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

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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 dyspnnoeic 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?
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 lipid 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 (x40) 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, first described in 1958 by Rosen et al., is a distinct clinical entity with an estimated prevalence of 0.1 case per 100,000 individuals. 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. 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.

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. The first ever description of “Crazy-paving” pattern on HRCT was in a patient of PAP 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. “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 or due to deposition of material in the alveoli at the borders of the acini (periacinar pattern) while the GGO occur due to deposition of PAS-positive material in the alveoli. 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.

**DISCUSSION**

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. 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 with four of them being males. Cough and dyspnea were the predominant presenting symptoms seen in almost all patients. Respiratory failure, on presentation, was noted in 9/30 patients (30%). Our patient too presented with type I respiratory failure. Of the 26 patients in whom CT chest was performed, HRCT was done in 23. Characteristic “Crazy-paving” pattern was documented in 18 of them. Bilateral “Crazy-paving” was seen in 14/18 patients. Information regarding the distribution of “Crazy-paving” was not available in 4 patients. 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. The disease was classified as idiopathic in 9/30 patients and in five patients as secondary PAP. 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 | 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 and OLB | BAL: Milky fluid which stained positively to PAS | 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 and OLB | 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 | 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 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 |
| 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: Alveolar filling with amorphous, granular, eosinophilic PAS positive material | N/A | 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 |
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 thoroscopic lung biopsy | BAL: Eosinophilic material with granular appearance and PAS stain positive Video assisted thoroscopic lung biopsy: Eosinophilic granular infiltrates in the alveoli 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 | 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 | | Idiopathic | Supplemental oxygen + inhaled bronchodilators + injectable steroids + GM-CSF for 21 day + co-trimoxazole + antituberculous drugs Bronchoscopic SLL |

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### Table 2: Contd...

| Study/year/number of patients | Age/ gender | Symptoms | Radiology | Diagnosis | Histopathology | Etiology | Treatment |
|-----------------------------|------------|----------|-----------|-----------|----------------|----------|-----------|
| Bhattacharyya et al., 2013¹/² | 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 | 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 lipoproteinaceous material which stained pink with PAS stain TBLB: PAS stain positivity N/A B/L sequential WLL + GM-CSF |
| Bansal and Sikri, 2013¹/²    | 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 | Not done | Not done | N/A Nebulization with N-acetyl cysteine with oxygen inhalation Improved with alveolar aspiration. |
| Kumar et al., 2013¹/²        | 18 months/ female | Dyspnea, cyanosis, cough, and respiratory failure | CXR: Consolidation in right upper and middle lung fields HRCT: “crazy-paving” | Not done | N/A | N/A |
| Redkar et al., 2014¹/²       | 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-paving” pattern | Bronchoscopic aspiration lavage | N/A | N/A |
| Hasan et al., 2014¹/²        | 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., 2014¹/²          | 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: 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) BAL cytology: Macrophages showed PAS positive material in the cytoplasm which was resistant to diastase treatment | Tracheal aspirate; Positive for P. jiroveci on both staining and MSG-PCR | Secondary | Mechanical ventilation + intravenous cotrimoxazole for 4 weeks + oral steroids and intravenous clindamycin Therapeutic lung lavage was attempted weekly |
| Baro et al., 2015¹/²         | 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 | | Secondary | Total lung lavage + hydroxychloroquine and prednisolone |
| Davis et al., 2015¹/²        | 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 reticulon 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 |

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Diagnosis was established by cytopathological examination and staining of the BAL fluid in 6/30 patients while in a pediatric patient, tracheal aspirate was used to confirm the diagnosis. In another seven patients, apart from BAL additional transbronchial biopsy was done. OLB was confirmatory in 11/30 patients and in one patient video assisted thoracoscopic lung biopsy was done. Autopsy proved the diagnosis in one patient. In three patients information regarding the treatment modality was not available.

WLL as a therapeutic modality was used in 18/30 patients while serial lobar lung lavage was done in one patient. Of these 18 patients, seven in addition received GM-CSF therapy. GM-CSF therapy alone as a treatment modality was used in one patient. In all patients who had undergone WLL, response to therapy was considered to be satisfactory. 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. The only patient who had received GM-CSF therapy alone showed clinical response but had no radiological improvement. One patient who was symptomatic even after five sessions of WLL showed significant benefit post-GM-CSF therapy. Repeated bronchoscopic lavage was the treatment modality in two patients of whom one died. Conservative management was done in five patients with mortality seen in one patient. Treatment resulted in remarkable improvement in 25/30 patients. In one patient, information regarding the treatment modality was not available while two other patients were lost to follow-up. 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.

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