CLINICAL MEETING 19TH JANUARY 2017

Clues from the blood

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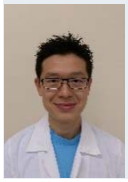


Case history

Patient 1

Patient 1 was a 59 year-old man with 15 pack-year history of smoking. He was a social drinker, and worked as a lorry driver all along. He has chronic hepatitis B infection on Entecavir, without other past medical diseases.

He was admitted for increasing exertional dyspnoea for 4 weeks, with reduction of exercise tolerance to less than 1 flight of stair. He also suffered from persistent dry cough, on and off fever, making him unable to work due to his symptoms.

On admission, his blood pressure and pulse were normal, with oxygen desaturation (SpO2 85% on room air, improved to 96% on 2L/min O2 via nasal cannula). He also had low grade fever. Physical examination did not show cyanosis or finger clubbing. Chest auscultation detected bilateral basal fine crackles. Cutaneous signs were evident, including periungal telangiectasia, cracks over finger tips and rash over upper chest (V-neck sign). There was no muscle weakness or tenderness.

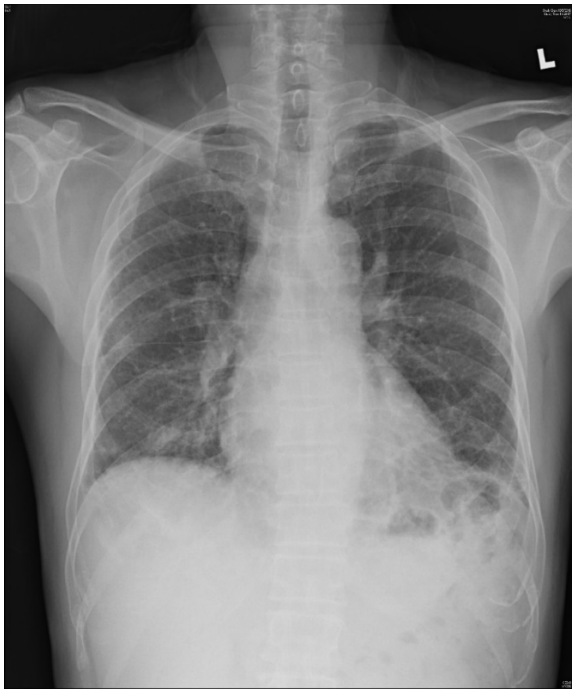
Chest X-ray on admission (Fig. 1A) showed bilateral lower zones interstitial shadows. Initial blood tests showed leucocytosis (total white cell counts 12.4 x 10^9/L, neutrophil 10.8 x 10^9L, eosinophil 0.1 x 10^9/L), elevated inflammatory markers (ESR 96mm/hour, CRP 20 mg/L).

Patient 1 was initially given Augmentin, but still had persistent low grade fever, cough and dyspnoea. Further investigation showed normal serum creatinine kinase and negative autoimmune profile (ANA, anti-ENA, ANCA, RF, anti-CCP, C3, C4, Anti-GBM were unremarkable). Microbiological work-up did not show any specific pathogen. CT thorax (Fig. 2) showed bilateral lung bases reticular opacities, ground glass opacities and consolidation, suggestive of non-specific interstitial pneumonia (NSIP). Spirometry showed restrictive lung pattern, while he failed diffusion capacity testing. Six minute walk distance was 286m, with lowest SpO2 at 86% on 2L/min oxygen. Echocardiogram was unremarkable, with no signs of pulmonary hypertension. Bronchoscopy revealed no endobronchial lesion, with bronchial aspirate negative for microbiological and cytological tests. Transbronchial biopsy showed myoxid fibroblastic focus in the alveolar space, with no background fibrosis and no pathogen, suggestive of organizing pneumonia (OP).

