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Case Series

Antiphospholipid syndrome in women: Case series and review of literature

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Summary:

Antiphospholipid syndrome (APS) is an autoimmune disorder consisting of components like thrombosis of arteries and veins, adverse outcomes of pregnancy affecting both mother and fetus, and raised levels of antiphospholipid (aPL) antibodies. Found only in 5 persons per 100,000 populations. We are reporting three patients who presented with severe chest pain and breathlessness of acute onset, history suggestive of recurrent 2nd-trimester abortions. All basic investigations were done along with ECG, chest x-ray, D-dimer, CECT, and APLprofile. Clinical, radiological and laboratory data were in favor of Anti-phospholipid syndrome in all the patients. They were managed conservatively with anticoagulant therapy and other supportive measures. This case series is reported with review of some relevant literature. We conclude that young women with history of recurrent abortions presenting with acute onset of breathlessness and chest pain should be investigated in the line of pulmonary thromboembolism due to antiphospholipid antibody syndrome.

Keywords: Antiphospholipid antibody syndrome, Anti-cardiolipin, Lupus anticoagulants, anti-β2Glycoprotein I

INTRODUCTION:

Antiphospholipid antibodies are the immunoglobulin produced to react against the phospholipids which are mostly present in the plasma membranes of human cells. [1]

These antiphospholipid antibodies namely anticardiolipin (aCL), lupus anticoagulant (LA), anti-b2 glycoprotein-I (anti-b2GPI) antibodies and few more are characteristically present in an autoimmune condition called as 'Antiphospholipid antibody Syndrome' or APS. [2]

Long back, in 1983 Harris E N and co-workers found a significant relationship between the presence of lupus anticoagulants (LA) and increased level of anticardiolipin antibodies in the serum of patients with Systemic Lupus Erythematosus (SLE). They also established a strong relationship between raised cardiolipin level and venous thrombosis. [3]

Later it was proved that the level of this antibody is raised in non-SLE patients too. The term Primary Antiphospholipid Syndrome was coined by Mac worth-Young and colleagues for this group of conditions. [4]

Clinical manifestations of arterial, venous, or small vascular thrombosis of any organ with or without pregnancy morbidities are the criteria for describing this disease entity. [5]

In this case report, we are presenting a case series of three patients with features of APS, and all of them had pregnancy morbidities.

CASE SERIES:

CASE-1

A 23-year-old female presented with left-sided, pricking type, non-radiating chest pain since 15 days, grade 2 mMRC shortness of breath, low-grade fever for 4 days, 4 episodes of scanty hemoptysis for 2 days. She had no other co-morbidities. She has one live child. She had past history of two second-trimester spontaneous abortions. The last event occurred one week before the presentation which was at her twenty-eighth week of gestation. For this she underwent dilatation and evacuation for retained products. There was no significant family history.

On general examination, she was well built, well-nourished with pallor present. On respiratory examination, bilateral normal vesicular breath sounds were heard, fine crepitations present over left infra-scapular and infra-axillary areas. Laboratory reports of hemogram, liver and renal function tests were within normal range. There was no evidence of infection with HIV. Chest x-ray showed wedge-shaped lesion in left lower zone suggestive of infarction. 2D echo was normal. CECT (Contrast Enhanced Computerized Tomography)of chest showed diffuse long segment thrombus noted involving bilateral lower lobes segmental, subsegmental pulmonary artery branches, Atoll sign with feeding vessel sign suggesting pulmonary infarcts. Diffuse fluffy ground-glass opacities in basal segments of both lungs suggesting alveolar hemorrhages. APLA profile - D-Dimer 2527 ng/ml [Normal <855], anti-thrombin 3.162% [Normal

80-120], protein C 105% [Normal 70-150], protein S 87% [Normal 70-150], homocysteine 6.2 micromol/lit [Normal 5-15], anti-cardiolipin antibodies IgG 26 GPL units [Positive >20], IgM 8 MPL units [Negative <20], anti-phospholipid antibodies IgG 0.45 COI [Positive>1.2], IgM 0.31 COI [Positive>1.2], anti-β_2 glycoprotein-1 IgG 4 U/mL [Normal <5], IgM 3 U/mL [Normal <5], anti-nuclear antibodies negative.

