"Crazy-paving" pattern: A characteristic presentation of pulmonary alveolar proteinosis and a review of the literature from India

Shekhar Kunal, Kamal Gera, Vikas Pilaniya, Sudhir Jain[1], Rajesh Gothi[2], Ashok Shah

Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, [1]Department of Pathology, Oncquest Laboratories Limited, New Delhi, [2]Department of Radiology and Imaging, Saket City Hospital, New Delhi, India

Address for correspondence: Prof. Ashok Shah, Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi - 110 007, India. E-mail: ashokshah99@yahoo.com

CASE REPORT

An 18-year-old female student, a never smoker, HIV-negative, was referred to our Institute for evaluation of exertional breathlessness, cough with minimal mucoid sputum and fever of 1.5 years duration. She had lost 15 kg weight over the past 6 months. Prior to the presentation, based on her clinical and radiological profile, she had received antituberculous therapy for 4 months with no relief.

On examination, she was tachypnoeic and dyspnoeic but afebrile. Digital clubbing was observed. Vesicular breath sounds with fine inspiratory crackles were audible in all areas of the chest wall. Oxygen saturation on room air was 54%. Arterial blood gas analysis on oxygen (4 lt/min) showed pH 7.40, PCO_2 38.7 mmHg, PO_2 57.6 mmHg, and SaO_2 of 90%. The total leucocyte count was 5.43×10^3 cells/μL with a normal differential count.

Chest radiograph is shown in Figure 1 and high resolution computed tomography (HRCT) of the thorax is shown in Figure 2. Sputum stains and cultures for *Mycobacterium tuberculosis*, fungi and other aerobic organisms were negative. Fiber-optic bronchoscopy did not visualize any gross abnormality. Bronchoalveolar lavage (BAL) was milky in appearance but stains and cultures were negative for aerobic organisms including *M. tuberculosis* and pathogenic fungi. The BAL fluid was sent for a special investigation.

QUESTIONS

Q1: What is the radiological description?
Q2: What is this characteristic pattern on HRCT known as?
Q3: What is the differential diagnosis of "Crazy-paving" pattern on HRCT?
Q4: What was the clinical diagnosis in this patient?
Q5: How was the diagnosis achieved?
Q6: What are the current modalities available for treatment of this condition?

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.180936

How to cite this article: Kunal S, Gera K, Pilaniya V, Jain S, Gothi R, Shah A. "Crazy-paving" pattern: A characteristic presentation of pulmonary alveolar proteinosis and a review of the literature from India. Lung India 2016;33:335-42.

ANSWERS

A1: Chest radiograph [Figure 1] showed bilateral, diffuse alveolar opacities having a perihilar and basal distribution with sparing of the apices while the HRCT of the thorax [Figure 2] demonstrated bilateral diffuse ground-glass opacities (GGO) superimposed with interlobular and intralobular septal thickening in a geographical distribution resembling irregularly laid cobblestones on a pavement. These areas of "Crazy-paving" were bilateral and sharply demarcated from the normal lung parenchyma creating a "geographic" pattern.

A2: This appearance is characteristically described as "Crazy-paving" pattern. The reticular network in "Crazy-paving" pattern is thought to represent the thickened interlobular septa while the GGO reflect the alveolar filling with periodic acid-Schiff (PAS) positive material.[1] The mechanisms thought to be responsible for this pattern include alveolar filling processes, interstitial fibrotic processes, or a combination of both.[2]

A3: "Crazy-paving" pattern on HRCT was at one time considered diagnostic of pulmonary alveolar proteinosis (PAP). However, this pattern has now been recognized in several other conditions which are listed in Table 1.[1,3,4]

A4: PAP.

A5: The diagnosis was suspected due to the characteristic features seen on HRCT supported by the milky appearance of BAL. It was substantiated by the microscopic examination of the bronchial aspirate which showed granular eosinophilic exudate that was PAS stain positive [Figure 3]. The diagnosis of PAP is commonly established on the basis of the characteristic imaging feature on HRCT along with cytopathological evaluation of the BAL fluid. However, open lung biopsy (OLB) continues to remain as the gold standard for diagnosis of PAP.

