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False-positive Serum IgM/IgG to SARS-CoV-2 in a Rare Pulmonary Neuroendocrine Carcinoma with Ocular Metastasis: A Case Report

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Abstract

The Coronavirus disease 2019 (COVID-19) pandemic impacts pulmonary cancer management since it shares similar clinical features and creates fear among patients to visit hospitals due to possible in-hospital disease transmission. We report a patient who presented with a rare case of a pulmonary neuroendocrine tumor with an ocular involvement, which, unfortunately, experienced a delay in diagnostics. The first hospitalization was due to superior vena cava syndrome, pleural and pericardial effusions, and swollen left eye. The patient was diagnosed with pulmonary cancer, released after the symptoms were relieved, and expected to visit a referral hospital for further diagnostics and treatments. The patient returned two weeks later with progressing disease, an ocular metastasis, and a reactive serum IgM/IgG to SARS-CoV-2; serial qPCR tests consistently returned negative. The patient was treated with the best supportive care before succumbing to death. Biopsy showed pulmonary tumor cells consistent with a neuroendocrine tumor. Fear of the pandemic makes patients reluctant to seek help from medical facilities. Pulmonary TB has similar symptoms to pulmonary cancer, which can pose another challenge in diagnosing pulmonary cancer in TB-endemic countries. Thus, patients often present with advanced-stage pulmonary cancer with rare ocular metastasis, as in this report.

Keywords: SARS-CoV-2 infection serological testing; delayed diagnostic; neuroendocrine tumor; false-positive reactions

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic impacts the healthcare system worldwide. Almost all patient care was affected as fear of infection results in patients being reluctant to visit a hospital, further complicating the early diagnosis of pulmonary cancers.^{1,2,3} In high prevalence tuberculosis (TB) countries such as Indonesia, pulmonary cancer is also complicated by pulmonary TB, where misdiagnosis and mistreatments are unfortunately common as both could present similar symptoms.⁴ Consequently, patients often present with advanced pulmonary cancer.

Pulmonary neuroendocrine carcinoma is a broad spectrum of pulmonary malignancy with various clinical features and is less common than adenocarcinoma or squamous cell carcinoma. Additionally, ocular metastasis is a rare clinical feature in pulmonary cancer, with an incidence of 0.1 – 0.7%. The uvea, the choroid, iris, and ciliary body are the most common site for intraocular metastasis, respectively.^{5,6}

We report a rare case of pulmonary neuroendocrine tumor (NET) with ocular metastasis, experiencing a delay in diagnosis due to misdiagnosed pulmonary tuberculosis and presenting with an advanced stage due to fear of COVID-19 transmission.

Case illustration

A 58-year-old male was admitted to the hospital due to progressive shortness of breath for three months and left eyesore for two weeks. He visited a nearby hospital five months prior due to chronic cough and weight loss, without night sweating and fever. He was a heavy smoker, and none of his close family has a history of cancer or TB. He was diagnosed with tuberculosis based on symptoms and chest x-ray (CXR) (Figure 1A), and sputum acid-fast bacilli smear (AFB) was negative. Fixed-drug combination anti-TB treatment was given for two months, but there was no clinical improvement, as shown from the follow-up CXR (Figure 1B).

He was reluctant to visit the hospital due to the COVID-19 pandemic, so he decided to continue anti-tuberculosis treatments although the symptoms were progressing. Unfortunately, he was not receiving the COVID-19 vaccination as it was unavailable then. During the emergency ward visit, the examination showed he was fully awake. His blood pressure was 110/90 mmHg, heart rate was 110 bpm, respiratory rate was 36 bpm with a noted work of breathing, and peripheral oxygen saturation was 95%. Physical examination showed a non-axial proptosis of the left eye with no light perception, no light reflex, multi-direction ophthalmoplegia (Figure 2A), and enlargement of the left supraclavicular lymph node. Thoracic examination showed

asymmetrical left hemithorax with narrowed left intercostal space and dull percussion. Rales were heard on the right hemithorax. CXR showed generalized radiodensity at the left hemithorax (Figure 1C).

