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Acute Respiratory Distress Syndrome in A 32-Year-Old Man with Newly Diagnosed Wegener's Granulomatosis C-ANCA Positive Pauci Immune Crescentic Glomerulonephritis with Leucopenia Treated Successfully: A Rare Case Report

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ABSTRACT

A 32-year-old man presented with myalgia, polyarthritis, hearing problem, sneezing, erythematous rash, episcleritis for one month. As serum creatinine was high, renal biopsy was done; it was compatible with pauci immune glomerulonephritis. Blood c-ANCA was positive; and, both anti-glomerular basement membrane antibody and p-ANCA were negative. Therefore, he was diagnosed as a case of Wegener's Granulomatosis with rapidly progressive glomerulonephritis, and treated with corticosteroids, cyclophosphamide and rituximab. Hemodialysis was initiated shortly after immunosuppressive treatment as serum creatinine was rising. He developed dyspnea and low SaO_2 due to acute respiratory distress syndrome (ARDS). Total WBC count was low ($2.1X10^9$ /L). He was successfully treated with continuous positive airway pressure (CPAP).

KEYWORDS: Wegener's Granulomatosis, serum creatinine, ARDS, c-ANCA related pauci immune glomerulonephritis, leucopenia, CPAP

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a fatal condition with insufficiently clarified etiology. Supportive care for severe hypoxemia remains the mainstay of essential interventions for ARDS. In recent years, adequate ventilation to prevent ventilator-induced lung injury (VILI) and patient self-inflicted lung injury (P-SILI) as well as lung-protective mechanical ventilation has an increasing attention in ARDS. Wegener's Granulomatosis (WG) is an uncommon autoimmune disease characterized by granulomatous

inflammation of the respiratory tract and systemic small vessel vasculitis that is usually associated with significant morbidity and mortality. Although WG is considered to be an autoimmune disease, its pathogenesis is not fully understood. The diagnosis of WG is made based on clinical features of illness associated with the presence of c-ANCA and vasculitis in small arteries and veins, with the presence of giant cells and epithelioid cell granulomas.

Common presenting features of WG were reported as glomerulonephritis (88%), diffuse alveolar hemorrhage (DAH) (44%) and venous thrombotic events (12%).

The following case report illustrates the diagnostic difficulties encountered by physicians facing dyspnea in young man with recently diagnosed WG with crescentic glomerulonephritis.

CASE PRESENTATION

A 32 years old doctor was previously healthy till September 2023. He had sneezing , feeling of blockage in both ears more on right and epistaxis for 1 week duration; and, he was treated as a case of acute suppurative otitis media. He was given co-amoxiclav 625mg 3 times a day for 10 days and topical nasal steroid. It was followed by episcleritis of left eye, myalgia and polyarthritis involving large joints: both knee joints, elbow joints multiple joint pain especially in large joint. They were swollen; very tender; non-migratory in nature; and, disturbing sleep even with diclofenac 50 mg 3 times a day. The clinical impression was acute polyarthritis due to virus (Chikungunya infection) or bacterial (acute rheumatic fever) in etiology. Blood for complete picture showed normal total WBC count, hemoglobin and platelet count. Inflammatory markers were slightly raised; ESR was 10 mm in 1st hour; and CRP 6.7 mg/L. ASO titer was 200 units; serum creatinine was normal (0.93 mg/dl); uric acid was high normal (7.4 mg/dl). Anti-CCP was negative and RA test was positive. As RA test was positive; the likelihood of seropositive RA was considered though several points were against it. They were male sex; relatively short duration of joint symptoms of less than 2 weeks; involvement of large joints. Rheumatologist suggested to start steroids, methotrexate, calcium supplements for possible seropositive rheumatoid arthritis and allopurinol for hyperuricemia.

One month later, erythematous maculo-papular rash appeared on both shin and chest; they were tender. It is shown in photo (15) and (16). He had poly-chondritis of both ears. It is demonstrated in photo (17) and (18). Episcleritis improved though myalgia and polyarthritis were worsening. Then, he had puffy face; serum creatinine suddenly rose to 7.2 mg/dl. ANA was negative. Features were highly suggestive of acute interstitial nephritis or analgesic nephropathy. His urine output was normal. Meanwhile, he was having low grade fever. Full blood count showed normal; total WBC count was upper normal limit ($12X10^9$/L); hemoglobin was 12.9 gm/dl; platelet count was 406 $X10^9$/L. Inflammatory markers were rising rapidly; ESR became high (70 mm in 1st hour); CRP rose to 89 mg/L. Uric acid was remained high 8.2 mg/dl; liver function tests were normal; and random blood sugar was 103 mg/dl. Blood urea was very high 142 mg/dl; and, serum creatinine was very high too 7.2 mg/dl; serum potassium was 5.58 meq/L. Chest radiograph was normal. Serial chest radiographs are shown in photo (1) to photo (7). Ultrasound kidney was suggestive of bilateral mild nephropathy. All features pointed to acute kidney injury due to acute interstitial nephritis or analgesic induced nephropathy. In ANCA testing, p-ANCA was negative and c-ANCA was positive. Regarding ANCA profile, both Proteniase 3 and Myeloperoxidase were negative. Renal biopsy was suggestive of a pauci- immune crescentic glomerulonephritis. He was given aggressive treatment to save kidney with rituximab, methylprednisolone and cyclophosphamide.

Nonetheless, he continued to have oliguria, rising serum creatinine and fluid overload. Therefore, hemodialysis was initiated on 02-02-2024 after fourth dose of rituximab. The patient suffered dyspnoea at rest at the day after last (third) dose of intravenous cyclophosphamide. He continued to have orthopnea, falling SaO2 even after removal of fluids with hemodialysis. Therefore, high flow oxygen was initiated. ECG revealed sinus tachycardia; echocardiogram was normal. Chest radiograph was normal. Serial chest radiographs are shown in photo (1) to photo (7). High resolution CT (HRCT) and CT pulmonary angiogram were normal. Serial HRCT chest in comparison (Figure A, Figure B & Figure C) are revealed in photo (8), (9) and (10). Photo (13) demonstrates HRCT (Chest) coronal view (Figure A & Figure B). CT pulmonary Arteriograms in comparison (Figure A & Figure B) are illustrated in photo (11) and (12).

Doppler lower limb was normal. Then, total WBC count dropped to $2.1X10^9$/L; hemoglobin decreased 6.9 gm%; and platelets count was $240X10^9$/L.

The possibilities for dyspnoea were severe COVID-19 pneumonia, pulmonary embolism, pulmonary hemorrhage and ARDS. Intensive care physician put him on respiratory support with non-invasive ventilation; continuous positive airway pressure (CPAP). Photo (14) shows patient on CPAP. As he was immunocompromised, bacterial bronchopneumonia as well as *Pneumocystic carinii* pneumonia was possible. For infection control, vancomycin, meropenum and septrin were initiated. Echocardiogram on 04.03.24 revealed normal heart valves and chambers; no vegetation; normal LV systolic and diastolic function with LVEF 66%; normal RV systolic function; trace MR; trace TR; no pulmonary hypertension; minimal pericardial effusion in postero-lateral region (1.2cm).

Chest radiograph revealed bilateral opacities. HRCT was repeated; it showed bilateral relatively symmetrical ground glass opacification with a normal sized heart. They were

suggestive of non-cardiogenic pulmonary oedema or acute respiratory distress syndrome. It is demonstrated in photo (13). CT pulmonary angiogram revealed no evidence of pulmonary embolism. Minimal pericardial effusion with non-cardiogenic pulmonary oedema is noted. Photo (14) shows CTPA. The CT paranasal sinuses examination revealed a small mucosal polyp in the right maxillary with bilateral maxillary sinusitis. Photo (12) shows CT of nasal sinuses in various view.

The condition was in desperate situation for several days; then, he improved gradually. HRCT recheck done on 18.03.24 showed improvement; there were residual ground-glass opacities at non-dependent portions of both lung fields. New findings of fibrotic changes, bilateral minimal pleural effusion and minimal air in the mediastinum were seen.

DISCUSSION

This patient had positive testing for c-ANCA; an antiproteinase 3 antibody (PR3-ANCA) was negative and an anti-myeloperoxidase antibody was negative too. ANCA with a cytoplasmic pattern (c-ANCA) is not a diagnostic criterion of WG according to The American College of Rheumatology; the specificity and sensitivity in the diagnosis of WG with c-ANCA positivity was 96% and 92% respectively. Being low-income country, the exact titer could not be done. In this case having upper respiratory symptoms and renal manifestation with c-ANCA positivity established the diagnosis WG. Blood test for c-ANCA was an important feature for the diagnosis. This is one reason for doing case report.

This patient was on rescue hemodialysis; nonetheless, he was dyspneic even after hemodialysis. Clinically, tachypnoea, low SaO2, tachycardia and very few crackles were recorded; they made the physician to have several challenges for cause of dyspnoea. The reasons for having dyspnea in this patient, on hemodialysis, may be multi-factorial. The possibilities were as follows: (1) ARDS; (2) rituximab induced acute lung injury; (3) severe bacterial bronchopneumonia; (4) severe viral bronchopneumonia; (5) fungal bronchopneumonia; (6) heart failure; (7) pulmonary hemorrhage; (8) pulmonary embolism; (9) severe COVID-19 pneumonia; and, (10) thiamine deficiency (cardiac beriberi).

It was important to identify exact cause of dyspnoea/hypoxia in this situation which may be immune-related or non-immune cause. If it was due to immune-related cause, aggressive immunosuppressants were indicated. On the other hand, it was better to avoid unnecessary immunosuppressive therapies if the cause was non-immune like infective cause. Gibelin et al found that non-immune causes attributed 43% in patients with small-vessel vasculitis having acute respiratory failure (Gibelin et al., 2021).

