A little more than just air and fluid: an uncommon disease underlying a simple hydropneumothorax

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A LITTLE MORE THAN JUST AIR AND FLUID: AN UNCOMMON CASE OF HYDROPNEUMOTHORAX

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Case report:

A non-hypertensive, non-diabetic, euthyroid young female of 25 years age from rural Coochbehar presented to us at MJN Medical College and Hospital, with 1 year history of mild cough and mMRC grade 1 dyspnea, with the dyspnea worsening acutely since last 1 week. It was associated with low grade fever. Her shortness of breath was not associated with wheezing, diurnal, seasonal or postural variation; her cough was non-productive and had no diurnal or seasonal variation. She denied any chest pain, joint pain, history of cyanosis, paroxysmal nocturnal dyspnoea, history of prior tuberculosis, or any history suggestive of allergy or atopy. She had no addiction, no exposure to any known agents that might cause hypersensitivity; her menstrual history was normal and she has one living issue of 16 months age.

During examination it was noted that she had a tall stature (height: 170 cm) but no features of joint hyperextensibility, loose, lax skin, eye or heart problems. Her vitals were all stable except for her respiratory rate being 30/ minute and pulse rate being 110/minute. Her accessory muscles of respiration were visibly working.

She had multiple brownish nodular skin lesions localized around her nasolabial folds and surrounding areas of the face **(FIG 1.A).**

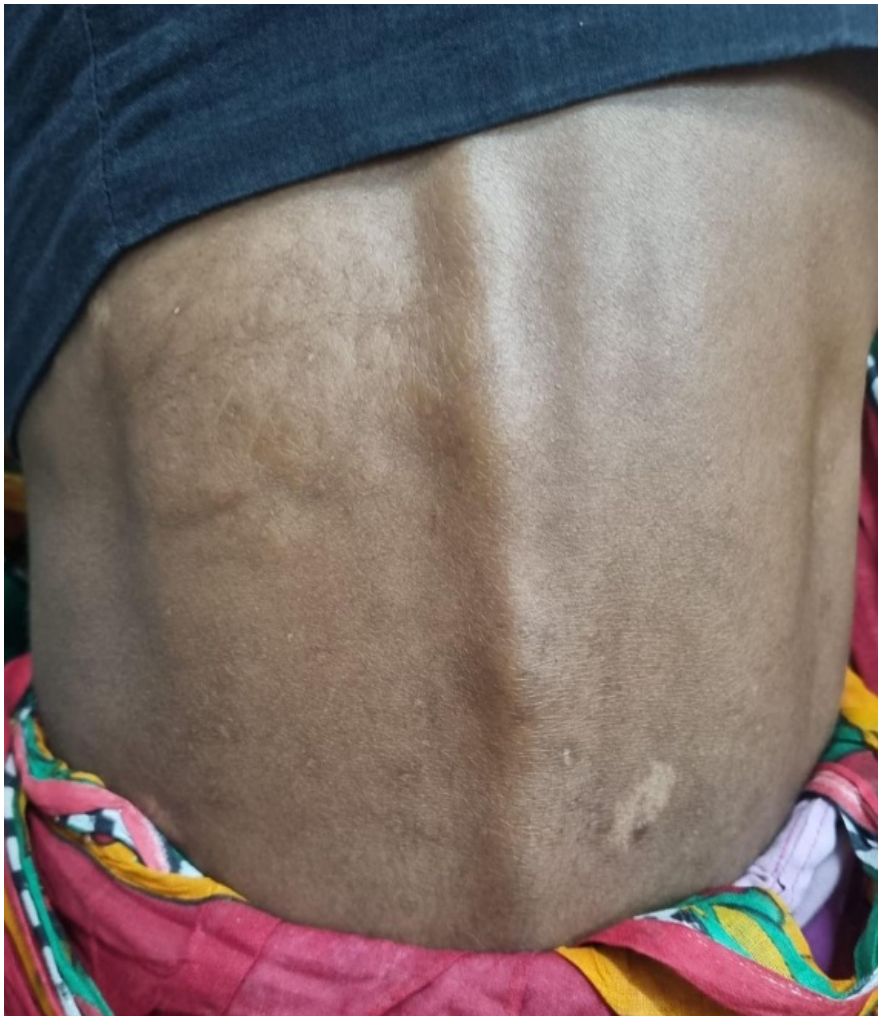
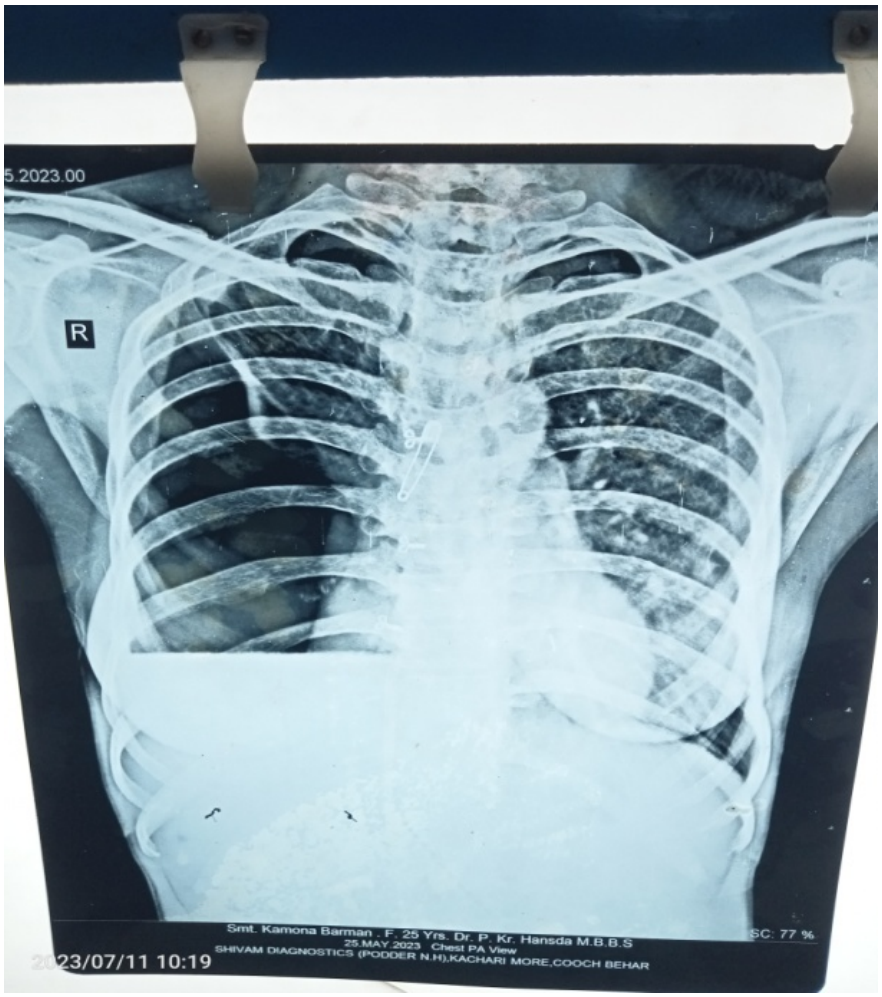


