

# Incidental diagnosis of lung adenocarcinoma following coronavirus OC 43 severe pneumonia

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## Abstract

Viral infections are frequent among patients with thoracic malignancies prompted by dysregulation of innate and adaptive immune response. Clinical symptoms and radiological findings of both viral pneumonia and lung adenocarcinoma may overlap resulting in diagnostic and clinical challenges. We present the case of a woman admitted to our department presenting with an acute manifestation of coronavirus OC43 pneumonia with underlying undiagnosed lung adenocarcinoma.

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## Introduction

Cancer patients are particularly susceptible to develop lung infectious diseases, mainly caused by viruses and bacteria. The recent outbreak of SARS-CoV-2 infection has highlighted that patients with cardiovascular, respiratory and metabolic pre-existing diseases experience poor outcomes once infected [1-4]. Adenocarcinoma is the most common subtype of lung cancer particularly in young women who have never smoked [5]. Clinical presentation is often aspecific and differential diagnosis includes a broad spectrum of nosological entities [6,7]. Computed tomography (CT) scan in invasive adenocarcinoma usually shows heterogeneous patterns including consolidations, ground glass opacities (GGOs) or partly solid hyperdense lesions, single or multifocal. Differential diagnosis between viral pneumonia and malignant disease progression in patients suffering from lung cancer can be very challenging due to the similar radiological characteristics [8,9]. We present a case that highlights difficulties in differential diagnosis of a patient with acute lower respiratory viral infection superimposed on lung adenocarcinoma.

## Case Report

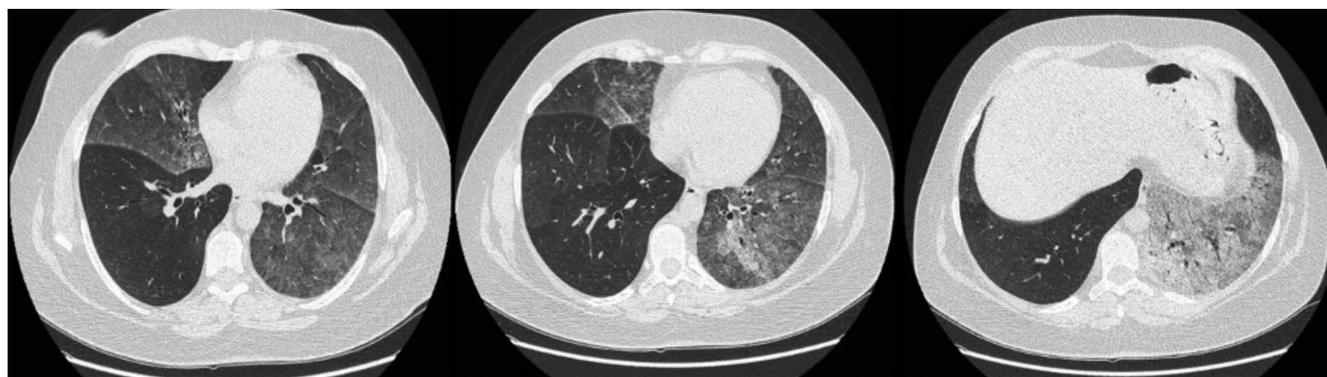
In December 2019, a 42-year old female non-smoker was seen in outpatient setting complaining of 10-day history of chest pain, nocturnal fever and mild dyspnea. Past medical history included gastroesophageal reflux, gastritis and uterine myomas. CT scan showed left lower lobe parenchymal consolidation with signs of air bronchogram. The patient was treated with antibiotic therapy including ceftriaxone and ciprofloxacin. Following a transient clinical improvement, after 14 days the patient exhibited relapsed dyspnoea with asthenia and mild cough, mucoid expectoration; peripheral saturation was 88% on room air, heart rate 100 bpm, arterial pressure 110/70 mmHg. She was therefore admitted to the Respiratory Unit at the University L. Vanvitelli, Monaldi Hospital. Blood gas analysis showed acute hypoxic respiratory failure (pH 7.45, pCO<sub>2</sub> 32 mmHg, pO<sub>2</sub> 59 mmHg, HCO<sub>3</sub><sup>-</sup> 22.2 mmol/L). Physical examination revealed inspiratory gasps partially modified by coughing in the lower right field, wheezing and inspiratory gasps in the upper left field, reduced vesicular murmur in the middle and lower left field. Chest X-ray showed only a left retrocardiac basal opacity whilst chest CT scan exhibited persistence of left lower lobe opacity, and a novel middle lobe parenchymal