A6: Whole-lung lavage (WLL) developed by Ramirez and Campbell[5] has been the standard of care for the treatment especially, in patients with idiopathic PAP. This procedure is done under general anesthesia and involves removal of lipo-proteinaceous material from the alveoli using saline solution and chest percussion. This leads to symptomatic, radiological, and functional improvement in 85% of patients of

Table 1: Radiological differential diagnosis of "crazy-paving" appearance on HRCT[1,3,4]

Conditions having "crazy-paving" on HRCT
PAP
Pneumonia (especially pneumocystis pneumonia)
ARDS
UIP
Cardiogenic pulmonary edema
Alveolar hemorrhage
Radiation-or drug-induced pneumonitis
BAC
Lymphangitic carcinomatosis
Chronic eosinophilic pneumonia
Hypersensitivity pneumonitis
Exogenous lipoid pneumonia
BOOP
Pulmonary veno-occlusive disease

ARDS: Acute respiratory distress syndrome, BAC: Bronchioloalveolar carcinoma, BOOP: Bronchiolitis obliterans organizing pneumonia, HRCT: High resolution computed tomography, PAP: Pulmonary alveolar proteinosis, UIP: Usual interstitial pneumonia

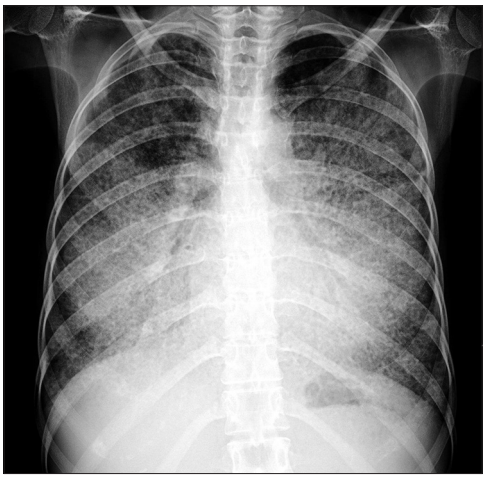

Figure 1: Chest X-ray posteroanterior view showing showed bilateral, diffuse alveolar opacities having a perihilar and basal distribution with sparing of the apices

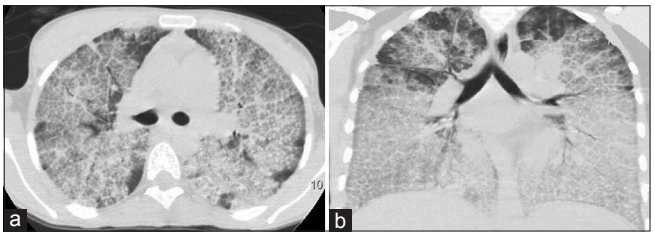

Figure 2: High-resolution computed tomography chest (a) (lung window) and (b) (coronal section). The anterior part of both the lung fields show typical crazy-paving pattern with central ground-glassing and peripheral interlobular septal thickening. In the dependent part of the lung, there is an increased density secondary to the gravitational accumulation of lipo-proteinaceous fluid

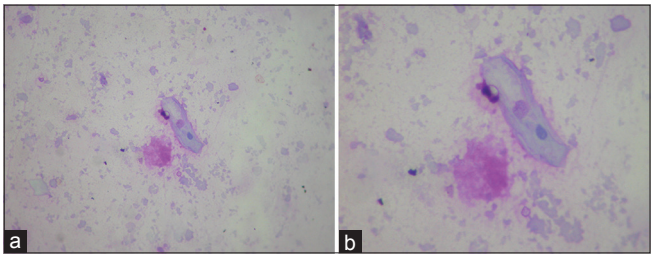

Figure 3: (a) High power view (×40) showing a benign squamous epithelial cells and periodic acid-Schiff positive granular material. (b) Zoom of the previous picture showing the epithelial cell and granular material

PAP.[6] Following WLL, the median symptom-free period is 15 months and if required repeat sessions of WLL can be done.[7] The major complication associated with this procedure is hypoxemia with other less common ones being pneumothorax, pleural effusion, and hydropneumothorax[8]

- Granulocyte-macrophage colony stimulating factor (GM-CSF) supplemental therapy has a role in the management of idiopathic PAP.[9] GM-CSF therapy can be given either by inhaled or subcutaneous route and it can be considered supplemental to WLL with response rates of 50%[9]
- Newer modalities of treatment include administration of Rituximab, a monoclonal antibody directed against the CD20 antigen of B-lymphocytes. It helps in decreasing the concentration of anti-GM-CSF antibodies through the depletion of B-cells.[4] Rituximab is useful in patients not responsive to WLL or GM-CSF therapy. Plasmapheresis is a novel technique which involves removal of the anti-GM CSF antibodies. It leads to improvement in symptoms, oxygen saturation and radiological appearance. Lung transplantation has been attempted in patients with congenital PAP.[4]