Figure 1: A. brownish nodular lesion over nasolabial region; B. Hypopigmented macule over back

Further clinical examination revealed mediastinal shift towards left, right sided hyper resonant percussion notes till right 4^{th} intercostal space and stony dull below, presence of shifting dullness, and absent breath sounds over right hemithorax- all suggestive of right sided hydropneumothorax. Abdominal examination, neurological examination, examination of the genitourinary tract and other systems did not reveal any significant finding.



A chest X-ray was readily performed and established the diagnosis of right sided hydropneumothorax with mediastinal shift to the left side. The left lung field showed few non-homogenous opacities and cystic changes but could not be characterized with certainty **(FIG 2**).

Figure 2: the initial chest X-ray of the patient showing right sided hydropneumothorax.

Although spontaneous hydropneumothorax in a young female of reproductive age group is not that uncommon, especially in a lean, thinly built, tall individual, the finding of specific skin lesions in association with the aforementioned clinical profile raised possibility of some underlying disease as the cause of the hydropneumothorax.

The prime candidates were lymphangioleiomyomatosis with tuberous sclerosis (with the skin lesions being

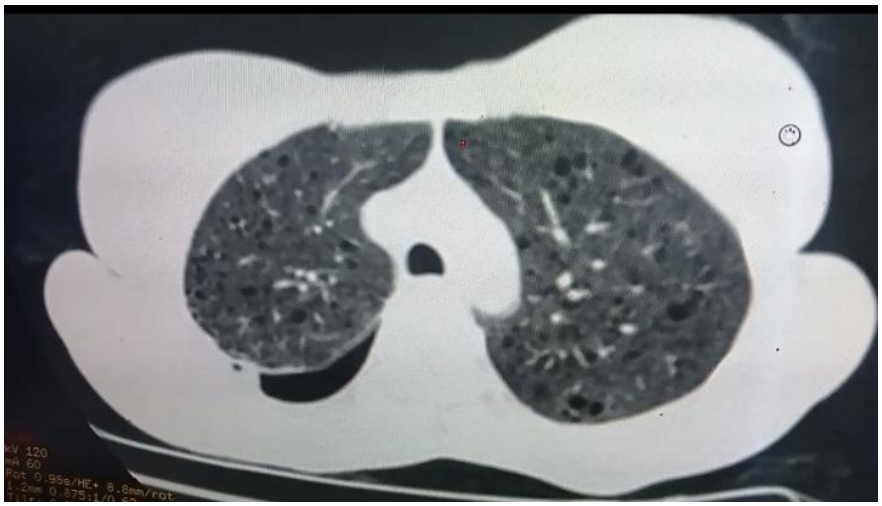
that of adenoma sebaceum) and Birt-Hogg-Dube syndrome (BHD) (skin lesions could be fibrofolliculoma). The other possibilities included Marfan's syndrome (associated with hereditary predisposition to pneumothorax and tall, thinly built people with hyperextensible joints and multiple other deformities), Cutis Laxa, alpha-1-antitrypsin deficiency along with common differentials of hydropneumothorax such as bronchopleural fistula due to infective causes, secondary infection of a primary spontaneous pneumothorax etc. The latter ones had little clinical evidence to gain any support as plausible diagnoses.

