

Case Report / Olgu Sunumu

Ciliated muconodular papillary tumor masked by COVID-19 infection and aspergilloma

COVID-19 enfeksiyonu ve aspergilloma ile maskelenmiş silyalı mukonodüller papiller tümör

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ABSTRACT

Novel coronavirus disease-2019 (COVID-19) continues to pose a threat all over the world with the effect of new variants. The frequency of other secondary infections such as aspergilloma in patients with COVID-19 disease is not uncommon. Extremely rare lesions such as ciliated muconodular papillary tumor can be masked by radiological images caused by COVID-19 infection or secondary pathologies associated with it, leading to difficulties in diagnosis. Herein, we report a case in whom a diagnosis of aspergilloma and ciliated muconodular papillary tumor after six months of COVID-19 infection was made.

Keywords: Aspergilloma, ciliated muconodular papillary tumor, coronavirus disease-2019.

Novel coronavirus disease-2019 (COVID-19) emerged in December 2019 from Wuhan City and rapidly spread around the world, leading to a pandemic.^[1] Despite the current focus on understanding the mechanism of pathogenesis to manage and prevent the spread of COVID-19, appropriate treatment measures are still unclear.^[2]

The relationship between COVID-19 and other respiratory pathogens and the resultant possibility of co-infection have become a major concern in the treatment of patients with COVID-19.^[2] Aspergillosis

ÖZ

Yeni koronavirus hastalığı 2019 (COVID-19) tüm dünyada yeni varyantların da etkisi ile tehlike yaratmaya devam etmektedir. COVID-19 hastalığı geçiren hastalarda aspergilloma gibi sekonder enfeksiyonların da sıklığı nadir değildir. Silyalı mukonodüller papiller tümör gibi oldukça nadir görülen lezyonlar, COVID-19 enfeksiyonunun veya bununla ilişkili sekonder patolojilerin neden olduğu radyolojik görüntülerle maskelenebilmekte ve tanıda güçlük yaşatabilmektedir. Bu makalede, COVID-19 enfeksiyonundan altı ay sonra aspergilloma ve silyalı mukonodüller papiller tümör tanısı konan bir olgu sunuldu.

Anahtar sözcükler: Aspergilloma, silyalı mukonodüller papiller tümör, koronavirus hastalığı 2019.

is a well-known disease which is typically seen in severely immunocompromised patients. There is a limited number of literature data on COVID-19 and aspergillosis co-infection, and the form of aspergilloma is rarely reported after COVID-19 infection, as COVID-19 is a newly described illness.^[3]

Ciliated muconodular papillary tumor (CMPT) of the lung is a newly described low-grade malignant tumor which has ciliated columnar cells and goblet cells with basal cell proliferation.^[4] It has a rare pathology, and the etiopathogenesis is unknown. In

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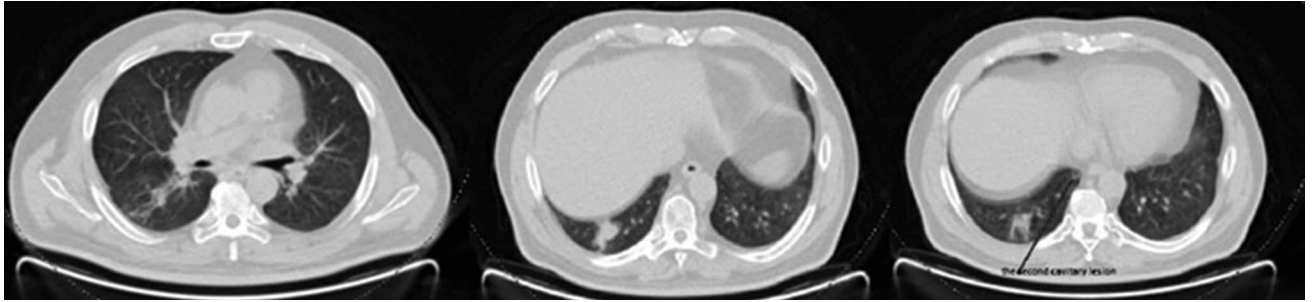


Figure 1. Images of computed tomography. In the first image, there is an atelectatic area, in the second image the largest (3×2 cm) lesion on lower lobe is seen behind this lesion, a 1-cm cavitory lesion can be seen on the inferior segment of lower lobe.

this article, we present a case in whom a diagnosis of aspergilloma and CMPT after six months of COVID-19 infection was made.