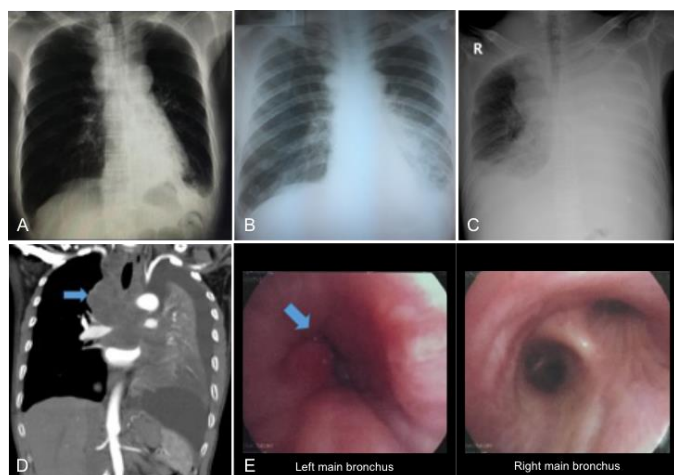


Figure 1. Serial photo showing: (A) Initial CXR, which represents the diagnosis of pulmonary tuberculosis. (B) Two months of follow-up CXR after initiation of anti-tuberculosis treatment showed no improvement. (C) CXR by the time at the emergency unit, five months after the first CXR. (D) Chest CT scan showed a central pulmonary mass (pointed by the blue arrow) obliterating the right thoracic space, resulting in SVCS and obstructing the left main bronchus and pleural and pericardial effusion. (E) The bronchoscopy imaging showed total left main bronchus obstructed by infiltrative tumor mass (pointed by the blue arrow).

Blood tests showed leucocyte count of 9,000 cells/dL, lymphocyte count of 20%, neutrophil: lymphocyte ratio of 3.1, and platelet counts of 165,000 cells/dL. We suspect pulmonary malignancy with pleural effusion and ocular metastasis in this case.

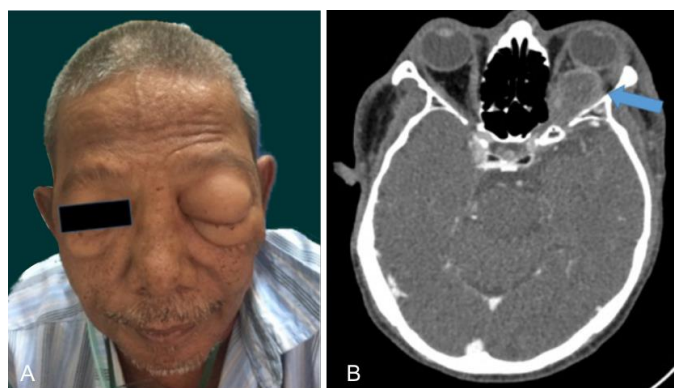


Figure 2. (A) Left eye proptosis. (B) Brain axial CT scan shows left intra-ocular mass (pointed by the blue arrow)

Due to the COVID-19 pandemic, the patient was screened for COVID-19 through a rapid serological test of IgM/IgG for SARS-CoV-2. He was ruled out of COVID-19 as the serological test result returned as non-reactive, and the follow-up nasopharyngeal SARS-CoV-2 qPCR test results were negative. A thoracic CT scan showed a central pulmonary mass and pleural and pericardial effusion (Figure 1D).

A brain CT scan showed an intra-orbital mass suspected as a metastasis (Figure 2B). Left thoracentesis was performed, with the results of cytological and cells block examination from the pleural fluid that was negative for malignant cells. The bronchoscopy evaluation showed total left main bronchus obstruction with infiltrative tumor mass (Figure 1E). Intra-bronchial biopsy was performed, with the results being inconclusive, although suspected malignant cells were detected (Figure 3A). During the two-week hospitalization, the patient was relieved from his symptoms. His family decided to bring him home for supportive

care, as doctors instructed them to visit a referral hospital for further diagnostics and treatments.