Even among the first two, LAM associated with TSC was far more likely than the others. But tuberous sclerosis patients usually show a spectrum of mental retardation, gives some history of seizure or other neurological symptoms, none of which was found in this patient despite meticulous history taking.

On closer examination, the patient also had hypopigmented macules on her back **(FIG 1:B)** , and confetti-like patches of hypopigmented lesions scattered over her back and extremities.

Patient's dyspnea was managed with insertion of an intercostal drain in her right 4^{th} intercostal space at the midaxillary line and over time her right lung gradually re-expanded. Her pleural fluid analysis showed characters of an exudate rich in mixed inflammatory cells predominantly lymphocytes (55%) with an ADA value of 7 mg/dl. Lipid analysis of the fluid revealed that the triglyceride levels was 39 mg/dl. Pap smear and Malignant cell block did not reveal any evidence of malignancy.

In the meantime, further investigations were planned including a contrast enhanced CT scan of the thorax along with a thin slice high-resolution CT thorax, MRI brain, CT abdomen and echocardiography. Spirometry with bronchodilator reversibility test was delayed until the full expansion of the right lung.. A dermatologist's opinion was sought along with that of a neurologist and radiologist in interpreting the clinico-radiological spectrum of the patient from their perspectives.



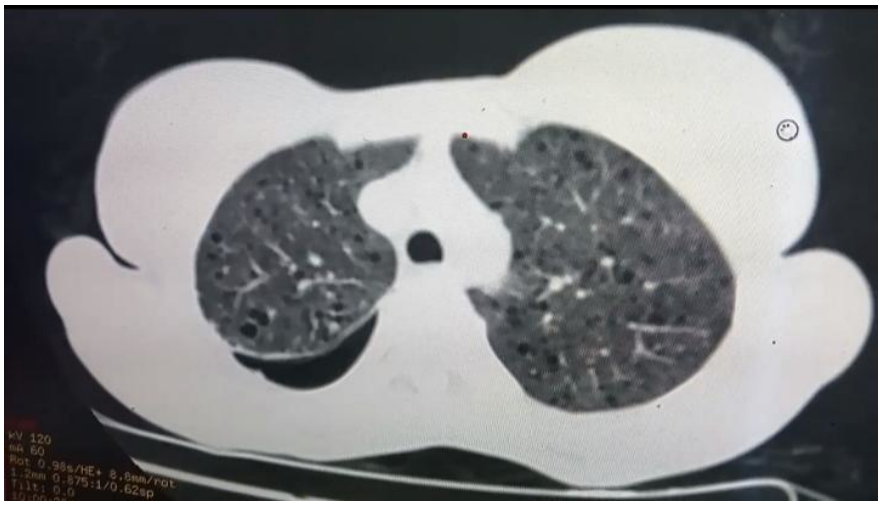
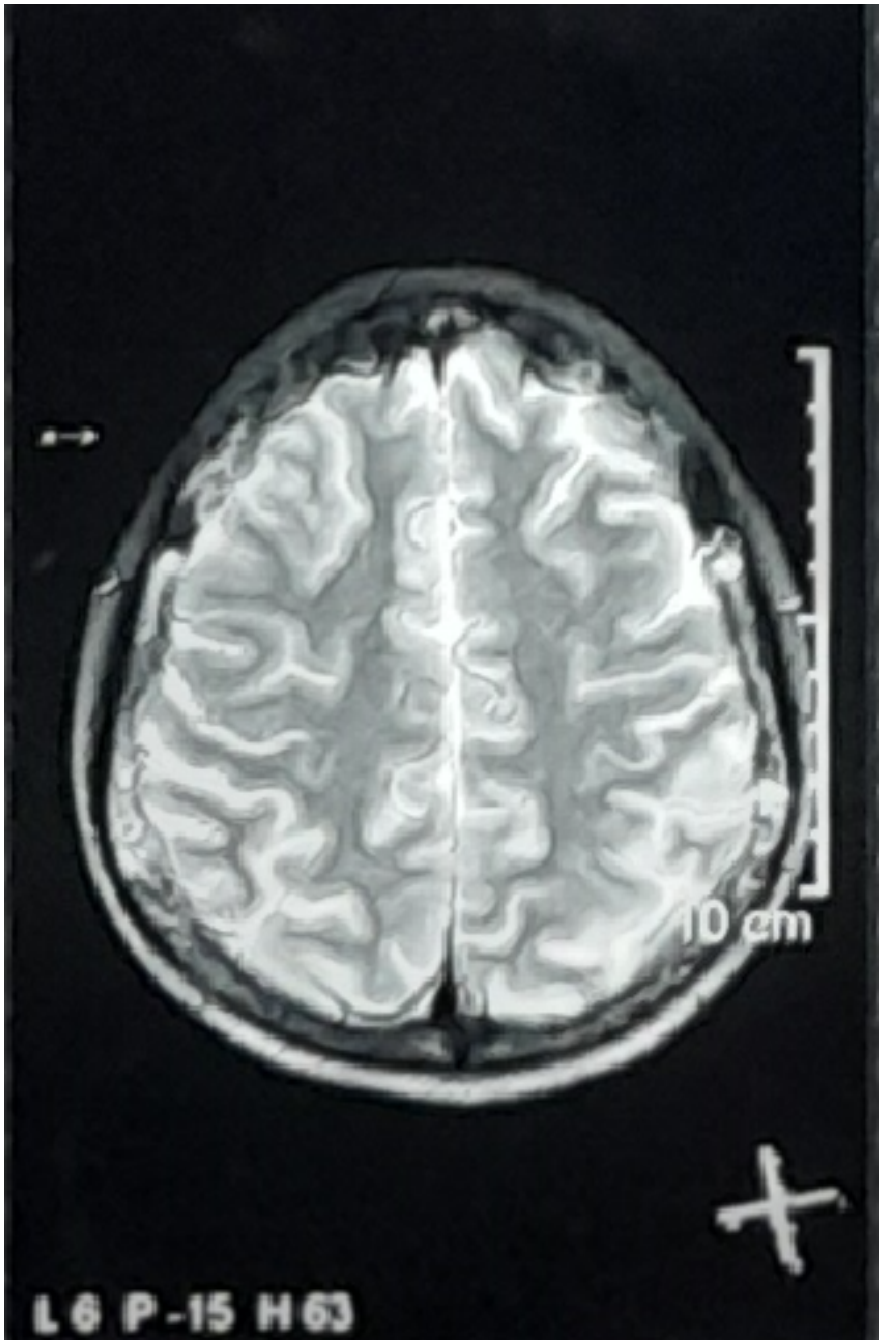
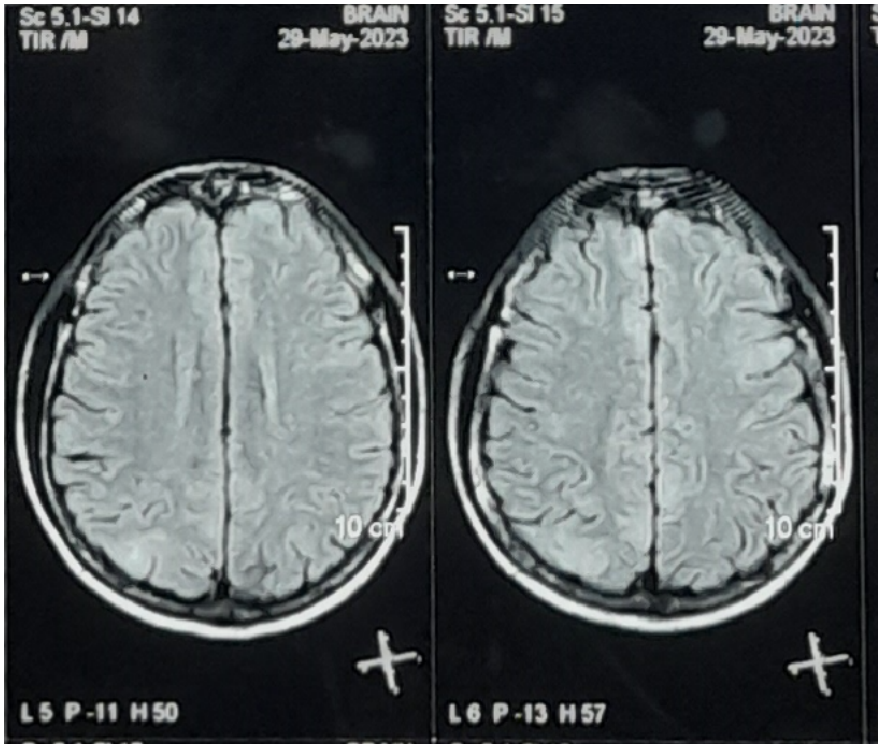


Figure 3: HRCT thorax of the patient





The CT thorax revealed that, in addition to the now resolving hydropneumothorax with the intercostal drain in-situ, the lung parenchyma was riddled with multiple randomly distributed thin-walled round cysts of various sizes, but predominantly small (<2cm). The intervening lung was predominantly normal. A few fibrotic bands and resolving consolidation as evidence of prior infection were also seen. The findings were highly suggestive of pulmonary lymphangioleiomyomatosisin this clinical context **(FIG 3).** MRI brain revealed multiple cortical tubers and subependymal signal-intense white matter nodules strongly suggestive of tuberus sclerosis

(FIG 4).

Figure 4: MRI brain of the patient

The CE abdomen identified large renal angiomyolipomas encircling both the kidneys **(FIG 5).** The dermatologist opined that the skin changes are that of adenoma sebaceum and ashleaf macules, consistent with cutaneous signs of tuberus sclerosis. The pleural fluid bacteriology and NAAT reports virtually excluded infection as the primary cause of the hydropneumothorax.