In this patient, chest radiograph did not reveal gross lesion and echocardiogram was normal at the onset of dyspnea. Heart failure and cardiac beriberi were unlikely. Therefore, HRCT chest and CTPA were done urgently. They did not reveal gross lesion. As HRCT chest was normal pulmonary hemorrhage and ARDS were not possible; pneumonia would be seen obviously in HRCT chest. Metabolic acidosis was excluded as serum HCO_3 was normal. We did not get a clue for his hypoxemia initially; nonetheless, his dyspnea was increasing.

According to report by Ahmad et al, even in the absence of disease-specific radiological signs of granulomatosis with polyangiitis, severe intrapulmonary granulomatosis with polyangiitis may be present (Ahmad et al., 2021). Therefore, this patient might have intrapulmonary granulomatosis with polyangiitis. However, to produce low SaO2, severe intrapulmonary granulomatosis with polyangiitis could be visible in HRCT chest. He had received 6 doses of rituximab and corticosteroids and cyclophosphamide. As the action of rituximab usually start at 2 to 6 months(Keogh et al., 2006), the action of rituximab was not evident in this case. Therefore, this patient could be a case of WG with severe intrapulmonary granulomatosis with polyangiitis refractory to corticosteroids and cyclophosphamide.

We kept him on high flow nasal oxygen, intravenous corticosteroids and antibiotics. Wegener's granulomatosis (WG) is an uncommon necrotizing vasculitis having variable presentations in the chest that are best seen on high resolution CT chest. Imaging findings are various pattern: nodules which may cavitate; ground-glass opacity secondary to pulmonary hemorrhage; and airway stenoses and ulcerations. Moreover, active WG can mimic pneumonia, septic emboli, and metastases (*ECMO Rescues Patients With Acute Respiratory Failure Related to GPA*, n.d.-c).

Chest radiograph was normal initially; however, recheck one done 10 days later revealed features of ARDS. HRCT chest repeated 10 days also showed features suggestive of ARDS; and, it ruled out pulmonary hemorrhage. It pointed out the value of repeating chest radiograph and HRCT chest if the cause of dyspnea was not solved. This is the learning point from this case. In fact, repeating HRCT chest was not easy in every hospital low resource setting.

Pulmonary hemorrhage in WG was frequently reported (Mirouse et al., 2020) (Arora, 2014); and the mortality rate was very high (66%). Repeating HRCT chest and CTPA were crucial for ruling out pulmonary hemorrhage and pulmonary embolism in this case. If HRCT chest showed features of pulmonary hemorrhage, he had to undergo plasmapheresis. On the other hand, he required anti-thrombolytic therapy and anti-coagulation if CTPA was compatible with pulmonary embolism.

After ruling out pulmonary hemorrhage and pulmonary embolism, he was treated as a case of ARDS. The underlying cause of ARDS was also challenging in this case. The likely causes of ARDS in this case were as follows: (1) ARDS resulting from WG itself; (2) rituximab induced acute lung

injury; (3) severe bacterial bronchopneumonia causing ARDS; (4) severe viral bronchopneumonia causing ARDS; (5) severe COVID-19 pneumonia with ARDS; (6) *Pneumocystic carinii* pneumonia; and, (7) fungal bronchopneumonia causing ARDS.

The patient had leucopenia; total WBC was $2.4X10^9$/L. Therefore, severe bacterial bronchopneumonia causing ARDS and severe viral bronchopneumonia causing ARDS were possible. He had dry cough and blood culture was sterile. The possibility of *Pneumocystic carini* pneumonia was not ruled out though he was negative for HIV serology.

Rituximab induced acute lung injury in lung transplant recipient was reported by Baughman et al (Baughman et al., 2012). On the other hand, rituximab was reported as a well-tolerated and effective remission induction agent for severe refractory WG. It was reported that full remission rates was achieved in two third of patients with WG ANCA-positive vasculitis refractory to corticosteroids and cyclophosphamide (Keogh et al., 2006) (Dolch et al., 2013); and, it was also good in non-refractory cases of WG (Powers et al., 2013). McAtee et al pointed out that rituximab was well tolerated among young people; and, it was associated with few serious adverse events commonly infections (McAtee et al., 2021). Therefore, the possibility of coexisting bacterial or virus or fungal pneumonia was worrisome in this patient. Hence, he was treated with meropenem, vancomycin, fluconazole and trimethoprim-sulpharmethoxazole. The study in China pointed out that infection rate during induction therapy was high in patients with WG ANCA-associated vasculitis; among them, bacterial pneumonia was the main type of infection encountered (Yang et al., 2018). Thus, giving antibiotics in this patient was justifiable with their findings. Yang et al also found that age at the time of diagnosis, history of smoking, baseline high serum creatinine (≥5.74 mg/dl), low $CD4^+$ T cell (< 281 μl), and intravenous cyclophosphamide were identified as risk factors for infection. This patient had all risk factors; rapidly rising serum creatinine, leucopenia and he received intravenous cyclophosphamide. Therefore, he was very vulnerable to infection.

Regarding management of ARDS, mechanical ventilation and ECMO were applied for more severe ARDS (Ohshimo, 2021). Determining oxygenation targets in ARDS remained a challenge among intensive care physicians (Capellier et al., 2023). Oxygen therapy was routinely administered to mechanically ventilated patients. However, there were controversial issues on the optimal oxygen titration target in patients with ARDS. Boyle et al reported that mortality was lowest when the average time-weighted PaO_2 was between 12.5 and 14 kPa (93.8–105.0 mmHg), suggesting this was a reasonable oxygenation target for clinicians to aim for (Boyle et al., 2021). Ohshiomo et al found that early exposure to a conservative-oxygenation strategy with a Pao_2 between 55 and 70 mm Hg in patients with ARDS did not increase survival at 28 days (Ohshimo, 2021). Anyhow, this patient improved with CPAP.

According to Yokoyama, the purpose of noninvasive respiratory management in ARDS, such as noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) oxygen therapy, was to prevent unnecessary intubation and worsening of the disease severity. The lung protective strategy, mainly including low tidal ventilation, was important in the respiratory management of ARDS (Grieco et al., 2021). The effect of NIV and HFNC for ARDS was limited because of the lack of strict limitation of tidal volume. He said that both NIV and HFNC were effective as respiratory management in mild and early ARDS (Yokoyama & Kondoh, 2022). This patient recovered with CPAP and HFNC, supporting Yokoyama. If maximum mechanical ventilation is unable to maintain oxygenation, extracorporeal membrane oxygenation (ECMO) should be considered as the final respiratory supportive method, if available (*ECMO Rescues Patients With Acute Respiratory Failure Related to GPA*, n.d.-a). Luckily, this patient recovered with CPAP and HFNC. ECMO has a life-saving role in the management of patients with severe respiratory failure due to ANCA-associated pulmonary capillaritis.The benefits of ECMO in severe hypoxemic respiratory failure secondary to diffuse alveolar hemorrhage from Wegener granulomatosis was reported (Ahmed et al., 2004) (Sánchez-Escuredo et al., 2011) (Wang et al., 2021) (Delvino et al., 2019).

CONCLUSION

If patient with WG, ANCA associated vasculitis, presented with dyspnea, various pulmonary manifestations of WG should be find out seriously. Immune-related cause as well as non-immune cause have specific treatment. Awareness of acute respiratory distress syndrome (ARDS) is important if patient has dyspnea and low SaO2. Repeating chest radiograph and CT imaging are essential if hypoxia persists and initial one does not give clue. CPAP and HFNC are successful oxygen therapy in ARDS.

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ETHICAL CONSIDERATION

Informed consent was taken from patient for case reporting.

CONFLICT OF INTEREST

There was no COI.