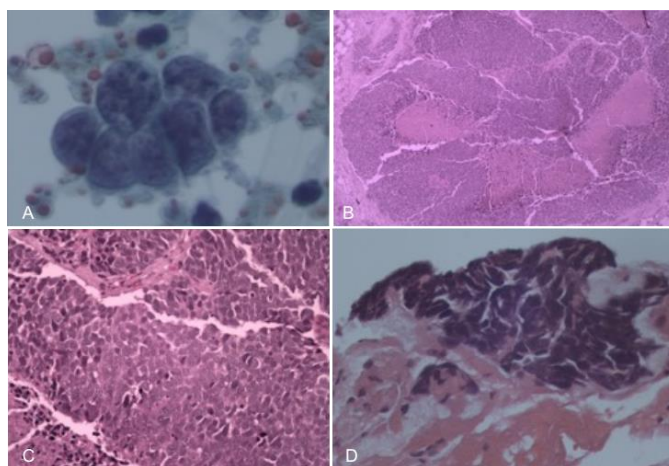


Figure 3. Cytological and histopathological specimens: (A) Cytological specimen from the lung shows malignant cells (Pap stain). (B to E). Biopsy of supraclavicular lymph nodes show the clusters of infiltrative tumor cells with pleomorphic nuclei, hyperchromatic, salt-and-pepper chromatin, molding, and necrosis (H&E stain).

Ten days later, he was re-admitted to the emergency ward due to difficulty breathing, chest pain, and neck and face swelling, suggesting superior vena cava syndrome (SVCS). The patient also complained of fever and productive cough. Another COVID-19 screening was performed; this time, the serological test of IgM/IgG for SARS-CoV-2 came back reactive, and consequently, the patient was isolated in the isolation ward. Two nasopharyngeal SARS-CoV-2 qPCR tests were taken three days apart and resulted in a negative then, the patient was ruled out as COVID-19 and transferred to a non-isolation ward. CXR showed a left pleural effusion with a midline shift. Echocardiography showed significant pericardial effusion. Pericardiocentesis was performed to evacuate 350 mL fluids and followed by pericardiodesis. Left thoracentesis was performed using a large-bore catheter, resulting in daily pleural fluid production between 750 and 1,000 mL. Biopsy from supraclavicular lymph nodes showed clusters of infiltrative tumor cells with pleomorphic nuclei, hyperchromatic, salt-and-pepper chromatin, molding, and necrosis. The microscopic features were consistent with carcinoma suggestive of NET (Figure 3B-D). Radiotherapy to alleviate SVCS required transportation to another hospital; thus, it was impossible due to the worsening condition. His condition deteriorated, and the patient died after two weeks of hospitalization.

Discussion

Indonesia is among the regions with a high TB prevalence, where pulmonary malignancy is often misdiagnosed as TB since both share similar symptoms. Delayed malignancy diagnostics could impact its therapy and outcome. Therefore, pulmonary cancer should always be considered a differential diagnosis in TB cases refractory to anti-TB treatments.^{4,7} In this case report, the patient was initially diagnosed with pulmonary TB based on clinical symptoms and CXR despite negative sputum AFB. Suspicion of pulmonary cancer was raised, as two months of anti-TB drugs resulted in no clinical improvements.

