonary cancer • COVID-19 • SARS-CoV-2

Influența Infecției Cu Virusul SARS COV2 Asupra Cancerului Pulmonar Sub Imunoterapie

Rezumat

Romanian:

Pacienții cu neoplasm pulmonar au o vulnerabilitate crescută față de infecția cu virus SARS-CoV2, asocierea celor două boli amplificând severitatea infecției. Prezentăm cazul unui pacient în vârstă de 72 de ani, fost fumător 30 pachete-an (PA), sevrat de 12 ani, nevaccinat anti SARS-CoV-2, cu BPOC stadiul II GOLD, hipertensiune arterială, diagnosticat recent cu neoplasm bronhopulmonar stâng, sub imunoterapie. Pacientul a prezentat o infecție SARS-CoV2 cu evoluție rapidă către o formă critică complicată cu embolie pulmonară acută, infecție fungică nosocomială, sindrom mielodisplazic, sindrom anemic moderat, multifactorial și afectare cardiacă. Evoluția nefavorabilă a stării pacientului a dus la suspendarea temporară a tratamentului oncologic pe toată perioada critică, însă fără progresia bolii neoplazice. Deși neoplasmul bronhopulmonar potențează severitatea infecției SARS-CoV-2, nu este obligatorie și evoluția oncologică nefastă în lipsa tratamentului corespunzător, în special al imunoterapiei.

Cuvinte-cheie

neoplasm bronhopulmonar • COVID-19 • SARS – CoV-2

Introduction

The impact of the COVID-19 pandemic in the oncology field means increased attention as a result of the newly identified comprehensive relationship between the two diseases (1). The most affected oncological patients were by far the ones

with lung cancer. The factors that put them at risk of severe COVID-19 were their advanced age (median age >65 ani), smoking status and having been diagnosed with concurrent obstructive or restrictive pulmonary diseases (2–4).

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Furthermore, the presence of the aberrant expression of the functional angiotensin-converting enzyme 2 (ACE2) found in the malignant tissues of lung cancer, compared with the normal tissues, regardless of the stage of disease, makes this population of patients more vulnerable to COVID-19 (5–8).

Immunodepression is another main feature of bronchopulmonary cancer (BPC). The T cells that target and suppress the cancerous cells can become functionally drained in neoplastic tissue due to the persistent stimulation by the proinflammatory cytokines in the tumour microenvironment (9). Immunodepression is further emphasised by the fact that tumour cells have the capability to target and specifically deactivate the T cells that target cancer by an increased level of CTLA-4 and PD1; these markers of cellular depletion also function as inhibitors of activity, proliferation and survival of T cells, ultimately leading to immune suppression.

From the clinical point of view, the increased expression of PD1 ligand on the cancerous cells is associated with a significantly worse prognosis in patients diagnosed with BPC (10).

Therefore, the association of COVID-19 infection with acute respiratory distress syndrome (ARDS) and BCP shows that aberrant inflammation and immune dysregulation seem to play an important role in increasing the severe form of these two diseases. An increased inflammatory condition, characterised by monitoring the interleukin-6 (IL-6) and C-reactive protein (PCR) parameters, shows a negative prognosis for these patients (11).

Case description

We present a case of a 72-year-old patient, a former smoker of 30 packs per year (PA), who had quit the smoking habit 12 years ago, and who has had exposure to respiratory occupational pollutants in the field of construction materials for 45 years. The patient was unvaccinated against the SARS-CoV-2 infection.

The patient was also known with GOLD 2 COPD, B class of risk with a 4-year anticholinergic/beta-2 adrenergic (LAMA LABA) treatment, hypertension and seasonal allergic rhinitis (with a sensibility to *Ambrosia elatior*; under intermittent treatment with levocetirizine for 2 years).

The related symptoms were cough with mucopurulent expectoration, weight loss (≈10 kg in the last month) and moderate exertion dyspnoea onset for approximately 3 months. He followed repetitive drug treatments, following several consultations in the ambulatory unit, without any improvement.

Owing to the persistence of symptoms despite treatment as aforementioned, the patient had decided to present himself at the emergency department of our pulmonology service.

At the submission date, the physical examination revealed a patient with affected general status, afebrile, ECOG score = 1, BMI = 26.5 kg/m², bilateral vesicular murmur with discrete bronchial rales, equidistant equipotent heart sounds, without increased cardiac murmurs, without leg oedema and with normal vital signs (BP = 130/80 mmHg, AV = 78 bpm, SpO₂ = 95% at rest).

