

Haemodialysed patient with lung cancer in the COVID-19 era: a clinical challenge

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SUMMARY

A 66-year-old man was referred to the oncological pneumology consultation due to a mass in the right upper lobe observed in a routine X-ray of the chest. The CT scan confirmed a mass in the same location. The biopsy revealed a lung adenocarcinoma. It was decided to start chemotherapy adapted to kidney function. In April 2020, the patient contracted SARS-CoV-2 infection and developed bilateral pneumonia with partial respiratory failure. He was transferred to the intensive care unit, where he had a positive evolution. In the next 5 months, there was a clinical improvement; however, the CT scan of the chest showed disease progression. After a new multidisciplinary approach, it was decided to start a second line with atezolizumab. After four cycles of atezolizumab, there was a clear clinical improvement, and a reduction by more than 50% in the tumour size, without significant adverse effects.

BACKGROUND

COVID-19, caused by the SARS-CoV-2, was considered pandemic in March 2020. One year later, more than 120 million cases had been reported across the world, and more than 2.5 million people died.¹ In January 2021, Portugal became one of the most affected countries worldwide concerning the number of new cases per million inhabitants, exceeding 16 000 daily cases.²

Patients with lung cancer, given their commitment to underlying lung function, represent a particularly vulnerable group to COVID-19. Furthermore, the most common symptoms of COVID-19 and lung cancer, such as cough and dyspnoea, can overlap, thus delaying diagnosis. The most common imagiological changes of COVID-19 can also be confused with those caused by pneumonitis associated with immunotherapy, tyrosine kinase inhibitors (TKIs), and radiotherapy (RT).³

Renal impairment in patients with cancer can often condition antineoplastic treatments, on the other hand, antineoplastic agents themselves can also be a cause of renal failure.⁴

Atezolizumab is a humanised monoclonal antibody directed to the ligand of the programmed cell death receptor 1 (PD-L1) that inhibits its interactions with the PD-1, and the B7-1 receptor (CD80), thus restoring anticancer cell immunity.⁵ This drug, as well as other immune checkpoint inhibitors (ICIs), can be used in chronic kidney patients, even under haemodialysis, without the need for dose adjustment.⁶

The approach of COVID-19, in the presence of multiple serious comorbidities, such as those

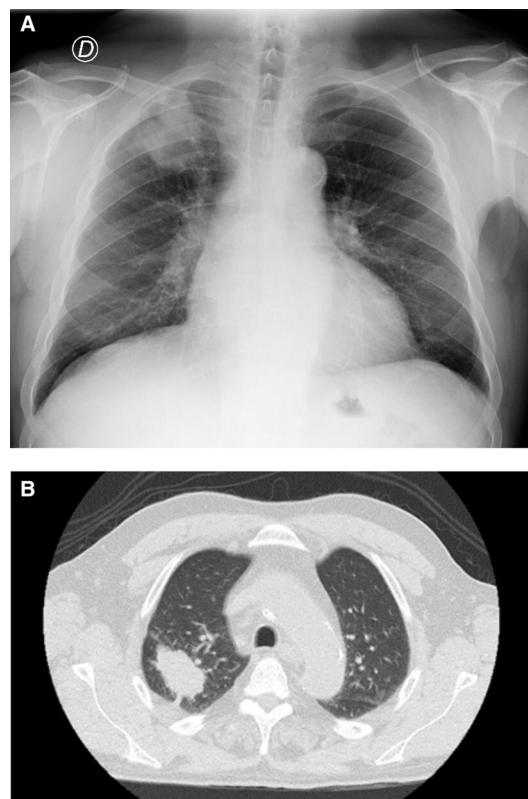


Figure 1 (A) February 2020. The routine X-ray of the chest showed a mass in the right upper lobe (RUL). (B) February 2020. The CT scan of the chest showed a spiculated mass in the RUL measuring 46×30.6 mm.

presented here, represents a clinical challenge. In these cases, a multidisciplinary perspective in decision-making is crucial, to improve, not only the survival but also the quality of life of our patients.