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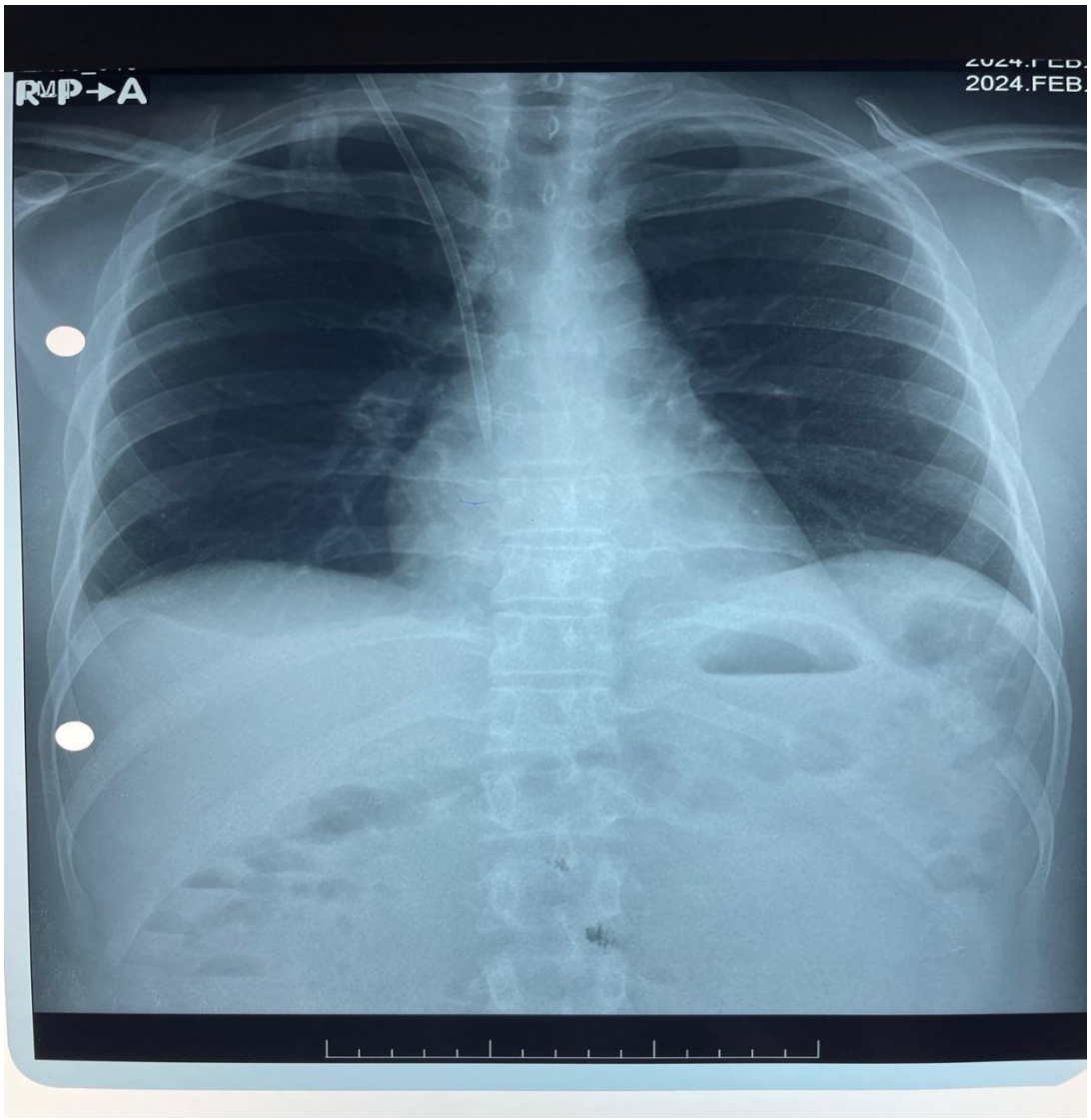

Photo (1) Chest radiograph (02.02.2024) showing normal with a catheter in SVC and right atrium for rescue hemodialysis

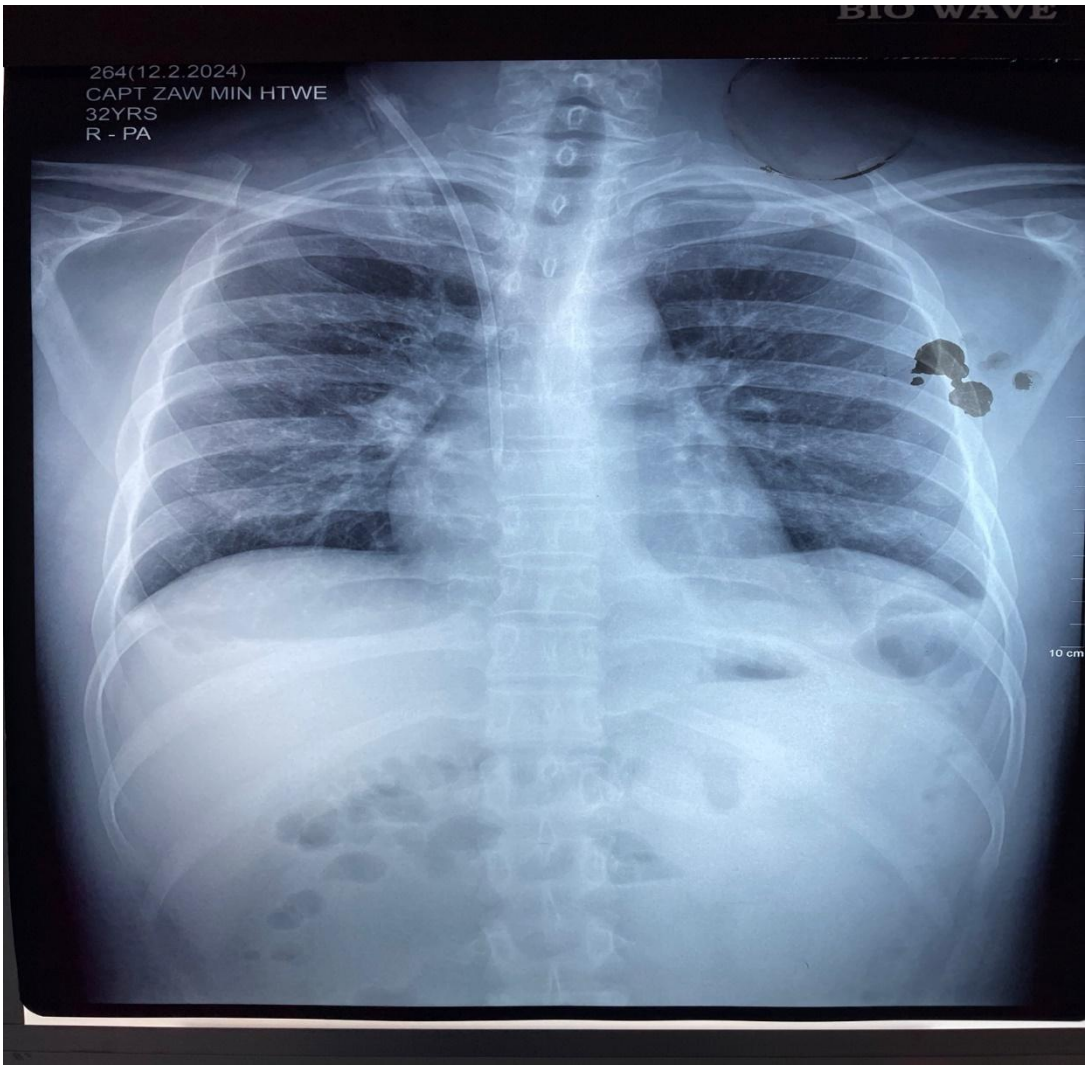

Photo (2) Chest radiograph (12.02.2024) showing very faint patchy opacities over right middle and lower zone with a catheter in SVC and right atrium

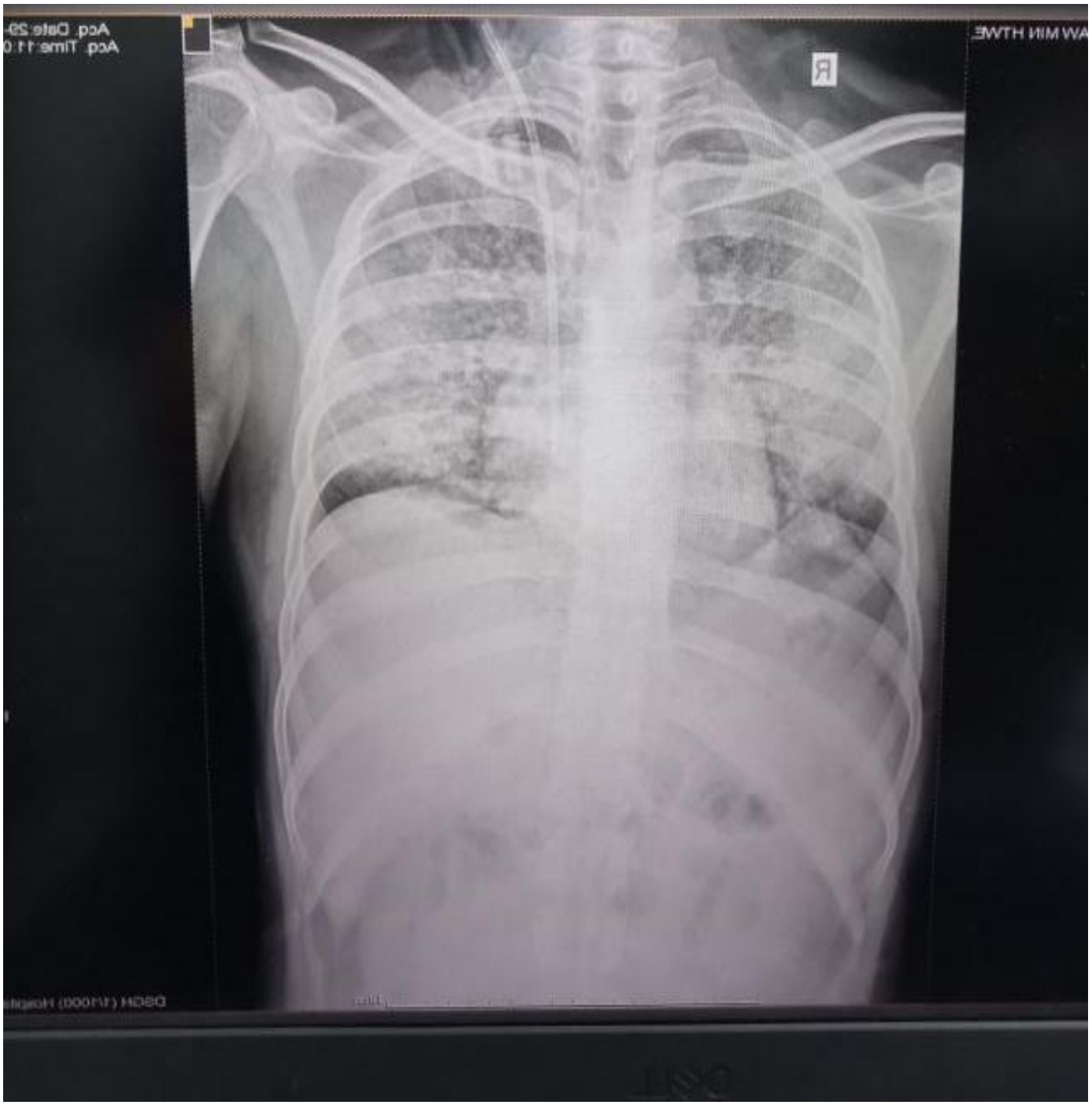

Photo (3) Chest radiograph (22.02.2024) showing opacities over both middle and lower zone with a catheter in SVC and right atrium