DISCUSSION

PAP, first described in 1958 by Rosen *et al*.,[10] is a distinct clinical entity with an estimated prevalence of 0.1 case per 100,000 individuals.[8] This disorder is characterized by intraalveolar accumulation of lipo-proteinaceous material due to defective clearing by the alveolar macrophages. Three distinct subtypes have been recognized: Auto-immune (idiopathic), secondary, and congenital. The auto-immune (idiopathic) form, seen in 90% of the patients, is the most common subtype.[11] Anti-GM-CSF antibodies plays a central role in the pathogenesis of auto-immune (idiopathic) subtype while secondary type is seen in various pulmonary infections, hematological malignancies, and industrial dust exposure.[6]

Chest radiography, a useful screening test, shows a typical perihilar or "batwing" distribution of alveolar opacities. These findings can be confused with those of pulmonary edema, however, absence of cardiomegaly, pleural effusion, Kerley-B lines on chest radiograph usually rules in the favor of PAP. Other less common radiological abnormalities include reticular or reticulonodular shadows, multifocal consolidation, or ground-glassing.[4] The first ever description of "Crazy-paving" pattern on HRCT was in a patient of PAP[12] and has been considered as a hallmark of the disease. HRCT shows areas of patchy alveolar opacification with superimposition of a network of reticulations. These areas of air-space opacification, seen as GGO, are clearly demarcated from the surrounding normal lung parenchyma.[1,4] "Crazy-paving" pattern results from a combination of these reticular networks and GGO. These reticular networks are due to the interlobular, as well as intralobular septal thickening[4] or due to deposition of material in the alveoli at the borders of the acini (periacinar pattern)[3] while the GGO occur due to deposition of PAS-positive material in the alveoli.[4] Together these resemble a pavement lined with irregular shaped stones laid in a polygonal fashion. Apart from the characteristic "Crazy-paving" pattern, other features seen on HRCT include interlobular septal thickening and GGOs without "Crazy-paving" pattern, diffuse bilateral GGOs without septal thickening, consolidation, pulmonary nodules, mediastinal lymphadenopathy, and pleural effusion.[13]

BAL has an important supportive role in the diagnosis of PAP. It has a milky appearance due to the presence of lipo-proteinaceous material consisting of phospholipids and surfactant proteins. On staining the BAL fluid, the presence of PAS-positive, eosinophilic, granular, acellular material with occasional enlarged foamy macrophages generally establishes the diagnosis. OLB reveals the deposition of PAS-positive, eosinophilic material within the alveoli without any architectural distortion.[6] Detection of anti-GM-CSF antibodies is an important tool for differentiating autoimmune (idiopathic) form from other subtypes of PAP with a high sensitivity and specificity.

Pulmonary alveolar proteinosis in India

A search of the literature on the subject from India using the PubMed, IndMed databases and Google revealed 25 reports documenting 30 patients of PAP. All 30 documented patients from India were reviewed and are tabulated in Table 2.

The first documented report of PAP from India was in a 35-year-old man, a sailor from the armed forces.[14] Of the 30 patients, 22 were males (73%) and the age group varied from 4 months to 54 years in males while in female patients ranged from 18 months to 58 years. There were six patients in the pediatric age group[15,17,24,33,36,37] with four of them being males.[15,17,24,36] Cough and dyspnea were the predominant presenting symptoms seen in almost all patients. Respiratory failure, on presentation, was noted in 9/30 patients (30%).[24,25,27,32,35,37] Our patient too presented with type I respiratory failure. Of the 26 patients[14,16,18,20-25,27-38] in whom CT chest was performed, HRCT was done in 23.[14,16,18,20-23,27-35,37,38] Characteristic "Crazy-paving" pattern was documented in 18 of them.[18,21-23,27-34,37,38] Bilateral "Crazy-paving" was seen in 14/18 patients.[18,21-23,27-32,34,37,38] Information regarding the distribution of "Crazy-paving" was not available in 4 patients.[27,33] Our patient too had a distinctive bilateral "Crazy-paving" pattern on HRCT. In 16/30 patients information regarding classification either as idiopathic or secondary was not available.[15-20,22-25 ,29, 32-34,37,38] The disease was classified as idiopathic in 9/30 patients[21,27,28,30,31] and in five patients as secondary PAP.[14,26,28,35,36] Our patient too was classified as idiopathic.