He was subject to a chest chemotherapy (CT) with contrast substance in the ambulatory unit that revealed a tumoural process with infiltrative edges at the bifurcation of the left primitive pulmonary bronchi with extension to the lobular bronchi almost completely obstructed. Mediastinal adenopathy close to 1 cm, located at the level of the left hilar and precarinal region, was also associated (Figure 1). The chest CT was completed with a cerebral and abdominal CT, which did not detect distant lesions. The biological parameters were normal.

Lung function tests revealed a mixed ventilatory dysfunction (FEV1 = 73.7% pred), with moderately decreased diffusing capacity for carbon monoxide (DLCO = 56.3% pred). In the case of possible surgery, a cardiopulmonary effort test (CPET) was also performed. The CPET showed a slightly reduced exercise tolerance, due to impaired ventilation, but with the maximum value of oxygen consumption (VO₂ peak = 17.52 mL/min/kg) allowing to perform the pulmonary resection. The ECG and echocardiography were within normal limits.

The fibrobronchoscopy identified, at the primitive left bronchus, an infiltrate starting from the fourth posteromedial cartilage and a tumoural process that completely obstructed the distal portion. At this point, a biopsy sample and a bronchial aspirate were harvested for cytological examination, tuberculosis and bacterial flora.

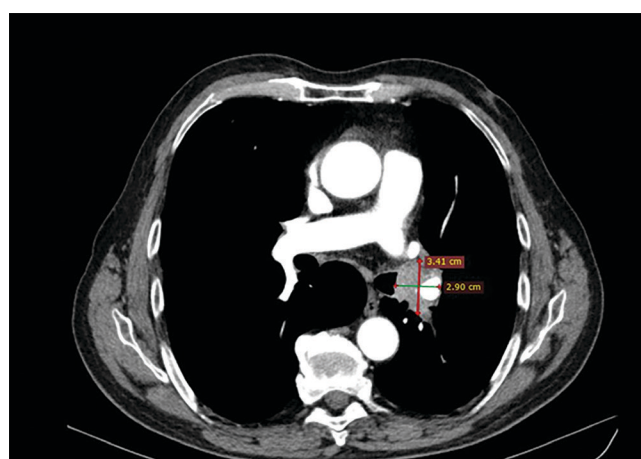
The cytologic examination revealed a neoplastic cell population, and the bronchial biopsy confirmed a grade 2 squamous cell carcinoma. The bacteriological examination was negative for imposed infections.

The anatomopathological examination was completed with the immunohistochemical test, which showed the presence of PDL-1 in up to 70%. The genetic tests for EGFR, ALK and ROS-1 were not performed due to the patient's smoking history.

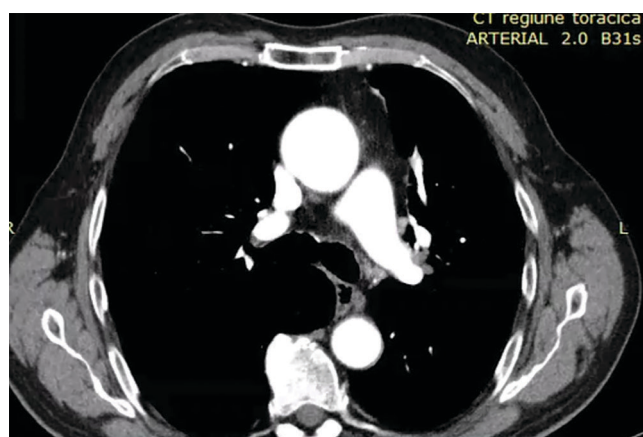
Finally, the patient was diagnosed with left hilar squamous bronchopulmonary carcinoma stage IIIa (T2aN2M0) with PDL-1 positive in up to 70%.

Since the patient declined the surgery during the pandemic period, pulmonary resection was postponed.

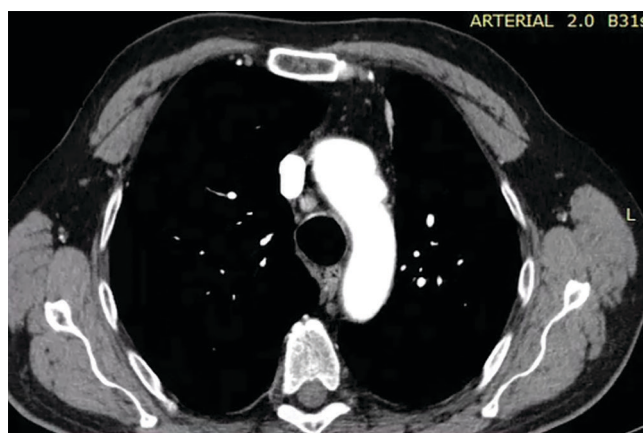
In this context, the patient was referred to an oncologist, where curative treatment was initiated – platinum salt-based neoadjuvant polychemotherapy (four series of gemcitabine and carboplatin), which was well tolerated. The evolution was marked by worsening dyspnoea, by an atelectatic syndrome at the left Fowler's segment and by the appearance of two