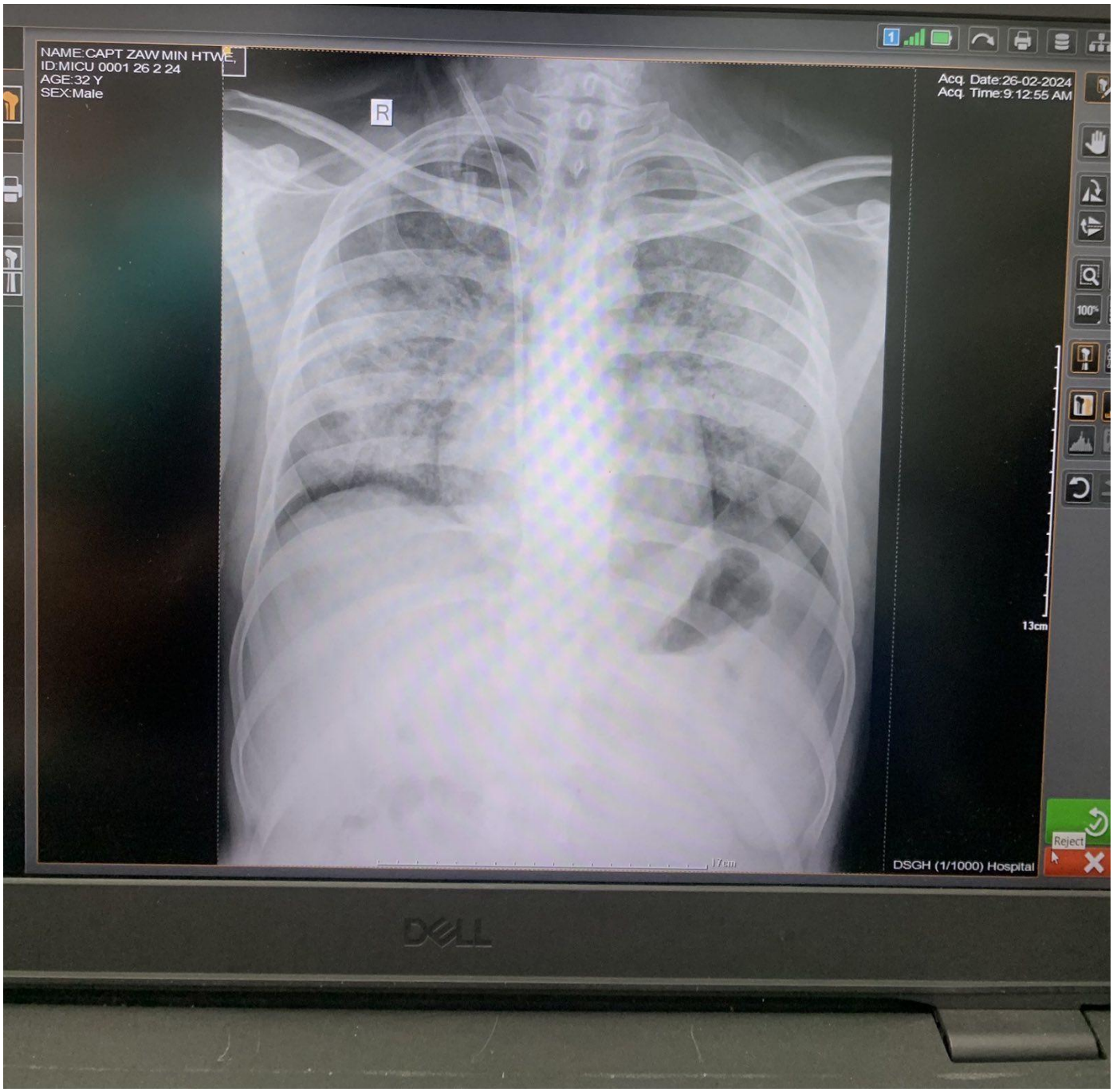

Photo (4) CXR taken on 26.02.2024 showing improvement

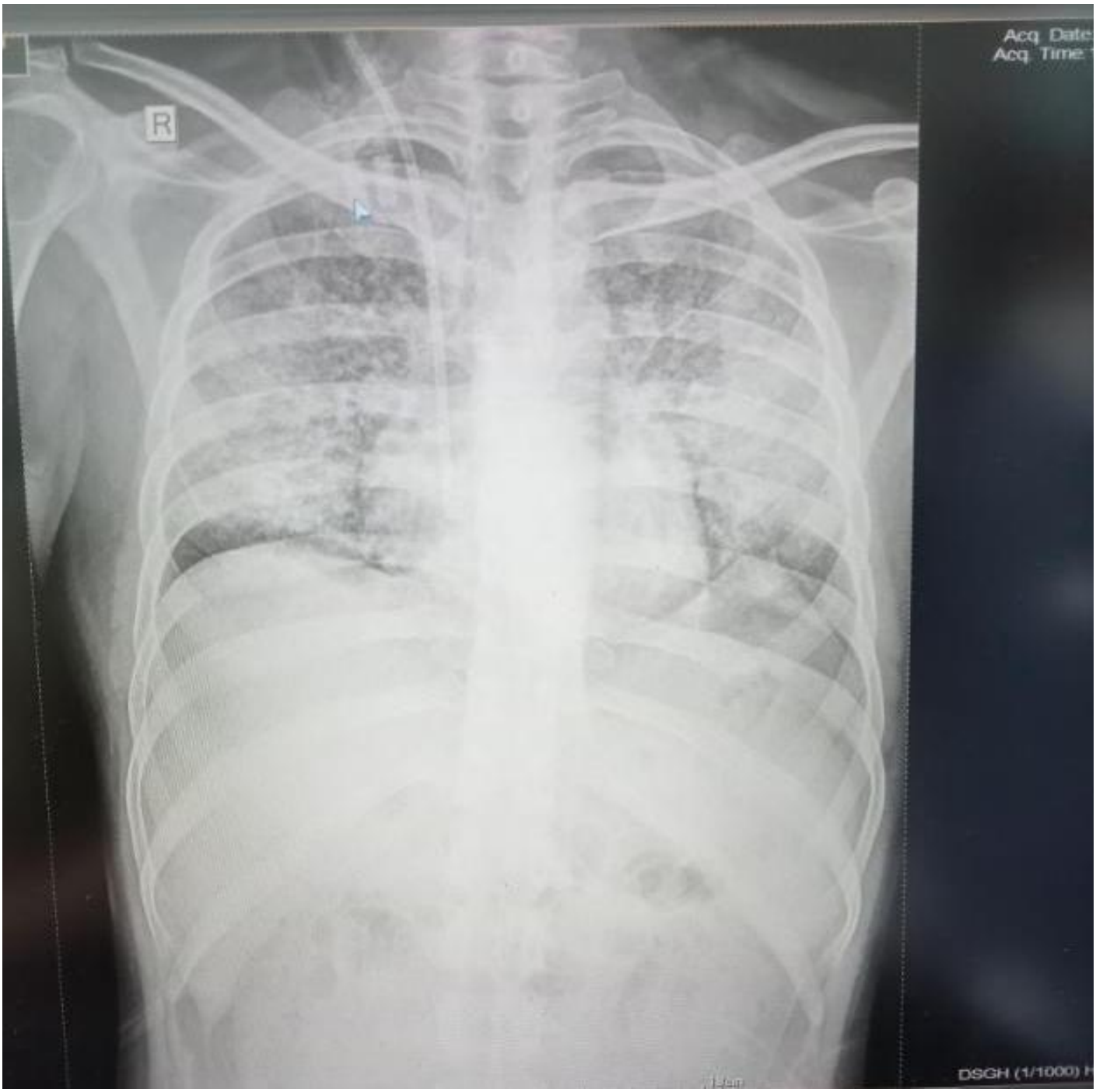

Photo (5) Chest radiograph (29.02.2024) showing opacities over both middle and lower zone with a catheter in SVC and right atrium