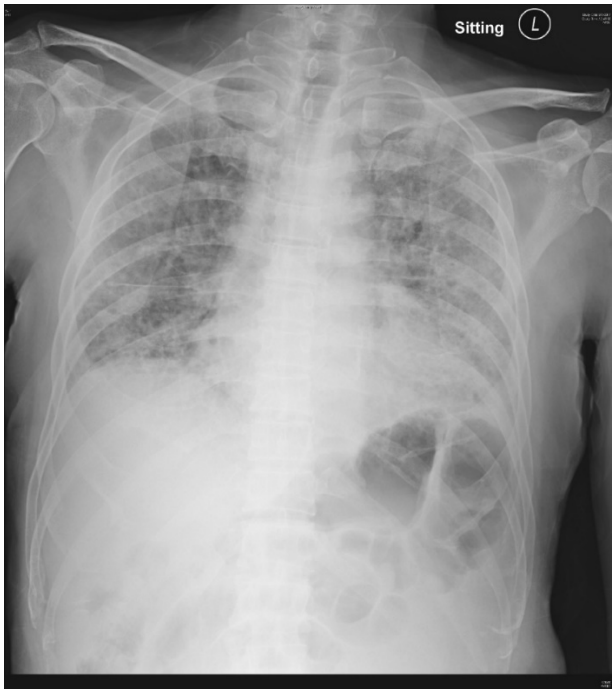
In view of the rapidly progressive chest symptoms over 1 month, dermatomyositis-like

skin signs, elevated inflammatory markers, discrepant radiological (NSIP) and histological (OP) findings, interstitial lung disease (ILD) related to rheumatological disease was suspected. Myositis specific antibody panel was arranged after discussion with rheumatologist. Anti-MDA5 was strongly positive, and a diagnosis of ILD associated with clinically amyopathic Dermatomyositis (CADM) was made. Strong immunosuppression, including pulse methylprednisolone followed by prednisolone and tacrolimus was started, together with monthly intravenous cyclophosphamide. Yet the patient did not respond, with increasing dyspnoea and radiological progression (Fig. 1B), needing long term oxygen therapy. Intravenous immunoglobulin (IVIG), Rituximab were tried without much effect. The patient passed away 8 months after presentation.

