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Commentary

Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: A diagnostic challenge

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A 73-year old Italian man with a history of diabetes, hypertension, hyperthyroidism, atrial fibrillation and obesity was transferred to our hospital on March 1, 2020 due to pneumonia associated with confirmed diagnosis of SARS-CoV-2 infection. On February 29, he was initially admitted, to the Emergency Department of another city hospital complaining of a 3 days high fever (38,5 °C) and non-productive cough. A chest X-ray showed a picture of interstitial pneumonia with enlarged heart.An arterial blood gas demonstrated a pH of 7.45, PaO_2 61 mm Hg, PCO_2 44 mm Hg, HCO3 29 mmol/L; he was put on oxygen supplementation and the following day transferred to our hospital. On admission he was alert, with a BMI 32,72, blood pressure 135/80 mm Hg, respiratory rate 24/min, heart rate 72/bpm with an oxygen saturation of 95% with 2 L O_2/m administered by nasal cannula. A chest X-ray showed interstitial opacities with focal consolidation in the upper right lobe (Fig. 1A). His medical treatment comprised bisoprolol 2.5 mg/day, methimazole 5 mg/day, rosuvastatin 10 mg/day, dabigatran 150 mg BID, insulin lispro 20 + 25 + 20 U/day and insulin glargine 40 U/day at bedtime. The patient was given antibacterial treatment (levofloxacin 750 mg/day plus ceftriaxone 2 g/d) for 3 days plus lopinavir/ritonavir 400/100 mg twice daily and hydroxychloroquine 200 mg twice daily; dabigatran was substituted by low molecular weight heparin (8000 UI). On hospital day (HD) 5, he was transferred to the ICU requiring endotracheal intubation and mechanical ventilation for progressive worsening of the radiological picture (Fig. 1B) with refractory hypoxia despite non-invasive positive pressure ventilation; at this time laboratory exams were as follow: white blood cells (WBC) 8300/μL, total bilirubin 1,46 mg/dL, aspartate aminotransferase (AST) 194 U/L, alanine aminotransferase (ALT) 81 U/L, serum creatinine 2,26 mg/dL, C-reactive protein 109,7 mg/dL, procalcitonin (PCT) 8,9 μg/L. On HD 8 of hospitalization an increase of WBC (13,620/μL) and PCT (15,8 μg/L) was observed together with altered liver enzymes (AST 323 U/L, ALT 238 U/L), total bilirubin (3,1 mg/dL) and renal failure requiring continuous renal replacement therapy (CRRT); a picture of septic shock was evident from HD 9 and antibiotic therapy was changed from piperacillin-tazobactam to meropenem (2 g every 8 hour) and ceftaroline (600 mg every 8 hour). Blood cultures were repeatedly negative. A bronchoalveolar aspirate done on HD 9, grew *Aspergillus fumigatus* 10^4 CFU/mL prompting the request for serum galattomannan antigen. On HD 11, on the basis of a positive (8.6 OD index) serum galactomannan (GM) antigen the patient was started with antifungal therapy with liposomal amphotericin B because of severe liver dysfunction (ALT 323 U/L, ALT 238 U/L, total bilirubin 4,36 mg/dL) and concomitant therapy with amiodarone (1200 mg/24 h) due to the onset of high frequency atrial fibrillation. WBC count increased from 28,980/μL (81% neutrophils) on HD10 to 45,250/μL (83% neutrophils) on HD 13 with very high CRP (323 mg/dL); A chest X-ray on HD 13 showed an improvement of the bilateral interstitial picture (Fig. 1C). The patient deceased on the morning of HD 14 due to respiratory and hemodynamic instability (after having received an initial dose of isavuconazole initially unavailable in our pharmacy). Post-mortem lung examination confirmed invasive pulmonary aspergillosis, that was characterised by bronchial wall ulceration associated with multiple spots of necrotizing pneumonia. Septate, dichotomously and progressively branching hyphae (stained with haematoxylin and eosin) consistent with *Aspergillus* spp (Fig. 1D) were more easily recognizable on Grocott-Gomori stain (Fig. 1E). The residual lung parenchyma displayed an acute lung injury pattern with diffuse alveolar damage, both in the exudative and in the proliferative phases; reactive atypical enlarged type II pneumocytes with large nuclei, prominent nucleoli and finely granular cytoplasm were present. Furthermore *Aspergillus* spp DNA was confirmed by PCR-amplification on paraffin block tissue.