CASE PRESENTATION

A 66-year-old man, previously healthy, retired from civil construction, was referred to the oncological pneumology consultation in February 2020 due to a change in a routine X-ray of the chest.

The main clinical antecedents were a chronic kidney disease (CKD), under haemodialysis in the last 12 years ischaemic stroke in 2015, with full recovery without sequelae, dilated cardiomyopathy, anaemia associated with CKD and a 60 pack-year smoking history. The CKD has originated by an obstructive condition. In 2008, this patient suffered several signs of prostatism, with pollakiuria, dysuria, urinary urgency and tenesmus. After 4 days with marked oliguria, it worsened to anuria, having



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only then gone to the hospital; however, his kidney function was already irreparably affected.

In the first consultation, he had a good Eastern Cooperative Oncology Group (ECOG) performance status (0) with no respiratory complaints. Concerning the complementary diagnostic exams, from November 2019, he had a routine X-ray of the chest that showed a mass in the right upper lobe (RUL), echocardiogram with 43% Left Ventricle (LV) ejection fraction, haemoglobin (Hb) of 10.4 g/L (figure 1A). The CT scan of the chest showed several lymphadenopathies (right hilar and paratracheal, and left hilar), with a spiculated mass in the RUL measuring 46×30.6 mm, with probable pleural invasion and peritumour lymphangitis (figure 1B).

The Positron Emission Tomography (PET)–CT scan showed a 46×31 mm lesion in the RUL, with pleural contact with an Standardized Uptake Value (SUV) of 27.4, and several suspicious lymph nodes, such as right paratracheal, infra-carinal and bilateral hilar, with a minimum SUV of 16. Clinically staged as T2bN3M0 (Stage IIIB).

The transthoracic needle biopsy revealed a TTF1+ lung adenocarcinoma, with intermediate PD-L1+, and with no Epidermal Growth Factor Receptor (EGFR) mutations or Anaplastic Lymphoma Kinase (ALK) rearrangements.

The case was discussed in a multidisciplinary tumour board. It was decided to start chemotherapy (CTx) adapted to renal function, with carboplatin (Area Under the Curve, AUC 5)+ vinorelbine 40 mg/m² orally, followed by RT in a sequential setting.

He started CTx in March 2020. In the laboratory examinations, he had: Blood Urea Nitrogen (BUN) 25.92 mmol/L, creatinine 590 µmol/L and Hb 11.3 g/L. In X-ray of the chest of March 2020, compared with the previous month, there was a slight increase of the mass in the RUL, now measuring 49×43 mm.

On 11 April 2020, he performed a SARS-CoV-2 test with a positive result. Three days later, he had the first symptoms (dry cough, dyspnoea, myalgia and fever). Hospital admission was decided on the same day. On admission to the hospital, in arterial blood gas analysis, with oxygen at 1L/min, a pO₂ 81 mm Hg, with pCO₂ 27.7 mm Hg, pH 7.44 and arterial oxygen saturation (SaO₂) of 96.4% (PaO₂/FiO₂=386). Analytically, he had a lymphopenia of 0.5×10⁹/L, C-Reactive Protein (CRP) 257 nmol/L, interleukin-6 140 pg/mL, ferritin 2.67 nmol/L, creatinine 1740 µmol/L and BUN 60.24 mmol/L. The X-ray of the chest, in addition to the lesion in the RUL, already known, presented a new hypotransparency in the left base.

Treatment with hydroxychloroquine was initiated, according to the protocol approved at that time, maintaining haemodialysis.

On 21 April 2020, the 10th day after the diagnosis, there was a clinical worsening, with breathing difficulties and a fever of 40°C. Despite oxygen supplementation (FiO₂ 60%), he had partial respiratory failure, with pO₂ 53 mm Hg and SaO₂ 88%. The X-ray of the chest showed a worsening with evidence of bilateral pneumonia (figure 2A).

Given clinical and imagiologic worsening, the case was discussed again in a multidisciplinary board and, attending to the good clinical condition of the patient before de SARS-CoV-2 infection (ECOG 0), the transfer to an intensive care unit (ICU) was decided. The patient began invasive ventilation and was placed in the prone position for about 24 hours, with a positive evolution. On the 3rd day of the ICU, it was possible to extubate, with good tolerance. On the 4th day, he was transferred back to the nursery, ending up being discharged after 21 days of hospitalisation.