Table 2: Pulmonary alveolar proteinoses in India

Study/year/ number of patients	Age/ gender	Symptoms	Radiology	Diagnosis	Histopathology	Etiology	Treatment
Chauhan *et al*., 1988[14]/1	35/male	Asymptomatic, referred for evaluation of radiological opacities detected on medical examination	CXR: B/L reticulonodular opacities CT chest: B/L reticulonodular opacities extending from the hila toward periphery and being denser at the bases	Rigid bronchoscopic lavage and OLB	Bronchoscopy: Negative for AFB, fungus and malignant cells OLB: Alveoli filled with eosinophilic, granular material. Detached septal cells with light colored cytoplasm were PAS positive	Secondary	Discharged on advice of further follow-up
Sangani *et al*., 1993[15]/1	14/male	Reduced appetite, failure to gain weight, dyspnea, and cough	CXR: B/L fluffy alveolar shadows in hilar and perihilar distribution CT chest : N/A	Bronchoscopic aspiration lavage and TBLB	BAL: PAS stain positive amorphous, eosinophilic material TBLB: Alveoli filled with granular, eosinophilic PAS positive material with cleft-like spaces	N/A	N/A
Chaudhuri *et al*., 1996[16]/1	26/male	Relatively asymptomatic with occasional dry cough and Grade I dyspnea	CXR: B/L acinar opacities in mid and lower zones CT chest: B/L, patchy, soft tissue shadows, with no cavitation, calcification or lymphadenopathy	Bronchoscopic aspiration lavage and OLB	BAL: Plenty of eosinophilic proteinaceous material OLB: Large areas of alveoli filled with granular pink material with occasional small clefts. Proteinaceous material was PAS stain positive and diastase resistant	N/A	Patient was relatively asymptomatic so therapeutic lavage was not performed Later on superimposed tuberculous infection treated with antituberculous drugs
Dixit *et al*., 1998[17]/1	14/male	Dyspnea, fever, and cough	CXR: B/L alveolar shadows CT chest: N/A	Bronchoscopic aspiration lavage	N/A	N/A	B/L sequential WLL
Ravi *et al*., 2006[18]/1	22/female	Dyspnea, cough	CXR: B/L airspace disease with ill-defined nodular lesions HRCT chest: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage	BAL: Scattered macrophages, PAS positive eosinophilic bodies, few lymphocytes and endobronchial cells	N/A	N/A
Kumar *et al*., 2007[19]/1	45/female	Dyspnea	N/A	N/A	N/A	N/A	B/L WLL
Sengupta *et al*., 2007[20]/1	36/female	Dyspnea, cough, and fever	CXR: B/L diffuse alveolar infiltrates HRCT: Diffuse intraalveolar ground glass opacities and interlobular thickening	Bronchoscopic aspiration lavage	BAL: Milky fluid which stained positively to PAS	N/A	B/L sequential WLL
Indira *et al*., 2007[21]/1	53/male	Dyspnea, cough	CXR: Perihilar alveolar opacities with relative sparing of the upper zones HRCT: B/L alveolar filling pattern with a lower zone involvement with "crazy paving appearance"	Bronchoscopic aspiration lavage and OLB	BAL: Inconclusive OLB: Eosinophilic granular, PAS positive material filling the alveoli with thickened alveolar walls and preserved parenchymal architecture	Idiopathic	B/L sequential WLL
Udwadia and Jain, 2007[22]/1	45/male	Dyspnea, cough	CXR: B/L alveolar and interstitial opacities HRCT chest: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage and TBLB	TBLB: Alveolar filling with amorphous, granular, eosinophilic PAS positive material	N/A	B/L sequential WLL
Naidu and Sridhar, 2008[23]/1	26/male	Dry cough, dyspnea, weight loss, and fever	CXR: B/L diffuse reticulonodular pattern HRCT: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage and OLB	BAL: Eosinophilic material with granular appearance with PAS stain positive OLB: Eosinophilic secretions with granular appearance	N/A	B/L sequential WLL
Garg *et al*., 2009[24]/1	4 months/ male	Dyspnea, respiratory failure	CXR: B/L hazy lung fields CT chest: Diffuse opacification with air bronchogram in B/L lung fields	Bronchoscopic aspiration lavage and OLB	BAL: Lipid-laden macrophages OLB: Distended alveoli containing pale eosinophilic granular material and scattered foamy macrophages. PAS positive alveolar material present	N/A	Repeated large volume bronchoalveolar lavages with trial of surfactant given

Contd...

Table 2: Contd...

