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Case Report

Ground Glass Appearance During the Pandemic Period: Everolimus Induced Interstitial Pneumonia

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ABSTRACT

Ground glass appearance is a nonspecific finding that can see in diseases such as chronic interstitial disease, acute alveolar disease or infection; however, it is most commonly encountered in COVID-19 pulmonary involvement today. The mammalian target of rapamycin (mTOR) plays a regulatory role in cell proliferation and growth. Everolimus is an allosteric mTOR inhibitor used in ER+ breast cancers and inhibits the mTOR functional complex. Here, we present a case of interstitial pneumonia due to everolimus, which can be confused with COVID-19 pneumonia due to its ground-glass appearance during the pandemic period.

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Introduction

Interstitial lung diseases (ILD) are diseases that include many non-infectious diseases affecting the lung parenchyma. Etiologically, ILD is divided into nine main groups: idiopathic interstitial pneumonia, connective tissue disease, smoking-related, vasculitis, granulomatous disease, environmental/occupational, drug-induced, hereditary, and other causes.[1] In drug-induced interstitial pneumonia, the drug causes inflammation in the lung interstitium, resulting in fibrosis in the lung.

Ground glass appearance is a nonspecific finding that can see in COVID-19 lung involvement (which we see most today), pulmonary oedema, aspiration, *Pneumocystis jirovecii* pneumonia, nonspecific interstitial pneumonia, alveolar haemorrhage, and drug-related lung toxicity.[2] Dominant computed tomography (CT) findings in COVID-19 pneumonia include ground-glass opacification, consolidation, bilateral involvement, peripheral and diffuse distribution.[3] Herein, we wanted to present one of the etiologies that can be confused with the ground glass appearance, one of the radiological findings of COVID-19 pneumonia.

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Case Report

A 48-year-old female patient who received hormonal therapy and chemotherapy due to breast cancer and bone metastasis was admitted to the emergency room with low saturation, dyspnea, and worsening general condition. The patient had fever, cough and sputum. On the physical examination, her general condition was good. She was conscious, oriented, and cooperative. On the lung auscultation, basal and midline fine rales were present. There were no tenderness, rigidity or rebound in the abdominal examination. Oxygen saturation was 97% with 3 L/min oxygen support from the nasal cannula and 85% at rest in room air. The patient was started on teicoplanin and ciprofloxacin as antibiotic therapy. Lung computerized tomography (CT) on 23.06.2021 has been reported as "In addition to the COVID-19 sequelae identified in the examination on 12.06.2021 (*Image 1*), ground-glass consolidations in the lung parenchyma from the apex to the basal and vascular-bronchial clarifications in these areas are compatible with the second COVID-19 infection and active inflammation and it appears to be progressive compared to the examination on 12.06.2021." (*Image 2*). The patient was previously treated with a diagnosis of lung CT positive COVID-19 pneumonia. However, all of the patient's COVID-19 polymerase chain reaction (PCR) test results were negative. On 24.06.2021, the SARS-CoV-2 antibody test and PCR test were negative, and we excluded the diagnosis of COVID-19 from the patient. She had been using everolimus for the past four months. The reason for the ground-glass appearance in low-dose thoracic CT was thought to be related to interstitial pneumonia. We evaluated the patient with the oncology department and considered having interstitial pneumonia due to everolimus. Interstitial lung involvement, occasional pneumonic consolidation, ground-glass appearances and hyperaeration findings suggested bronchiolitis and interstitial pneumonia in the patient after consultation with chest diseases. Bronchoscopy, transbronchial biopsy or bronchoalveolar lavage were recommended to the patient to distinguish between agents and pathogens and to determine whether there was a drug lung or not. The patient refused. In the other tests, CMV IgM was negative and IgG positive. Candida beta-glucan antigen was negative. Aspergillus Galactomannan antigen