(A)



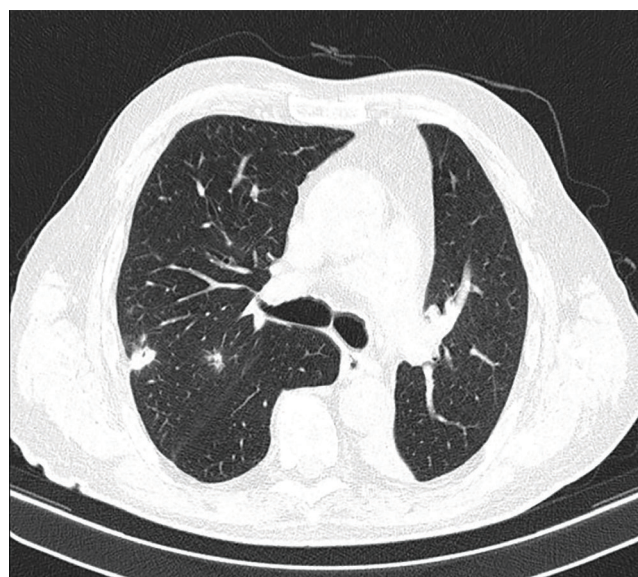
(B)



(C)

Figure 1. Chest CT with contrast substance (15 April 2020). (A) Expansive tissular process with infiltrative edges with inhomogeneous iodophilic infiltration with a maximum axial diameter approx. 3 cm, localised at the bifurcation of the left primitive pulmonary bronchi with extension to the lobular bronchi almost completely obstructed; (B) mediastinal adenopathy close to 1 cm located at the level of the left hilar and (C) precarinal region. CT, computer tomography.

pulmonary nodules of 24/19 mm and 18/11 mm, respectively, at the anterior and posterior right superior lobar segments (Figure 2). The tumour was restadialised in stage IV and the oncologist's orientation was towards another treatment. Owing to the presence of positive PDL-1, the systemic treatment based on immunotherapy (nivolumab 240 mg) was initiated every 2 weeks, associated with radiotherapy (RT)



(A)



(B)

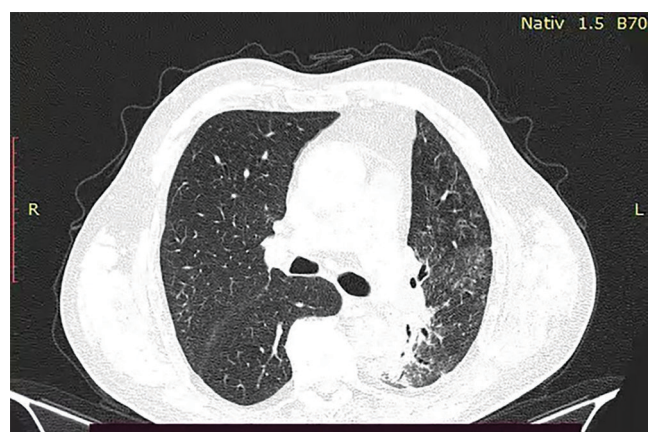
Figure 2. Chest CT with contrast substance (15 September 2020). (A) Pulmonary nodules of 24/19 mm and 18/11 mm, respectively, at the anterior and posterior segments of the right superior pulmonary lobe; (B) dimensional regression of the left hilar tumoural formation (20/14 mm), but with atelectasis of the Fowler segment; unchanged adenopathy. CT, computer tomography.

for the symptomatic atelectatic syndrome (IMRT – VMAT technique, DT = 39 Gy). The tolerance was good, marked by dimensional regression of the tumour, with a reduction of the atelectatic process in the left Fowler segment, and the disappearance of the two nodules, but without changing the size of the adenopathy (Figure 3).