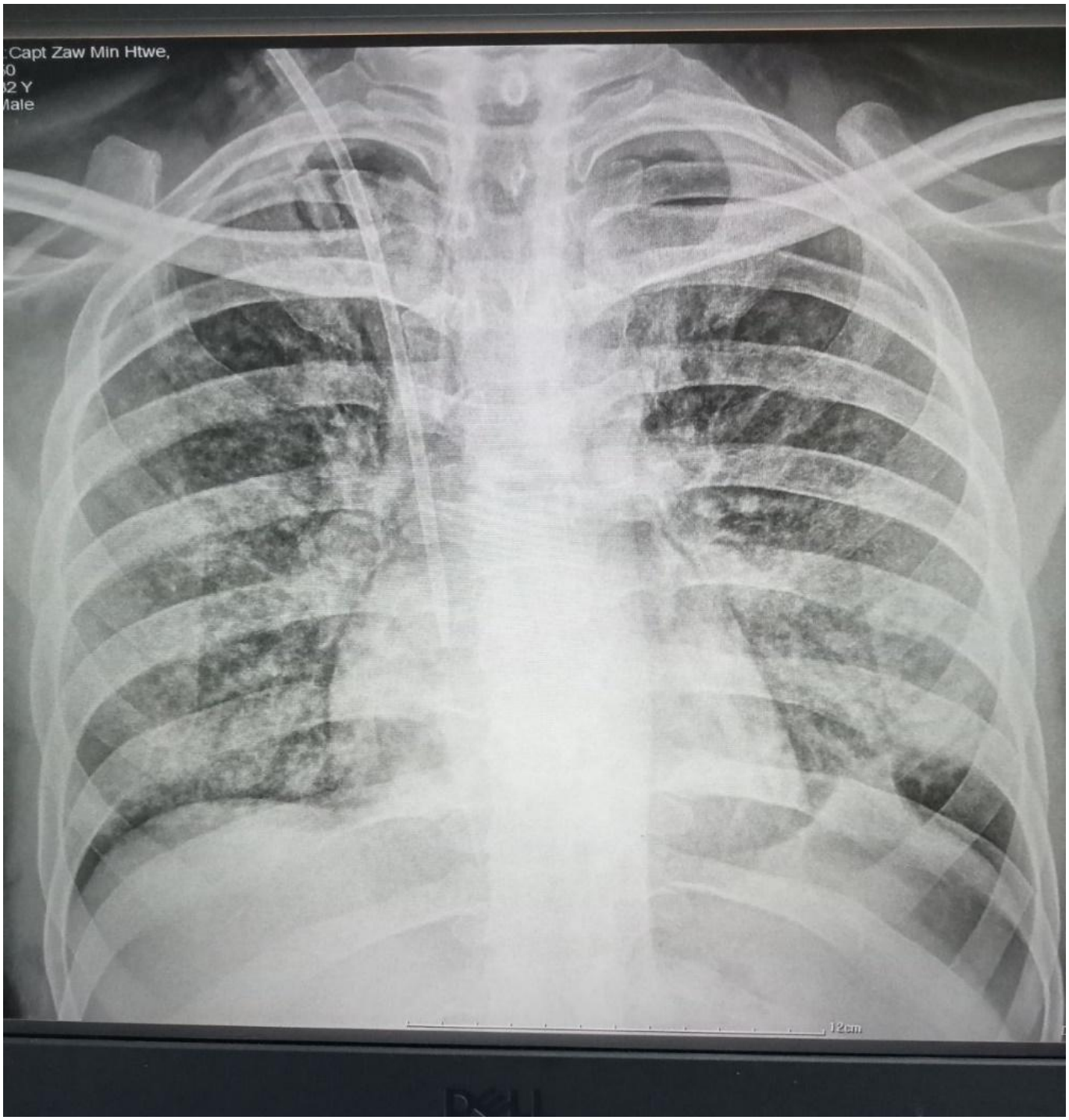

Photo (6) Chest radiograph (18.03.2024) showing improvement

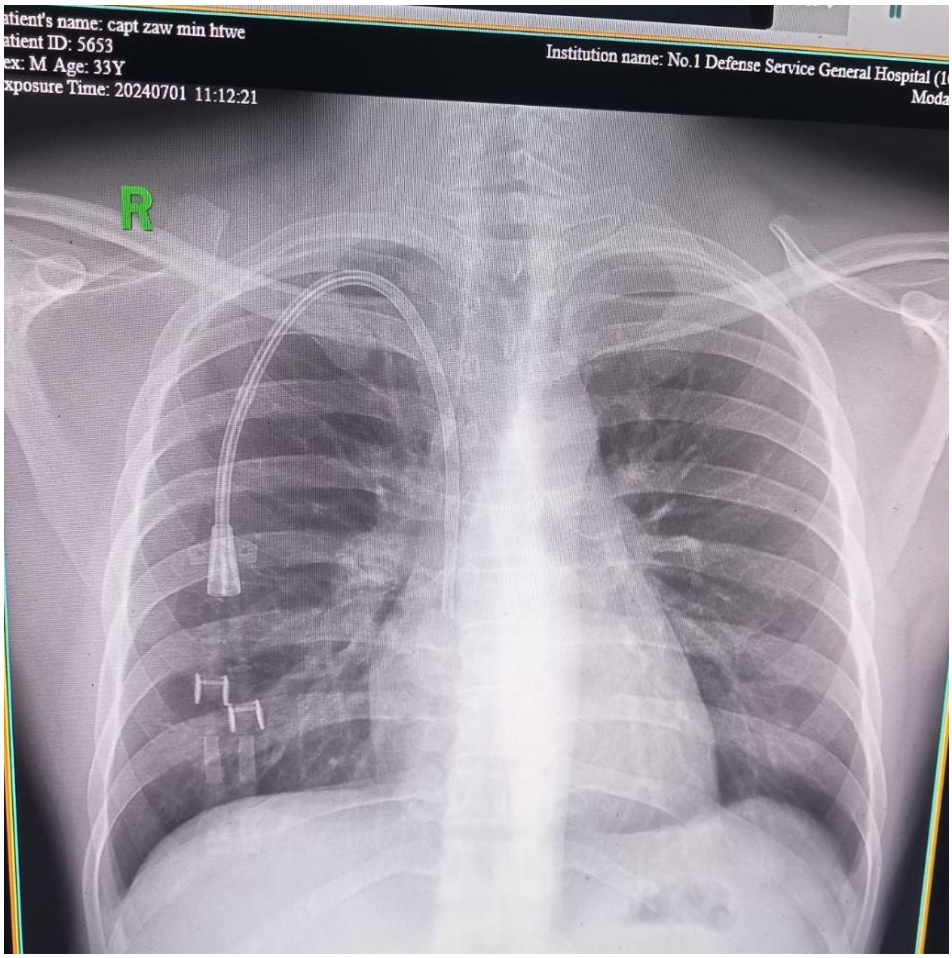

Photo (7) Chest radiograph (01.07.2024) showing almost clear lung fiel

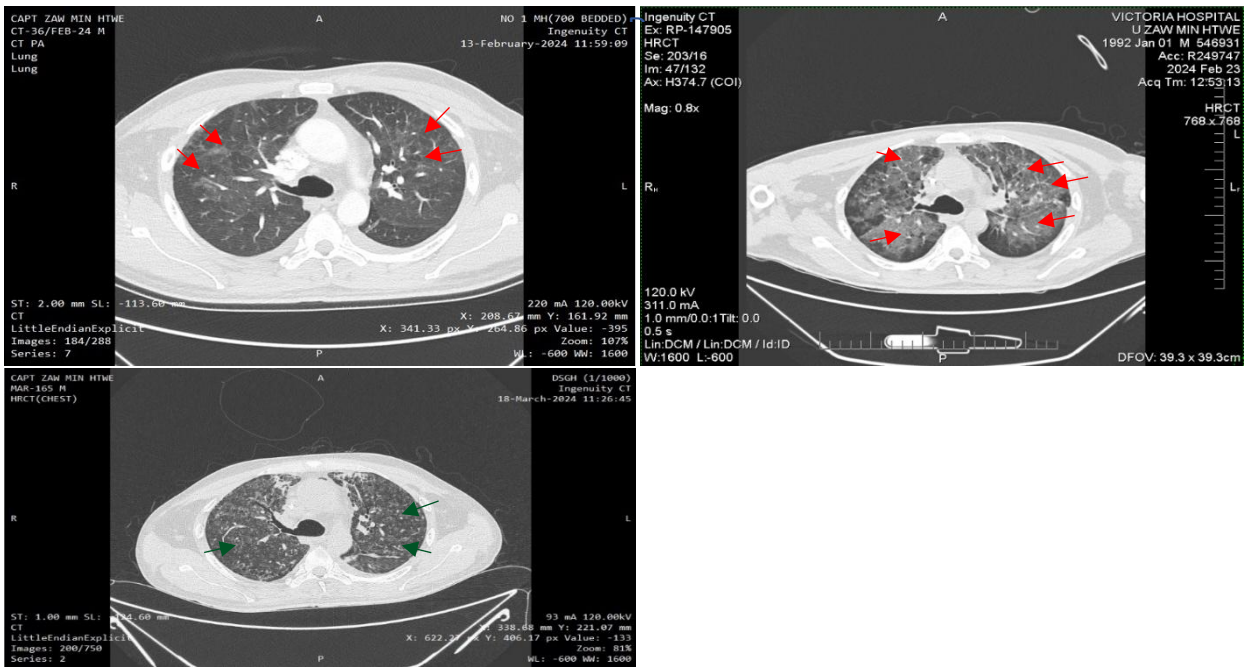

Photo (8) Comparison of serial HRCT chest (Figure A, Figure B & Figure C)

HRCT (Chest) lung window axial view at the level of the carina showing images in Figure (A, upper right), taken on 13th February 2024, showing the patient's lungs with signs of diffuse alveolar damage. Ground-glass opacities are present in both lung fields, with bilateral patchy areas of increased attenuation (indicated by red arrows). Figure (B, upper left),

taken 10 days later, showing a progressive increase in ground-glass opacities and expansion of consolidation areas. These changes are bilateral and relatively symmetrical (indicated by red arrows) and Figure (C, lower left) was taken in 18th March 2024 showing Ground-glass opacity present bilaterally and relatively symmetrical was still present but reduced in density and presence of aerated regions exhibited (green arrow).