Fig 1. Chest X-ray of patient 1

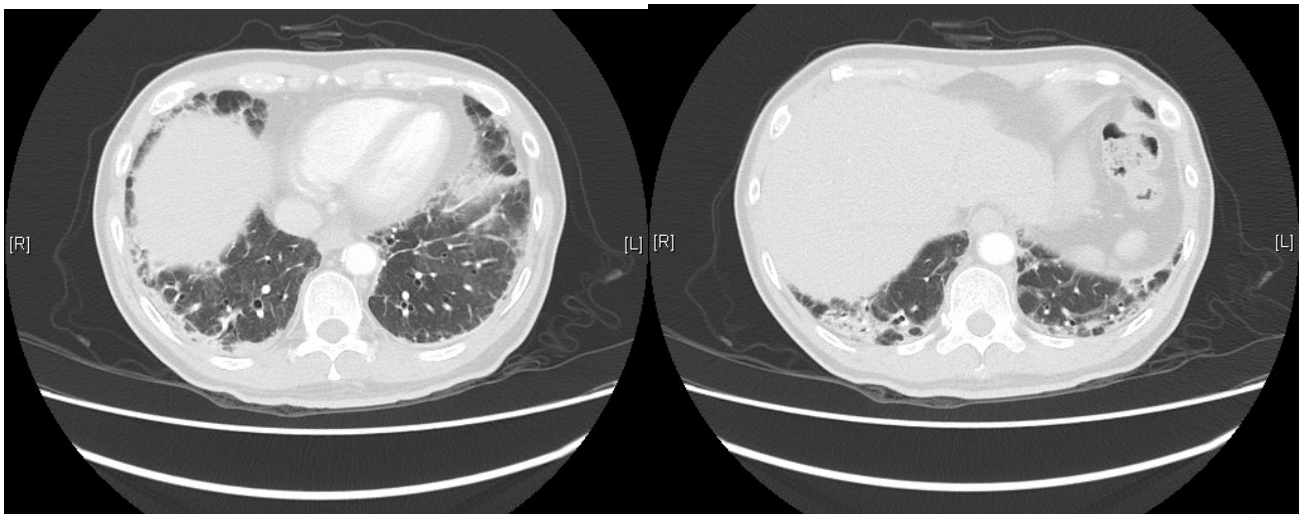


1A: Chest X-ray on admission



1B: Chest X-ray 8 months after diagnosis

Fig 2. CT thorax of patient 1 at presentation



Patient 2

Patient 2 was a 63 year old lady with no history of smoking and had unremarkable past health. She was presented with increasing cough and dyspnoea for 3 months. She also had dry thickened skin with cracks over her fingertips. Her muscle power was full, with no muscle tenderness.

Her initial chest X-ray (Fig. 3) showed bilateral lower zones reticular shadows. Blood tests showed leucocytosis (WBC 9.8 x 10^9/L, neutrophil 7.1 x 10^9/L, eosinophil 0.2 x 10^9/L), elevated inflammatory marker (ESR 70mm/hour). Serum creatinine kinase was normal. Basic autoimmune profile (ANA, Anti-ENA, Anti-ds DNA, C3, C4, RF, ANCA) was unremarkable. Lung function showed restrictive lung defect with reduced diffusion capacity (36% of predicted value). Six minute walk distance was 250m. CT thorax showed diffuse consolidation and ground glass opacities predominantly over bilateral lower lobes, suggestive of ILD (Fig. 4).

Myositis specific antibodies was arrange in view of her skin changes and ILD. Anti-PL 12 antibody was strongly positive, and a diagnosis of anti-synthetase syndrome with ILD was made. Prednisolone together with monthly intravenous cyclophosphamide were commenced. Her cough and dyspnoea improved, with WBC and ESR normalized. Subsequent CT thorax showed reduction in consolidation (Fig. 4).

Fig. 3. Patient 2's chest X-ray on presentation

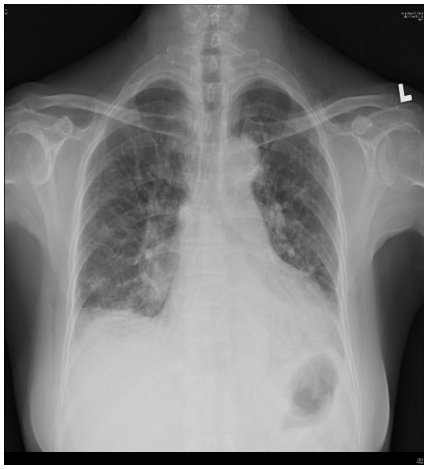
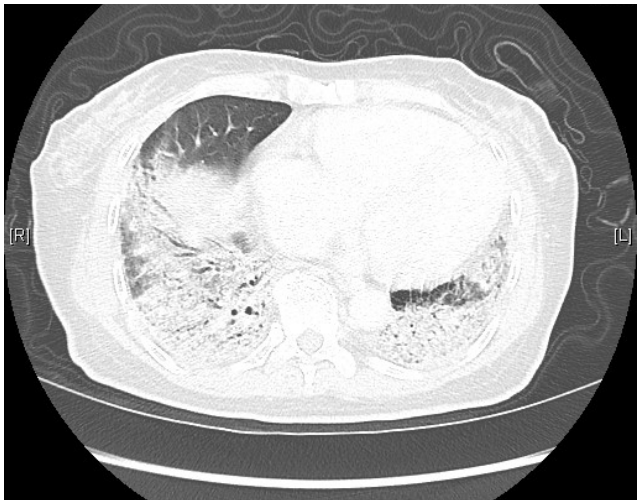
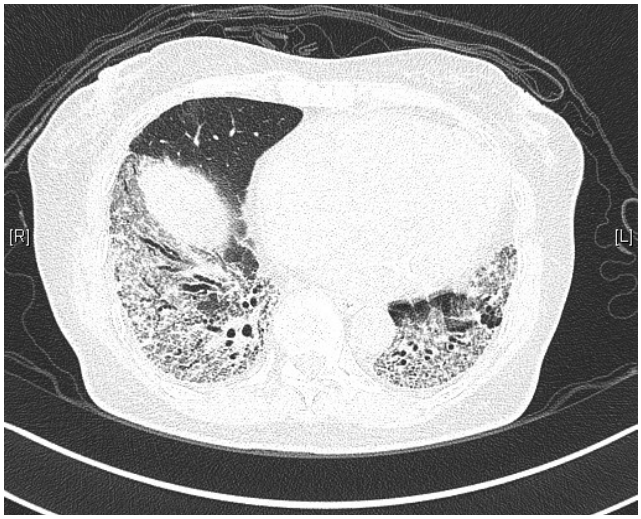


