

Novel COVID-19, Many Faces of a New Menace: Experience with a Male, 54 Years of Age, on the Ventilator, Treated by ECMO

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Abstract: A novel Corona virus disease (COVID-19) associated with a severe acute respiratory syndrome and originated from Wuhan city, in the Hubei province of China, in late 2019. Its spread was so rapid around the globe that consequently, in March 2020, the World Health Organization (WHO) declared a COVID-19 pandemic. Although the lungs are the organs most affected because the portal of entry is via inhalation, this bug spares no organ of the body, including the nervous system, which is involved in the viremia manifesting as meningoencephalitis or intracerebral hemorrhage or even as a complication necessitating management with anticoagulants, and Extracorporeal Membrane Oxygenation (ECMO). We describe our experience with a Saudi male, 54 years of age, who had been admitted to another hospital with COVID-19 positive pneumonia, septicemia, and severe respiratory failure. Initially, he required Non-Invasive Mechanical Ventilation (NIMV), and was later put on Invasive Mechanical Ventilation (IMV) because he had developed COVID-19-induced Adult Respiratory Syndrome (ARDS) and continued to show desaturating, despite being on high flow 100% FIO₂. Therefore, being critically sick, he was started on veno-venous ECMO as rescue therapy, after the critical stage of the illness of the patient was discussed with his family.

Keywords: Novel-COVID-19, Acute respiratory distress syndrome, NIMV, ECMO, brain-hemorrhage

1. Introduction

Novel COVID-19 infection slowly began from December 2019 onwards in China [1]. At present, the disease has spread, affecting the whole world as a pandemic. An infected person may have no symptoms or may experience mild illness, but which could progress to pneumonia complicated with incapacitating respiratory failure. Some patients may develop septicemia and even succumb to the illness. This highly contagious bug can result in increased patient morbidity and mortality. Therefore, in March 2020, the World Health Organization (WHO), declared global emergency [2-4]. By September 2020, approximately over 3 million people were infected, among whom nearly one million succumbed. Among the chief symptoms of COVID-19, respiratory distress is the commonest and most distressing. Severe inflammatory response, such as a cytokine storm, very critically affects the lungs, greatly reducing the diffusion of oxygen, a condition termed Acute Respiratory Distress Syndrome (ARDS) requiring non-invasive to invasive mechanical ventilation, and in some cases, even ECMO. As we continue to encounter this new menace, we recognize its many faces, which affect almost all the body systems, without being limited to the respiratory

system alone; in fact, even the nervous system is not exempt [5-7]. The involvement of the nervous system can manifest as hyposmia, loss of taste, anorexia, or even skeletal muscle damage [8-13]. The more severe form can be observed as cerebrovascular accidents, both ischemic and hemorrhagic, gait defects, decreased cognition, and seizures. Until May 2020, only one case was reported with intracerebral hemorrhage (14). Subsequent to that report, our patient managed in July 2020, stands out as one of the first few COVID-19 cases, which reported extensive scattered multiple fluid level hemorrhagic brain lesions, in addition to having intractable respiratory failure and requiring IMV despite high flow oxygen, and 100% FIO₂, failing to achieve acceptable O₂ saturation, and thus ultimately necessitating the application of rescue therapy with V.V.ECMO (Extra-Corporeal Membrane Oxygenation). We present the details of our experience in treating this patient from the initial stage until the end.

2. Case Report

A Saudi male, 54 years of age, non-smoker, and no past medical history of any illness, was admitted in mid-July 2020 to a local hospital, with the chief complaints being

