UNIVERSITI TEKNOLOGI MARA

DIAGNOSIS OF GRANULOMATOSIS WITH POLYANGIITIS-IS IT THAT DIFFICULT?

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Discussion:

GPA is a rare disease with reported annual incidence and prevalence is estimated 23.7-156.5 per million and 3.0-14.4 per million, respectively (1). GPA is more common in European populations and slightly more in male with male to female ratio 1.5:1 (2). It may occur at any age but typically at age 35-55 years old. It classically involved upper and lower respiratory tract and glomerulonephritis. According to American College of Rheumatology (ACR) classification the diagnosis is made when 2 out of 4 criteria are present, which includes nasal or oral inflammation, abnormal chest radiograph, urinary sediment and granulomatous inflammation on biopsy. This test has a sensitivity of 88.2 percent and specificity of 92 percent.

Otological manifestation are found in 19 to 61 percent of cases with GPA (3). The commonest presentation is otitis media (4). It is due to eustachian tube dysfunction caused by nasopharyngeal involvement but commonly misdiagnosed as infection (5). Up to 50 percent of GPA cases presented with hearing loss (6). Bakthavachalam et al reported that both sensorineural and conductive hearing loss are common in GPA (7). However, audiogram was not done for our patient to determine the type of hearing loss.

The finding of full pathologic triad of granulomatous inflammation, vasculitis and necrosis in nasal biopsy is one of the criteria to diagnose GPA. Our patient was not advised for nasal biopsy. Initially, her presentation was mainly otitis media but she developed epistaxis later and the focus shifted to lung masses and she was advised for lung biopsy. Lung biopsy has better yield compared to nasal biopsy (8). Upper respiratory tract tissue biopsies are frequently non-diagnostic (9). However, in our case, histopathological finding is not required for diagnosis as she already fulfilled diagnostic criteria for GPA according to American College of Rheumatology (ACR) classification.

Lower respiratory tract involvement is commonly seen in GPA. The most common symptoms are cough, haemoptysis, dyspnoea and pleuritic chest pain. The most common radiographic and CT findings of GPA nodules and masses (10). The other differential diagnosis for lung masses are metastasis, sarcoidosis and infections (11). Especially in a moderate tuberculosis burden country such as ours it can be mistaken as pulmonary tuberculosis. The lung masses in GPA are usually described as multiple and bilateral and mainly involves subpleural regions and less common in peribronchovascular region (11). The prominent features of nodule in GPA are radiating linear scarring, spiculation and tags to the adjacent pleura which not usually seen in other peripheral lung mass pathology such as lung metastases (12). Although our patients' CT scan was typical of GPA, the diagnosis was not entertained in the beginning probably due to lack of experience of the radiologist and failure to correlate with clinical findings. The management was further compromised when the patient refused lung biopsy.

Gastrointestinal involvement in GPA has been reported in some case reports (13,14,15). The most common gastrointestinal manifestations are oral mucosa ulcerations, gum mucosa hypertrophy, dyspepsia, vomiting, abdominal pain, gastrointestinal haemorrhage, diarrhoea and gastrointestinal perforation (16). Apart from oral ulcers, our patient presented with post prandial abdominal pain, which suggest mesenteric ischemia. In our patient, there were lack of typical CT finding of mesenteric ischemia and vasculitis, described as thickening of the affected bowel wall and vessel engorgement, respectively. Instead, there were presence of

inflamed mucosa and deep ulcers at the small and large bowel. The common causes of generalised ulcers along the gastrointestinal tract includes inflammatory bowel disease, Non-steroidal anti-inflammatory drugs-induced and tuberculosis of the colon, while the rarer causes are gastrointestinal manifestation of vasculitis, cytomegalovirus infection and colon malignancy. The findings of granuloma inflammation in gastrointestinal biopsy would support the presence of GPA. However, Masiak et al reported that the role of histopathology examination in GPA with gastrointestinal vasculitis are limited, where among 34 patients only 2 patients had histopathological evidence of vasculitis (16).

Neurological manifestations of GPA are not rare. 15 to 50 percent of patients have peripheral nervous system involvement and 5 to 15 percent have central nervous system involvement (17). The most common peripheral nervous system manifestation is peripheral neuropathies such as mononeuritis multiplex while central nervous system manifestations depend on site of lesion and varies from headache, memory deficits, cognitive impairment, seizures, paresis and impaired consciousness (17). Nerve conduction study of this patient showed axonal polyneuropathy which give rise to the distal weakness and reduce sensation of bilateral feet. However, again the diagnosis of GPA was not entertained. This may be due to lack of discussion between the attending physician and neurologist and also because the neurologist may not be familiar with GPA as a cause of polyneuropathy compared to other causes of such diabetes, Guillain-Barre syndrome and chronic alcohol.

Urgent intervention is the key success in the management ANCA-associated vasculitis. In life threatening or organ threatening disease such as patient who has severe pulmonary haemorrhage, rapidly deteriorating renal function or motor neuropathy, cyclophosphamide combined with glucocorticoids is an established treatment modality as the initial immunosuppressive therapy. This combination induce remission in 85 to 90 percent of patients with 75 percent achieved complete remission. Plasma exchange has been shown to help increase the rate of renal recovery in ANCA associated vasculitis in patient with serum creatinine more than 500 micromol/L (18). Other patients who may benefit from plasma exchange are concurrent anti-glomerular basement membrane antibody disease and pulmonary hemorrhage. Rituximab has been showed to be equally effective as cyclophosphamide in RAVE and RITUXVAS trial (18). PEXIVAS is an ongoing trial regarding plasma exchange in treatment of ANCA associated vasculitis (19).

Conclusion:

As a conclusion, we should treat a patient as a whole and use a holistic approach in managing the disease. One of the pitfall in the modern healthcare era where subspecialty is the rule is highlighted in this case, where the diagnosis of GPA was still delayed even when the constellation of symptoms were present for almost 4 months. Healthcare provider must be in constant communication with each other when faced with complex and rare case. Thorough history taking and physical examination should be the usual practice and interpretation of investigations should not be done in isolation, without clinical correlation.