He was evaluated in a pulmonology consultation in May 2020, appearing emaciated (−3 kg), with moderate dyspnoea,

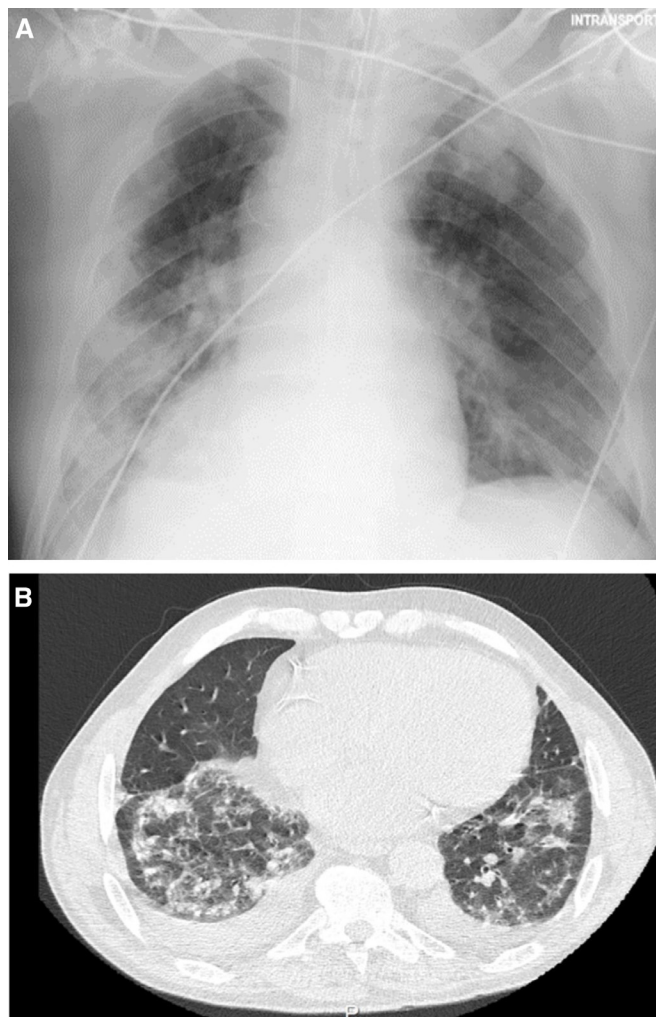


Figure 2 (A) April 2020. The X-ray of the chest showed a worsening with evidence of bilateral pneumonia. (B) May 2020. The CT scan of the chest showed bilateral consolidation areas in ‘ground glass’.

corresponding to level 2 on the modified medical research council scale and permanent oxygen needs (2L/min). Much more debilitated (ECOG 3), with anaemia of 7.3 g/L. The CT scan of the chest showed bilateral consolidation areas in ‘ground glass’ (figure 2B). It was decided to increase the dose of erythropoietin and to maintain CTx with oral vinorelbine until October for further evaluation.

In October 2020, there was an improvement of the dyspnoea, with no need for supplemental oxygen. A global clinical improvement (ECOG 1) was observed. Analytically, there was also an improvement of the anaemia (Hb 10.6 g/L); however, there was an imaging progression in the CT scan of the chest, with an increase in the mass located in the RUL, now measuring 51×64×55 mm and presenting contact with the pleural surface in the lateral and posterior sides, with a ‘ground glass’ area surrounding. There were also six micronodules with dimensions between 20 and 60 mm, in the apical segment of the right lower lobe and the posterior segment of the RUL. Prevascular, pretracheal and lateral tracheal lymphadenopathies.

Taking into account, the progression of the disease under the first-line CTx, on 30 October, it was decided to start a second-line treatment with atezolizumab (PD-L1 <50%).

