

# Miliary nodules on chest radiographs: A diagnostic dilemma

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Busy respiratory clinicians from tuberculosis endemic area are frequently faced with a question of attributing a patient's illness to tuberculosis. Missing a diagnosis of a potentially fatal disease like miliary tuberculosis may prove disastrous. Also, a falsely ascribed diagnosis may prove unfortunate as the underlying disease is left unaddressed and the burden is amplified by avoidable potential side effects of anti-tubercular drugs.

So, what would actually help in such a situation? The only answer is to stick to the rules and plan out a pragmatic approach for an individual case based on the best evidence available. The approach should be comprehensive and at the same time it should be planned in a way not to exhaust resources, mainly the financial ones.

This issue of Lung India contains an article on a patient presenting with fever and chills of 3-months duration.<sup>[1]</sup> She also had respiratory symptoms in form of cough and breathlessness for 3 weeks. She was found to be human immunodeficiency virus (HIV) positive with a CD4+T cell count of only 23 cells/ $\mu$ L. In addition, she also had pancytopenia and raised liver function tests.

She had miliary shadows on her chest X-ray and HRCT. She was put on ATT which was continued for 6 days without any response. Meanwhile, a bone marrow examination done for cytopenia revealed the presence of *Histoplasma*. Thus miliary shadows on her chest radiographs were due to acute histoplasmosis in setting of HIV infection.

*Histoplasma* is a heat-responsive dimorphic fungus which is found on decaying organic matter. Infection is acquired by inhalation of microconidia followed by generation of mycelia and yeast forms. Yeast forms are engulfed by immune cells leading to either curtailment or dissemination of infection depending on the status of host response. Infection may be particularly severe and prolonged in immunocompromised patients.<sup>[2]</sup>

Clinical presentation of histoplasmosis depends on whether it involves lungs locally or systemic dissemination has occurred in liver, kidney and bone, etc. Pulmonary involvement of histoplasmosis may very closely mimic tuberculosis. The features that resemble tuberculosis include upper lobe cavitation, nodular shadows, miliary nodules, mediastinal adenopathy and a more sinister form - the fibrosing mediastinitis.<sup>[2,3]</sup>

Miliary nodules are generated when the cellular defense mechanism to an infectious agent is either ineffective or there is an underlying infiltrative process which tends to spread through lung interstitium. Thus, this pattern is representative of a lymphohematogenous dissemination of disease process.

Radiograph is usually the initial and one of the most cost-effective diagnostic tools for a patient with respiratory disease. Out of various radiographic patterns described for tuberculosis the miliary mottling is the most curious one that can be picked up easily from plain chest radiographs on the most of occasions.

The causes of miliary pattern on chest radiographs are many including infections like miliary tuberculosis (TB), histoplasmosis, mycoplasma, nocardia and blastomycosis; immune and inflammatory disorders like sarcoidosis, tropical pulmonary eosinophilia and hypersensitivity pneumonitis (HP); malignant disorders like bronchoalveolar carcinoma and hematogenous metastases from carcinoma of thyroid, kidney or lymphagitic carcinomatosis. Other causes of miliary shadows include pneumoconiosis especially silicosis and pulmonary siderosis.<sup>[4,5]</sup>

Miliary nodules have also been reported in association with very unusual causes. The diseases like allergic bronchopulmonary aspergillosis (ABPA) presenting as miliary nodules is very rare and only a few cases have been reported in the standard medical literature. Otherwise also, the ABPA is often misdiagnosed as tuberculosis.<sup>[6]</sup> Leiomyoma, which is considered to be a benign disease process, may also cause multiple bilateral miliary nodules.<sup>[7]</sup> Pulmonary alveolar microlithiasis is a disease characterized by deposition of microliths in the alveoli. The disease may be misdiagnosed as miliary tuberculosis or sarcoidosis especially in its initial stages. Histological confirmation of the diagnosis may be required in some cases.<sup>[8]</sup>

The utility of a well-performed high-resolution computed tomograph (HRCT) in specifying the disease pattern in a case of miliary nodules on chest X-ray cannot be undermined. Ideally, 1-2 mm HRCT films should be ordered in order to get a proper picture of lung parenchyma and delineate secondary pulmonary lobule. The nodular patterns are divided into three groups based on the relationship of nodules to the secondary pulmonary lobule: Centrilobular, random, and perilymphatic distribution.<sup>[9]</sup>