Fig. 4. A: Patient 2's CT thorax on presentation. B: Patient 2's CT thorax after 2nd dose of intravenous cyclophosphamide.

A 

B 

Discussion

Idiopathic inflammatory myopathies (IIM) is a rare, heterogeneous group of connective tissue disease (CTD) with chronic inflammation of skeletal muscles with unknown aetiology (Table 1). Polymyositis and dermatomyositis are the two prominent diseases in this group. Other notable examples including clinically amyopathic dermatomyositis (CADM) and anti-synthetase syndrome. CADM is a subset of dermatomyositis, characterized by the classical cutaneous features of dermatomyositis (e.g. Heliotrope rash, Gottron's papules, V-neck sign, periungal telangiectasia, etc), with no clinically significant muscle involvement for at least 6 months prior to presentation. Majority of the reported CADM cases are from East Asia, many of which had rapidly progressive ILD associated with grave prognosis. Anti-synthetase syndrome was first described by Targoff in 1992[1]. Clinical features include ILD (67-100%), myositis (2-30%), polyarthritis (60%), mechanics hands sign (70%), Raynaud's phenomenon (60%) and fever. Presence of auto-antibodies against aminoacyl-tRNA synthetase was key to the diagnosis of this syndrome.

Table 1. Examples of Idiopathic Inflammatory myopathies (IIM)

Dermatomyositis - clinically amyopathic dermatomyositis (CADM) - anti-synthetase syndrome - juvenile dermatomyositis
Polymyositis
Necrotizing autoimmune myositis
Sporadic inclusion body myositis

Despite the low prevalence and the fact that many of the cases are managed by rheumatologists, IIM remains highly relevant to respiratory physicians. One reason is that ILD is common in IIM, with a prevalence of 20-65%[2-4]. Also, 10-20% of IIM present with ILD as the first and sole manifestation, while the delay in the appearance of muscle or skin manifestation can be up to years[2-3]. As a result, a significant proportion of so called "idiopathic" ILD may actually have underlying IIM. In a retrospective cohort of 114 patients with ILD, 15% had new CTD diagnosed during the index ILD evaluation, of which 59% were IIM[5].

Whether or not an ILD patient has associated IIM can have a major impact on his prognosis. In a large retrospective cross-sectional study involving 831 patients with IIM[6], presence of ILD was associated with significant higher risk of death (Hazard ratio 2.13).

<u>Work-up for idiopathic inflammatory myopathies</u>

Patients suffering from IIM usually have the classical skin changes, or symmetrical proximal muscle weakness. Blood tests can show elevated muscle enzymes like creatinine kinase (CK) or lactate dehydrogenase (LDH) if muscle involvement was present. Typical electromyographic (EMG) findings are

increased spontaneous and insertional activity with fibrillation potentials, positive sharp waves, complex repetitive discharges, early recruitment and small polyphasic motor unit potentials. Magnetic resonance imaging (MRI) can identify muscle oedema in muscle inflammation and muscle atrophy in late cases, and to guide muscle biopsy site. Muscle biopsy in polymyositis reveals endomyisal inflammatory cells infiltrate mainly consisting of $CD8^+$ T lymphocytes. In dermatomyositis, the inflammatory infiltrates usually localize in the perivascular site, consisting of $CD4^+$ T lymphocytes. Skin biopsy reveals interface dermatitis, and occasionally lymphocytic inflammatory infiltrates at the dermal-epidermal junction. Care should be exercised in excluding other causes of myositis e.g. infection, metabolic disorder, muscular dystrophies, etc.