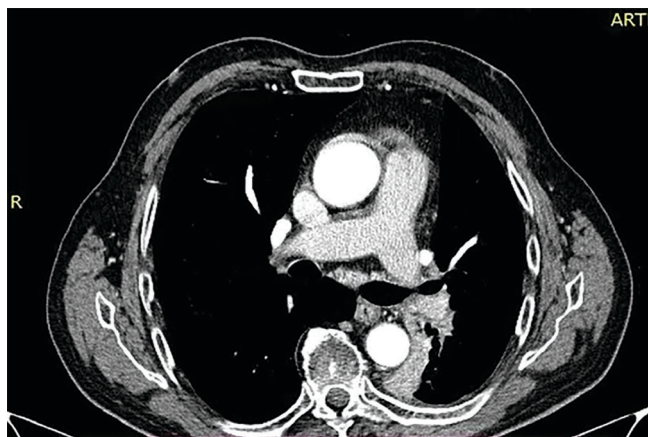
The oncological evolution was favourable, but in March 2021 the patient was confirmed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection, with

persistent symptoms for about 5 days (odynophagia, chills, fatigue), for which he received symptomatic treatment at home. The patient's condition worsened at home, with a $\text{SaO}_2 = 85\%$ in ambient air at rest, which led to hospitalisation in the intensive care unit, in order to correct the marked desaturation. From the chest CT scan, bilateral pulmonary lesions could be discerned, a discovery of significance in the context of COVID pneumonia, seeing that it has affected approximately 50% of the parenchyma (Figure 4).

The biological evaluation revealed lymphopaenia, thrombocytopenia, moderate multifactorial anaemia, biological inflammatory syndrome, liver cytolysis syndrome, elevated muscle cytolysis enzymes, nitrate retention, mild hypocalcaemia, hypokalaemia, hypoalbuminemia, hyperglycaemia, increased

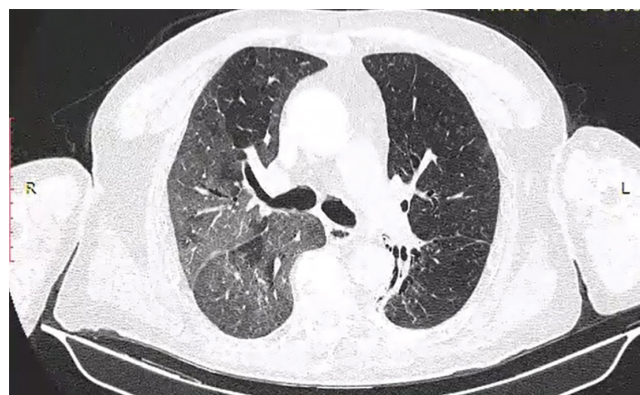


(A)

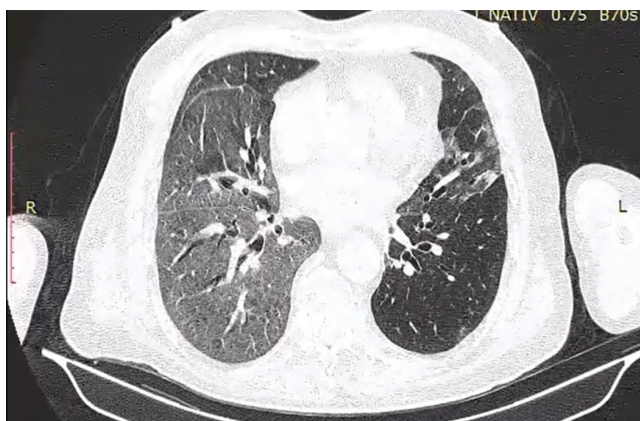


(B)

Figure 3. Chest CT with contrast substance (11 January 2021). (A) Dimensional regression of the tissue expansive process located at the bifurcation of the left main bronchi; reduction of the atelectatic process at the level of the left Fowler's segment, currently partially aerated; the disappearance of the bilateral pulmonary nodules from the previous examination; minimal areas of infiltration are presented in ground glass; extensive ground glass infiltration areas at the level of the left pulmonary parenchyma; (B) mediastinal adenopathy located in the left hilar (maximum 9 mm), precarinal (maximum 10 mm) unchanged. No pleural or pericardial effusion. The pulmonary arterial and venous vascular axes are homogeneously opacified with contrast material on their segments. CT, computer tomography.



(A)



(B)

Figure 4. Chest CT with contrast substance (26 March 2021). (A) Middle third parenchymal window and (B) lower third parenchymal window. Ground glass appearance lesions at the level of both lungs' parenchyma, more extensive in the right lung field; without areas of pulmonary consolidation; mediastinum in normal position; without mediastinal adenopathy; without pericardial or pleural fluid accumulations. CT, computer tomography.