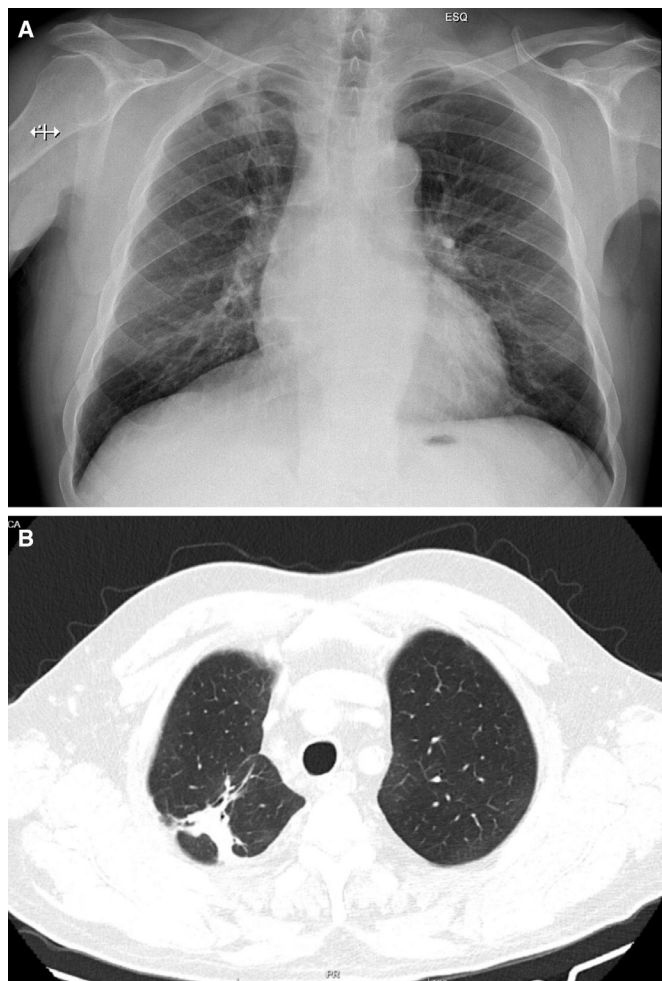


Figure 3 (A) February 2021. A reduction, by more than 50%, of the tumour mass, evaluated with an X-ray of the chest. (B) April 2021. The CT scan of the chest confirms a clear tumour shrinkage.

DIFFERENTIAL DIAGNOSIS

At our centre, patients are regularly tested for SARS-CoV-2 by reverse transcription (RT)-PCR before each new CTx cycle. In this case, the previous existence of a positive test simplified the diagnosis of COVID-19, when the first symptoms (dry cough, dyspnoea, myalgia and fever) appeared, 3 days later.

However, these symptoms are non-specific and not exclusive to COVID-19, being present in many other conditions. In a patient with lung cancer, the possibility of disease progression should be taken into account from the beginning, as well as other diagnostics, such as pulmonary embolism, which is a relatively common condition among patients with cancer, particularly among those with lung cancer.^{7,8} Also, the toxic effects of CTx can seriously damage the lung, causing similar symptoms.⁹

In our patient, the imagiological findings, showing left-sided basal pneumonia, as well as characteristic analytical changes, together with a positive RT-PCR test, clearly confirmed the diagnosis of COVID-19.

OUTCOME AND FOLLOW-UP

The patient was reassessed in February 2021, after completing four cycles of atezolizumab, showing a clinical improvement (ECOG 0) and a reduction, by more than 50%, of the tumour mass, evaluated with an X-ray of the chest (figure 3A). The patient had an excellent tolerance to atezolizumab, without

changes in thyroid function, or other immune-related adverse effects.

At the last consultation, on 21 April 2021, more than a year after de diagnosis, the patient had an excellent general condition, being completely asymptomatic, and maintains treatment with atezolizumab. The CT scan of the chest confirms a clear tumour shrinkage, already evidenced in the X-ray of the chest performed in February (figure 3B).

DISCUSSION

In this clinical case, we present a patient with non-small-cell lung cancer (NSCLC), receiving haemodialysis and CTx, who contracted SARS-CoV-2 infection. Several serious comorbidities overlap in the same patient, at the same time.