cough, fever, and breathlessness of one week. He was diagnosed as having community-acquired pneumonia, acute respiratory failure and suspected COVID-19. He reported positive for COVID-19. At first, he was started on standard anti-COVID-19 therapy, namely the MOH protocol, antibiotics (meropenem, vancomycin, azithromycin, dexamethasone), and anticoagulants for deep vein thrombosis (prophylaxis dose), as well as given respiratory support, starting with BiPAP (NIMV) with high flow oxygen. The patient did not respond and deteriorated, with severe respiratory failure, needing mechanical ventilation, which was complicated with subcutaneous emphysema and pneumomediastinum. Subsequently, he required V.V.ECMO on 27 July, 2020. The V. V. ECMO insertion was smooth, without any complications. He received a single dose of anticoagulation with 800 units of heparin, aiming for a target activated coagulation time of 40 seconds. On the same day, 27 July, 2020, as per the request of the family and administrative orders, the patient was shifted to the Adult Intensive Care Unit (AICU) in our hospital by our AICU team. On arrival, he was discovered to have type 2 diabetes mellitus, and his pupils were noted to be unequal and dilated. An urgent plain CT scan reported multiple scattered air fluid levels containing hemorrhagic brain lesions, as shown in **Figure 1 (a, b and c)**. After a multidisciplinary meeting, it was decided that anticoagulants were not to be administered to protect him against any further brain hemorrhage. The family was also kept on board during management. Hence, despite the V.V.ECMO, he was maintained off anticoagulants after the first single dose of unfractionated heparin.

3. Investigations

On 27-7-2020, the laboratory testing revealed WBC 26.96x10.3/uL, HB 12.6 g/dl, PLT 113x3/uL, INR 1.56, PPT 39.8 seconds, PT 19.4 seconds, N 86%, L 5%, D-Dimer 17.23 micrograms/ml, G6PD NA, S. Ferritin 1650 ng/ml, BU 19 mmol, S. CR 173 micromol/L, CRP 2.32 millimol/L, S. Sodium 145 mmol/L, K 5.2 mmol/L, Lactic acid dehydrogenase 1054 units/L, AST 278 units/L, ALT 270 units/L, T. BIL 251, Direct 26 micromol/L, Creatinine kinase 771 units/L, S. Albumin 26 g/L, T. protein 50 g/L, and S. troponin I 0.21 nano g/ml; blood culture showed no growth. On 28-7-2020, the tracheal aspirate showed no growth; PCR sputum for Mycobacterium was negative. On 24-8-2020, the WBC 8.5x10.3/uL, Hb 11.7 g/dl, platelets 56%, BU 46.76 mmol/L, SCR 245 mmol/L, CRP 14.30 mg/L, Lactic acid dehydrogenase 1448 units/LCK 612, Troponin I 0.12 ng/ml. ECG was normal; ECHO was normal, except for mild pericardial effusion.

On 28-7-2020, the non-contrast CT-brain as seen in **Figure 1 (a, b and c)** reported sub-arachnoid hemorrhage bilaterally. Extensive intracranial hemorrhage with multiple, innumerable, variably sized, hyperdense, intracranial, fresh blood density foci are evident in the cortical and subcortical, frontal, parietal and occipital regions being observed more in both front parietal lobes, showing multiple fluid/blood levels (bleeding at different stages). The extension of the hemorrhage into the corpus callosum anteriorly and the occipital horns of both lateral ventricles diffuse axonal injury cannot be excluded. Generalized cortical and

subcortical cerebral edema also noted, with effacement of the cortical sulci and gyri. No midline shift. Effacement of the pre-pontine cisternae, as well as around the medulla; from edema or ischemic for clinical correlation.

Non-Contrast CT-chest done on 28-7-2020 (**Figures 2 a, b, and c**) which reported both lung fields were almost replaced by extensive pneumonic consolidation patches, with air bronchogram within, as well as diffuse ground-glass attenuation and patchy subsegmental areas of crazy-paving pattern, typical of diffuse COVID-19 changes. Both lungs hypovoluminous overlying bilateral pleural effusion could not be excluded. Bilateral pneumothorax (mild on the right and minimal on the left) and pneumomediastinum were noted. Minimal pericardial effusion

4. Treatment Course in the Hospital

Multi-disciplinary meetings, including an intensivist, pulmonologist, infectious diseases consultant, neurologist, neurosurgeon, cardiologist and nephrologist, were held periodically to monitor the management and the patient's responses to management. After the first meeting post the CT-SCAN of the brain, the neurosurgeon recommended no neurosurgical intervention. That patient is treated conservatively due to the number of differential diagnoses, where no invasive approach is without extra risks in the likelihood of serious brain damage. No anticoagulants were to be used in therapeutic doses. The family was kept informed at every step of the management and investigation, with a guarded prognosis.