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Introduction:

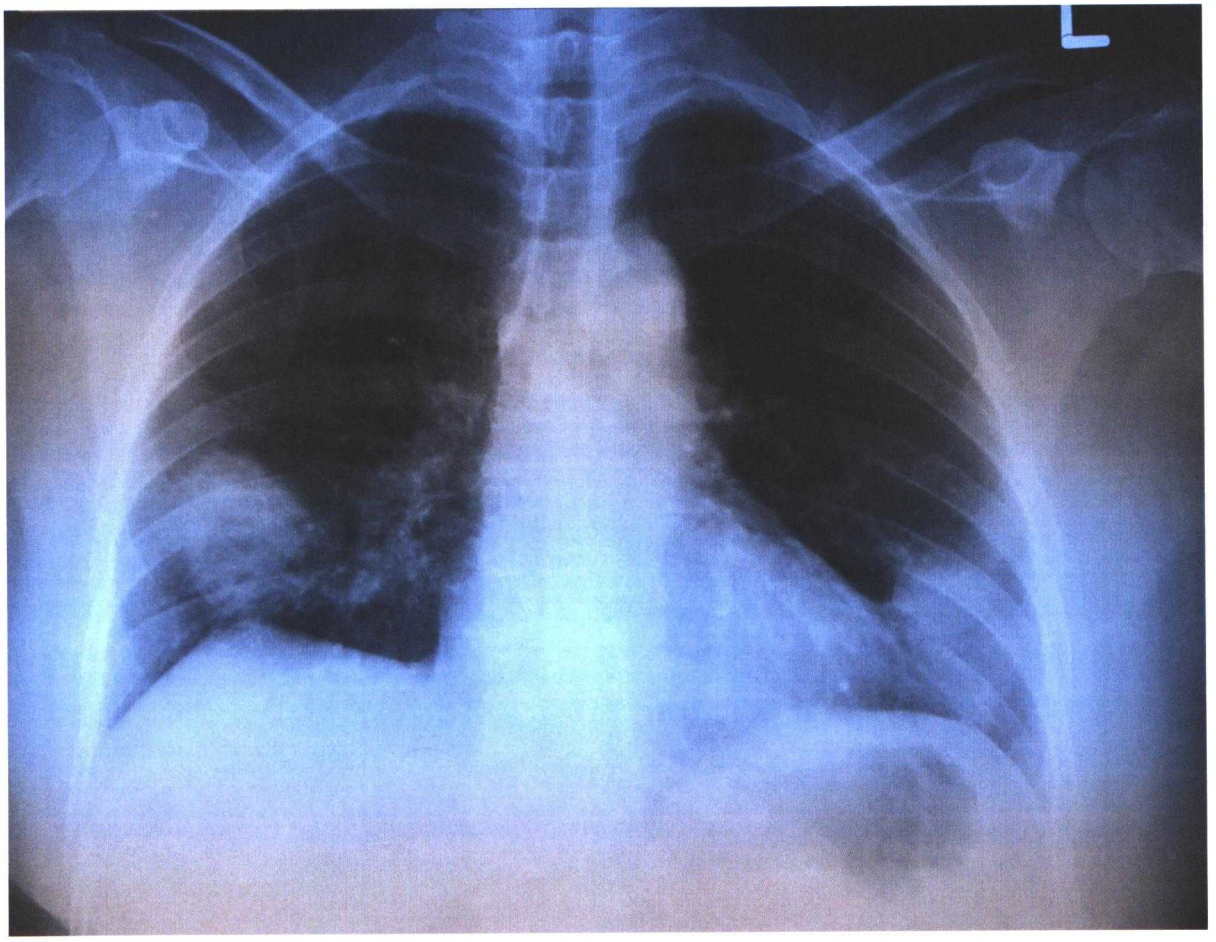
Granulomatosis with polyangiitis is an ANCA-associated vasculitis. Making a diagnosis of GPA can be difficult due to the rarity of this disease and the involvement of multisystem which may result in patients to be presented to various specialities. However, it becomes more challenging when the presentation is atypical. Here we presented a case of GPA with initial presentation of tinnitus followed by array of symptoms involving majority of the body systems.

Case presentation:

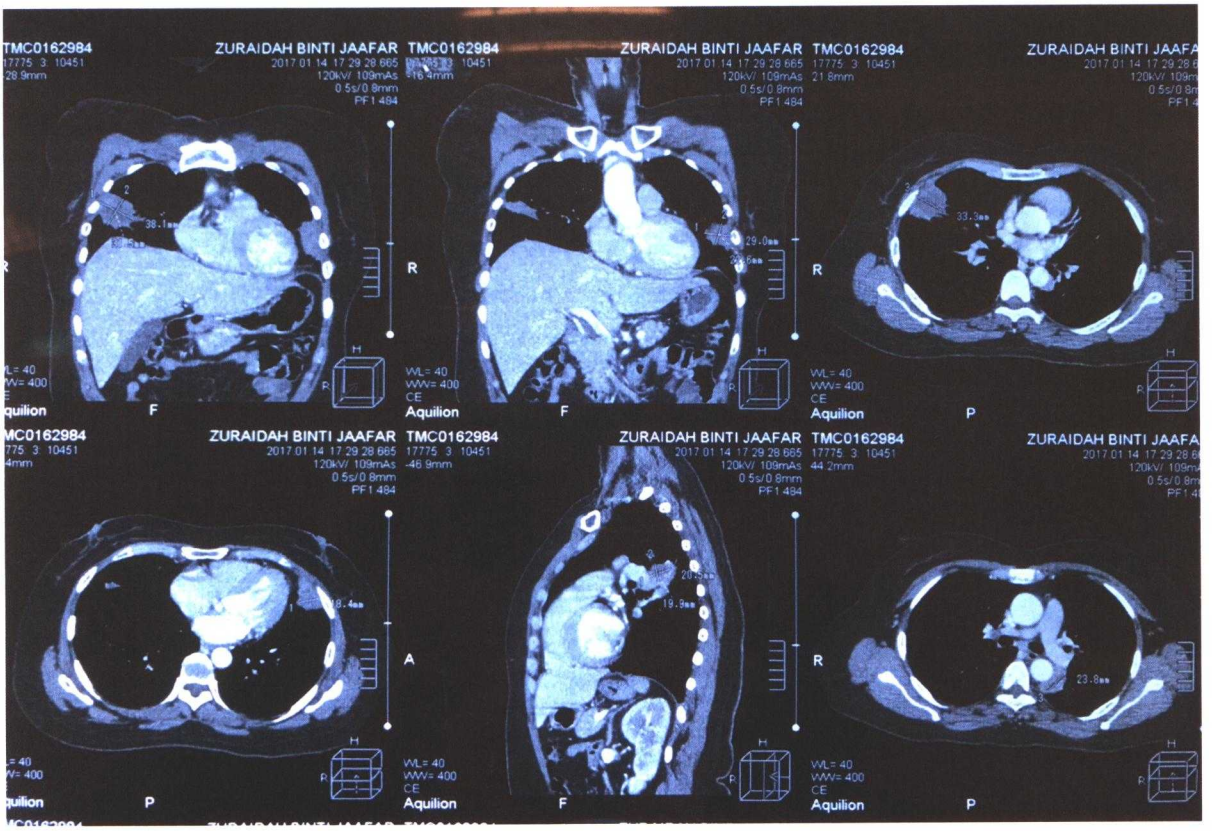
A 46 year old lady was referred to our centre for colonoscopy and respiratory consult for investigation of bilateral lung masses. 4 months earlier, she presented with left ear tinnitus associated with reduce hearing. She only sought medical advice after 4 months to an otolaryngologist and was treated for otitis media. At the same time, she complained of epistaxis, haemoptysis, bilateral lower limb numbness associated with weakness, arthralgia involving multiple joints and intermittent fever which led to hospital admission 2 weeks later. Chest radiograph showed a homogenous, rounded consolidation over right lower zone with patchy consolidation over left lower zone (Fig 1). She was treated as pneumonia and completed a course of antibiotic. Despite treatment, these symptoms persisted. A non-contrasted CT thorax revealed a pleural base mass noted at the right middle lobe, measuring 38mm x 31mm x 33mm and at the left lower lobe measuring 29mm x 27mm x 18mm. Another mass at the perihilar region abutting the descending aorta measures 20.5mm x 19.9mm x 23mm. This partially encasing the left pulmonary trunk and descending aorta. A lung nodule with spiculation noted at right lobe anterior segment, measures 19.5mm x 15mm and another nodule at right lower lobe measuring 8.6mm x 16mm. No infiltration to adjacent ribs. No pleural effusion. No pathological lymph nodes at carina and mediastinum. No axillary mass. Other organs are normal (Fig 2). She was advised for biopsy but refused. She was referred to a neurologist for investigation of the bilateral lower limb weakness and numbness. A nerve conduction study performed which showed severe axonal type of motor polyneuropathy involving lower limbs more than upper limbs. She was diagnosed with Guillain-Barre Syndrome. She subsequently requested for self-discharge. She continued to deteriorate further and six weeks later, she was readmitted to another hospital due to ongoing epistaxis, haemoptysis, joint pain and limb weakness. New symptoms include loss of weight and appetite, multiple oral ulcers and post prandial abdominal pain. During that admission, she had blood transfusion due to epistaxis and haemoptysis with drop in haemoglobin level. CT abdomen and pelvis revealed alveolar shadowing within lateral segment of the right middle lobe and the superior segment of the lingula. A short segmental circumferential narrowing at the ascending colon is seen for a length of 2cm. the liver, gallbladder, pancreas, spleen and both kidneys are normal. No space occupying lesion seen. Esophago-duodenoscopy showed multiple areas of gastritis, erosion at antrum and duodenitis at first and second part. No ulcer or growth seen. She was then referred to our centre for colonoscopy and further investigation.

On examination, she was hemodynamically stable with blood pressure 152/94 mmHg, pulse rate 108 beats per minute, temperature 37 degree Celsius and oxygen saturation 99 percent on room air. Respiratory examination showed bilateral coarse crepitations up to midzone while cardiovascular and abdominal examinations were unremarkable. Neurologically, the cranial nerves were intact. There was evidence of sensorimotor polyneuropathy with 4/5 ankle

dorsiflexion and 3/5 plantar flexion bilaterally and loss of sensation up from midtarsal distally. All the peripheral pulses were normal and strong. A small vasculitic lesion seen on the lateral part of the right lateral malleolus (Fig 3).