CASE-2

A 19-year-old female presented with right-sided chest pain, cough with expectoration and shortness of breath, fever, and pain in upper abdomen for one week. She had no associated comorbidities. She had history of three first-trimester abortions and twice dilatation and evacuation. There was no significant family history.

On general examination, she was well built and well nourished, vitals were stable. On respiratory system examination, diminished vesicular breath sounds over right infra-axillary, mammary areas and few fine crepitations over right infra-scapular, infra-axillary areas were found. Laboratory investigations showed normal hemogram, liver and renal function and non-reactive HIV status. Chest x-ray showed right lower lobe consolidation. CECT thorax showed right lower lobe posterior basal segment infarct with feeding vessel thrombosis and right adrenal gland infarction. APLA profile - D-Dimer 1625 ng/ml [Normal <855], anti-thrombin 3 92% [Normal 80-120], protein C 95% [Normal 70-150], protein S 107% [Normal 70-150], lupus anticoagulant positive, Russel viper venom positive, anti-cardiolipin antibodies IgG 9.4 GPL units [Positive >20], IgM 3.66 MPL units [Negative <20], anti-phospholipid antibodies IgG 0.63 COI [Positive>1.2], IgM 0.22 COI [Positive>1.2], anti-β_2 glycoprotein-1 IgG 2 U/mL [Normal <5], IgM 1.8 U/mL [Normal <5], anti-nuclear antibodies 0.32 [Negative<0.8].

CASE-3

A 26-year-old female presented with high-grade fever associated with chills and rigors, cough with expectoration of 5 days and shortness of breath fortwo days. She had no chest pain. There is history of abortion ten days back. She had no comorbidities. She attained menarche at the age of 13. Cycles are regular, no history of consanguinity, married at age of 20 years. She had history of 3 first trimester abortions, 2-second trimester abortions and no single live child. There was no significant family history.

On general examination, she was well built and well-nourished, vitals were stable, and pallor was present. On respiratory system examination, bronchial breath sounds were present over right mammary, infra-axillary, infra-scapular areas, crepitations present in those areas. On investigating, hemogram showed leucocytosis, thrombocytopenia, and anemia. Chest x-ray showed right lower lobe consolidation with pleural effusion. CT thorax showed right lower lobe consolidation with loculated effusion. By CECT small focal filling defect was noted in proximal left subclavian vein, partial thrombotic occlusion. APLA profile - D-Dimer 3200 ng/ml [Normal <855], anti-thrombin 3 96% [Normal 80-120], protein C 85% [Normal 70-150], protein S 122% [Normal 70-150], lupus anticoagulant positive, anti-cardiolipin antibodies IgG 22.34 GPL units [Positive >20], anti-phospholipid antibodies IgG 14.2 COI [Positive>1.2], anti-β_2 glycoprotein-1 IgG 2.3 U/mL [Normal <5], IgM 3.8 U/mL [Normal <5].

In this case series, all the three patients were diagnosed as antiphospholipid syndrome. They were kept on Warfarin with target INR of 2 to 3. All of them were called for follow up, and only the first two cases turned up. In both the cases the follow-up blood investigations showed raised anti-phospholipids levels.