Study/year/ number of patients	Age/ gender	Symptoms	Radiology	Diagnosis	Histopathology	Etiology	Treatment
Nandkumar *et al*., 2009[25]/1	43/male	NYHA Grade IV dyspnea, respiratory failure	CXR: Diffuse B/L asymmetrical infiltrates CT chest: B/L patchy alveolar filling shadows with air bronchogram	N/A	N/A	N/A	Single lung lavage in 2 sitting
Thind, 2009[26]/1	24/male	Dyspnea, productive cough	CXR: Diffuse B/L alveolar opacification, more marked in middle and lower zones CT chest: N/A	Autopsy	Alveolar spaces and respiratory bronchioles filled with eosinophilic PAS positive material typical of PAP, with cleft-like spaces scattered throughout Polarized microscopy showed a number of birefringent bodies due to the cotton particles	Secondary	Conservative with antibiotics, bronchodilators and oxygen therapy
Jayaraman *et al*., 2010[27]/1	26/male	Dry cough, dyspnea, weight loss, and fever	CXR: B/L diffuse reticulonodular pattern HRCT: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage and OLB	BAL: Eosinophilic material with granular appearance with positive PAS stain OLB: Eosinophilic secretions with granular appearance	Idiopathic	B/L sequential WLL
Khan *et al*., 2012[28]/5	46/female	Dyspnea, cough respiratory failure	HRCT: Geographical areas of interlobular septal thickening superimposed on background of ground-glass opacities involving entire lung (B/L "crazy paving")	OLB	OLB: Eosinophilic granular material filling alveolar spaces with intact alveolar septum	Idiopathic	B/L simultaneous WLL with ECMO + GM-CSF
	42/male	Dyspnea, cough respiratory failure	HRCT: Crazy paving appearance	OLB	OLB: N/A	Idiopathic	B/L sequential WLL + GM-CSF
	38/male	Dyspnea, cyanosis, respiratory failure	HRCT: Crazy paving appearance	OLB	OLB: N/A	Idiopathic	B/L sequential WLL + GM-CSF
	28/male	Dyspnea, fever, loss of appetite, respiratory failure	HRCT: Patchy crazy paving pattern, more so in the left lung	OLB	OLB: PAS-positive alveolar filling with intact septa, and typical crooked, branching, beaded, Gram-positive organisms consistent with *Nocardia*	Secondary	Trimethoprim-sulfamethoxazole
	34/male	Dyspnea, cough	HRCT: Interlobular septal thickening with patchy ground glassing in the perihilar regions	Bronchoscopic biopsy	Bronchoscopic biopsy: N/A	Idiopathic	Subcutaneous GM-CSF
Shende *et al*., 2013[29]/1	58/female	Cough with milky white sputum and dyspnea	CXR: N/A HRCT: B/L "crazy- paving" pattern	Bronchoscopic aspiration lavage and video assisted thoracoscopic lung biopsy	BAL: Eosinophilic material with granular appearance and PAS stain positive Video assisted thoracoscopic lung biopsy: Eosinophillic granular infiltrates in the alveoli	N/A	B/L sequential WLL + GM-CSF
Baldi *et al*., 2013[30]/1	38/male	Dry cough, dyspnea, weight loss and fever	CXR: B/L reticular markings predominantly in mid and lower zones HRCT: Ground-glass opacities with superimposed septal thickening (B/L "crazy-paving" pattern)	Bronchoscopic aspiration lavage	BAL cytology: Numerous amorphous globules of varying sizes that were PAS positive and diastase resistant. Also positive for acid fast bacilli Gomori methenamine silver stain: Occasional cysts resembling those of *P. jiroveci*	Idiopathic	Supplemental oxygen + inhaled bronchodilators + injectable steroids + GM-CSF for 21 day + co-trimoxazole + antituberculous drugs Bronchoscopic SLLL

Contd...

Table 2: Contd...