(Fig 1)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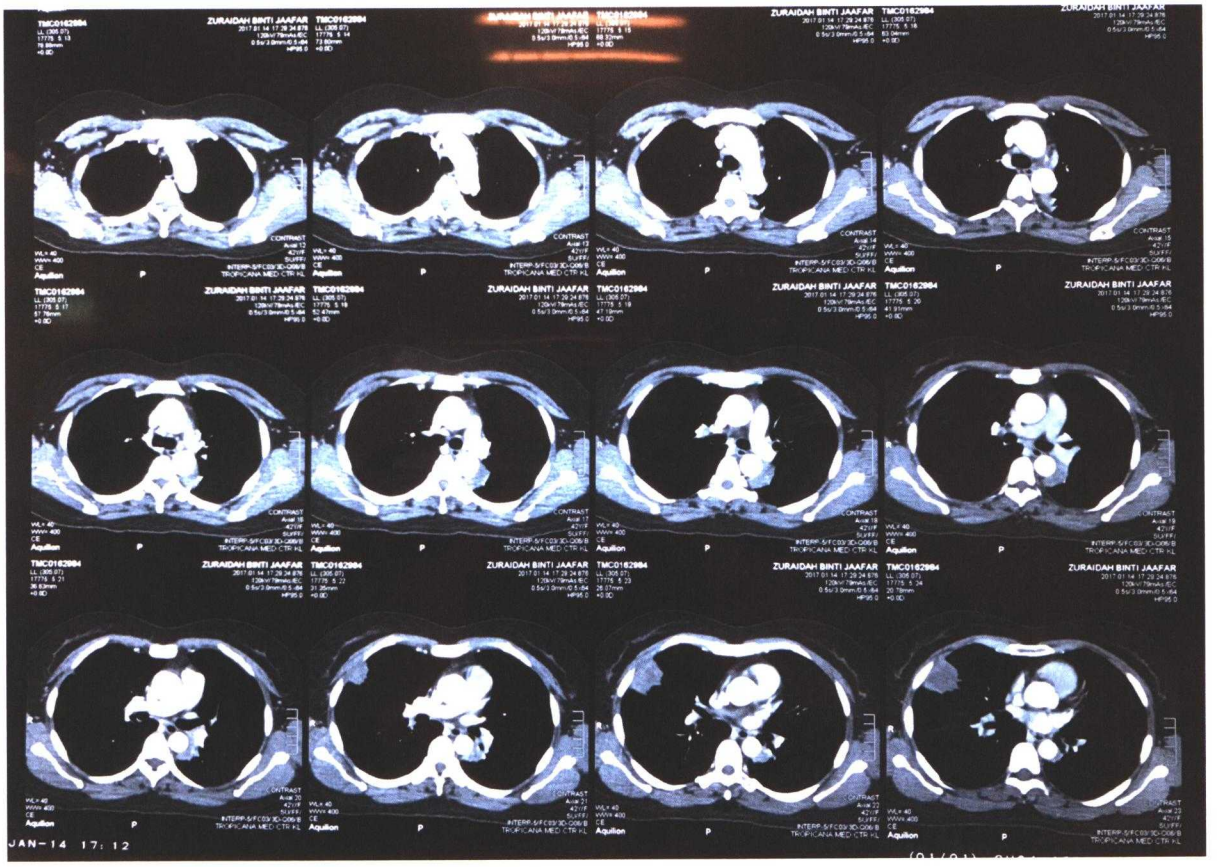
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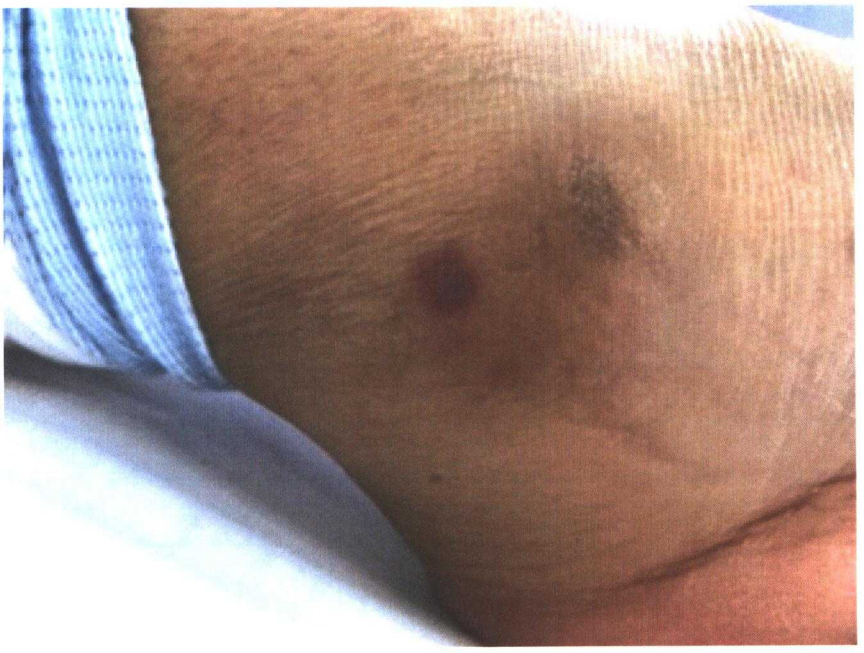
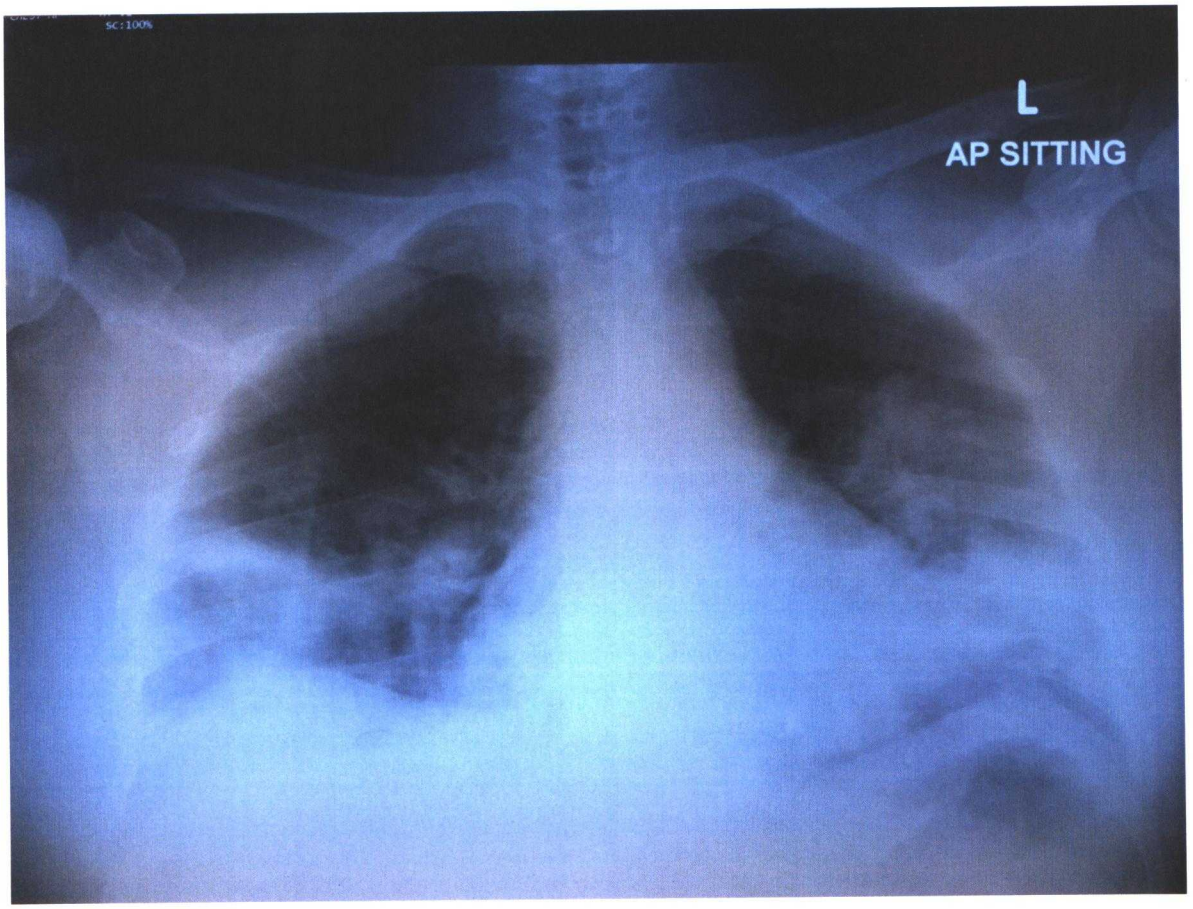
(Fig 2)