LITERATURE REVIEW:

The international Consensus statement 2006 has defined Anti Phospholipid Syndrome in a patient if there is a presence of clinical evidence(s) of vascular thrombosis and/or pregnancy-related morbidities along with persistent detection of a high level of anti-phospholipids antibodies in the plasma or serum. [5]

The arterial, venous or small vessel thrombosis should be confirmed based on radiological or histopathological evidences. The pregnancy-related morbidities include unexplained fetal death even after ten weeks of gestation in the absence of any fetal morphological abnormalities. It also includes features like eclampsia, severe preeclampsia or placental insufficiency leading to premature childbirth. Spontaneous abortions before ten weeks of gestation for three times or more without any obvious cause also come under these criteria of pregnancy morbidity. Some other clinical conditions like cardiac valve diseases, thrombocytopenia, nephropathy, livedo reticularis, and neurological manifestations,etc are also associated with APS in many instances. The actual mechanism why thrombosis occurs in APS is still unclear. According to literature,heterogeneity of the antibodies might be responsible for the pathophysiology. B2-Glycoprotein I (β2 GPI) is the most common phospholipid-binding protein and its most frequently encountered by these antibodies. Various mechanisms of action have been proposed.This may a result of sequence of events like activation ofendothelial cells, platelets, and monocytes, activation of the coagulation cascade, inhibition of the fibrinolytic system, inhibition of natural anticoagulant pathways and activation of the complement system. [6, 7, 8]

The β2GPI also binds the low-density lipoprotein molecules (LDL), and the oxidized form of LDL in combination with β2GPI cross-reacts with the anti-phospholipids antibodies consequently leads to vasculopathy, severe intimal hyperplasia, thrombus formation, and atherosclerotic changes. [9, 10, 11]

The same phenomenon may also lead to vascular occlusion and pregnancy-related morbidities. These thrombophillic effects of antiphospholipid antibodies may lead to thrombosis inside the intra-placental vessels hinder the feto-maternal blood exchange and subsequent fetal loss. [12]

Patients with anti-phospholipids syndrome will present with varieties of clinical manifestations. [13, 14]

Those may be associated with arterial thrombosis causing aortic occlusion, cerebrovascular accident, mesenteric infarction or gangrene of extremities. They may also present with features of venous thrombosis manifested by pulmonary embolism, deep vein thrombosis, mesenteric, renal or hepatic vein thrombosis or adrenal insufficiency. Females may present with recurrent pre-embryonic or embryonic, fetal loss, Intra-uterine growth retardation, preeclampsia, etc. [15]

In a systemic review and meta-analysis conducted by Santos et al. it was established that anti-phospholipids antibody in blood has a significant relationship with recurrent miscarriages in women between age 20 to 45 years. [16]

There may be hematological manifestations like Haemolytic anemia, thrombocytopenia, thrombotic microangiopathic hemolytic anemia, Evans syndrome, etc. Cutaneous manifestations like Livedo reticularis; cutaneous necrosis; pyoderma-like ulcerations; digital gangrene may be observed in many patients. There may be evidence of renal complications like Nephropathy with glomerular thrombosis; cortical necrosis; renal infarction etc. Cardia complications like valvular insufficiencies, intracardiac thrombosis, coronary artery thrombosis etc may also be found in some cases. Some patients may manifest with multi-systems failure which is termed as catastrophic APS. [17]

To call it an Anti-Phospholipid syndrome the clinical manifestations should satisfy the revised criteria for classification of APS (Table-1). It is necessary to have a combination of at least one clinical criterion and one laboratory criterion. [5]

Table-1: Revised criteria for the classification of APS (Adapted from S Miyakis et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS-2006). [5]

S. No.	Clinical Criteria	Laboratory Criteria
1	Involvement of any tissue or organ with one or more clinical episodes of arterial, venous, or small vessel thrombosis that must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). Histopathologic confirmation, by presence of thrombosis in the vessel wall, without significant evidence of inflammation.	Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipids-dependent antibodies).
2	Pregnancy morbidity (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency–, or (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b or c above.	2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. 3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titre> the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures. Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa- LA present alone; IIb- aCL antibody present alone; IIc- anti-b2 glycoprotein-I antibody present alone.