Study/year/ number of patients	Age/ gender	Symptoms	Radiology	Diagnosis	Histopathology	Etiology	Treatment
Bhattacharyya *et al*., 2013[31]/2	33/male	Dyspnea, cough, loss of weight	CXR: B/L extensive alveolar opacities HRCT: B/L extensive ground-glass opacities with interlobular septal thickening within areas of ground-glass opacities: Crazy pavement pattern	Bronchoscopic aspiration lavage and TBLB; OLB	TBLB: Inconclusive OLB: Alveoli filled with amorphous, eosinophilic material showing cholesterol clefts with well-preserved alveolar structure	Idiopathic	B/L sequential WLL
	28/male	Productive cough, dyspnea	CXR: B/L alveolar opacities HRCT: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage and TBLB	BAL cytology: Acellular, amorphous eosinophilic PAS positive material TBLB: Alveoli were filled with granular lipo-proteinaceous material which stained pink with PAS stain	Idiopathic	B/L sequential WLL
Bansal and Sikri, 2013[32]/1	54/male	Dyspnea, fever, and cough	CXR: B/L reticular shadows affecting the lower zones (left > right) HRCT: B/L "crazy-paving" pattern	Bronchoscopic aspiration lavage and TBLB	TBLB: PAS stain positivity	N/A	B/L sequential WLL + GM-CSF
Kumar *et al*., 2013[33]/1	18 months/ female	Dyspnea, cyanosis, cough, and respiratory failure	CXR: Consolidation in right upper and middle lung fields HRCT: "crazy-paving"	Not done	Not done	N/A	Nebulization with N-acetyl cysteine with oxygen inhalation
Redkar *et al*., 2014[34]/1	53/male	Dyspnea, cough, loss of weight, and anorexia	CXR: Bat wing appearance with B/L infiltration with spared lung apices HRCT: B/L "crazy-pavement" appearance	Bronchoscopic aspiration lavage	N/A	N/A	Improved with alveolar aspiration.
Hasan *et al*., 2014[35]/1	36/male	Dyspnea, cough	CXR: B/L perihilar and lower zone infiltrates HRCT: B/L diffuse ground glass haziness with superimposed interlobular septal thickening	Bronchoscopic aspiration lavage and TBLB	TBLB: Dilated alveoli filled with PAS positive granular eosinophilic material along with deeply eosinophilic structures	Secondary	Azathioprine (75 mg/day) with prednisolone (5 mg/day) and continuous oxygen
Raj *et al*., 2014[36]/1	8 months/ male	Fever, cough, and respiratory failure	CXR: B/L white out lung fields HRCT: B/L extensive infiltrates with almost complete white out appearance of the lung fields	Tracheal aspirate Serum immunoglobulin levels	Tracheal aspirate: Positive for *P. jiroveci* on both staining and MSG-PCR Cytopathology: Pneumocystis cysts along with extracellular PAS positive diastase resistant amorphous material Serum immunoglobulin: Hypo-gamma globulinemia (IgG and IgA)	Secondary	Mechanical ventilation + intravenous co-trimoxazole for 4 weeks + oral steroids and intravenous clindamycin Therapeutic lung lavage was attempted weekly
Baro *et al*., 2015[37]/1	10/female	Dyspnea, fever, cough, and weight loss	CXR: Miliary pattern with infiltrates more on the basal area HRCT: Extensive interstitial septal thickening, suggestive of B/L crazy-paving pattern in lower lobes	Bronchoscopic aspiration lavage	BAL cytology: Macrophages showed PAS positive material in the cytoplasm which was resistant to diastase treatment	N/A	Total lung lavage + hydroxychloroquine and prednisolone
Davis *et al*., 2015[38]/1	33/female	Dyspnea, cough, and respiratory failure	CXR: B/L diffuse alveolar opacity HRCT: Extensive ground glass opacities with superimposed interlobular septal thickening producing a reticular pattern (crazy pavement) appearance in B/L upper and lower lobes of lung	Bronchoscopic aspiration lavage and biopsy	BAL: PAS positive materials TBLB: Consistent with pulmonary alveolar proteinosis	N/A	Therapeutic lung lavage under local anesthesia + GM-CSF

Contd...

Table 2: Contd...

Study/year/ number of patients	Age/ gender	Symptoms	Radiology	Diagnosis	Histopathology	Etiology	Treatment
Present case, 2015/1	18/female	Dyspnea, fever, cough, weight loss, and respiratory failure	CXR: B/L, diffuse alveolar opacities having a perihilar and basal distribution with sparing of the apices HRCT: B/L diffuse ground glass opacities superimposed with interlobular and intralobular septal thickening in a geographical distribution "crazy-paving" pattern	Bronchoscopic aspiration lavage	BAL: Granular eosinophilic exudate that was PAS stain positive	Idiopathic	Lost to follow-up

AFB: Acid-fast bacilli, B/L: Bilateral, BAL: Bronchoalveolar lavage fluid, CT: Computed tomography, CXR: Chest X-ray, GM-CSF: Granulocyte-macrophage colony-stimulating factor, HRCT: High resolution computed tomography, MSG-PCR: Major surface glycoprotein-polymerase chain reaction, N/A: Not available, NYHA: New York Heart Association, OLB: Open lung biopsy, *P. jiroveci: Pneumocystis jiroveci*, PAS: Periodic acid-Schiff, SLLL: Serial lobar lung lavage, TBLB: Transbronchial lung biopsy, WLL: Whole-lung lavage