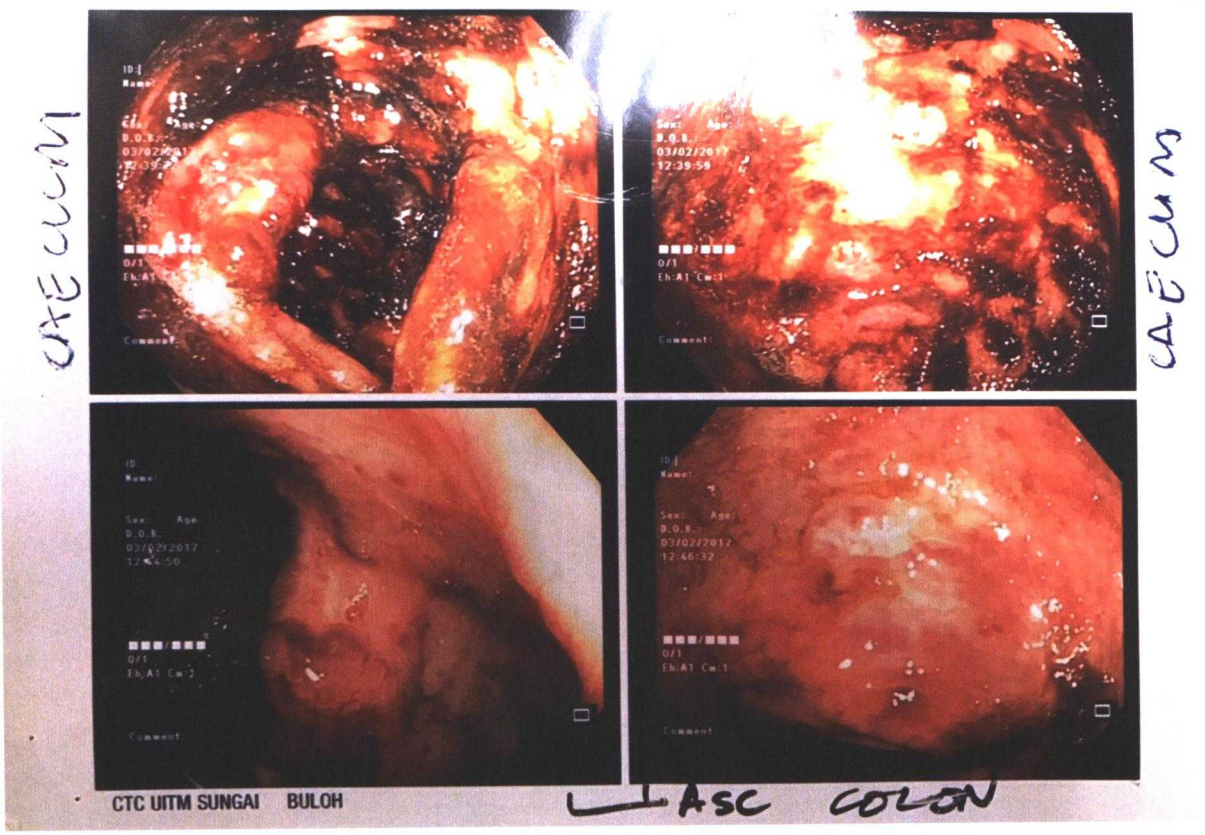


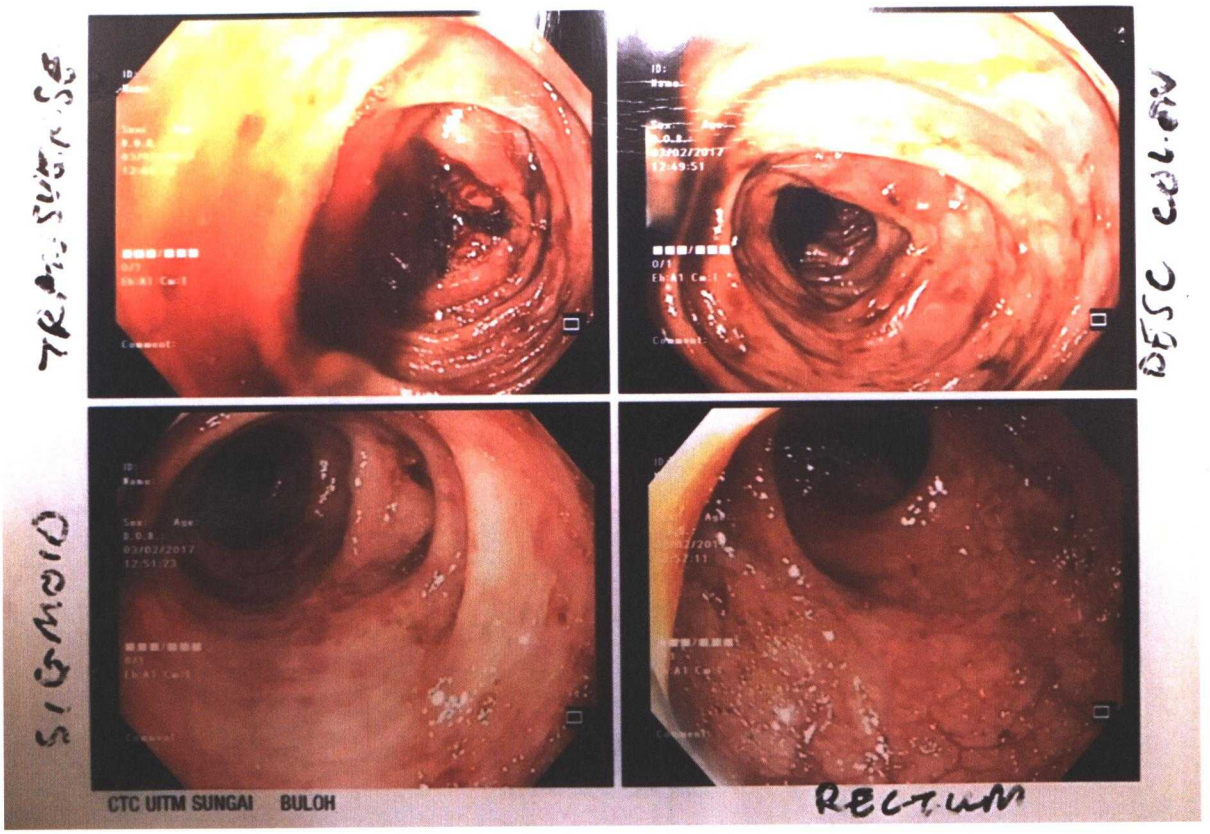
(Fig 3)

