A post-COVID-19 Aspergillus fumigatus posterior mediastinitis: Case report

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Abstract
Invasive aspergillosis is a life-threatening condition of the immunocompromised, with a low occurrence reported in the immunocompetent. Although usually made by invasive methods, its early diagnosis is the cornerstone of a better prognosis as it yields a timely management and thus a lower mortality risk. Mediastinal invasion by Aspergillus is, like any fungal mediastinitis, uncommon and usually results from a hematogeneous or a contiguous spread, a postoperative fungal infection, a complication of a descending necrotizing fasciitis, or from an esophageal perforation. We report a case of a diabetic patient with a previous history of hospitalization 2 months earlier for a COVID-19 infection, otherwise healthy, presenting with an unresolving dorsal pain. A malignancy was expected but further work-up showed in fine a posterior mediastinitis due to Aspergillus fumigatus. Thus, fungal etiologies are to be included as a differential while diagnosing a posterior mediastinitis even in a relatively immunocompetent patient and with no evident route of entry.

Keywords
Aspergillus fumigatus, COVID-19, pathology, posterior mediastinitis, radiology, surgery

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Introduction
COVID-19 pandemic has spread throughout the world at an alarming pace since December 2019. It generated a spectrum of illness presentations, ranging from mild to severe, even fatal. It has been also associated with several complications throughout its course, mainly respiratory, sepsis, hypercoagulability, cardiac events, which can occur either in an acute setting or a delayed form. Unlike influenza, which is known to be complicated by invasive aspergillosis (IA), there has not been to date a direct association between COVID-19 infection and IA, although some cases have been reported. We report here a new case of COVID-19 complicated by IA of the posterior mediastinum.

Case presentation
A 70-year-old male non-hypertensive, non-smoker, well-controlled diabetic (HbA1c = 6.83%), presented for an unresolving back pain 2 months following a COVID-19-induced pneumonia. All routine blood investigations were normal except a slightly elevated white blood cell (WBC) (15,200/mm³). No abnormal monoclonal gammopathy was detected on the serum protein electrophoresis for a suspected multiple myeloma. A contrast-enhanced chest–abdomen–pelvis computed tomography (CT) scanner showed mediastinal calcified lymph nodes and a dense infiltrative retroesophageal prevertebral lesion of the mediastinal adipose tissue from T2 till T8. The lung fields were clear except for some retractile subpleural fibrous bands (Figure 1).

While a stepwise increase in WBC and C-reactive protein (CRP) had been observed, a broad spectrum antibiotherapy was initiated. A dorsal MR was conducted 3 days later...
showing an expanding prevertebral lesion from T2 till T9 (Figure 2).

Tuberculosis, HIV, and brucellosis testing along with blood culture came out negative. Serum galactomannan assay and reverse transcription polymerase chain reaction (RT-PCR) COVID-19 were also negative. A first percutaneous CT-guided biopsy of the prevertebral lesion was inconclusive. Rising WBC count and CRP were still reported. A control dorsal MR was carried out 10 days later, depicting a slight progression of the lesion without an intraspinal extension.

Empirical antifungal therapy with fluconazole 400 mg b.i.d. and amphotericin B 400 mg q.d. was initiated 2 days before a second CT-guided biopsy was performed. On light microscopy, necrotic lesions containing fungal organisms with acute-angle-branching hyphae were observed suggesting a mycotic infection. Culture showed growth of *Aspergillus fumigatus* (Figure 3).

At this stage, antifungal therapy was switched to voriconazole upon reception of culture, with a dosage of 400 mg b.i.d. for the first day reduced to 200 mg b.i.d. the day after for 14 consecutive days. An optimal treatment also required a surgical thoracotomy which was not executed due to the refusal of the patient’s family members. While CRP levels decreased, the patient developed increasing levels of creatinine right after initiation of voriconazole and progressive oliguria, requiring hemodialysis sessions. Ten days after the last dorsal magnetic resonance imaging (MRI), the patient acutely developed paraplegia with an altered mental state mandating an intensive care unit (ICU) transfer. A head CT performed did not show any focal abnormality in the brain parenchyma with an adequate gray matter–white matter differentiation. In addition, lumbar puncture was normal with sterile cultures. A dorsal MR performed in an urgent setting showed a recent spinal cord compression at the level of T6 to T8 (Figure 4).
Outcome and follow-up

Despite the antifungal treatment which was expectedly insufficient by itself without concomitant surgical intervention, the renal and neurological functions of the patient kept deteriorating, with him becoming comatose and intubated for the following 2 weeks before passing away.