Diagnosis was established by cytopathological examination and staining of the BAL fluid in 6/30 patients[17,18,20,30,34,37] while in a pediatric patient, tracheal aspirate was used to confirm the diagnosis.[36] In another seven patients, apart from BAL additional transbronchial biopsy was done.[15,22,28,31-33,38] OLB was confirmatory in 11/30 patients[14,16,21,23,24,27,28,31] and in one patient video assisted thoracoscopic lung biopsy was done.[29] Autopsy proved the diagnosis in one patient.[26] In three patients information regarding the diagnostic modality was not available.[19,25,33]

WLL as a therapeutic modality was used in 18/30 patients[17,19-23,25,27-29,31,32,36-38] while serial lobar lung lavage was done in one patient.[30] Of these 18 patients, seven in addition received GM-CSF therapy.[28-30,32,37] GM-CSF therapy alone as a treatment modality was used in one patient.[28] In all patients who had undergone WLL, response to therapy was considered to be satisfactory.[17,19,20-23,25,27-29,31,32,36-38] In patients who had received GM-CSF therapy in addition to WLL, it could not be ascertained whether the response to therapy was due to WLL or due to GM-CSF.[28-30,32,37] The only patient who had received GM-CSF therapy alone showed clinical response but had no radiological improvement.[28] One patient who was symptomatic even after five sessions of WLL showed significant benefit post-GM-CSF therapy.[29] Repeated bronchoscopic lavage was the treatment modality in two patients[24,34] of whom one died.[24] Conservative management was done in five patients[16,26,28,33,35] with mortality seen in one patient.[26] Treatment resulted in remarkable improvement in 25/30 patients.[16,17,19-23,25,27-38] In one patient, information regarding the treatment modality was not available[18] while two other patients were lost to follow-up.[14,15] Our patient too was lost to follow-up.

PAP is rare but a distinct clinical entity and presents characteristically with "Crazy-paving" pattern on HRCT. In India, PAP does not appear to be as rare as initially thought and state of the art therapy has been administered with gratifying results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lee CH. The crazy-paving sign. Radiology 2007;243:905-6.
2. Maimon N, Heimer D. The crazy-paving pattern on computed tomography. CMAJ 2010;182:1545.
3. De Wever W, Meersschaert J, Coolen J, Verbeken E, Verschakelen JA. The crazy-paving pattern: A radiological-pathological correlation. Insights Imaging 2011;2:117-32.
4. Frazier AA, Franks TJ, Cooke EO, Mohammed TL, Pugatch RD, Galvin JR. From the archives of the AFIP: Pulmonary alveolar proteinosis. Radiographics 2008;28:883-99.
5. Ramirez J, Campbell GD. Pulmonary alveolar proteinosis. Endobronchial treatment. Ann Intern Med 1965;63:429-41.
6. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, *et al*. Pulmonary alveolar proteinosis. Eur Respir Rev 2011;20:98-107.
7. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: Progress in the first 44 years. Am J Respir Crit Care Med 2002;166:215-35.
8. Campo I, Kadija Z, Mariani F, Paracchini E, Rodi G, Mojoli F, *et al*. Pulmonary alveolar proteinosis: Diagnostic and therapeutic challenges. Multidiscip Respir Med 2012;7:4.
9. Ioachimescu OC, Kavuru MS. Pulmonary alveolar proteinosis. Chron Respir Dis 2006;3:149-59.
10. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958;258:1123-42.
11. Soma P, Ellemdin S, Roche NJ. A crazy cause of dyspnoea: Pulmonary alveolar proteinosis. Lancet 2014;384:714.
12. Murch CR, Carr DH. Computed tomography appearances of pulmonary alveolar proteinosis. Clin Radiol 1989;40:240-3.
13. Mehrian P, Homayounfar N, Karimi MA, Jafarzadeh H. Features of idiopathic pulmonary alveolar proteinosis in high resolution computed tomography. Pol J Radiol 2014;79:65-9.
14. Chauhan MS, Jayaswal R, Rajan RS, Chopra RK, Bhalla IP, Tewari SC. Pulmonary alveolar proteinosis (with review of literature). J Assoc Physicians India 1988;36:445-6.
15. Sangani BK, Prabhudesai PP, Tandon SP, Vidyeeswar P, Bijur S, Mahashur AA. Pulmonary alveolar phospholipoproteinosis. Indian Pediatr 1993;30:917-9.