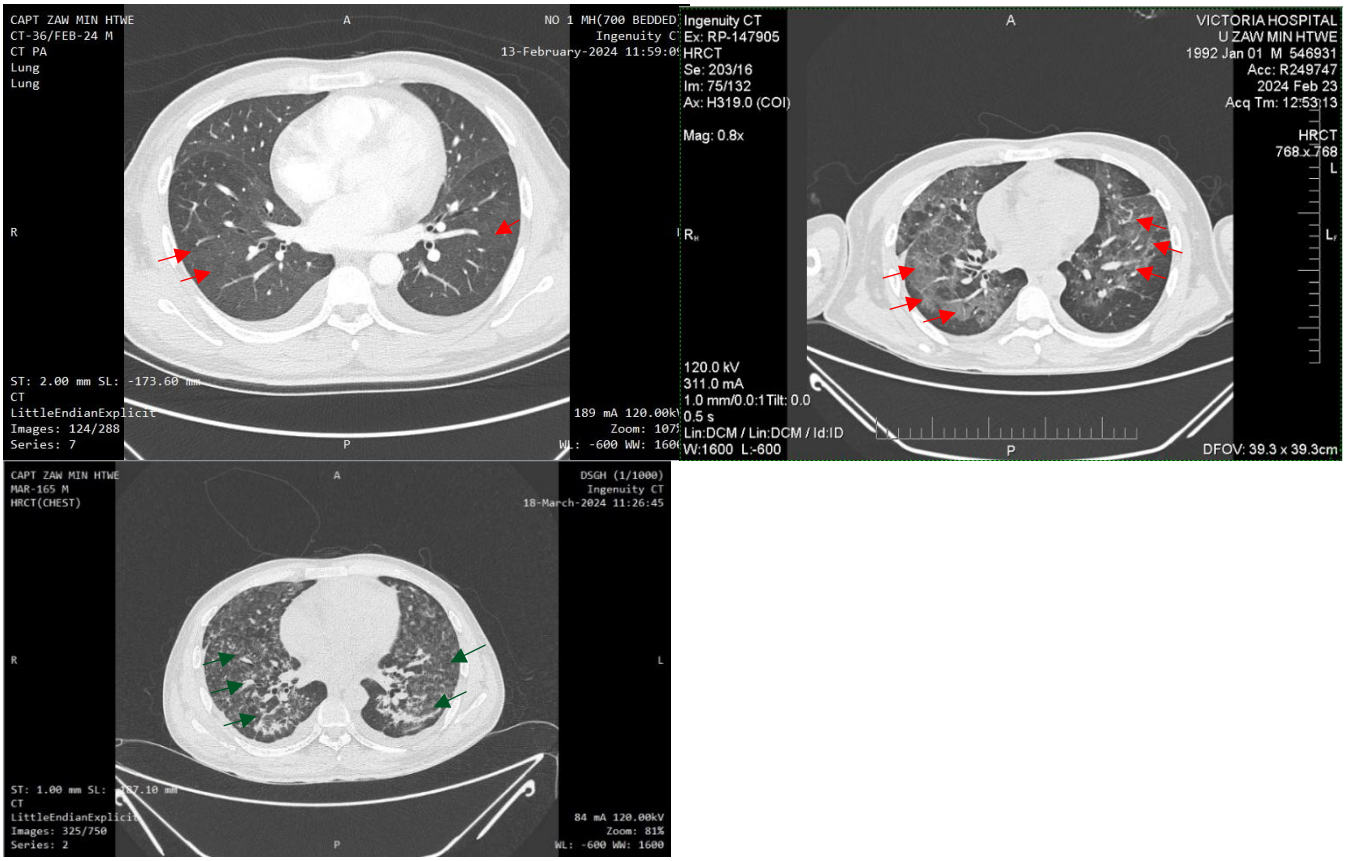

Photo (9) Comparison of serial HRCT chest (Figure A, Figure B & Figure C)

HRCT (Chest) lung window axial view at the level of the pulmonary vein level showing images in Figure (A, upper right), taken on 13th February 2024, showing the patient's lungs with signs of minimal diffuse alveolar damage. Ground-glass opacities are present in both lung fields, with bilateral, patchy areas of increased attenuation (indicated by red arrows). Figure (B, upper left), taken 10 days later, showing a progressive increase in ground-glass opacities and expansion of consolidation areas. These changes are bilateral and relatively symmetrical (indicated by red arrows), Figure (C, lower left) was taken in 18th March 2024 showing Ground-glass opacity present bilaterally and relatively symmetrical was still present but reduced in density and presence of aerated regions exhibited (green arrow).

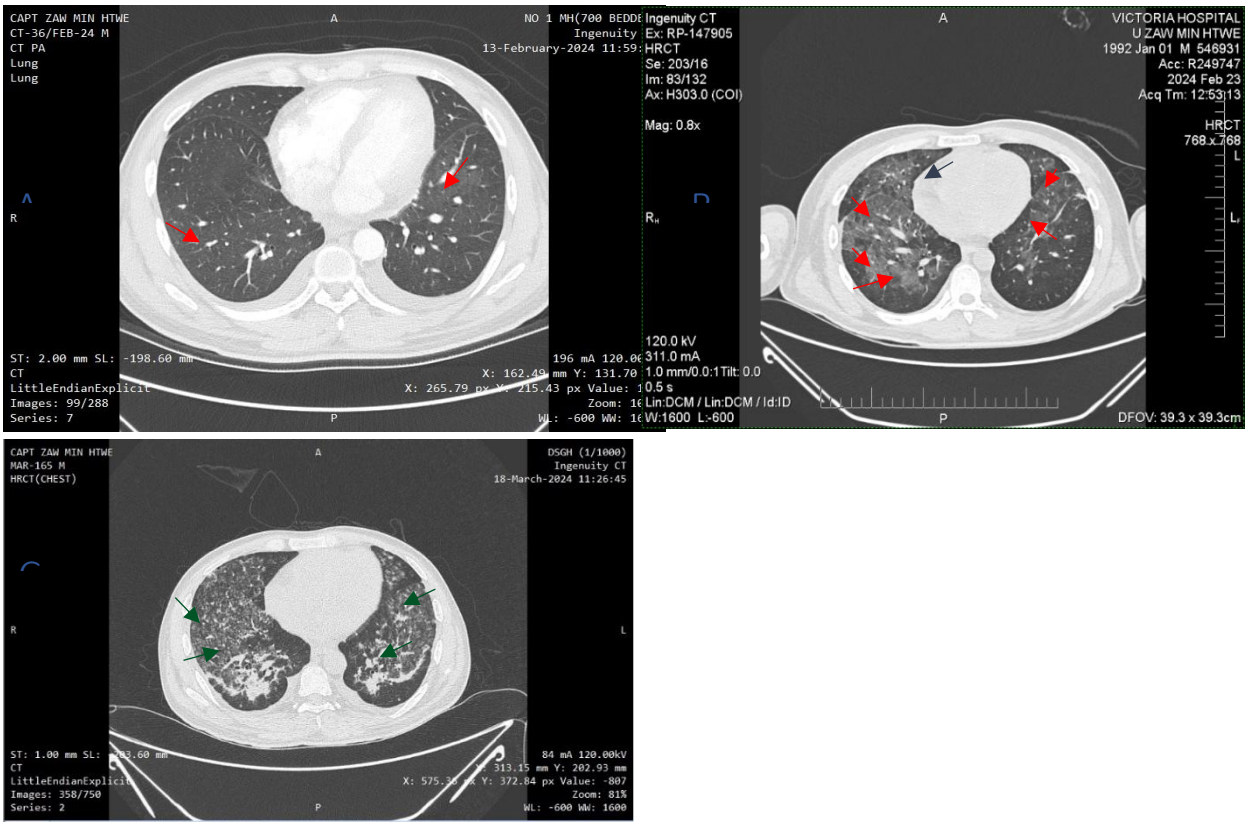

Photo (10) Comparison of serial HRCT chest (Figure A, Figure B & Figure C)

HRCT (Chest) axial view at the level of the heart in Figure (A, upper right), taken on 13th February 2024, showing the patient's lungs with signs of diffuse alveolar damage. Ground-glass opacities are present in both lung fields, with bilateral, patchy areas of increased attenuation (indicated by red arrows). Figure (B, upper left), taken 10 days later, showing a progressive increase in ground-glass opacities and expansion of consolidation areas. These changes are bilateral and relatively symmetrical (indicated by red arrows) and minimal pericardial effusion (blue arrow), Figure (C, lower right) was taken in 18th March 2024 showing Ground-glass opacity present bilaterally and relatively symmetrical was still present but reduced in density and presence of aerated regions exhibited (green arrow).

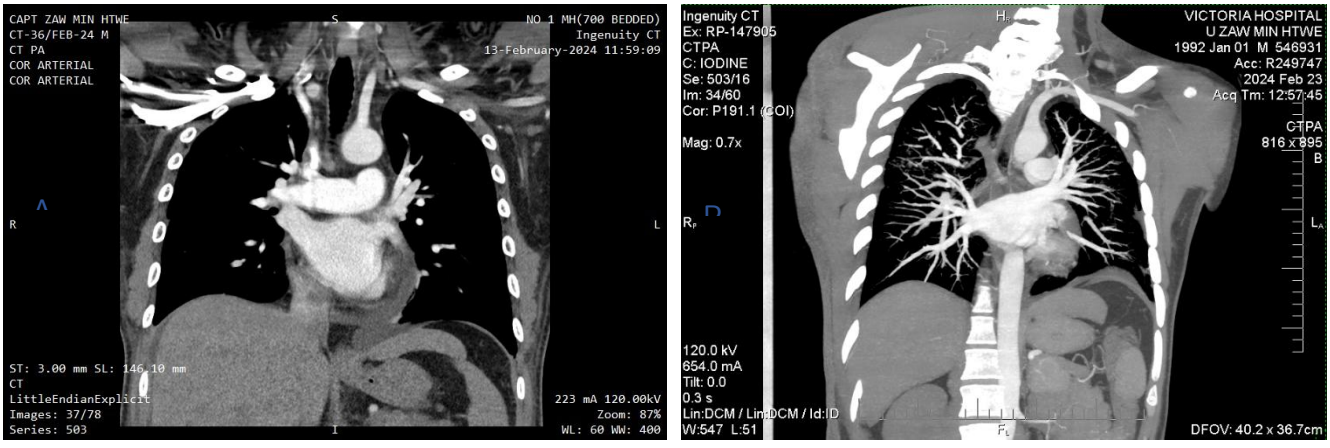

Photo (11) Comparison of CT pulmonary Arteriogram (Figure A & Figure B)

CT pulmonary Arteriogram was taken in 13th Feb2024 (Figure A, left side) and 23rd Feb 2024 (Figure B, right side) showing the normal flow and no evidence of pulmonary embolism.