Discussion

IA is a life-threatening infection that commonly targets individuals with chronic granulomatous disease, prolonged or profound neutropenia, solid organ or stem cell transplant, HIV/AIDS, chronic steroid, or tumor necrosis factor (TNF)-alpha antagonist use.\textsuperscript{3–6} However, it has been, although rarely, encountered in healthy individuals.\textsuperscript{7–9}

Mediastinal involvement with \textit{Aspergillus} is by itself an extremely rare condition like any other fungus in the mediastinum, resulting from a direct spread from a contiguous pulmonary infection, a hematogeneous inoculation, a post-operative fungal infection, a complication of a descending necrotizing fasciitis, or from an esophageal perforation.\textsuperscript{10–15}

To our knowledge and based on the literature review, this is the first sporadic posterior mediastinitis to \textit{Aspergillus fumigatus} following COVID-19 infection in a relatively immunocompetent patient.

Many IA cases have been described following a COVID-19 infection, most of them presenting as a COVID-19 \textit{Aspergillus} pneumonia (CAPA).\textsuperscript{16–18} The main risk factors reported are a severe illness requiring a long hospital stay, mechanical ventilation, an admission to ICU, corticosteroid therapy.\textsuperscript{19,20} However, even though it needs larger registries to be confirmed and since the pandemic is still taking a toll on a worldwide scale, COVID-19 may be by itself an independent risk factor for subsequent \textit{Aspergillus} infection.\textsuperscript{17}

Our patient, although he did not fulfill other classic host criteria for invasive fungal infection, had received during his COVID-19 hospitalization a 3-week corticosteroid therapy (dexamethasone 20 mg daily) which is his main predisposing risk factor for IA. Steroid therapy increases host immune vulnerability by impairing the frontline defense

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\includegraphics[width=\textwidth]{figure3}
\caption{Figure 3. (a) Necrotic tissue. (b) Mycelial filaments within necrotic tissue. (c) and (d) Branched and septated hyphae in favor of \textit{Aspergillus} infection.}
\end{figure}
against mold infection.\textsuperscript{21} His previous hospitalization for COVID-19 pneumonia lasted 2 weeks, did not mandate mechanical ventilation nor an admission to the ICU, and was not complicated by invasive pulmonary aspergillosis based on the findings of the SCAN.

We determined the immunocompetent status of our patient based on the medical history, the laboratory work-up, and the absence of underlying malignancy or chronic immunosuppressive drug use. His only predisposing factor was a 2-week dexamethasone course. No otherwise primary infection sites were detected (negative initial blood cultures, no surgical history of the mediastinum, no retropharyngeal or parapharyngeal abscess, and no esophageal perforation).

Since histopathological and culture are the mainstay for diagnosing \textit{Aspergillus fumigatus} infection and knowing the fastidious nature of \textit{Aspergillus}, a high index of suspicion and prompt diagnosis have to be attempted as they yield a better prognosis.\textsuperscript{6,7,22}

\section*{Conclusion}

IA should be suspected in case of clinical deterioration in patients with current or previous recent history of SARS-CoV-2. The virus itself might be a predisposing factor for IA in relatively immunocompetent patients. Prospective studies are needed to determine whether mycosis screening should be systematically performed in a post-COVID-19 complication presentation.

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N.E.H. contributed to the writing of the whole manuscript. J.G. and D.J. participated in the clinical data collection and the inpatient

\begin{figure}[h]
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\caption{Progression of the peridural spread measuring 12 mm responsible for a recent spinal cord compression at the level of T6 to T8 with a high signal abnormality on T2-weighted images. The previously reported enhancement as well as the T2-signal abnormality of the vertebral bodies is significantly increased in addition to the prevertebral lesion thickness currently measuring 7.5 mm.}
\end{figure}
follow-up. G.N. and I.D. provided all the radiologic imaging. N.M. contributed to the writing of the histopathology section, in addition to providing original histopathology figures. All authors had full access to all of the data in the study. All authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Ethical considerations
We obtained the consent of the patient’s family for the publication of his medical data. Patient privacy was fully protected, and personal information was handled such that the patient could not be identified.

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