If ILD is present, patients can have the usual clinical features of ILD like dyspnoea, cough, finger clubbing and pulmonary hypertension. Characteristic HRCT thorax pattern usually shows a non-specific interstitial pneumonia (NSIP) or organizing pneumonia (OP) pattern. Lung function classically shows restrictive lung defect, with reduced diffusion capacity and 6-minute walk distance. Caution is needed during interpretation as there can be pseudo-normalization of lung volumes if the patient has co-existing obstructive lung diseases. In such case, diffusion capacity will be disproportionally low. Another scenario with disproportionally low diffusion capacity is the presence of complications like pulmonary hypertension. Surgical lung biopsy remains a gold standard in classifying different subtypes of ILD. But it is less frequently done in the context of CTD related ILD as the presence of other CTD features often justifies immunosuppressive therapy before the surgical lung biopsy.

Auto-antibodies

As with other CTD, auto-antibodies are important in confirming the diagnosis and predicting prognosis. Auto-antibodies were reported to be present in 50-60% of IIM[7], and is broadly classified into myositis-associated antibodies (MAA) and myositis-specific antibodies (MSA).

Myositis associated antibodies [Table 2]

As the name suggests, these antibodies are associated with IIM (40%)[8], but can be present in other CTD as well.

Table 2. List of myositis-associated antibodies (MAA) [w/ associated CTDs listed]

Auto-antibodies	**Clinical correlations**
Anti-nuclear antibodies (ANA)	Dermatomyositis (24-60%) ; polymyositis (16-40%)[7, 9]
Anti-Scl	Systemic sclerosis
Anti-centromere	Limited scleroderma
Anti-Ku	Systemic sclerosis, SLE
Anti-Ro(SSA), Anti-La(SSB)	SLE , Sjogren's syndrome
Anti-U1RNP	Mixed CTD

SLE - Systemic lupus erythematosus; CTD - connective tissue disease

Myositis specific antibodies [table 3]

Myositis specific antibodies (MSA) are present in 35-50% of IIM[8, 10]. They are highly specific for IIM, with specificity of 76-100%[8, 10]. Apart from diagnosing IIM, MSA can help predicting clinical phenotype, prognosis and response to treatment.

Table 3. List of myositis specific antibodies (MSA)

Auto-antibodies	**Clinical feature**
Anti-synthetase antibodies - Anti-Jo1, anti-PL7, anti-PL12, anti-KS, anti-EJ, anti-OJ, anti-Ha, anti-Zo	Anti-synthetase syndrome
Anti-MDA5	CADM, Rapidly progressive ILD with poor prognosis
Anti-SRP	Acute onset necrotizing myopathy (severe weakness, high CK) May be refractory to treatment
Anti-Mi2	Adult and juvenile dermatomyositis ILD uncommon Favourable prognosis
Anti-SAE	May present with CADM first
Anti-NXP2	More common in juvenile dermatomyositis Commonly associated with malignancy in adult cases
Anti-p140	Juvenile dermatomyositis with calcinosis
Anti-p155/140	Severe cutaneous disease

CADM – clinically amyopathic dermatomyositis; ILD – interstitial lung disease;

Anti–Melanoma Differentiation–Associated Gene 5 Antibody (Anti-MDA5) is initially called anti-CADM-140 antibody, is a polypeptide weighing around 140-kilodaltons and is highly associated with CADM. It was first discovered and reported by Sato in 2005[11], where all patients positive for anti-MDA5 had CADM. Further studies show that anti-MDA5 is the most common MSA in dermatomyositis or CADM, present in up to 48% of Asian patients and 13% of Caucasian patients[10].