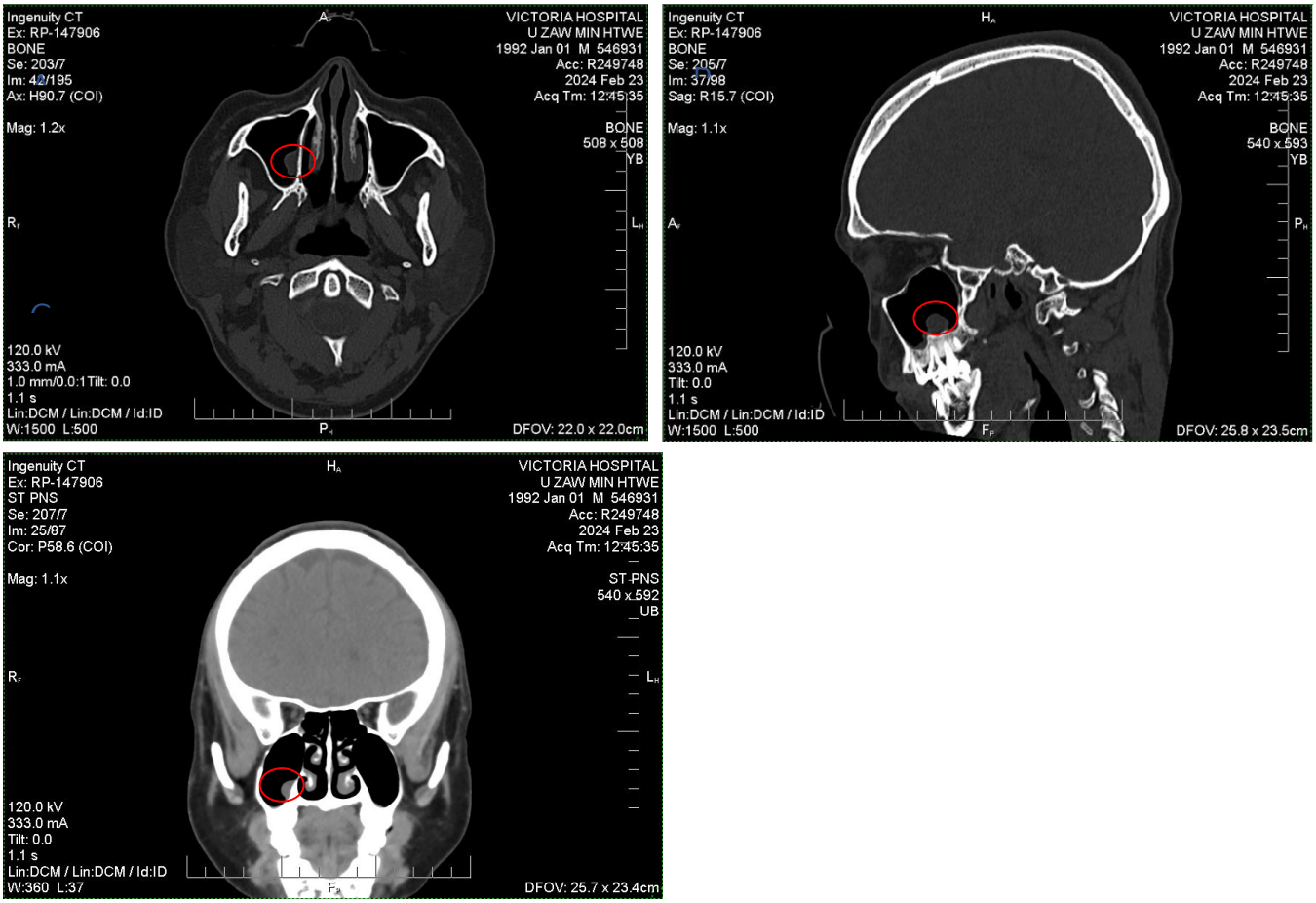

Photo (12) CT scan of nasal sinuses

Sinus CT taken in 23rd Feb 2024 showing axial view (figure A, upper left), sagittal view (figure B, upper right) and coronal view (figure C, lower right) of the maxillary and ethmoid sinuses. Mucosal thickening in the floor of both maxillary sinuses and a small polyp (red circle) in the right maxillary sinus.

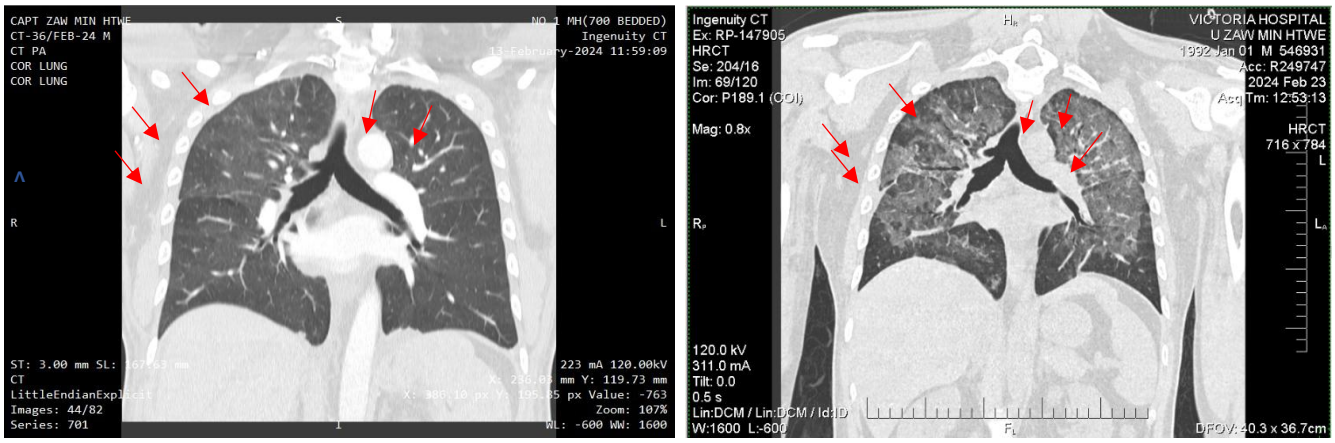

Photo (13) HRCT (Chest) Coronal view (Figure A & Figure B)

HRCT (Chest) Coronal view image in figure (A, right side), taken on 13th February 2024, showing the patient's lungs with signs of diffuse alveolar damage. Ground-glass opacities are present in both lung fields, with bilateral, patchy areas of increased attenuation (indicated by red arrows). Figure (B, left side), taken 10 days later, showing a progressive increase in ground-glass opacities and expansion of consolidation areas. These changes are bilateral and relatively symmetrical, predominantly affecting the mid and upper zones (indicated

by red arrows), with relative sparing of the basal and subpleural regions.