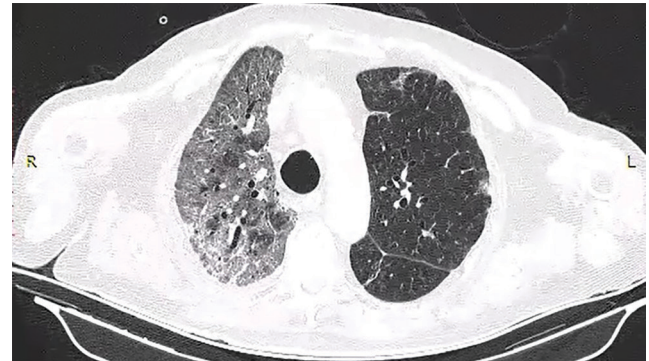
D-dimer (positive >20 Ug/mL) and an increase of red cell distribution width (RDW) up to 15.40% (normal value 11%–15%). The increase in IL-6 and PCR is directly related to the level of systemic inflammation impacting oncology disease progression. In Graphics 1A and 1B, we see values increase in PCR to 231.97 mg/L and IL-6 to 65.49 pg/mL respectively with a gradual descent (record during the period of infection with the SARS-CoV-2 virus).

Corroborating the clinical, biological and imaging data (Figure 5), the patient was treated as a case of acute hypoxemic respiratory failure associated with bronchopneumonia as a result of infection with the SARS-CoV-2. Non-invasive ventilation was initiated for a period of 3 weeks, and also initiated were antiviral therapy with remdesivir, antibiotic therapy (levofloxacin and carbapenem), anticoagulant therapy in a prophylactic dose (fondaparinux followed by enoxaparin sodium), corticosteroid therapy, rapid insulin therapy in doses adjusted according to glycaemic levels, personal cardiac medication, rehydration solutions, hydro electrolytes and oxygen therapy.

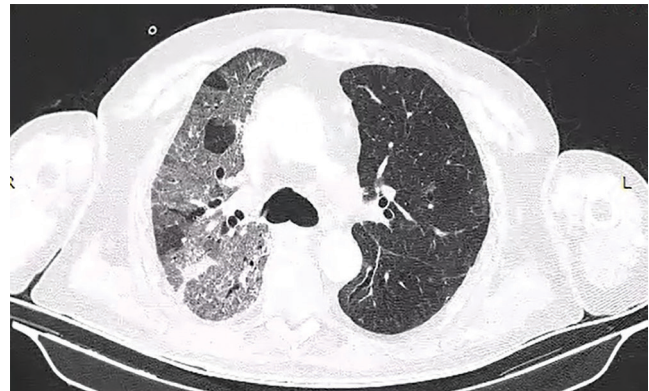
Although the therapy was maximal, the clinical progression was unfavourable, with the persistence of dyspnoea, the fact that imposes an imaging reassessment to exclude the pulmonary thromboembolism, pneumomediastinum or pneumothorax. The lung lesions from COVID-19 pneumonia are more extensive at the level of the right lung field, which is affected by approximately 90% (Figure 6).

The patient presented a worsening respiratory failure, with SaO_2 of 75% with 4 L/min during a chill without fever. Two sets of blood cultures were collected, isolating the germs of *Candida parapsilosis* and *Staphylococcus epidermidis*, sensitive according to the antibiogram to fluconazole and voriconazole. Antifungal treatment with fluconazole was added to the medication regimen. Oxygen therapy was instituted with a high-flow nasal cannula (HFNC) with a flow of 60 L with a FiO_2 of 51% for a SaO_2 of 95%.

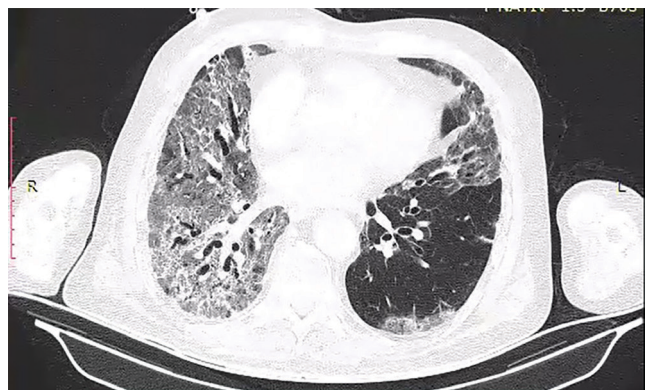
A tachycardic episode (170 bpm) lasting 3–5 min was caught on the monitor. An ECG was performed, revealing a slow-fast type nodal entrance to atrioventricular tachycardia with an AV of 180/min, with retrograde P wave in DI, DII, DIII and aVF. Also, left ventricular hypertrophy with ST repolarisation in V1–V5 was present. Beta-blocker was administered with a dose of 5 mg/day and continued until discharge from the hospital.