CASE REPORT

A 50-year-old man was admitted to our clinic after a 3×2-cm lesion on the right lower lobe on thoracic computed tomography (CT) identified during the evaluation of rare hemoptysis for one month (Figure 1). He had a history of smoking approximately 20 packs of cigarettes per year. During this six-months period, he had lost 20 kg. He also had diabetes mellitus and hypertension for 10 years.

Clinical examination findings, including auscultation, were normal. The saturation level was 95%. A complete blood count test, renal and liver function tests were normal. A 3×2-cm solid lesion on the right lower lobe posterior basal segment was discovered on a chest CT scan. Moreover, a 1×1-cm cavitory lung lesion in the medial basal segment and atelectatic area and bronchiectasis in the superior

segment of the same lobe were also present. The largest lesion in the patient was a middle-intensity fludeoxyglucose (maximum standardized uptake value [SUV_{max}] of 5) and no suspicious uptake was found in other areas (Figure 2).

His medical history revealed that he had COVID-19 infection, six months ago, and was hospitalized for one month in another country. The presence of ground-glass opacities (GGO) should be linked to COVID-19 infection on CT. However, no solid lesion was reported (Figure 3). Furthermore, his COVID-19 infection was treated with remdesivir, corticosteroids, and tocilizumab. Fiberoptic bronchoscopy was used during surgery. The bronchial system as a whole was normal. Lavage was performed for microbial and cytology purposes.

After the intubation with a double-lumen tube and placed in the left lateral decubitus position. A 1-cm port incision was performed at the seventh intercostal space. Then, a 3-cm utility incision was made from the fifth intercostal space. The largest lesion in the lower lobe was palpated. With a stapler, a wedge resection was performed on the largest lesion. The inferior ligament was divided, and wedge resection was performed on the second smaller lesion. Both of the lesions were aspergillomas that were confirmed by frozen-section analysis. The lesion on the lower lobe superior segment showed radiological similarities, as the leftover tissue was so small and anatomic resections, such as segmentectomy and lobectomy, have become more preferred than wedge resection, we decided to complete the lobectomy. We also collected samples from lesions and normal tissue for microbial evaluation. We dissected stations 7 and 9 lymph nodes during the exploration. The postoperative course of the patient was uneventful. The drains were removed on postoperative Day 2, and the patient was discharged without complications on the fifth postoperative day.

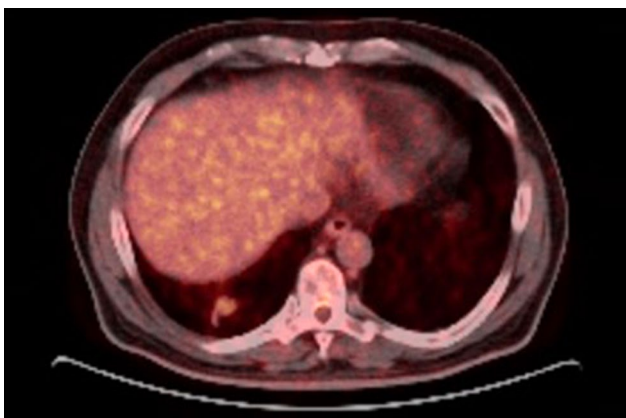


Figure 2. Only the largest lesion showing middle FDG uptake. FDG: F-18 fluorodeoxyglucose.