As it was a locally advanced and unresectable disease, the surgical option was ruled out. According to the current European Society for Medical Oncology (ESMO) guidelines, treatment with platinum-based CTx with RT in a concurrent schedule is the preferred approach.¹⁰ However, given the various comorbidities, as well as the multiple and relatively dispersed lymph nodes, it was decided to perform CTx and RT in a sequential approach, seeking to obtain a tumour downsizing before starting RT, thus decreasing the volume of irradiation required. The patient did not start RT on the scheduled date due to the complication of SARS-CoV-2 infection and ended up not getting started.

Regarding systemic therapies, there were not many options in the first-line setting. Cisplatin, considered the preferred regimen, was not viable because involves vigorous hydration, incompatible with haemodialysis due to the volume overload. Pemetrexed, also indicated in lung adenocarcinomas, exposes patients with CKD to greater toxicities, especially haematological, as such it is contraindicated.¹¹

According to the ESMO guidelines, ICIs, in association with CTx are currently indicated in the first-line setting, regardless of PD-L1 status. However, the only schedule with EMA approval is the combination of atezolizumab and pemetrexed, thus not advisable for this patient.¹² Finally, molecular therapies, such as TKIs, could also have been a possibility, as they are well-tolerated and have enteric excretion, being a good option in CKD, but EGFR mutations or ALK rearrangements would be needed.¹³

When contracting COVID-19, our patient had a particularly high risk since patients with cancer and COVID-19 showed to have a higher risk of complications.¹⁴ Both mortality rates and ICU admissions appear to be higher in patients with lung cancer.¹⁵

The severe forms of COVID-19 correspond to exacerbated inflammatory states with massive activation of immune cells. This may be associated with more severe cases in patients with cancer and the elderly since both are circumstances that favour inflammation.¹⁶ Patients with lung cancer have chronic lung inflammation, induced both by the tumour microenvironment and by the underlying pulmonary pathology.¹⁷ Notably, patients with cancer and COVID-19, treated with cytotoxic CTx, between 3 months and 2 weeks before the infection, as in this case, did not seem to have a greater risk of death or hospitalisation in ICU.¹⁸

Mortality in patients with lung cancer and COVID-19 appears to be associated with several factors such as low oxygen saturation at diagnosis, poor ECOG-PS, presence of distant metastasis and elevated levels of CRP and fibrinogen.¹⁹ These assessments may have been decisive in the decision of an ICU admission, as this patient was not metastasised and had a good performance status. Given the scarcity of beds in our ICU, it is always a delicate decision. Probably, if this patient had entered the peak of the

third wave of COVID-19, which took place at the end of January 2021, he would not have arrived at an ICU, and the outcome would certainly have been unfavourable.

The correct management of available resources, especially in small and medium-sized centres, is essential, and it requires an individualised approach to the patient, which must be supported by clinical data, preferably applying specific protocols for this purpose.^{20 21}

After overcoming COVID-19 infection, only oral vinorelbine was kept on monotherapy, since the weak clinical condition did not allow for more aggressive approaches. Vinorelbine has shown to be a safe and well-tolerated agent in elderly and debilitated patients.²²

As this patient ended up improving clinically, despite the imaging progression, became eligible to start immunotherapy. Atezolizumab monotherapy has an indication in a second-line setting in patients with NSCLC, regardless of the PD-L1 status and histological type, although those who had an intermediate PD-L1 (1%–50%) or higher (>50%) showed greater benefits from this therapy.²³

Learning points

- ▶ The clinical evolution of severe forms of COVID-19 infection is variable and unpredictable, related to multiple factors, some of which are still unknown.
- ▶ Patients with cancer and COVID-19 infection, as well as severe chronic kidney disease, even under haemodialysis, should not be excluded from intensive care unit admission based only on their previous comorbidities.
- ▶ The global assessment of patients with lung cancer taking into account their clinical condition and comorbidities must be done from a multidisciplinary and integrated perspective.
- ▶ Immune checkpoint inhibitors as monotherapy may offer a great benefit in the treatment of advanced non-small-cell lung cancer and can be used safely in a second-line setting.

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