Apart from diagnosing IIM, presence of anti-MDA5 predicts a high likelihood of lung involvement and a poor prognosis. A meta-analysis of 13 studies[12] showed anti-MDA5 has a sensitivity of 77%, specificity of 86% and AUC 0.89 in ROC analysis in predicting rapidly progressive ILD in dermatomyositis. Prognosis is especially poor for anti-MDA5 positive patients, with 6 month survival of 40-54% only[13, 14]. Level of anti-MDA5 may correlate with disease activity as well. In a case report, out of 11 patients with anti-MDA5 having ILD

and CADM, all 10 patients who achieved remission had disappearance of anti-MDA5, which the patient who died have persistent presence of anti-MDA5[15].

Anti-synthetase antibodies is a large group of autoantibodies and is a typical feature in anti-synthetase syndrome. Anti-Jo1 is the most common anti-synthetase antibody, being present in 20-30% of IIM, and has a strong association with muscle inflammation. Anti-PL7 and anti-PL12 are highly associated with ILD (up to 95%), with less association with muscle inflammation[16].

Testing for MSA, however, is not widely available in Hong Kong at present. The panel available in private hospital is a semi-quantitative assay, and cannot be used to monitor disease activity.

It can be tricky to detect ILD in IIM, or discovering underlying IIM in supposed "idiopathic" ILD. As mentioned, ILD can precede skin and muscle involvement in IIM by years, leading to a mislabelling of "idiopathic" ILD. Also, early symptoms of ILD like dyspnoea and reduced exercise tolerance are non-specific. They can be wrongly attributed to other associated conditions in IIM like deconditioning and muscle weakness, anaemia, and malignancy. A high index of suspicion is needed for an accurate diagnosis.

Management of idiopathic inflammatory myopathies

Systemic glucocorticoid is currently the corner stone in the treatment of ILD associated with IIM, with different regimens from oral prednisolone to pulse intravenous methylprednisolone. As response to steroid may not be satisfactory in many cases, additional immunosuppressants are frequently added. A small retrospective cohort showed better outcome if immunosuppressant is added to steroid at treatment initiation, instead of added after initial failure of steroid monotherapy[17].

Different immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine A, tacrolimus, and rituximab) were reported to have benefits in treating ILD asscociated with IIM in various case series or retrospective cohorts (Table 4). Other potential therapy includes intravenous immunoglobulin (IVIG), plasmapharesis and polymyxin B haemoperfusion, which can be considered as a salvage therapy[18-20].

Table 4. List of immunosuppressants used in ILD associated with IIM

Cyclophosphamide (CYC)	Ge (2015)[21]	Systematic review of 12 studies	58% ↑FVC 64% ↑DLCO 67% improved HRCT
	Kameda (2005)[22]	Prospective pilot study of 10 acute DM-ILD	50% survived with favourable outcome
Mycophenolate mofetil (MMF)	Fischer (2013)[23]	Retrospective cohort of 32 DM/PM-ILD	↑FVC ↑DLCO
Azathioprine (AZA)	Mira-Avendano (2013)[24]	Retrospective series of 13 DM/PM-ILD	↓dyspnoea Stabilize lung fx
Cyclosporine A (CsA)	Nagasaka (2003)[25]	Retrospective cohort of 32 DM/PM-ILD	Improved symptoms, auscultation, CXR, PaO2/FiO2 ratio
Tacrolimus	Ge (2015)[21]	Systematic review of 8 studies	89% ↑ or stabilize FVC 81% ↑ or stabilize DLCO
Rituximab	Andersson (2015)[26]	Retrospective cohort of 24 Antisynthetase syndrome & severe ILD	24% ↑FVC 17% ↑DLCO

Key: DM – dermatomyositis, PM – polymyositis, ILD – interstitial lung disease

Non-pharmacological therapies including smoking cessation, vaccination against influenza and pneumococcus, long term oxygen therapy and pulmonary rehabilitation should be considered in all patients with ILD associated with IIM.