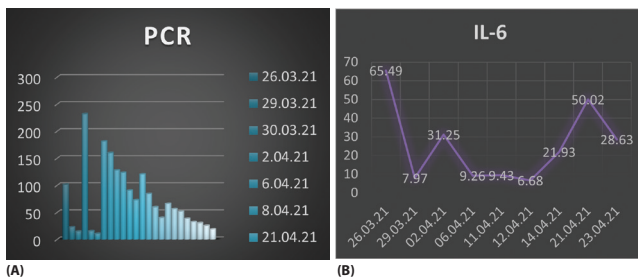
(A)



(B)

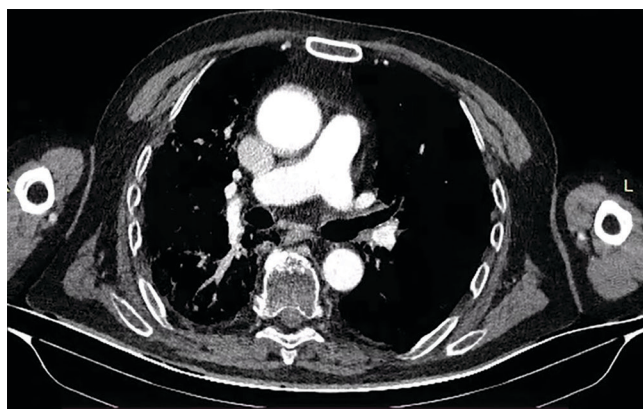


(C)



Graphics 1. Progression of levels of (A) PCR and (B) IL-6 during COVID-19 infection. (A) PCR progression and (B) IL-6 progression. IL-6, interleukin-6; PCR, C-reactive protein.

Continued.



(D)

Figure 5. Chest CT with contrast substance (12 April 2021). (A) Parenchymal window – upper third, (B) mediastinal window – middle third, and (C) parenchymal window – lower third. Compared with the examination performed on 26 March 2021: progression of lung lesions compatible with COVID-19, both dimensionally and in density (with global damage estimated at up to 60%); associated bronchial ectasias; no pulmonary nodular images suspicious for tumour substrate; (D) mediastinal window – without mediastinal adenopathy; without pleural or pericardial fluid; without lacunar punctiform intraluminal pulmonary arterial bilateral images, segmental ramifications, compatible for micro thrombosis. CT, computer tomography.

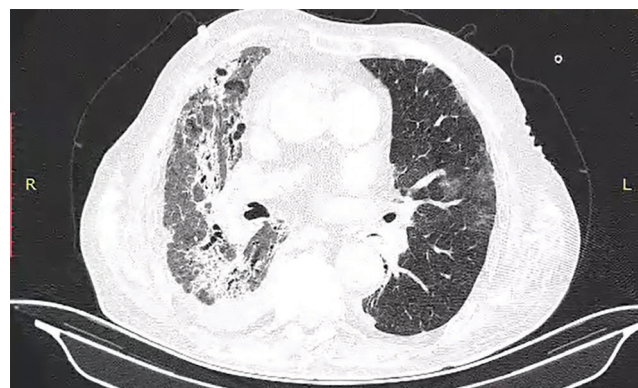
The progression of the anaemia was fluctuating with variations between 9.5 g/dL and 6.8 g/dL. The patient required two transfusions due to the absence of a source of bleeding, without intramuscular hematomas, and with negative repeated tests for occult haemorrhages.

Although the patient had an indication for anticoagulation in a therapeutic dose, low-weight heparin (LMWH) was administered first, in a prophylactic dose due to thrombocytopenia. On the background of the thrombocytopenia improvement and of high values of D-dimers, the dose of HGGM was increased to the therapeutic dose.

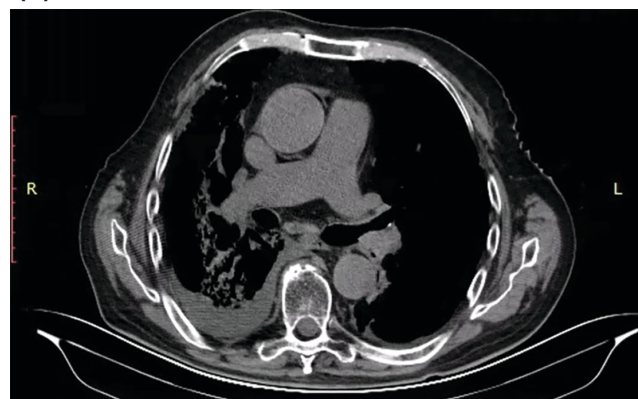
The hypoxemia progressively improved, with HFNC suppression and oxygen demand of 1–2 L/min by nasal cannula on successive days. Subsequently, both the ambient and the rest saturations became $\geq 95\%$, although accompanied by slight desaturation on exertion, and accordingly the need for further external oxygen supplementation was obviated.