The patient was maintained on ventilator support along with ECMO (without anticoagulants), which was later discontinued on the improvement of his respiratory functions. Membrane oxygenation fortunately remained functional, despite no anticoagulants being used in therapeutic doses. He was managed with antibiotics (inj. meropenem, inj. vancomycin, inj. azithromycin), diuretics, anti-COVID-19 antiviral therapy with Favipiravir standard dose starting at 1,800mg q.12h on the first day, then 800mg BID for 4 days, inj. Dexamethasone 6mg IV daily x 10 days, with NGT feeding and intravenous fluids. Supplements of vitamin-B complex, zinc oxide, vitamin-D and vitamin-C were given. After two weeks of being on the ventilator, the patient required tracheostomy after the family agreed, once we explained the indications. The patient's respiratory condition improved gradually and he was able to maintain a safe range of O₂ saturation above 90% with 45% FIO₂. At this stage the ECMO was stopped as he was able to maintain satisfactory oxygen saturation. Despite no sedation, he was not able to be weaned from off the ventilator due to his low Glasgow Coma Scale of 3-4/15. Besides severe brain damage, he developed multiorgan failure with deteriorating renal and liver functions.

The patient was re-assessed by Neurology for possible brain death by clinical assessment and EEG (electroencephalogram). He was confirmed to be brain dead and after a family-physician meeting he was declared DNR (Do Not Resuscitate). The patient expired on 24-8-2020 due to cardiopulmonary arrest resulting from multiorgan failure caused by COVID-19.

5. Discussion

The common symptoms of COVID-19 include sore throat, cough, fever, dyspnea, anosmia, muscle pains, fatigability. All ages are vulnerable, but old age and those with pre-existing comorbidities are at high risk and have a less favorable prognosis. Patients having cancer, chronic renal disease, chronic obstructive airway diseases, heart failure, coronary heart disease, immunocompromised conditions, diabetes, obesity and pregnancy, as well as those having sickle cell disease, smokers, and the old and frail are vulnerable to experiencing severe illness and poor outcomes(15). Mortality has been in the range of 3.8% in the new COVID-19, whereas it was 11% in the SARS-CoV epidemic and 35-50% in the MERS-CoV epidemic(16). The pandemic of COVID-19 infection started in late 2019, and is known for mainly involving the respiratory system; however, over time, multisystem involvement, including the nervous system, has been reported in the recent literature. Neurological manifestations include meningoencephalitis, intracerebral hemorrhage, and subarachnoid hemorrhage, as observed in our patient.

No specific medication is available at present, except preventive measures like isolation of those infected, wearing a mask and observing social distancing. Those experiencing mild symptoms are quarantined and given symptomatic treatment. Those requiring hospital admissions are treated with antibiotics, corticosteroids, anticoagulants, multivitamins, vitamin-C, zinc-oxide, antiviral medicines including, hydroxychloroquine in the event of mild disease, and triple therapy (a combination of Interferon Beta-1b, Lopinavir-Ritonavir), all of which have shown good response in patients who are more ill. Favipiravir, Tocilizumab, Remdesivir, as used in France, on five patients, especially in those having the cytokine storm have shown good response, as well (17). Immunoglobulin's are also being used in those with the cytokine storm and are critically sick and cared for in Intensive Care Units(ICUs). Those with COVID-19 pneumonia and respiratory failure requiring high oxygen FIO₂ are kept under close observation, preferably in the ICU.

Those having intractable respiratory failure are given oxygen therapy ladder starting via nasal cannula (1-5liters/min) or simple face mask (6-10liters/min) or non-rebreathing face mask with reservoir bag (11-15liters/min). Many of them require NIPPV (Non-Invasive Positive Pressure Ventilation) via HFNC (High Flow Nasal Cannula) or BiPAP. The next stage is for patients unresponsive to NIPPV, the critically sick, having such severe respiratory failure that they require mechanical ventilation and, even ECMO as rescue therapy, in selected patients, as in the case of our patient.

Our patient was discovered having multiple brain hemorrhages, having low GCS (Glasgow Coma Scale) scores 3-4/15 on arrival, and having dilated pupils due to multiple brain lesions discovered on the CT-brain plain, as seen in **Figure 1 (a, b and c)**. On the 2nd day of ECMO therapy, he received only one dose of 800 units of anticoagulant unfractionated heparin. After CT-brain and the multidisciplinary meeting with the family, the patient was

kept only on DVT prophylaxis without therapeutic anticoagulation. The brain lesions were attributed to severe COVID-19 viremia and not to anticoagulation.