Investigations revealed mild normochromic normocytic anaemia with Haemoglobin 9.9 g/L, White blood cell count 12 x 10/L, haematocrit 27.4% and platelet 314 x 10/L, acute kidney injury with urea 13.5 mmol/L and creatinine 166 mmol/L (baseline creatinine two weeks earlier was 71), hypoalbuminemia 24 g/L, bilateral lower zone patchy consolidation on chest radiograph (Fig 4) and evidence of glomerulonephritis with presence of granular and hyaline cast and packed field red blood cells on urinalysis. Colonoscopy on admission revealed the presence of abnormal mucosa throughout colon, inflamed mucosa with loss of vascular marking and deep ulcers at terminal ileum, caecum, ascending colon and proximal transverse colon (Fig 5). Biopsy of caecum was reported as granulation tissue consistent with ulceration, with mucosal haemorrhage and injury, no significant pathology in biopsy of terminal ileum and mild haemorrhage and active colitis in random colon biopsy. Negative for granuloma, dysplasia or malignancy. Negative for Acid fast bacilli and fungal. We could not proceed with bronchoscopy and lung biopsy because the patient deteriorated a day after admission and subsequently intubated due to type 1 respiratory failure. She developed massive haemoptysis with drop in Hb from 9.9 g/L to 7.1 g/L. Platelet level remained normal but the initial Activated Partial Thromboplastin Time (APTT) was prolonged 58 sec which was corrected with fresh frozen plasma. Chest radiograph showed diffuse consolidation (Fig 6). An urgent CT angiogram revealed bilateral lung masses with extensive posterobasal and ground glass nodular consolidation suggestive of pulmonary haemorrhage. No pooling of contrast within lung to suggest active bleeding (Fig 7).

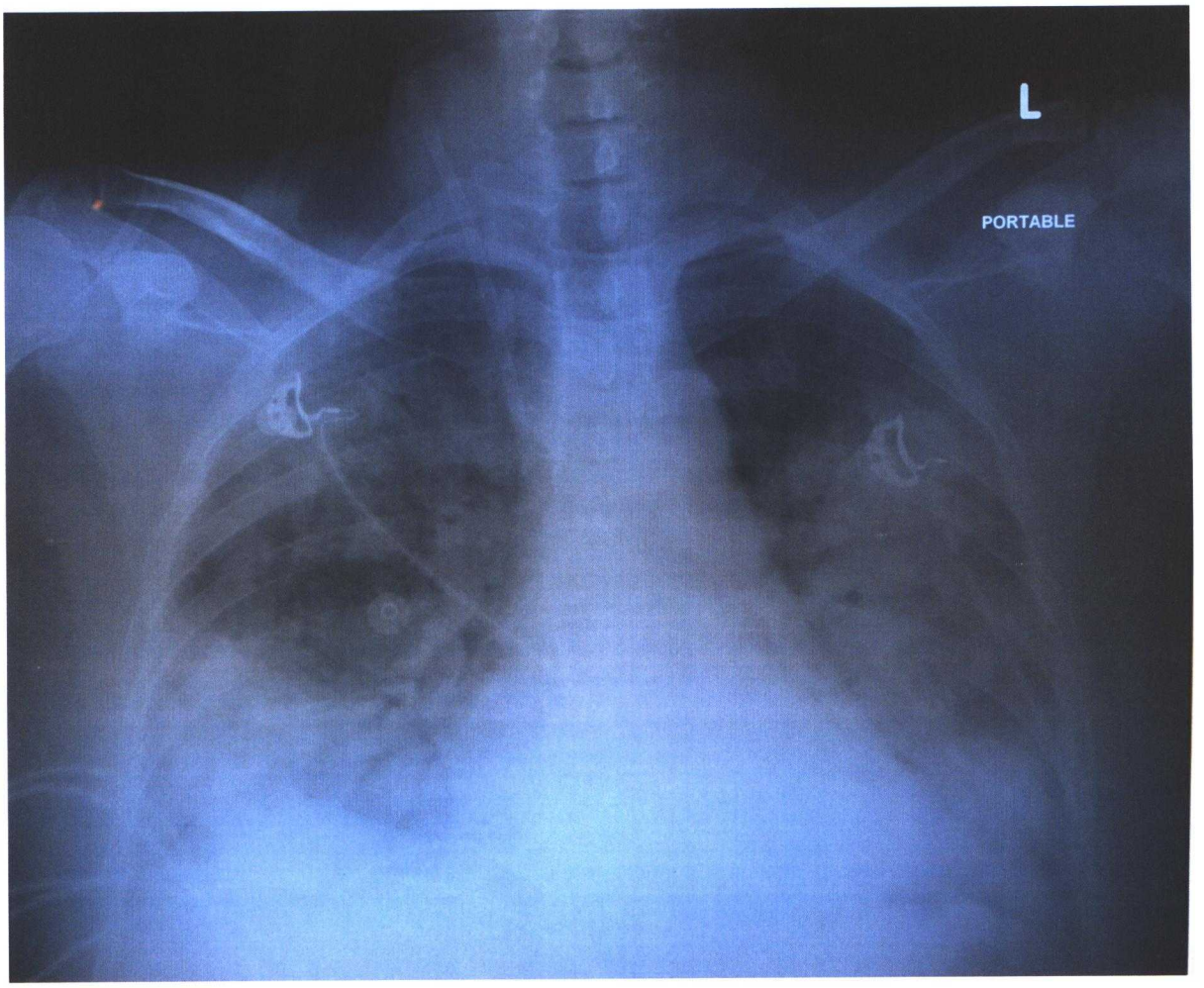


(Fig 4)