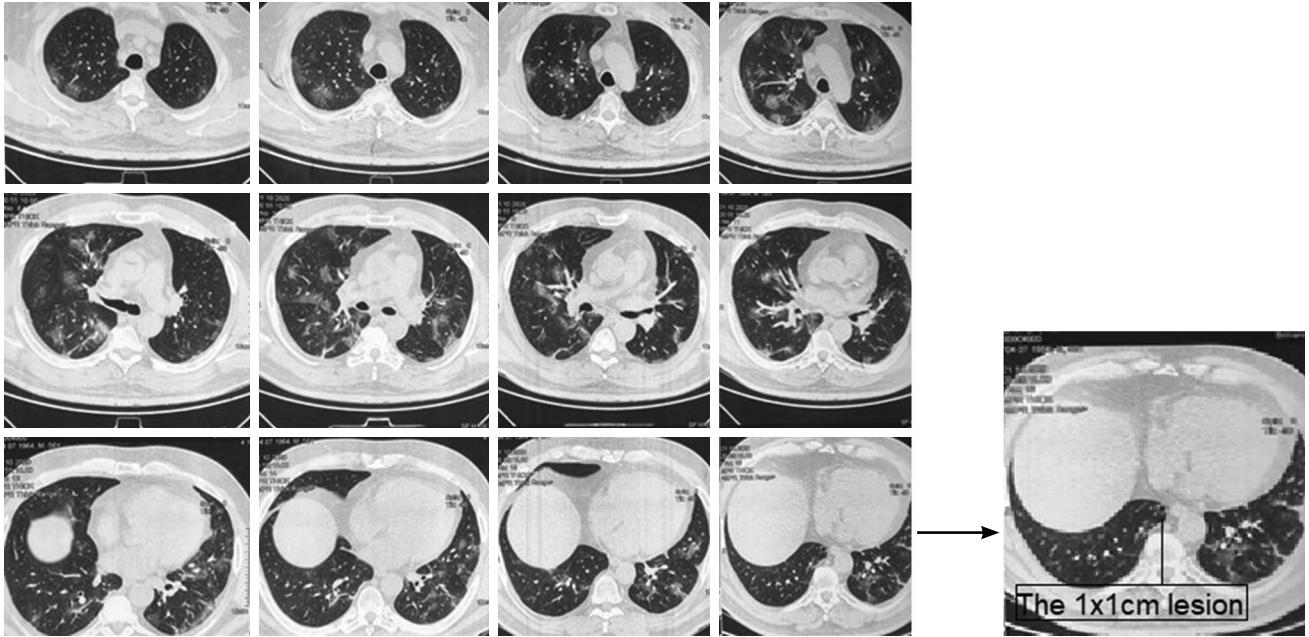


Figure 3. The previous computed tomography of patients showing ground-glass opacities linked to COVID-19 infection. However, no solid lesion was reported.

Although the medical treatment is uncertain, the patient's treatment began with intravenous voriconazole and, then, switched to an oral formulation.

The definite pathology result was reported that the largest lesion was classified as an aspergilloma, which is a fungus ball. There was a loss of bronchial epithelium. Fibrosis and inflammatory infiltration were present in the surrounding tissue, as well as inflammatory granulation tissue on the ground

(Figure 4). Microbiological culture of the tissue sample, there was no fungal or mould growth. Galactomannan in serum was found to be negative.

The second lesion, located in the medial basal segment, was classified as CMPT, as it contained both mucinous and non-mucinous ciliated cells with minimal cellular atypia (Figure 5). The lesion had a basal membrane that was immunohistochemically positive for p63 or p40, along with the presence of

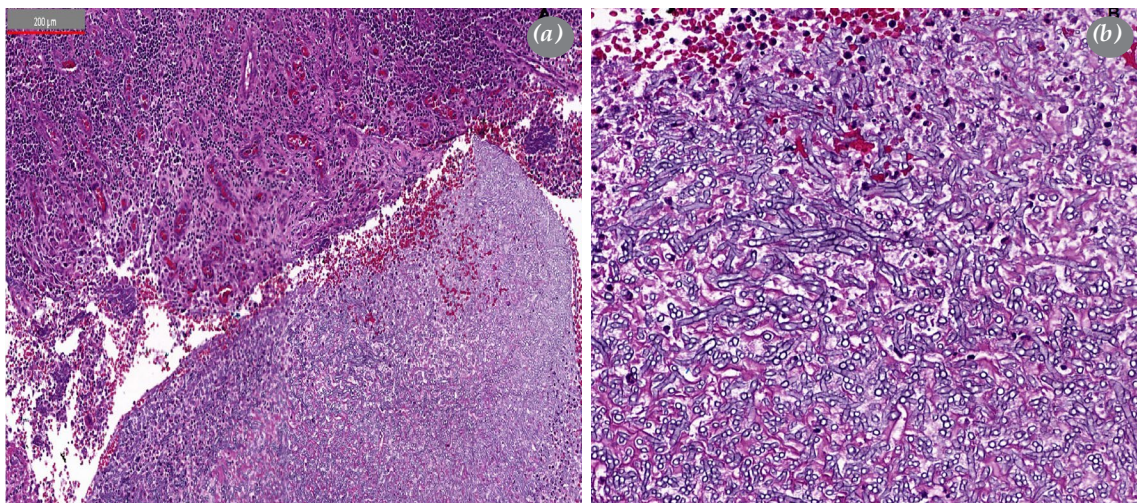


Figure 4. Fungus ball characterized by parallel, uniform hyphae which septate at regular intervals, branching at 45° angles. Granulation tissue due to the ulcerated bronchus mucosa is also noted. (a) H&E, $\times 15$ and (b) $\times 40$.