On the 59th day of hospitalisation, the patient, characterised by respiratory and hemodynamic stability, was discharged; and at that time, the following diagnoses were noted: bilateral SARS-CoV-2 pneumonia – critical clinical form; remitted acute hypoxemic respiratory failure; left bronchopulmonary neoplasm; pulmonary thromboembolism and nosocomial infection with *S. epidermidis* and *C. parapsilosis*.

After the COVID infection episode, the patient again underwent the thoracic CT scan, which revealed an absence



(A)



(B)

Figure 6. Chest CT with contrast substance (28 April 2021). (A) The lung lesions from COVID-19 pneumonia are more extensive at the level of the right lung field, which is affected by approximately 90%; the appearance of the lesions is slightly modified, denser in LSD and associated with more obvious traction bronchiectasis; global lung damage remains at approximately 60%; (B) without mediastinal adenopathy; no visible vacuum filling defect; right pleural fluid accumulation with a thickness of approximately 1.7 cm. CT, computer tomography; LSD, lobe inferior drept.

of the tumour process and left atelectasis, as well as an improvement of the postcovid parenchymatous infiltrations (Figure 7). The oncological treatment (immunotherapy) was resumed 3 months after its interruption. Further, the clinical and radiological evolution was favourable, with good tolerance (Figure 8).

Discussion

Over the past 3 years, studies have shown that patients with lung cancer have a higher sensitivity for SARS-CoV-2 infection, compared to people without associated pathologies. From the specialised literature, we have selected some papers with a theme related to the present case.

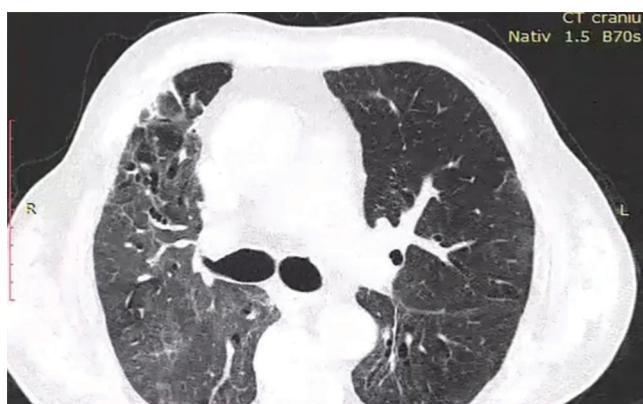


Figure 7. Chest CT with contrast substance (30 June 2021). The tumoural process at the level of the bifurcation of the left main bronchi is no longer obviously perceptible and only parietal thickening at the level of the lower lobar bronchi can be noticed, without its obstruction; the atelectatic process at the LIS level almost completely disappears; ground glass infiltrations are in the right lung parenchyma with reduction of the pre-existing ones on the left side. CT, computer tomography; LIS, lobe inferior stang.

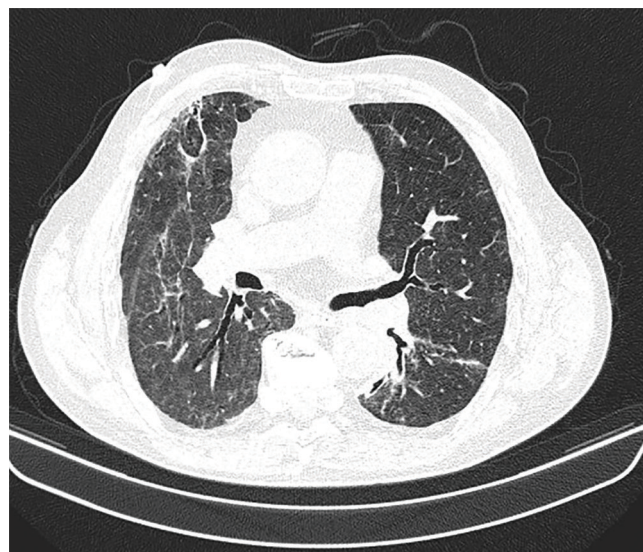


Figure 8. Chest CT with contrast substance (21 October 2022). Compared to the previous chest CT carried out on 30 June 2021, the image reveals a favourable evolution with discrete densifications in a band. CT, computer tomography.