The patient had had an increased risk of pulmonary cancer, as he was a 58 y.o. with a smoking history. A study by Sari et al. showed that among pulmonary cancer patients treated in an Indonesian pulmonary tertiary hospital, 41% had been misdiagnosed as pulmonary TB, and 29% had received anti-TB treatment resulting in at least a month of delayed diagnosis.⁸ We suggested that close clinical and radiological evaluations

be performed within one month for sputum AFB negative TB patients after initiating anti-TB drugs. Priority was to the patients possessing pulmonary cancer risk factors such as a male, elderly, heavy smoker, history of familial cancer, and exposure to occupational air pollutants.^{4,8}

The COVID-19 pandemic results in delayed diagnosis and treatments in pulmonary malignancy, leading to declining malignancy survival in the future.⁹ The UK projected a 4.8 to 5.3% increase in deaths, or 1,235 to 1,372 additional deaths, of pulmonary cancer due to delayed diagnosis during the pandemic.² Delayed malignancy diagnoses are attributed to the hospital overburden of COVID-19 cases and the attitude of patients and their family toward the COVID-19 pandemic.¹⁰ In this case report, suspicion of malignancy had been raised three months before hospital admission since symptoms were progressing. Still, the patient was reluctant to visit the hospital fearing in-hospital COVID-19 transmission. The patient showed pleural and pericardial effusion and left eye proptosis by hospital admission, suggesting an advanced stage of malignancy.

Pulmonary cancer may present with similar symptoms as COVID-19, and its patients are susceptible to SARS-CoV-2 infection; thus, timely screening is mandatory during the COVID-19 pandemic.^{10,11} Systematic review on rapid serological tests for COVID-19 concluded that the rapid IgM/IgG point-of-care testing possessed a risk of bias, heterogeneity, and limited discernibility, preventing its usage as a diagnostic tool for COVID-19.¹² The test might be suitable in epidemiological seroprevalence studies but not in clinical settings, as the gold standard for COVID-19 diagnosis remains the SARS-CoV-2 qPCR test. The test also should be used with caution in complicated cases, such as malignancy or autoimmune disease, since it could yield false-positive results.¹² In this case report, further delay in malignancy diagnostic occurred, as the patient was required to be screened by serological and qPCR tests. The delay in treatment had become problematic during the second hospitalization, as the patient was serologically reactive for IgM/IgG for SARS-CoV-2 and required brief hospitalization in an isolation ward before being ruled out of COVID-19 from the qPCR test. The screening process took at least three days on each of his hospitalization, which summed into approximately a week of pending diagnostics and treatments.

The NET is commonly found in the GI tracts, and less than 20% are of pulmonary origins. The prevalence of pulmonary NETs is around 1% to 2% of all pulmonary cancer. Primary pulmonary NETs consist of small cell lung cancer, large cell NET, and atypical and typical carcinoid with heterogenous behavior; the carcinoid behaves as a slowly indolent disease, and the small cell lung cancer represents an aggressive behavior.⁵ Ocular metastasis is a rare finding with the common primary sites of breast and pulmonary cancer and is mainly in the uveal tract, especially in the posterior choroid. Blurred vision, exophthalmos, visual loss, and ocular pain.¹³ NETs with ocular metastasis are extremely rare. A review by La Salvia et al. from 64 cases between 1966 and 2019 revealed the primary origin of NET with ocular metastasis was lung (43.7%), and the outcome of an advanced stage of NET was mainly poor.¹⁴ In this case, the patient was finally diagnosed with an advanced-stage of NET with ocular metastasis. The pathological examination was concluded to be NET, and he was presented with SVCS, pleural and pericardial effusion, and left eye proptosis.

Ensuring patients receive care consistent with their values and goals must be essential to advanced-stage pulmonary cancer management. Therefore, priority should be given to the wishes of patients and their families on the target of care, including resuscitation, ventilator support, and other best supportive care in the hospital setting or homecare setting.¹³ In this case report, the patient and his family were well-

informed of his condition during the hospitalization until his peaceful demise.

Conclusions

The COVID-19 pandemic has created unique challenges in diagnosing pulmonary cancer. Fear of the pandemic makes patients reluctant to seek help from medical facilities. Pulmonary TBC has similar symptoms to pulmonary cancer, which can pose another challenge in diagnosing pulmonary cancer in TB-endemic countries. Patients often present with advanced-stage pulmonary cancer with rare ocular metastasis.

Disclosure

The authors declare no conflict of interest

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