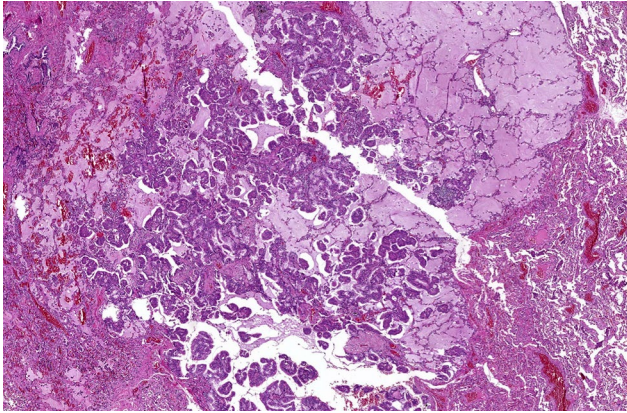


Figure 5. Ciliated muconodular papillary tumor (bronchiolar adenoma) of the lung is a peripheral lesion with mucin filled neighboring alveolar spaces. A papillary and micropapillary growth pattern with lepidic edges is characteristic of this lesion. H&E, $\times 15$.

papillarity, mucinous pools, and focal lepidic growth (Figure 6). Furthermore, bronchiectatic areas were found in other parts of the lobectomy tissue.

DISCUSSION

Ishikawa et al.^[5] first described CMPT of the lung in 2002. As only a few cases have been reported, the World Health Organization (WHO) has been unable to classify it. The cases in the literature are more often females (the ratio male-to-female 1:1.2), and no relationship between smoking histories and incidence of CMPT could be found. Ciliated muconodular papillary tumor is typically seen in middle-aged to elderly East Asian adults, but a teenage female case has also been reported.^[6]

Although CMPT is frequently localized peripherally, pleural retraction has not been described.^[7] Furthermore, microscopic examination typically reveals a lesion with predominantly glandular or papillary structures. The lesions are distinguished by a peripherally located discontinuous lepidic pattern and alveolar spaces containing mucin. To that extent, the lesion may have central mucin accumulation, which results in macroscopically visible central cavitation. Some pathological reports define fibrosis and disruption of the alveolar elastic framework. Ciliated columnar, mucous, and basal cells make up the epithelial component. Chronic inflammation, peribronchiolar metaplasia and, rarely, non-necrotizing granulomas can be typically seen at the periphery of the tumor.^[7,8] In our case, the lesion contained mucinous and non-mucinous ciliated cells with minimal cellular atypia. The lesion also had papillarity, mucinous pools, and focal lepidic growth.

Aspergillosis is a mycotic disease caused by the fungus *Aspergillus fumigatus*. Lung diseases related to *Aspergillus* manifest themselves in a variety of ways. Patients with asthma or cystic fibrosis are more likely to develop allergic bronchopulmonary aspergillosis. On the other hand, aspergilloma is a type of lesion of the lung that is more common in individuals who have abnormal airways (chronic obstructive pulmonary disease, bronchiectasis cystic fibrosis) or chronic lung cavities that can cause hemoptysis.^[9]

Aspergilloma is also classified into two types: simple or complex. The complex aspergilloma usually makes it difficult to manage necrotic cavitory lesions, particularly in tuberculosis. Patients with