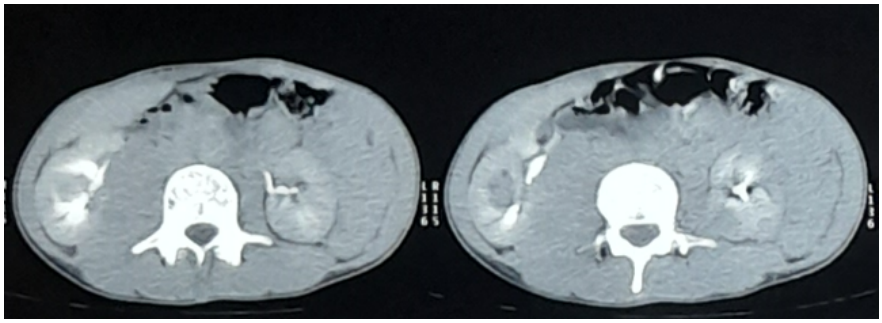


Figure 5: renal angiomyolipoma (stars) found on CT scan of abdomen

Taking all these into account, in accordance with the diagnostic criteria laid down by the American Thoracic Society, the patient was diagnosed as a case of pulmonary lymphangioleiomyomatosis associated with tuberus sclerosis complex (TSC-LAM).

After her right lung fully expanded, the sonological examination and X-rays both showed an automatic pleural thickening probably induced by prior infection and the presence of the intercostal drainage tube. Additional chemically induced pleurodesis was therefore deemed unnecessary (**figure 6**).

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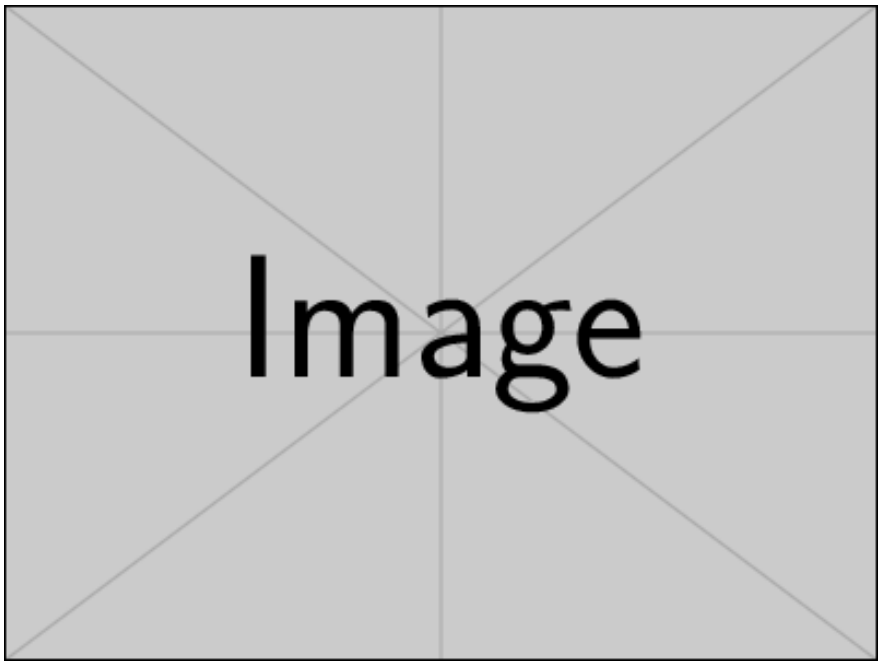