16. Chaudhuri R, Prabhudesai P, Vaideeswan P, Mahashur AA. Pulmonary alveolar proteinosis with pulmonary tuberculosis. Indian J Tuberc 1996;43:27-9.
17. Dixit R, Chaudhari LS, Mahashur AA. Anaesthetic management of bilateral alveolar proteinosis for bronchopulmonary lavage. J Postgrad Med 1998;44:21-3.
18. Ravi R, Mazharunissa A, Meenal JD, Sridharan K. Radiological quiz – Chest. Indian J Radiol Imaging 2006;16:983-4.
19. Kumar P, Sengupta S, Rudra A, Maitra G, Ramasubban S, Mukhopadhyay A. Bilateral whole lung lavage in the treatment of pulmonary alveolar proteinosis. Anesth Analg 2007;104:464-5.
20. Sengupta S, Kumar P, Rudra A, Ramasubban S, Mukhopadhyay A. Bilateral whole lung lavage in the treatment of pulmonary alveolar proteinosis. J Anesth Clin Pharmacol 2007;23:79-81.
21. Indira KS, Rajesh V, Darsana V, Ranjit U, John J, Vengadakrishnaraj SP, *et al*. Whole lung lavage: The salvage therapy for pulmonary alveolar proteinosis. Indian J Chest Dis Allied Sci 2007;49:41-4.
22. Udwadia ZF, Jain S. Images in clinical medicine. Pulmonary alveolar proteinosis. N Engl J Med 2007;357:e21.
23. Naidu IS, Sridhar. Pulmonary alveolar proteinosis. Apollo Med 2008;5:61-3.
24. Garg G, Sachdev A, Gupta D. Pulmonary alveolar proteinosis. Indian Pediatr 2009;46:521-3.
25. Nandkumar S, Desai M, Butani M, Udwadia Z. Pulmonary alveolar proteinosis with respiratory failure-anaesthetic management of whole lung lavage. Indian J Anaesth 2009;53:362-6.
26. Thind GS. Acute pulmonary alveolar proteinosis due to exposure to cotton dust. Lung India 2009;26:152-4.
27. Jayaraman S, Gayathri AR, Senthil Kumar P, Santosham R, Santosham R, Narasimhan R. Whole lung lavage for pulmonary alveolar proteinosis. Lung India 2010;27:33-6.
28. Khan A, Agarwal R, Aggarwal AN, Bal A, Sen I, Yaddanapuddi LN, *et al*. Experience with treatment of pulmonary alveolar proteinosis from a tertiary care centre in north India. Indian J Chest Dis Allied Sci 2012;54:91-7.
29. Shende RP, Sampat BK, Prabhudesai P, Kulkarni S. Granulocyte macrophage colony stimulating factor therapy for pulmonary alveolar proteinosis. J Assoc Physicians India 2013;61:209-11.
30. Baldi MM, Nair J, Athavale A, Gavali V, Sarkar M, Divate S, *et al*. Serial lobar lung lavage in pulmonary alveolar proteinosis. J Bronchology Interv Pulmonol 2013;20:333-7.
31. Bhattacharyya D, Barthwal MS, Katoch CD, Rohatgi MG, Hasnain S, Rai SP, *et al*. Primary alveolar proteinosis – A report of two cases. Med J Armed Forces India 2013;69:90-3.
32. Bansal A, Sikri V. A case of pulmonary alveolar proteinosis treated with whole lung lavage. Indian J Crit Care Med 2013;17:314-7.
33. Kumar N, Jyoti K, Ranjan S, Varshney AN, Anand A, Anand R. Pulmonary alveolar proteinosis a rare disease. Natl J Integr Res Med 2013;4:106-8.
34. Redkar NN, Rawat KJ, Agarwal V, Kolhe P, Shah J. Pulmonary alveolar proteinosis an underdiagnosed entity. Indian Pract 2014;67:574-6.
35. Hasan A, Ram R, Swamy T. Pulmonary alveolar proteinosis due to mycophenolate and cyclosporine combination therapy in a renal transplant recipient. Lung India 2014;31:282-4.
36. Raj D, Bhutia TD, Mathur S, Kabra SK, Lodha R. Pulmonary alveolar proteinosis secondary to *Pneumocystis jiroveci* infection in an infant with common variable immunodeficiency. Indian J Pediatr 2014;81:929-31.
37. Baro A, Shah I, Chandane P, Khosla I. Pulmonary alveolar proteinosis in a 10-year-old girl masquerading as tuberculosis. Oxf Med Case Reports 2015;2015:300-2.
38. Davis KR, Vadakkan DT, Krishnakumar EV, Anas AM. Serial bronchoscopic lung lavage in pulmonary alveolar proteinosis under local anesthesia. Lung India 2015;32:162-4.