As most of the current evidence is from retrospective cohorts or case series, no international treatment guideline is available. A recent review article[27] suggested steroids plus mycophenolate mofetil or azathioprine for mild to moderate ILD. For severe ILD, high-dose steroids plus cyclophosphamide or Rituximab or Cyclosporin A/Tacrolimus should be considered. After stabilization, prednisolone can be tapered down with steroid-sparing drugs remained. No consensus is available on the treatment duration.

Conclusion

ILD associated with IIM is not an easy diagnosis to make despite the strong association of the two conditions. High index of suspicion is required for evaluation of apparent idiopathic ILD, or known IIM patients with respiratory symptoms. Autoantibodies, especially myositis specific antibodies (MSA) like anti-MDA5 and anti-synthetase antibodies are important in making diagnosis, predicting clinical phenotypes and prognosis. Once diagnosis is made, early aggressive combination therapy with steroid and immunosuppressant should be considered.

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Pulmonary cavitation in a diabetic patient: TB or not TB

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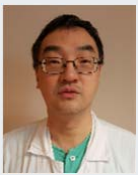

Case History

Mr CCY M/71, he was smoker and had history of diabetes mellitus. He complained of on and off cough for 2 months in 8/2015. There was no hemoptysis. He complained of exertional shortness of breath with exercise tolerance of 3 flights of stairs. There was no fever or night sweat.

He was referred from chest clinic to Kowloon Hospital for further care. Chest x-ray showed right upper cavitating shadow (fig 1). Blood result showed HbA1c 11, white cell count 9.3 and creatinine level of 112. Insulin was started for better glycemic control.

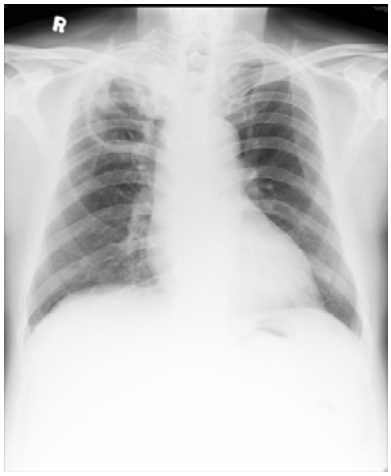

Figure 1. CXR on presentation

He was treated with empirical Rocephin but there was no radiological response. Bronchoscopy was arranged and it showed swollen right upper lobe bronchi and whitish lesion. The bronchial biopsy turned out to be chronic inflammation with mucormycosis. Among the inflammatory exudate covering the bronchial mucosa, non-septate wide-angled branching hyphae with admixed spores are demonstrated by PASD stain (Fig 2).No intra-vascular fungal invasion is noted. Computed tomogram of the chest was done and it showed 5.3 x5.3x 5.4 cm cavitation lesion with air-fluid level in right upper lobe of lung. Adjacent patchy consolidations seen at the apex and posterior aspect of the cavity (Fig 3)

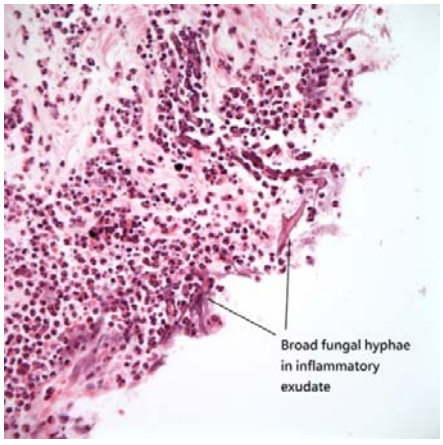

Figure 2. Histology of bronchial biopsy