Our case report illustrates the importance of considering invasive pulmonary aspergillosis as a possible complication of critically ill patients hospitalized in ICU for ARDS due to SARS-CoV-2 infection. Several laboratory findings observed in this case of IPA complicating COVID-19 pneumonia need to be emphasized; first our patient

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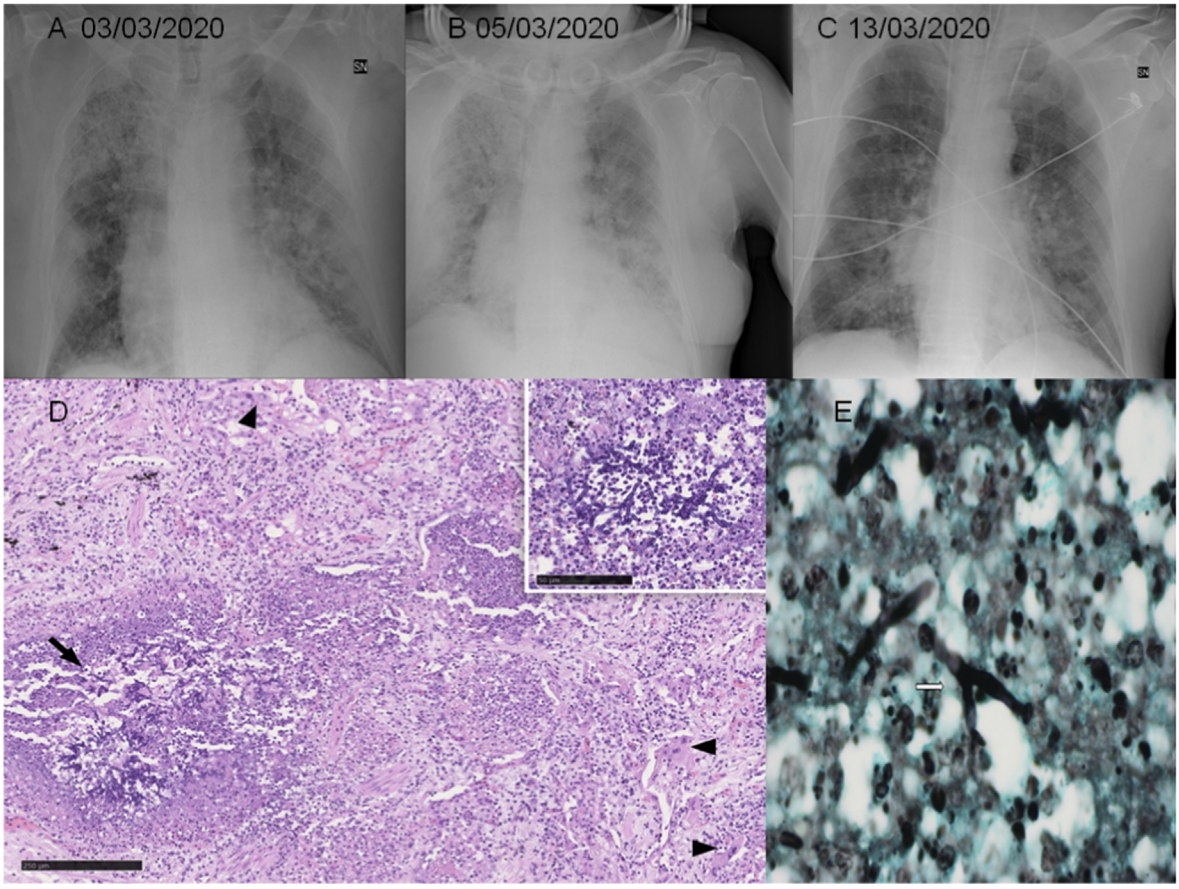

Fig. 1. (A,B,C) Sequential chest X-ray findings in a COVID-19 pneumonia complicated by invasive pulmonary aspergillosis. Interstitial opacities with focal consolidation in the right upper lobe (1A); worsening of the radiologic picture with involvement of the medium and upper right lobe and interstitial opacities in the left medium basal lobe (1B); partial regression of bilateral interstitial infiltrates (1C). 1D Autopsy lung section stained with haematoxylin and eosin showing spot of necrotizing pneumonia with several dichotomously branching septate hyphae consistent with *Aspergillus* spp (arrow and inset) surrounded by interstitial pneumonia with reactive atypical enlarged type II pneumocytes (arrow-heads) (H&E, 10x).1E Lung section stained with Grocott methenamine silver shows a branching septate hyphae (white arrow) 100x

presented with leucocytosis (up to 45,250/μL with neutrophilia), high value of PCT and C-reactive protein all of these findings generally associated with bacterial sepsis. Nevertheless, blood cultures were negative and despite aggressive empirical antibiotic therapy the patient rapidly worsened and eventually died. It should also be highlighted that high leucocytes and PCT values are more frequently detected among non-survivor patients with COVID-19 pneumonia and could be considered as a marker of disease severity thus making even more difficult to discriminate between a severe viral infection and a possible bacterial of fungal coinfection. If we consider the EORTC/MSG criteria our patient might have been classified as a possible case of IPA (only mycological criteria) whereas according to the clinical algorithm for ICU patients it would be classified as a colonized patient.

We treated our patient with liposomal amphotericin B, a drug that is considered a second-line option for IPA because of high liver enzymes value and renal failure. However, we started antifungal therapy with a delay of two days only when we received the result of GM antigen and it is unknown if an earlier treatment could have affected the outcome of our patient. We advise that even a positive sample for *Aspergillus* spp. from upper respiratory tract in a COVID-19 positive patient should prompt antifungal therapy.

Declaration of competing interest

All the Authors: no conflict of interests to disclose.

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