All patients with persistent anti-phospholipid level may not present with thrombotic or gestational symptoms. Their presentation may vary with effect to other systems like cardiovascular, neurological, skin, joints and pleura, etc. Ilgen et al. proved this in a series of 295 SLE patients, among whom 51 patients have persistent raised anti-phospholipid

antibodies. Twenty-five patients in this group did not have either of the thrombotic or gestational symptoms. [18]

Thorough history taking, physical examinations, routine imaging, and laboratory investigations are the requisites to come to a clinical diagnosis. But the mainstay of investigation is the laboratory detection of antiphospholipid antibodies in the blood. [19]

It is recommended to perform the following three types of laboratory tests:

1. Assays that detect the aPL as inhibitors of coagulation, the lupus anticoagulant (LAC),

2. Immunoassays that detect anticardiolipin antibodies (aCL) and

3. Immunoassays that detect anti-b2glycoprotein I antibodies (aβ2GPI).

If the laboratory reports show positive lupus anticoagulant or there is triple positivity, i.e. Positive lupus anticoagulant with positive anticardiolipin and anti-β2GPI or persistent medium to the high titer of isolated anti-cardiolipin, then it is considered to be. Isolated and intermittently positive aCL or anti-b2-GPI at low-medium titers is considered to be low risk. [20]

Anticoagulants are the mainstay of treatment in APS. Warfarin is the drug of choice for patient with primary APS and to be maintained with INR > 3.0. Long-term low molecular weight heparin, hydroxychloroquine or statins are recommended for patients with difficult management due to recurrent thrombosis and for those who have fluctuating INR levels, major bleeding or high risk for major bleeding. The duration of treatment for patients with APS with thrombosis is recommended to be indefinite. But for patients with low-risk anti-phospholipid profile the anticoagulation therapy is limited to 3 to 6 months. Long term thromboprophylaxis with Aspirin is recommended for patients with a high-risk antiphospholipid profile. [20]

DISCUSSION:

Every year only five new cases of Anti-phospholipid syndrome are reported, though 1 to 5% of the population has anti-phospholipids antibodies. [21] Patients in this case series were diagnosed as APS based on clinical, radiological and lab reports. According to the revised classification the first patient was having category II b APS, the second patient was having Category II b APS, and the third case was diagnosed as Category I APS (Table-2). But the repeat blood investigation could not be performed in the third case because she did not come for follow up.

Table-2: Categorization of the three cases according to the revised classification

Cases	Thrombosis	Pregnancy-related complications	Laboratory evaluation	Category
Case 1	Present	Present	aCL, D-Dimer positive	Category II a
Case 2	Present	Present	Lupus anticoagulant, Russell viper venom, D-Dimer positive	Category II b
Case 3	Present	Present	aPL, aCL, Lupus anticoagulant, D-Dimer positive	Category I

CONCLUSION:

Antiphospholipid syndrome is a less common disease entity affecting mostly women of childbearing age. We learned from the present case series that every woman with pregnancy-related morbidities should betested for antiphospholipid antibodies. Those patients with pregnancy morbidity approach the health facility with acute breathlessness should be investigated for pulmonary thromboembolism also.

REFERENCES:

1. Kutteh WH, Hinote CD. Antiphospholipid Antibody Syndrome. ObstetGynecol Clin N Am 2014;41:113–132.
2. Khamasta M, Taraborelli M, Sciascia S, Tincani A. Antiphospholipid Syndrome. Best Practice & Research Clinical Rheumatology 2016;30:133e148.
3. Harris EN, Gharavi AE, Boey ML, Patel BM, Young CGM, Loizou S et al. Anticardiolipin Antibodies: Detection By Radioimmunoassay And Association With Thrombosis In Systemic Lupus Erythematosus. Lancet. 1983:2(8361):1211-14
4. Mack worth-Young CG, Loizou S, Walport MJ. Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder. Annals of the Rheumatic Diseases. 1989;48:362-7.
5. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J ThrombHaemost2006;4:295–306.
6. Sikara MP, Grika EP, Vlachoyiannopoulos PG. Pathogenic Mechanisms of Thrombosis in Antiphospholipid Syndrome (APS), Thrombophilia, Prof. Prof. Andrea Tranquilli (Ed.), ISBN: 978-953-307-872-4, 2011. In: Tech, Available from: http://www.intechopen.com/books/thrombophilia/pathogenicmechanisms-of-thrombosis-in-antiphospholipid-syndrome-aps