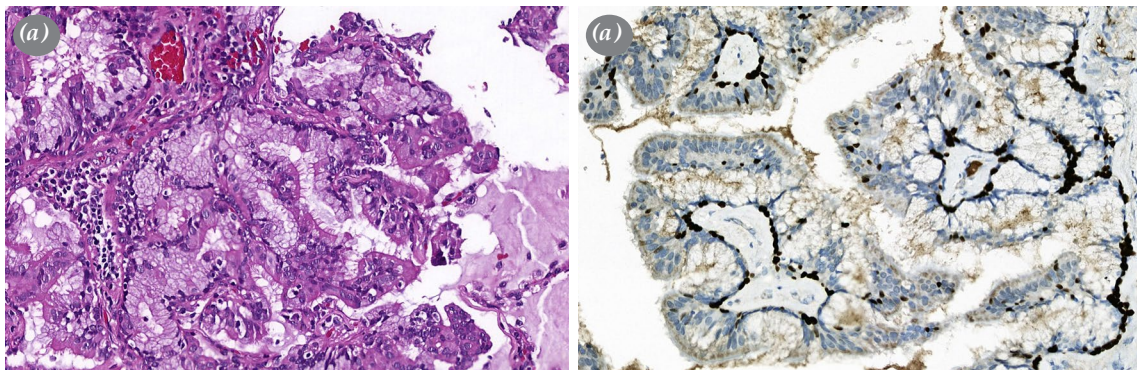


Figure 6. (a) Ciliated muconodular papillary tumor (bronchiolar adenoma) is characterized by ciliated columnar cells, as well as mucous and basal cells arranged in glandular, papillary and micropapillary configuration. H&E, $\times 40$. (b) The basal cells which are located beneath the others showing a layer which can be highlighted with basal cell markers immunohistochemically. P63, $\times 40$.

hematological neutropenia are more likely to develop simple pulmonary aspergilloma.^[10] Secondary fungal infections have been identified as a risk factor in COVID-19 patients and have been reported to occur in 33.3% of COVID-19 patients and 35.3% of critically ill patients. Following the reports from Europe, it appears that invasive pulmonary aspergillosis (IPA) may be associated with severe COVID-19.^[11] Furthermore, steroids are commonly used to improve survival among COVID-19 patients, but this may also lead to a predisposition to invasive aspergillosis. Tocilizumab, which is an interleukin-6 (IL-6) inhibitor that plays a role in modulating the cytokine storm, is used in the treatment of mild and severe COVID-19 infections. The high prevalence of invasive aspergillosis may be due to the widespread use of steroids and tocilizumab treatment.^[12,13] Despite the fact that our patient had no history of tuberculosis or another cavitary necrosis, the treatment outcome was favorable due to the previous treatment of corticosteroids and tocilizumab for mild COVID-19 infection. This treatment, as well as the infectious disease, should be considered while diagnosing aspergillosis.

The thickness of the cavity wall and inflammation of the surrounding parenchyma and pleura, as visible on CT scans, aid in the diagnosis of aspergilloma. In some cases, mycetoma with surrounding blood vessels can be seen.^[14] Although aspergilloma is usually found in the upper lobes and the superior segment of the lower lobe, it was discovered in the right lower lobe in our case. This could be the result of performing the prone position while infected with COVID-19.

For both aspergilloma and CMPT, resection is the most optimal treatment option. For aspergilloma, a wedge resection is an option, if the lesion is small and simple mycetoma. However, anatomic resections, such as segmentectomy and lobectomy, have become the preferred approach in recent years.^[14] In reported cases, patients with CMPT were mostly treated with lobectomy with the remaining cases undergoing wedge resection or segmentectomy. In both types of surgeries, no recurrences or metastases have been reported after a 10-year follow-up.^[15]

Of note, COVID-19 has been linked to fungal balls in aspergillosis.^[16] Our case was treated for COVID-19 six months ago, and there were no reported solid lesions on CT scans from that period. When we reviewed the CT scans from the study period, we discovered a 1x1-cm cavitary lesion in the medial basal segment that was masked and/or did not attract attention due to GGO. Tocilizumab and corticosteroids, which are

used to treat COVID-19, can increase the risk of aspergillosis and aspergilloma. Aspergilloma was the most severe lesion in our case at the end, and the patient was thoroughly examined for this lesion.

In conclusion, this case highlights that a rare tumor was masked and kept in the background by ground-glass opacities on a previous computed tomography scan and aspergilloma on the subsequent computed tomography scan. Therefore, we recommend that radiological examinations be thoroughly evaluated, even if there are too many ground-glass opacities lesions due to COVID-19 infection.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Control/supervision: C.K., Literature review: T.C., C.K.; Writing the article: T.C.; Critical review: H.Z.

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