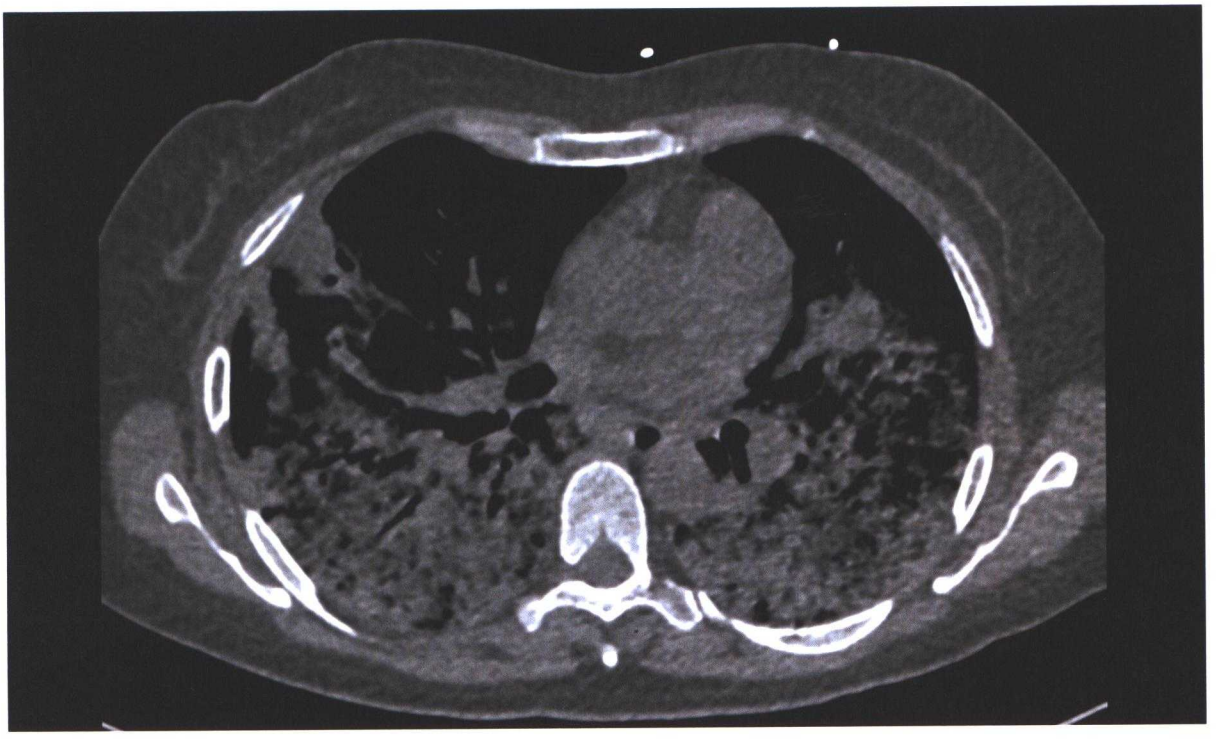




(Fig 5)