7. Mehdi AA, Uthman I, Khamashta M. Antiphospholipid syndrome: pathogenesis and a window of treatment opportunities in the future. Eur J Clin Invest 2010;40(5):451–64.
8. Pierangeli SS, Chen PP, Raschi E, Scurati S, Grossi C, Borghi MO et al. Antiphospholipid Antibodies and the Antiphospholipid Syndrome: Pathogenic Mechanisms. SeminThrombHemost 2008;34(3):236-50.
9. Vaarala O. Antiphospholipid antibodies and atherosclerosis. Lupus 1996;5:442-7
10. Christodoulou C, Sangle S, D'Cruz D P. Vasculopathy and arterial stenotic lesions in the antiphospholipid syndrome. Rheumatol2007;46:907–10.
11. Merashli M, Noureldine MA, Uthman I, Khamashta M. Antiphospholipid Syndrome: An Update. Eur J Clin Invest. 2015 Jun;45(6):653-62.
12. Meroni, PL, Borghi MO, Tedesco F. Pathogenesis of antiphospholipid syndrome: Understanding the antibodies. Nat Rev Rheumatol 2011;7(6):330–9
13. Di Prima FAF, Valenti O, Hyseni E, Giorgio E, Faraci M, Renda E et al. Antiphospholipid Syndrome during pregnancy: the state of the art. J Prenatal Med 2011;5(2):41-53.
14. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT et al. Antiphospholipid Syndrome Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients. Arthritis Rheum 202;46(4):1019–27
15. Vinatier D, Dufour P, Cossson M, Houpeau JL. Antiphospholipid syndrome and recurrent miscarriages. Eur J ObstetGynecolReprod Biol 2001;96:37-50.
16. Santos TDS, Ieque AL, de Carvalho HC, Sell AM, Lonardoni MVC, Demarchi IG et al. Antiphospholipid syndrome and recurrent miscarriage: A systematic review and meta-analysis. J Reprod Immunol 2017;123:78–87.
17. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry, Autoimmun Rev 2016;15(12):1120-4
18. Ilgen U, Yayla ME, Ates A, Yurteri EU, Torgutalp M, Kelesoglu ABD et al. Antiphospholipid antibodies and non-thrombotic manifestations of systemic lupus erythematosus. Lupus 2018;27(4):665-9
19. Devreese KMJ. Antiphospholipid antibody testing and standardization. Int J Lab Hematol2014;36:352–63.
20. Irastorza GR, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. Lupus 2011;20:206–18.
21. Gómez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. J Autoimmun 2014;48-49:20-5.