Photo (14) Patient on CPAP and neck line for rescue hemodialysis

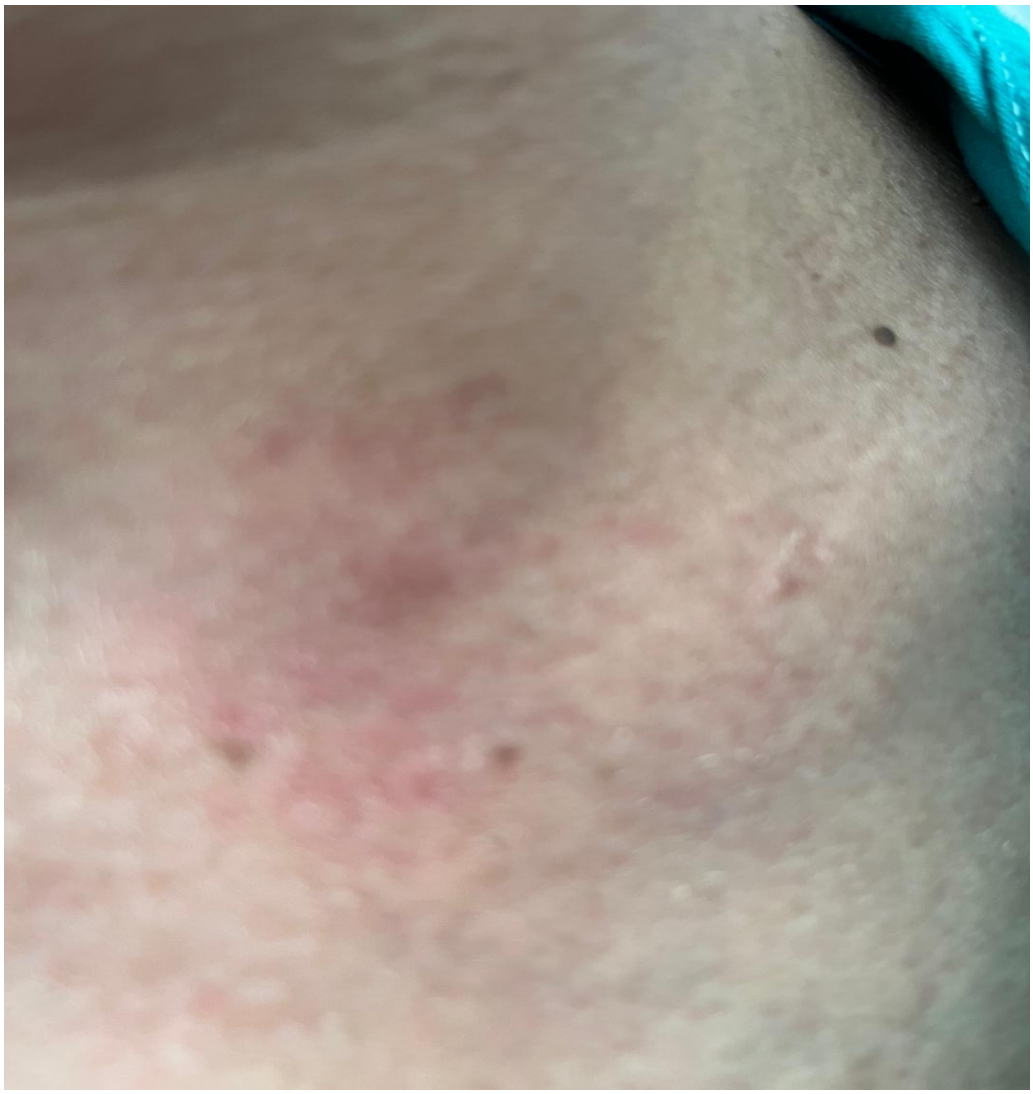

Photo (15) Erythematous rash over upper chest

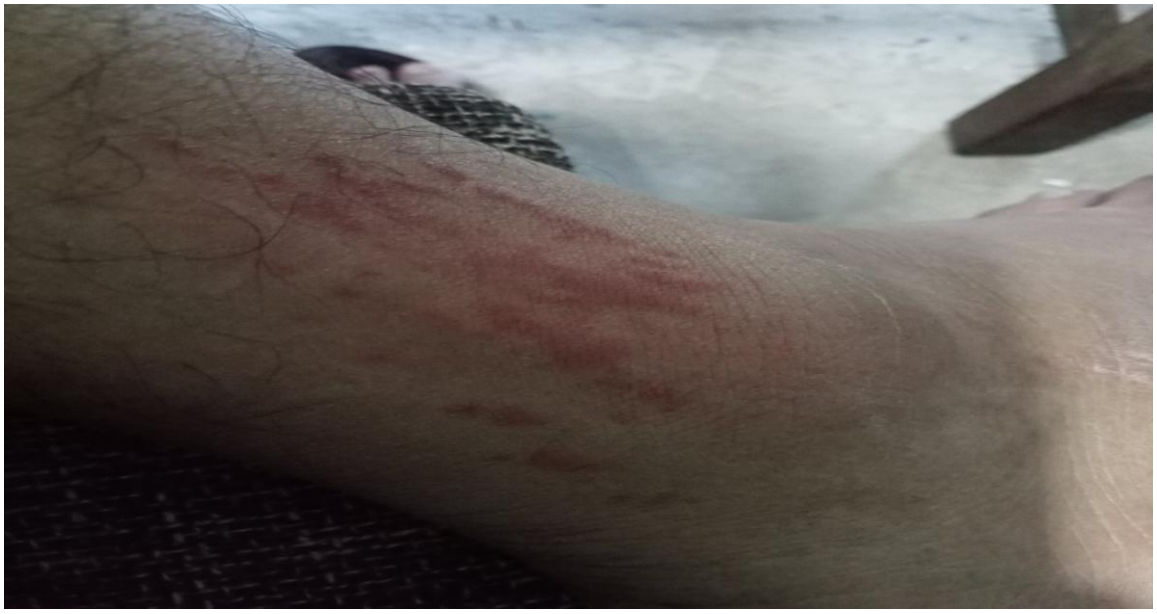

Photo (16) Erythematous rash over shin

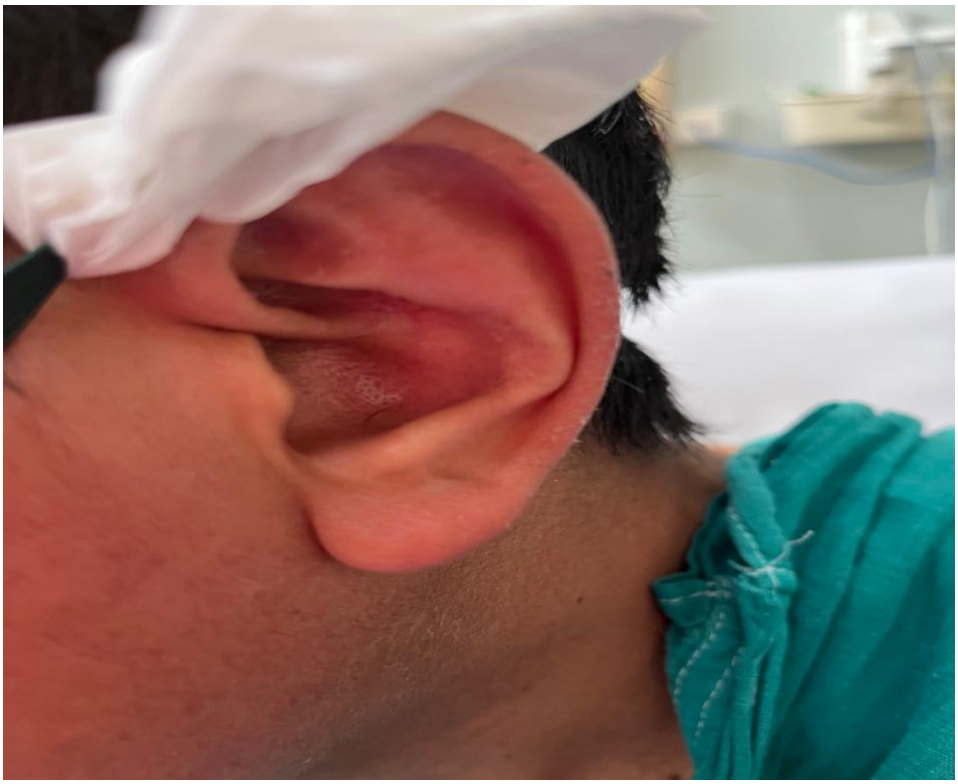

Photo (17) Patient having poly-chondritis left ear

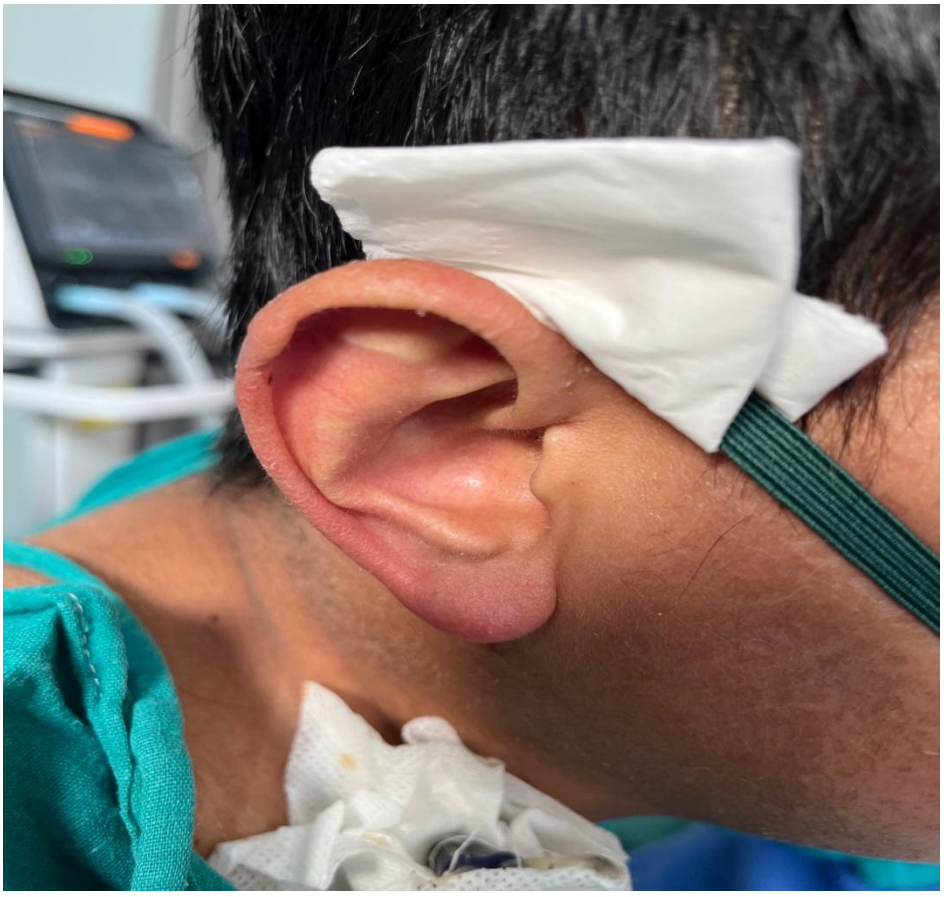

Photo (18) Patient having poly-chondritis right ear