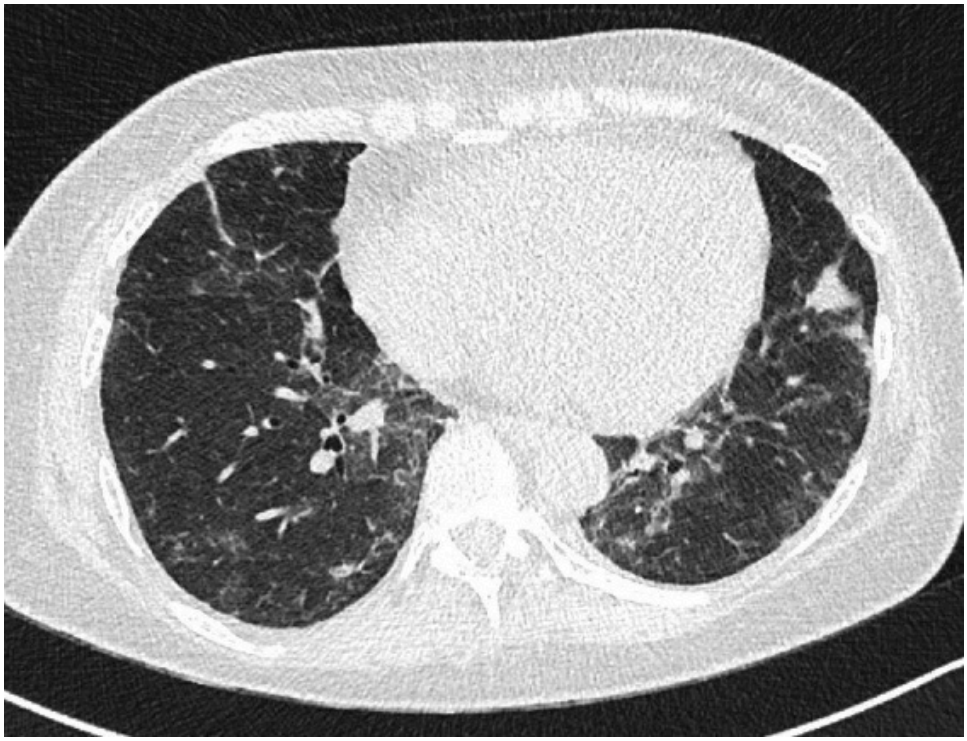

Image 1. Consolidation areas with ground glass appearance considered as a previous COVID-19 infection.

was negative. We started the patient with 100 mg of methylprednisolone and warned her not to use everolimus. On the 4th day of the patient's use of 100 mg methylprednisolone, the patient's room air saturation was 91%, and there were no rales or rhonchi on lung auscultation. The patient's admission CRP value was 33.05 mg/dL and decreased significantly after starting methylprednisolone. It was 1.31 mg/dL at the patient's discharge. The patient was ordered 100 mg of prednol for seven days on hospitalization. The patient showed significant improvement and did not get desaturated at room air and was discharged with the recommendation to continue using 32 mg methylprednisolone for 15 days at home.

Discussion

There are two mechanisms in drug-induced interstitial pneumonia; direct or dose-related toxicity and the other is an immune-mediated mechanism.[4] Mammalian target of rapamycin (mTOR) stimulates cellular anabolism and affects macromolecule formation with many mechanisms such as nucleic acid, protein, lipid production, ribosome biogenesis and protein translation. mTOR also inhibits catabolic processes such as lysosome biogenesis and autophagy. mTOR integrates anabolic processes induced by environmental stimuli by modulating metabolic pathways for cell proliferation, growth and metabolism.[5] mTOR is often downregulated in cancer, and activating somatic mutations of mTOR have recently been identified in several cancer types, thus making mTOR a therapeutic target. mTOR inhibitors have previously been widely used as immunosuppressants and are now approved to treat malignancies.[5] Everolimus inhibits mTOR functional complex 1 as an allosteric mTOR inhibitor used in ER+ breast cancers.[6]

Diagnosing interstitial pneumonia can be challenging for clinicians because the diagnosis is a diagnosis of exclusion. An analysis of data from three extensive controlled clinical studies of everolimus used in solid organ transplantation in one study found the incidence of everolimus induced interstitial lung disease to be 0.4%. (6 patients out of 1473). The onset of symptoms after patients started using everolimus was highly variable in these three studies, similar to the cases described in literature reviews. This period varies between 4 weeks and 15 months.[7]

The patient was diagnosed with everolimus-induced interstitial pneumonia because we excluded infectious causes. The patient's clinical status improved with steroid therapy, and the radiological and clinical findings were consistent with drug-induced pneumonitis. It is essential to consider other etiologies in the differential diagnosis, especially during the pandemic period, as the ground glass appearance leads clinicians to diagnose COVID-19.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SEY, IBG; Study Design: SEY, IBG; Supervision: YO, IBG; Materials: YO; Data Collection and/or Processing: IBG, SEY; Statistical Analysis and/or Data Interpretation: SEY; Literature Review: YO; Manuscript Preparation: SEY, IBG; Critical Review: YO, IBG.

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