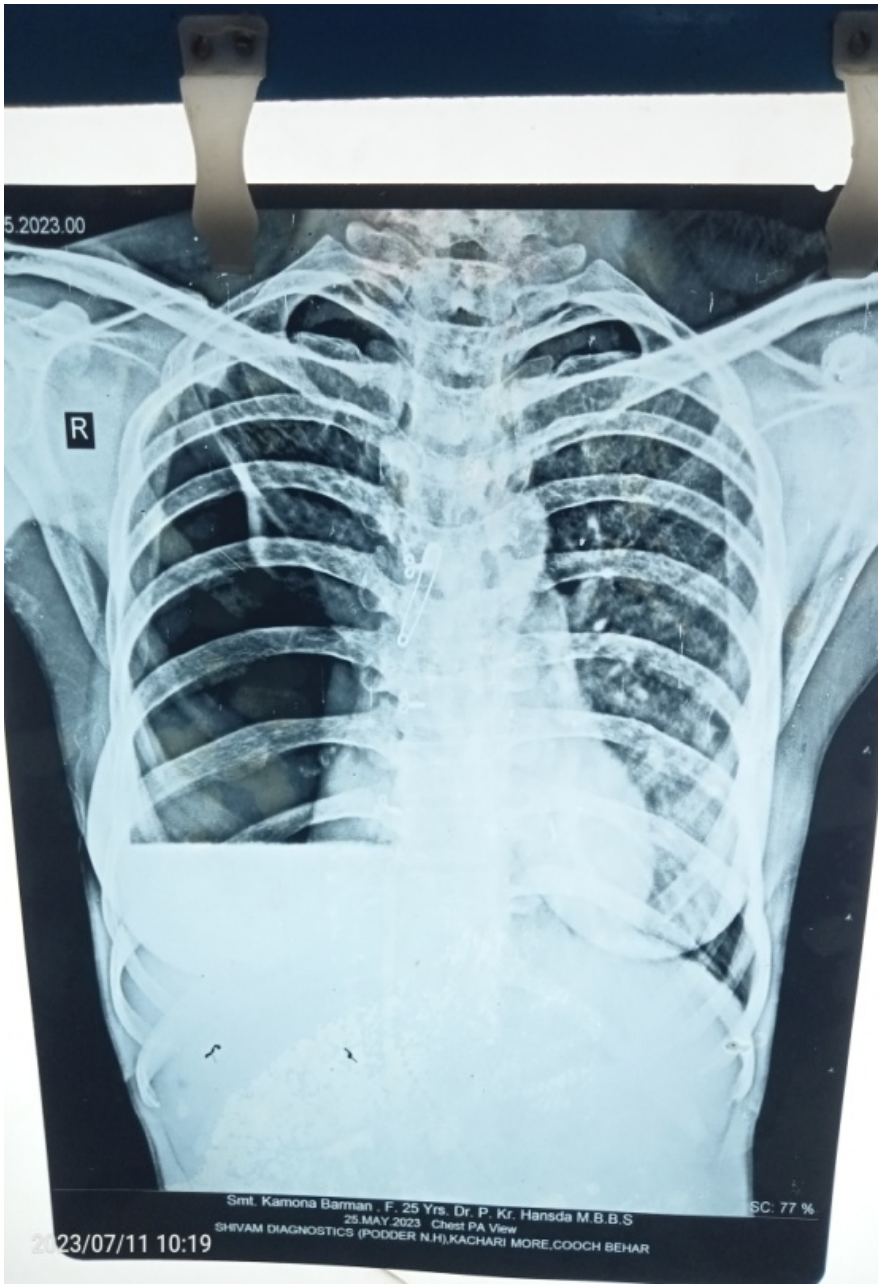

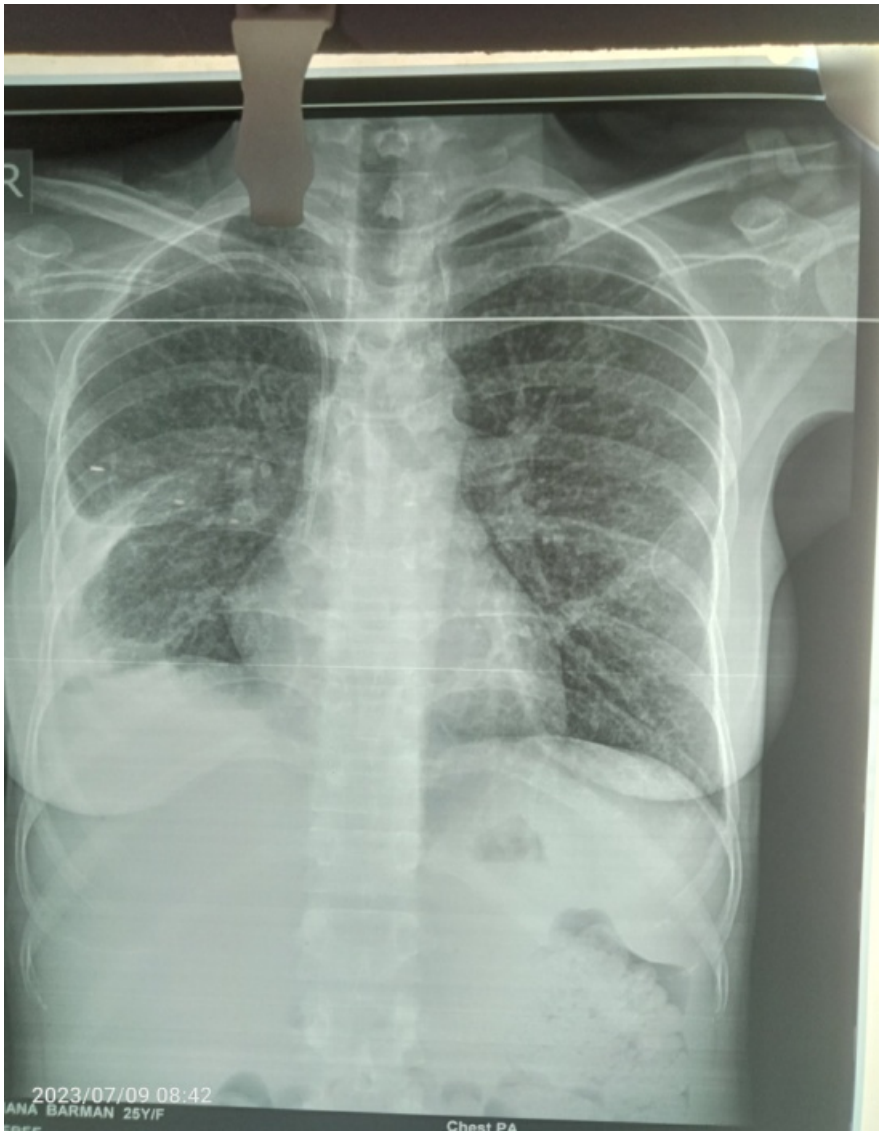

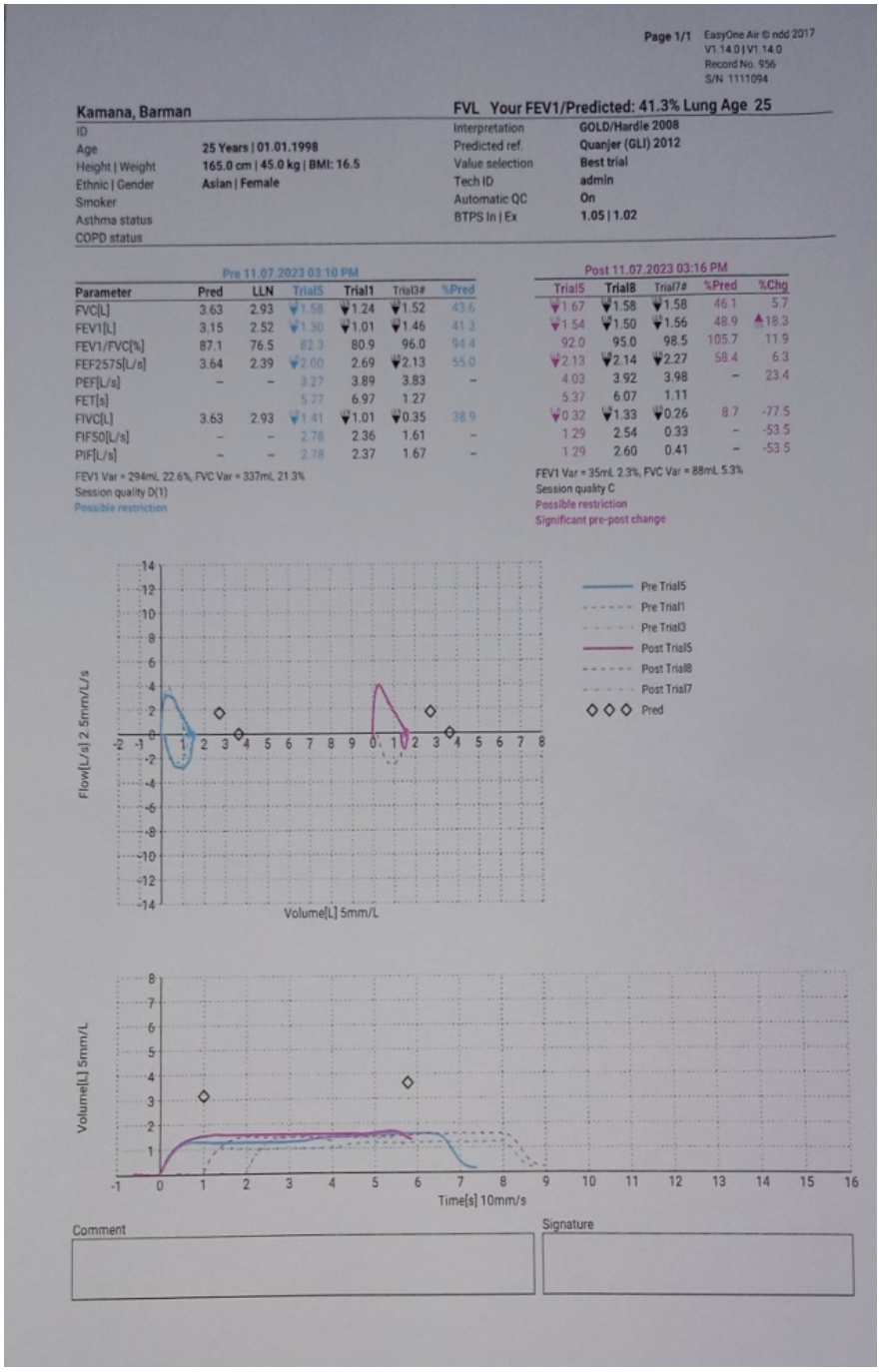

Figure 6: (a) chest X-ray at presentation (b) chest X-ray at discharge (c) spirometry at first visit (only visit)

Following removal of intercostal drainage, her oxygen saturation at room air improved, respiratory rate dropped to normal and she remained afebrile for the last one week preceding her discharge. Her spirometry however showed an FEV1 of 48% of predicted and FVC of 46% of predicted for her BMI, age, sex and ethnicity. Considering the poor initial lung function she was advised to start mTOr inhibitor sirolimus along with simvastatin pending their availability. The patient was also counselled about avoidance of activities

that might increase disease activity and/or risk of pneumothorax.