The risk factors associated with worsening COVID-19 outcomes in cancer patients were age over 65 years, comorbidities, smoking history and male gender.

The results of the TERA-VOLT study, conducted in 200 patients with thoracic malignancies and concurrent infection with COVID-19, demonstrate that smoking status and chronic obstructive pulmonary disease (COPD) were the main

predictive factors of the severity of SARS-CoV-2 infection. The preliminary results have shown a mortality rate of 33% (3). Our patient was 72 years old, had a diagnosis of COPD and also had a history of smoking that justifies this predisposition to a severe form of infection with SARS-CoV-2.

In the two large-scale studies realised by Chavez-MacGregor et al. (12) and Provencio et al. (13), CBP was associated with increased mortality due to COVID-19. Moreover, the patients with cancer had also more frequently severe COVID-19, with higher rates of hospitalisation and mechanical ventilation treatment than patients without cancer. Our patient, with a severe form of SARS-CoV-2 infection, also benefited from non-invasive ventilation in the intensive care unit for a period of 3 weeks.

We do not identify studies in the literature from this field that can prove an influence of oncological treatment on COVID-19, within therapies such as immunotherapy, targeted therapies, hormonal therapies and surgical resections.

On the other hand, chemotherapy (CT) and RT seem to have a negative impact on the evolution of patients with COVID infection (12,14).

In their researches, Sharafeldin et al. (14) (in an N3C report) and Chavez-MacGregor et al. (12) observed a significantly increased mortality in COVID-19 patients with recent CT compared to other studies (3,13,15,16). One meta-analysis showed that recent CT treatment increased the risk of COVID-19 mortality only in patients with haematological malignancies compared to solid tumour malignancies (17). This difference could be explained by the additive myelosuppressive effects of both haematological cancers and CT, which significantly increase the risk of lymphopaenia. Lymphopaenia has been identified as a major independent risk factor for COVID-19, as it could prevent adequate immune function against SARS-CoV-2 (18).

A significant association was identified also between severe COVID-19 and recent RT (12). It was noted that high doses of RT increase the risk of lymphopaenia in patients with advanced non-small cell lung cancer (NSCLC) (19,20).

Our patient received RT and CT in 2020 and presented with lymphopaenia, but we believe that the time between the two events (CT/RT and COVID-19) was too long to be able to accurately establish a cause-effect relationship.

Related to inflammation in lung cancer, it is known that can play a pivotal role in tumorigenesis and cancer progression (21). High serum levels of inflammatory markers such as IL-6, or PCR are associated with worse prognosis in NSCLC (22,23). Therefore, an increase in IL-6 was correlated with a lower 24-month survival rate and a more advanced tumour stage (23). Moreover, it was shown that IL-6 may herald the predisposition to CBP metastasis (24). Our patient presented high values of IL-6 in stage IV of PBC and this circumstance did not lead to the progression of the oncological disease.

Generally, stopping the oncological treatment has a negative effect on neoplastic diseases (25,26). Van Hanren et al. (27) ascertained a significant increase in suspected lung nodules following the screening program's restart in the hospital systems, from 8% before the pandemic period to 29% during the pandemic period. In our patient, it was necessary to interrupt his oncological treatment for a period of 3 months, during the COVID-19 infection. In this context, the lack of progression of the oncological disease could be explained by the long-term effect of immunotherapy compared to other types of oncological treatments (28,29). On the other hand, the patient did not experience interstitial changes in the context of immunotherapy, as described in some studies (30,31).

The lack of progression of neoplastic disease in the absence of oncological treatment in a patient with a severe form of COVID infection was considered a particularity of this case. Moreover, neither COVID infection nor immunotherapy led to important fibrous changes in the lung parenchyma.

Conclusions

Our case report demonstrates that, although there are several arguments in favour of the potentiation of SARS-CoV-2 viral infection in lung cancer patients, it is not always a rule to have neoplastic disease progression during COVID infection, especially in the context of immunotherapeutic treatment. However, interdisciplinary collaboration remains the key to managing these two pathologies, one acute and the other chronic.

Funding

None.

Authors' contributions

AAF and IEG have contributed equally to this work.

Conflicts of interest

The authors declare that no conflict of interest exists in relation to the present research.

Institutional review board statement

Not applicable.

Informed consent statement

Informed consent was obtained from the patient involved in the study.

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