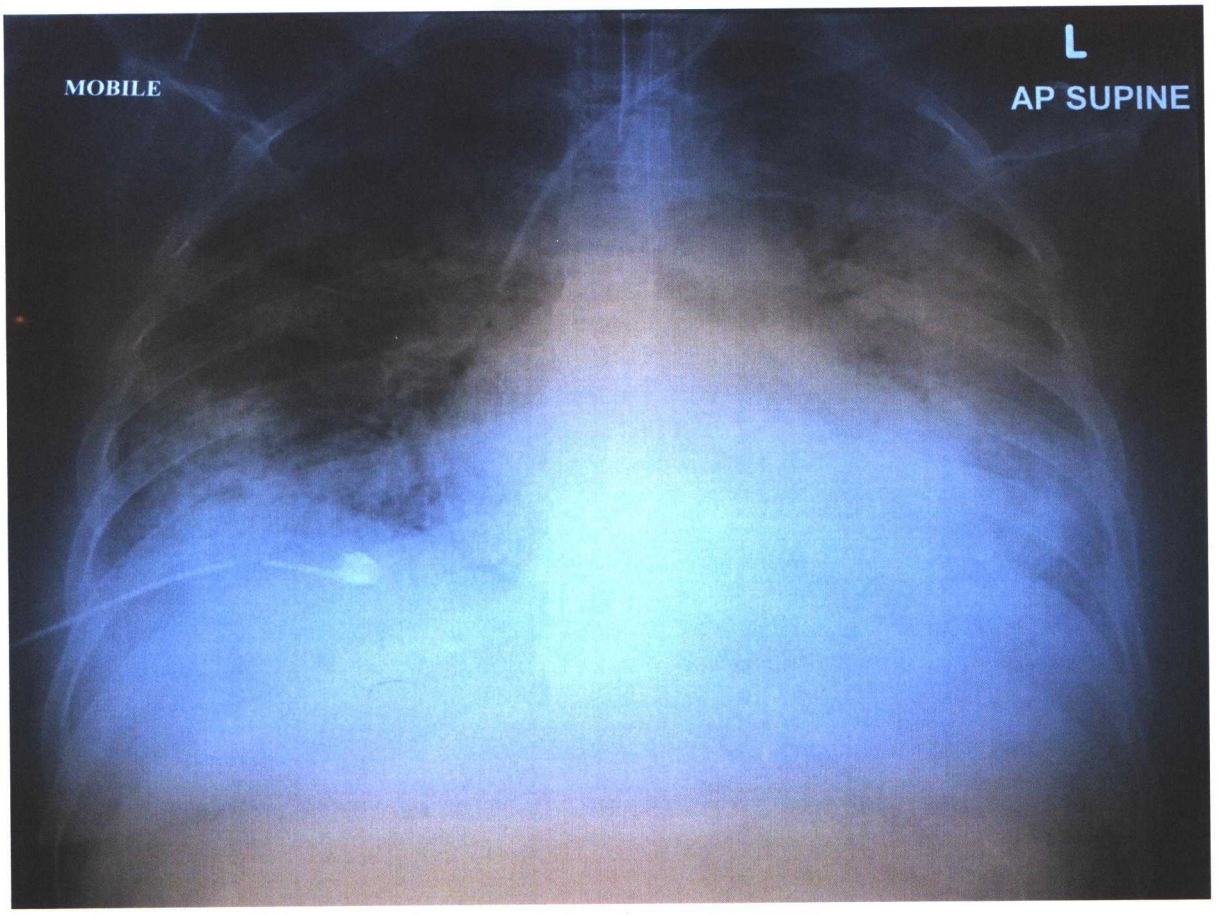


(Fig 6)

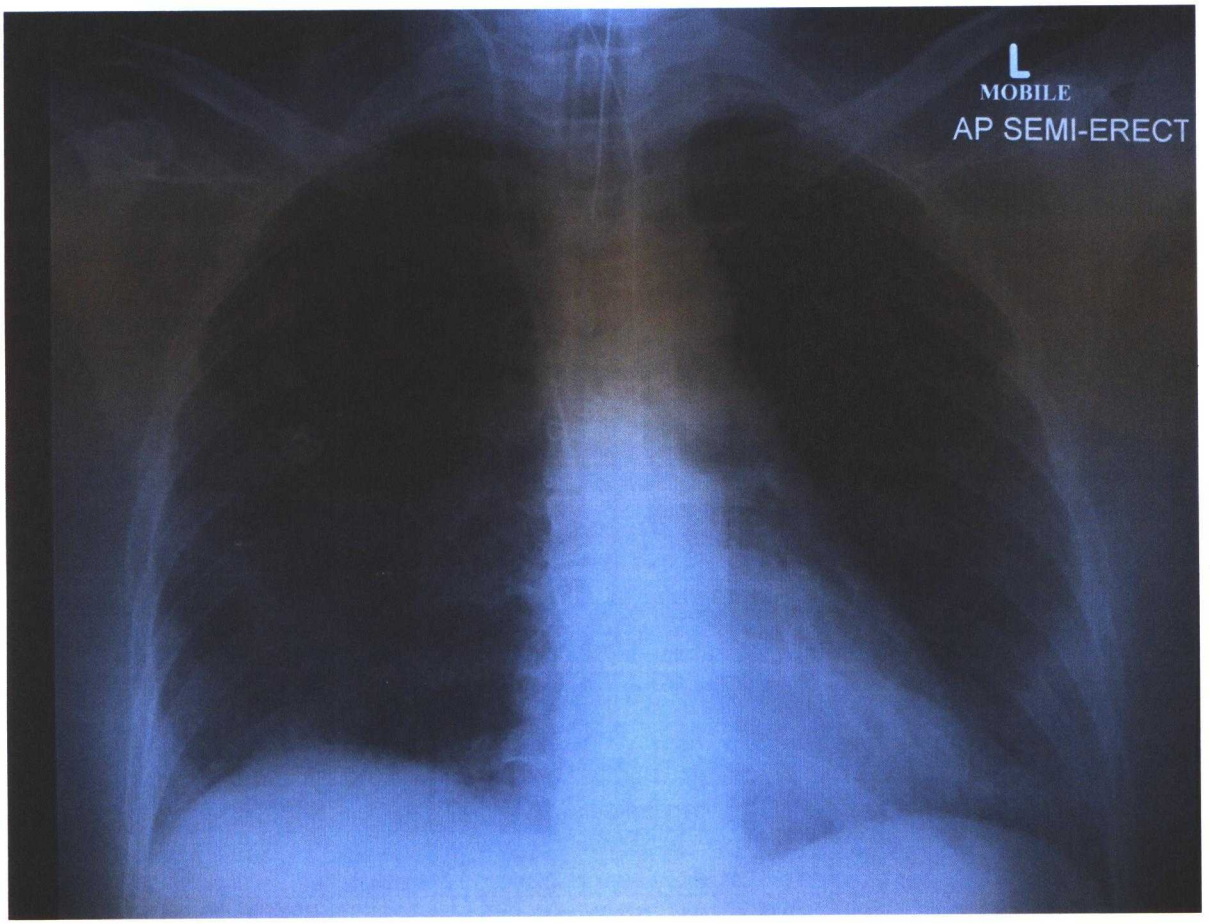


(Fig 7)

We diagnosed GPA based on clinical manifestations of pulmonary haemorrhage, acute renal failure with active sediments, epistaxis, otitis media, sensorimotor polyneuropathy, oral ulcers and multiple colonic ulcers which we postulated to be secondary to gut vasculitis. Although we did not have histopathological evidence and the result of c-ANCA and anti-PR3 were not yet available, treatment was initiated. Intravenous methylprednisolone 500 mg once daily was given for three days, followed by intravenous hydrocortisone 100 mg three times daily and plasma exchange was given for a duration of 7 days. On day 3 of methylprednisolone, anti-PR3 level came back at a high titre of 77 IU/ml (positive > 3.0 IU/ml) and c-ANCA was positive. After completion of a full course of antibiotics, intravenous cyclophosphamide 500 mg was given a day after completed plasma exchange. Serial chest radiographs showed marked improvement of the lung masses and bibasal opacities (Fig 8a and b: one week and two weeks post methylprednisolone). Creatinine level had reduced from 221 mmol/L to 129 mmol/L three days after cyclophosphamide.



(Fig 8a)



(Fig 8b)