Our patient had bilateral severe COVID-19 pneumonia and mild left-sided pleural effusion, as shown in his HRCT-chest (**Figure 2, a, b and c**). Where mechanical ventilation fails to achieve the desired oxygenation; ECMO can play the role of rescue therapy when used by experienced teams when it has shown rewarding outcomes, as in our case. We have an experienced team and even in the past pre-COVID times, the ECMO (V-V ECMO) therapy is used for our non-Covid patients with severe pneumonia, and ARDS (adult respiratory distress syndrome) on 100% FIO₂, has shown very good outcomes. (Al-Youm, the local newspaper Jan-2019 KSAFH Tabuk, K. S. Arabia).

In terms of intractable respiratory failure, the patient responded well to management and was weaned off the ECMO after two weeks. Fortunately, the oxygenator kept functioning well despite discontinuing the therapeutic anticoagulation from the first day. Due to this low GCS scores and despite being off of sedatives or analgesics, he could not be weaned off from the ventilator. A tracheostomy was performed at two weeks of mechanical ventilation. At this stage again, a multidisciplinary meeting was called, and a probable cause of low GCS scores was attributed to the severe brain insult leading to brain death, which was confirmed by the neurology team after clinical, radiological and physiological assessments.

The patient developed multiorgan failure and despite all measures, he expired on 24-8-2020. COVID-19-associated severe brain involvement was the major contributing factor towards the fatal outcome in this patient. After WHO declared the worldwide pandemic COVID-19 emergency in March 2020, many millions of people have been infected and millions have died. At the time of the writing of this case report, FDA (Federal Drug Authority) has approved the Pfizer/BioNTech COVID-19 vaccine for emergency use. Globally, more than 70 million patients have been reported infected by 17-12-2020. To date, in Saudi Arabia, out of the three hundred and sixty thousand people infected, more than six thousand COVID-19 infected patients have been reported dead. Europe suffered more during the first and second surges in the COVID-19 pandemic. Preventive measures have played a key role in stopping the spread of this virus, while efforts are being made to invent new medicines, including the development of an effective and safe vaccine. While worldwide travel has been banned, local schools, restaurants, and public meetings have been curtailed, either by total lockdown or partial smart lockdown (as practiced in Pakistan) which have shown a decline in the local spread of the disease (BBC).

At present, COVID-19 is being investigated as a new bug, affecting all the organs of the body. Therapeutic protocols have been evolving, sharing the experiences of clinicians worldwide. Trivial symptoms may resolve without any residual sequelae. In patients with COVID-19 pneumonia, and especially those cared for in the ICU (Intensive Care Unit), their oxygen dependency has been shown for some time and only a few of them required oxygen therapy for

prolonged periods. Respiratory failure associated with post-COVID-19 restrictive lung disease (based on a multitude of pathological issues) is a recognized entity in severe COVID-19 treated patients (18). Therapeutic bronchoscopy, although not recommended by WHO in the acute COVID-19 infected patients, has been of some benefit in selected patients experiencing intractable respiratory failure when they are negative and non-infectious in well-established Intensive Care Units (as in South Africa). Whereas efforts to discover an effective and safe vaccine are still underway, some of the countries have already begun vaccinating their population, England (UK) being the first in the world (BBC) followed by USA. Saudi Arabia has commenced using the vaccination by Pfizer in three phases—first, the healthcare workers and then those above 60 years will be vaccinated. In the second phase, those above 50 years and those desirous of getting the vaccine in the final phase. Pfizer has claimed the efficacy of the vaccine against the various strains of COVID-19 to be between 74 to 95.5% (19).