GGO with centrilobular tree in bud nodules and bronchiectasis; in both upper lobes ground glass opacities were reported. We started azithromycin, Vitamin C, N-acetylcysteine, prednisolone, aerosol therapy and enoxaparin 4000 IU once/day. Respiratory support through high flow nasal cannula oxygen therapy with FiO<sub>2</sub> 25% Flow 25 L/min was administered. Other tests were performed including QuantiFERON TB test, multiplex PCR nasopharyngeal swab for respiratory viruses, autoimmune profile and blood cultures. Blood examination revealed increase in CRP with normal white blood cell count; other tests were normal. The nasopharyngeal swab documented the presence of Coronavirus OC43. Daily chest monitoring was performed using lung ultrasound [10]. Clinical and physical examination improved after eight days of medical therapy; however high-resolution CT of the chest showed enlarged consolidation in left lower and middle lobe and more extensive ground glass areas in all lobes, overlapping of interlobar interstitial thickening, like *crazy paving*; no pleural effusion, no mediastinal or hilar lymph nodes were reported (Figure 1). Differential diagnosis, according to radiological pattern of CT scan diagnostic hypotheses were as follows: lung infection, alveolar proteinosis and lepidic heteroplastic growth. Multiple transbronchial biopsies, bronchoalveolar lavage, bronchoaspirate were subsequently performed. The left bronchial mucosa was hyperemic with profuse hematic suffusion from the basal segment. Tumor markers were also performed and strong positivity for CA 15-3 was recorded. At this stage a second Multiplex PCR nasopharyngeal swab for respiratory viruses confirmed the positive resolution of Coronavirus OC43 infection. The definitive histological diagnosis was micropapillary infiltrating adenocarcinoma, negative for EGFR, KRAS, BRAF, ROS1 receptor mutation, ALK translocation, with moderate PD-L1 expression (Tumor Proportion Score 1-49%). Staging was completed with CT-PET scan. Before starting chemotherapy on the basis of the atypical radiological pattern, we performed both serological immune test and RT-PCR on nasopharyngeal swab for SARS-CoV2 virus, which resulted negative.

## Discussion

The recent COVID-19 outbreak highlights the relevant role of viruses in prompting acute respiratory damage among lung cancer patients resulting in poor clinical outcomes. Several factors influence the enhanced risk of infection among lung cancer patients.

Firstly, the presence of central airway obstruction may favor atelectasis and/or distal pneumonia [11]. Secondly, the disruption of the innate and adaptive response induced by malignancy, malnutrition and active cancer treatment (chemotherapy, radiotherapy, immune checkpoint inhibitors) [12-17]. Thirdly, interaction site between viruses and host cell may offer further insights into the pathogenesis of viral infection among cancer patients [18-20]. Coronavirus OC43 spike protein binds to 9-O-acetylated sialic acids (9-O-Ac-Sias) attached as terminal residues to glycan chains on glycoproteins and lipids [21,22]. Sialic acids are constitutive components of cell surface glycoproteins and gangliosides and are frequently found in secreted glycoconjugates and in oligosaccharides, mainly of blood serum and mucus secretions [23]. Notably, the total sialic acid in serum or glycolipid-bound sialic acid are known to be elevated in different malignancies including lung cancer [24,25]. Furthermore, serum total sialic acid levels in lung cancer patients with metastatic disease were found higher than in patients with limited disease [25]. These findings suggest that coronavirus OC43-host cell interaction could play a relevant role both favoring viral infection and systemic spread among patients with lung cancer. In addition, viral pneumonia diagnosis in patients with lung adenocarcinoma is not straightforward. Symptom burden of both diseases – including fever, cough, dyspnea, asthenia – may overlap potentially mimicking other respiratory diseases, finally resulting in late diagnosis [26]. Likewise, the CT hallmarks of  $\beta$ -coronaviruses (SARS, MERS, HKU-1) include mild or extensive GGOs, consolidations or mixed patterns with predominantly peripheral distribution [9]. In these cases, early differential diagnosis with cancer disease progression can be difficult to deduce without a multidisciplinary approach. In our patient, the rapid symptom deterioration coupled with laboratory findings prompted the diagnosis toward an acute viral infection. Finally, identification of viral pathogen on biological samples through acid nucleic amplification may significantly differ based on specimens [27]. The development of broadly reacting pan-coronavirus primers while allowing rapid detection of several coronavirus strains, may however result in limited sensitivity when compared to primers designed for each of the human strains [28,29]. This is essential for treatment decision making in coronavirus related-pneumonia. Despite the established absence of licensed therapy, recent evidences suggest that some drugs may exert potential antiviral activity including macrolides, immunoregulatory and antiviral agents [30-32]. In our case the treatment prompted from initial pathogen identification led to early intervention with azithromycin and high dose of



**Figure 1.** Lung CT scan showing left lower lobe adenocarcinoma with mixed consolidative and GGOs pattern; in the middle lobe CT showed the presence of GGOs along with interlobular thickening configuring a *crazy paving* pattern.

antioxidants along with supportive high flow nasal cannula oxygen. In conclusion, our case demonstrates the relevance of coronavirus infection among patients with lung cancer and the challenges in defining adequate clinical management. recent outbreak of the novel coronavirus SARS-CoV-2 highlights the urgency of further studies in lung cancer patients.

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