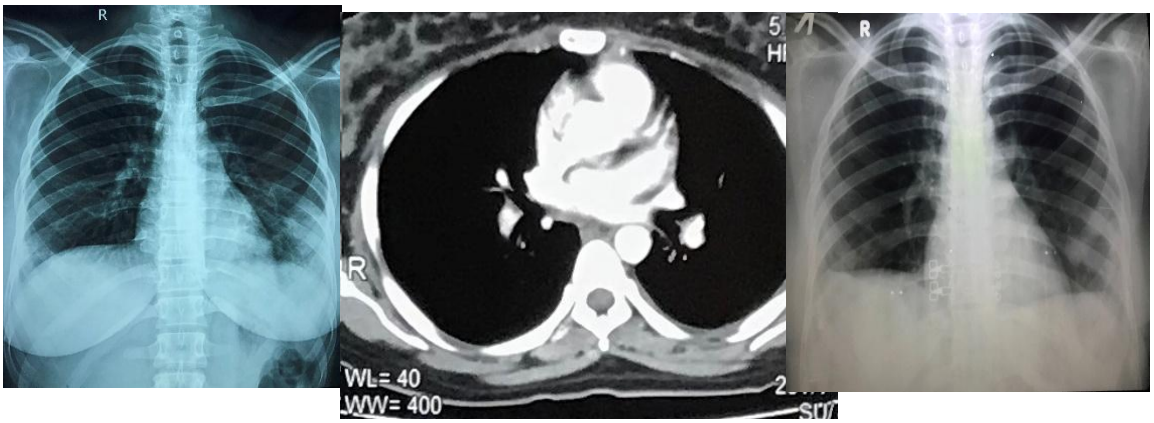

Fig 1: Case 1: Chest X-Ray PA view & CT image at the time of admission, CXR PA view after treatment

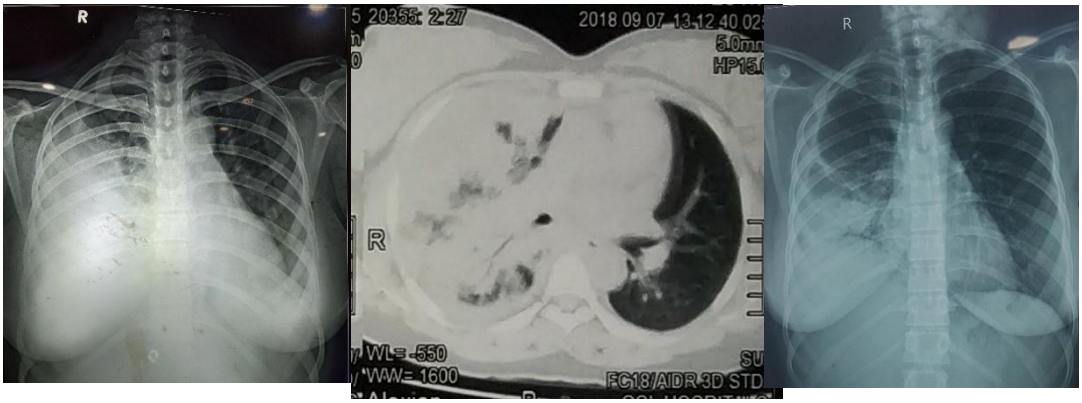

Fig 2: Case 2: Chest X-Ray PA view & CT image at the time of admission, CXR PA view after treatment

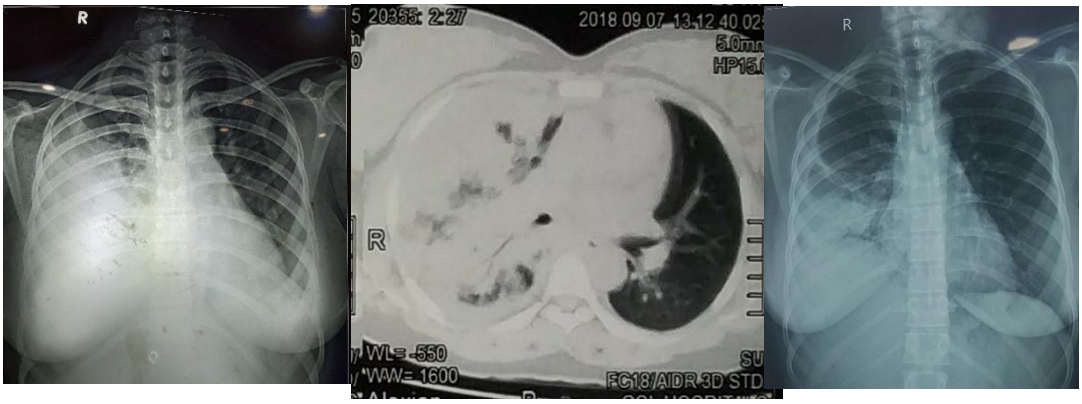

Fig 3: Case 3: Chest X-Ray PA view & CT image at the time of admission, CXR PA view after treatment

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