Conclusion: COVID-19 is unique in its vast clinical manifestations, sparing no system, including the nervous system. Its adverse effects on the health system and economy will be strongly felt for a long time. The medical community in general, and the respiratory specialists and intensivists need to play more effective roles in the early recognition of the COVID-19 complications, for better management and having sufficient resources. The clinical guidelines at both the global and regional levels have enabled consensus on the management to be reached. After the use of standard preventive measures, pharmaceutical, technical resources, clinical outcomes and data collection will facilitate developing better management strategies. Until the COVID-19 pandemic is over, preventive measures along with mass vaccination, remains the only way forward in tackling this new menace as, until now, no single specific antiviral therapy is available. Post COVID-restrictive lung disease, such as fibrosis, in patients treated in the AICU remains a new challenge, which keeps them oxygen-dependent, despite their negative conversion. As the whole world has been affected, worldwide collaborative efforts are urgently required, because no one is safe until everybody is safe.

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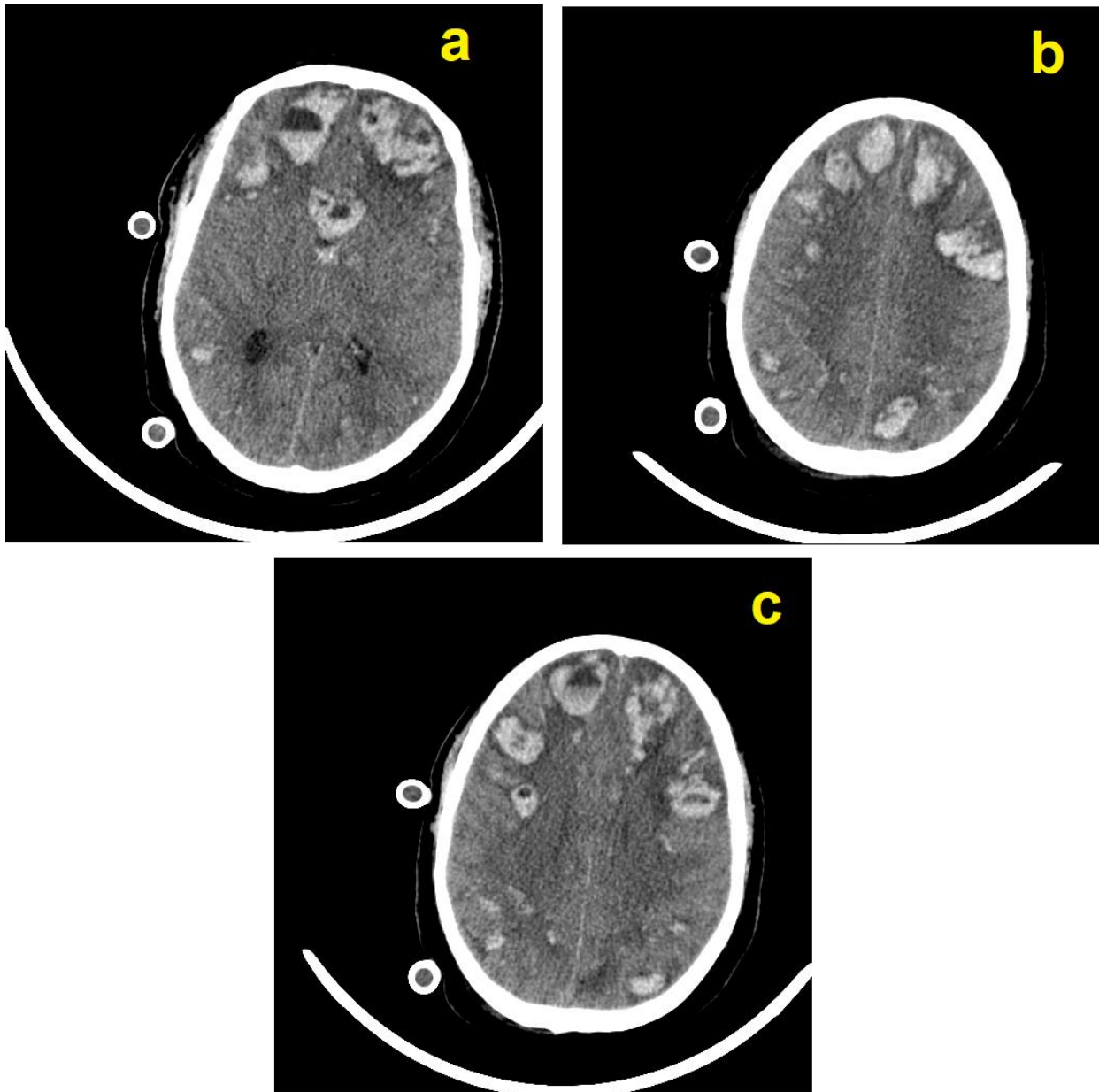