Discussion :

Pulmonary lymphangioleiomyoma or PLAM is a rarely reported diffuse parenchymal lung disease with the recent Indian ILD registry finding it in 0.2% of patients of DPLD[2]. Previously thought to be a disease exclusive in females of reproductive age group, it is now well-established that few male patients of tuberous sclerosis may have LAM-like lung radiology and even fewer may show characteristic LAM lesions[1]. PLAM is found in two forms: (1) sporadic form which is extremely rare (4.9 in 1000000 females) and (b) In association with tuberous sclerosis (1 in 6000-12000 live births). Although pathognomonic, the Vogt triad of mental retardation, seizure and adenoma sebaceum is not seen together in more than 30% patients of tuberous sclerosis, and most of the cases are suspected at childhood. It is estimated that a third of patients with tuberous sclerosis may have PLAM. PLAM patients are usually young females of reproductive age group who present with worsening shortness of breath and cough in absence of clinical improvement on bronchodilators and ICS for obstructive airway disease. The pulmonary manifestations include small nodules that ultimately cause airspaces to enlarge as result of proximal obstruction leading to formation of cysts of various size (0.2-2 cm). Cysts often rupture leading to formation of pneumothorax which may prompt the first hospital visit and diagnosis. Chylous pleural effusion and ascites are common associations. Also found are abdominal leiomyomas are renal angiomyolipomas. When associated with tuberous sclerosis, a neurocutaneous syndrome, these patients would show various degrees of mental retardation, history of seizure, cortical tubers and subependymal nodules and/or giant cell astrocyotoma along with cutaneous signs of ashleaf macule, shagren patches, periungual fibromas and adenoma sebaceum.

Studies suggest that a mutation of a tumor suppressor gene TSC2 (with some involvement of TSC1) leads to unopposed cellular signaling in favour of tumorigenesis, inappropriate growth, proliferation and evasion of apoptosis through the mTOR, mTORC1 and mTORC2 (intracellular serine/threonine kinase) activation, which are otherwise kept in check by a complex of tuberin, hamartin and TBC1D7, proteins coded by the healthy TSC2 gene. This leads to excessive proliferation of LAM cells, a group of smooth muscle cells suspected to be of uterine origin, in lung, kidney and abdomen, leading to formation of hamartomatous growths elsewhere and nodules in lung that eventually block small airways causing formation of cysts due to trapping of air. Relative over activity of matrix metalloproteinases in the face of reduce inhibitors (TIMP) also contribute to the damage. A strong association between estrogen and disease activity has been noted repeatedly, but remains to be proven by benefits in clinical trials[3].

Although the 2017 ATS guidelines suggest that a lung biopsy is necessary to diagnose the disease if other features of it are not evident, they also recognize the hazards associated with the invasive tests considering poor lung reserve in these patients. Current diagnostic criteria allow establishment of diagnosis in a patient with suggestive clinical profile and radiological evidence (classical characteristic HRCT thorax findings- diffuse thin-walled round cysts with normal intervening lung) in presence of any one of the following: (1) tuberous sclerosis complex (2)abdominal lymphangioleiomyoma (3)Renal angiomyolipoma (4)chylous effusion/ascites (5)serum VEGF-D levels in excess of 800 pg/ml[4]. As pneumothorax is a common and recurrent complication, pleurodesis is to be offered at the first instance of pneumothorax. Patient should also be cautioned about the poor outcomes of later pregnancies, risks of disease worsening with high estrogen states and risks associated with air travel. Complications like osteoporosis, chylous effusion/ascites and bleeding from angiomyolipomas/lymphangioleiomyomas are to be managed as necessary. ATS has strongly recommended that mTOR-inhibitor sirolimus be used as a first line agent whenever evidence of deteriorating lung function is there (FEV1<70% of predicted) with or without chylothorax or gradually enlarging lymphangioleiomyomas[5]. It recognized that simvastatin, hydroxychloroquine (autophagy inhibitor), and check-point (PD-1) inhibitors may hold a promising future as therapeutic options[6].

Conclusion :

Our patient was diagnosed entirely on the basis of findings of non-invasive modalities, yet in full accordance with the ATS guidelines. Her uniqueness lies in the fact that she showed no hint of any neurological

symptoms, she only had the adenoma sebaceum component of the classical Vogt clinical triad and was diagnosed in adulthood while most with this disease is diagnosed at early childhood. This highlights the fact that if high level of clinical suspicion is maintained in investigating the underlying disease process in every case of hydropneumothorax or pneumothorax in a young patient, who apparently do not have the classical risk factors, many cases of so called rare cystic lung diseases may be unveiled at a higher rate. There have been very few cases reported of this disease from India, a fact which has left us with little chance of making any stride in researching more about its management strategies[7]. As LAM is a treatable disease, this insight might be extremely beneficial for the unfortunate patients of this orphan disease.

INFORMED CONSENT:

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

CONSENT STATEMENT:

(TRANSLATED FROM BENGALI: THE MOTHER TONGUE OF THE PATIENT)

I, after being adequately informed about the extent and objectives of the article in consideration, give my full consent in sane mind and without any undue force, regarding using my clinical data and relevant images for the sake of advancing medical research and education activities.

Sd

Kamana Barman

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