A centrilobular pattern is found in diffuse panbronchiolitis and a lighter version with ill-defined borders is characteristic of HP. Pulmonary Langerhans cell histiocytosis (PLCH) also gives rise to a nodular pattern in the initial stages. Random distribution is usually seen in tuberculosis and silicosis. A perilymphatic distribution represents an increased number of thickened interlobular septa along with a noticeable thickening of interlobar fissures. The septa and fissures usually contain multiple tiny nodules. These small nodules are also found along the pleural surfaces. This pattern is characteristic of sarcoidosis and may be seen in silicosis and lymphangitic carcinomatosis.<sup>[10]</sup>

The presence of additional features, other than the lobular distribution of nodules, may be of help in making a more confident diagnosis. Ground glass opacities, multiple cystic lucencies with or without mosaic attenuation, also known as air trapping, are seen more commonly in HP. The upper middle zonal distribution of nodules is characteristic of HP and sarcoidosis. Silicotic nodules have upper and posterior distribution. These nodules are quite dense and have distinctive borders. The nodules tend to coalesce and form larger nodules, at times forming large masses indicative of progressive massive fibrosis. Calcification of mediastinal lymph nodes is found in silicosis, sarcoidosis as well as tuberculosis. The patterns described above are not highly specific of a particular disease and overlapping features are present in many of these illnesses.<sup>[11]</sup>

An excellent algorithmic approach to diagnosis of miliary nodules on HRCT is provided by Rauf *et al.*<sup>[12]</sup> Though the term miliary nodule has been used to describe a variety of CT patterns, it should be confined to randomly distributed nodules only. Miliary infections disseminated through blood or hematogenous metastases of some tumors tend to produce nodules that are randomly distributed in the secondary pulmonary lobules. In contrast to the centrilobular and perilymphatic pattern, the miliary nodules are found across the entire secondary lobule. Additionally, overall distribution of miliary nodules favors the lung bases.

An outstanding approach to diagnosis of suspected miliary tuberculosis is given by Sharma *et al.*<sup>[4]</sup> A focused clinical and laboratory workup for extra-pulmonary involvement should be undertaken in such patients. Because miliary pattern is represented by many disease processes, no single diagnostic feature is specific for miliary tuberculosis. However, a constellation of signs and symptoms may help in the confirmation of diagnosis. On general physical examination skin lesions, lymphadenopathy and choroid tubercles in eye or the presence of hepatosplenomegaly, signs of meningeal irritation, visceral effusions and cold abscess are highly suggestive tuberculosis as a factor generating miliary nodules.<sup>[4]</sup>

Though the HRCT may not specifically indicate toward a diagnosis of tuberculosis, immune status of the patient may alter certain HRCT findings especially occurring due

to miliary tuberculosis. HIV-seropositive patients may have a higher prevalence of interlobular septal thickening, necrotic lymph nodes and extrathoracic involvement as compared to seronegative patients. In addition, the seropositive patients may also have a lower prevalence of larger nodules of their HRCT.<sup>[13]</sup>

It is usually difficult to make a diagnosis of histoplasmosis. Though histoplasmosis may be confidently diagnosed by histopathology, the sensitivity of this technique is less than 50% in patients with disseminated disease. Pulmonary histoplasmosis is even more difficult to diagnose by histopathology. The sensitivity of polymerase chain reaction is less than that of histopathology. Culture is also met with certain difficulties like low sensitivity, a need for invasive procedure and delay growth of organism.<sup>[14]</sup>

The features that help us to distinguish objectively between tuberculosis and histoplasmosis are of great value in such a situation. A study was done in an area where both histoplasmosis and tuberculosis were endemic among HIV infected patients.<sup>[15]</sup> A study population of 99 participants with tuberculosis and 106 with histoplasmosis were selected in Cayenne, French Guiana. The analysis showed that tuberculosis was more strongly associated with higher prevalence of cough and C-reactive protein levels. Variables suggesting an association with disseminated histoplasmosis were  $\gamma$ -glutamyl transferase levels, origin from specific geographic area, disseminated disease, and presence of a concomitant opportunistic infection. A low neutrophil count, CD4 count, and platelet count were also associated with disseminated histoplasmosis.

Similar clinical and biochemical criteria need to be developed to diagnose and treat these potentially fatal conditions.

In conclusion, a variety of disease processes are responsible for generation of miliary pattern on chest radiographs. HRCT features are quite helpful in delineating the etiological process. The term miliary nodules should be confined to nodules with random and peripheral distribution. A focused diagnostic approach is usually rewarding and helps us in reaching a correct diagnosis so that an appropriate therapy can be instituted timely.

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