Figure 1 (a, b and c): CT-brain plain

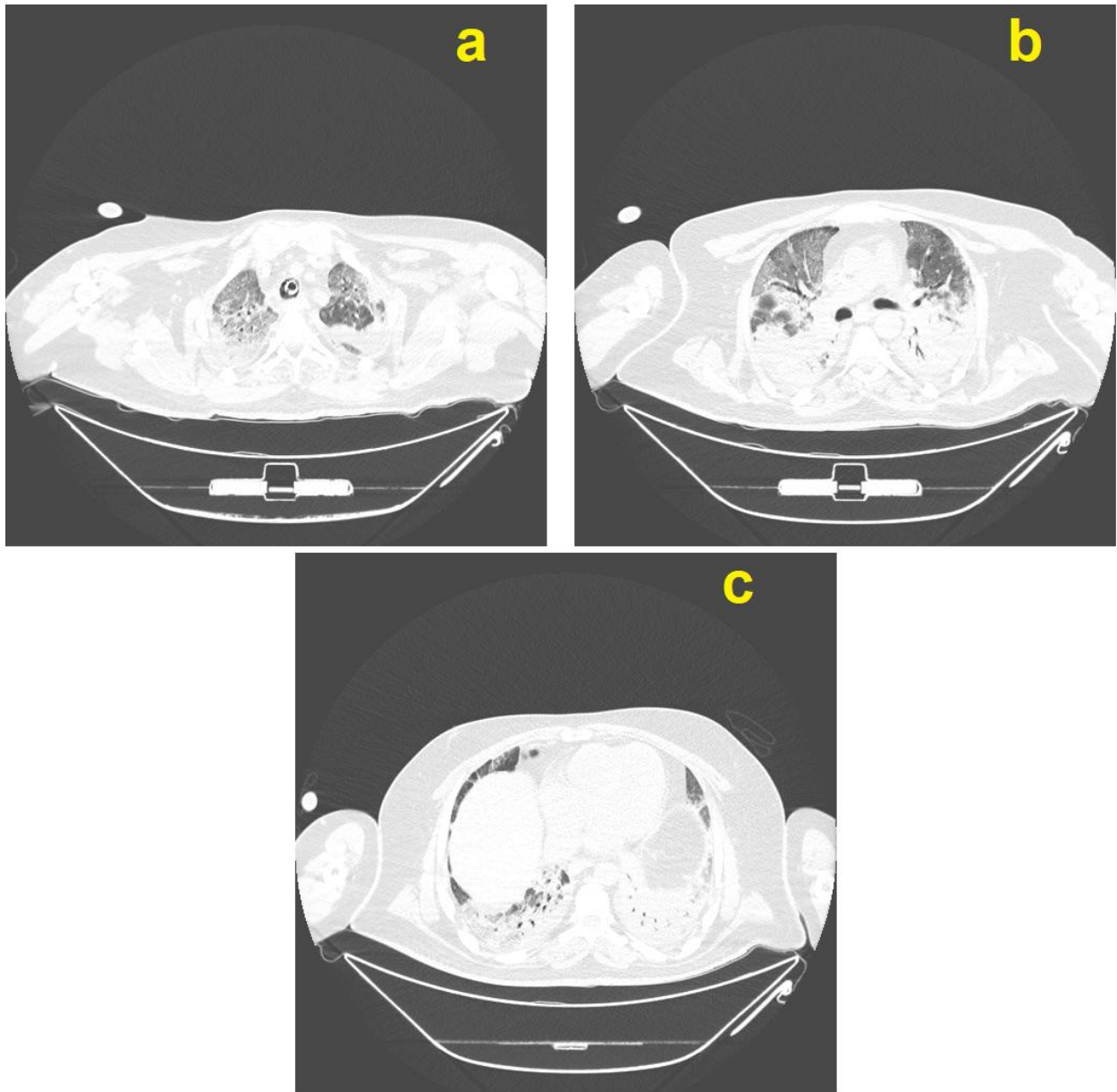


Figure 2 (a,b and c): HRCT-chest