Cough in a Young Non-smoker

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A 38 year-old male non-smoker presented for evaluation of a 4-5 monh history of dry cough, and fatigue. He denied any other constitutional symptoms including chest pain, dyspnea on exertion, paroxysmal nocturnal dyspnea, and gastrointestinal, genitourinary or musculoskeletal symptoms. Initially he did not disclose any significant exposure neither at his work place, home, nor to Tuberculosis.

On physical examination was a healthy appearing non-obese male, in no distress. Blood pressure was 138/78; heart rate 68 and regular sinus rhythm; respiratory rate was16 and oxygen saturation 99% on room air. Lung examination showed good air entry bilaterally with a few bilateral end-inspiratory dry rales. Cardiovascular, gastrointestinal, and neurological exams were negative for significant findings and no lymphadenopathy was present. His initial laboratory results including electrolytes, renal function, liver function, urinalysis, calcium, 2D-Echo, and ESR were within normal limits.

Chest x-ray (Fig 1.) showed diffuse micronodular changes while chest high resolution CT (Fig 2,3,4) scan showed diffuse micronodular infiltrate with predominant Lymphangitic and some hematogenous distribution, mainly affecting the upper and mid lung zones with hilar lymph node enlargement. Angiotensin converting enzyme level was within normal limits as was an eye exam.

Pulmonary function tests disclosed an FEV1 of 67%, FVC of 93%, PEF of 70% with improvement in PEF by 18% and FEV by 14% % following bronchodilator (mild obstructive changes with significant response to bronchodilator) and the DLCO was 65% (mildly decreased).

**Deferential Diagnosis:**
Sarcoidosis, metastatic carcinomatosis, tuberculosis, atypical mycobacterium and fungal infection.

Bronchoscopy with broncho-alveolar lavage and transbronchial biopsy from the left upper lobe was performed. (Fig 5, 6). BAL gram stain, acid fast and fungal stains were negative as was TB PCR for both TB and atypical mycobacterium.

**Microscopic Examination:**
Epithelioid cells associated with giant cells containing foreign polarizable material without caseation necrosis.

**Final Diagnosis:**
Sarcoid- like foreign body granulomas
Following communication of the biopsy results to the patient, he admitted to being part of special forces operating in a war zone for eighteen months during which time he had very significant exposure to sandy dust. (Post explosive).

The patient was started on oral prednisone 40 mg/day, and combined inhaled Steroid with long acting beta Agonist (fluticasone 500 mcg and the long acting beta agonist, salmeterol 50 mcg).

The goals of the treatment were to relieve the symptoms (Cough, fatigue), improve the lung function and prevent future deterioration.

The plan of management was to taper the Steroid in the same manner as in Sarcoidosis treatment regime, taking into account the aforementioned goals (i.e. to taper the dose by 5-10 mg every 6-8 weeks, till the dose reaches 5 to 7.5 mg/day, then evaluate possible slower tapering regime. this takes on average 9-18 months).

The patient was seen once every 6 weeks thereafter, and showed a remarkable improvement (significantly less cough and resolution of his fatigue), with a corresponding improvement of pulmonary function tests, such that prednisone was decreased to 30 mg/day with the goal of tapering down as long as his condition permits.

Unfortunately he lost follow up.

The anticipated length of the treatment would have depended on the above the factors.

**Discussion:**

Several mechanisms have been proposed for inhalational lung injury which include nonspecific accumulation of macrophages in alveoli with occasional granulomatous reaction (1), production of hydroxyl radicals resulting in DNA damage (2), T-cell alveolitis and particle induced NF-κB stimulation. Drent *et al* (3) demonstrated presence of activated NF-κB in Sarcoidosis as well.

Induction of disease by a foreign particle depends on cumulative exposure, clearance, dissolution, latency, genetic susceptibility, biologic plausibility and interaction with host factors. A single occupational agent may cause many diseases because of differences in susceptibility and metabolism of individual or several agents may produce only one type of illness (4).

Three types of parenchymal responses have been identified with occupational dust exposure: Interstitial fibrosis, nodular fibrosis and macule formation with emphysema. A lifetime occupational history should be obtained in such patients.

The goal of treatment is to suppress inflammation and halt the disease process. Systemic corticosteroids may provide benefit in improving symptoms, but relapses have been reported upon steroid tapering (4, 5), and long-term efficacy of steroid therapy is unknown.

Serial monitoring of pulmonary function tests provides objective assessment of a patient’s disease activity; however the most important step in caring of these patients is to avoid any exposure of the inciting agent.
This case illustrates very interesting findings and the conclusion is one of exclusion rather than definitive evidence.

The term “foreign body granulomatosis” is usually related to the intravenous injection of pulverized pharmaceutical tablets or injectable illicit narcotics from substances such as talc, microcrystalline, and cornstarch or sugars. In this case the injury was probably triggered by inhalation of sand modified by the explosives and the term “pulmonary foreign body granuloma” or “pneumoconiosis” is used to distinguish it from foreign body granulomatosis. Occasionally, a sarcoid like reaction with such exposure may be seen, as was present in this case.

In hypersensitivity pneumonitis, the granuloma formation is typically loose and peribronchial with a significant lymphocytic infiltrate, whereas well-formed granuloma, with clear giant cell and no vascular or bronchiolar involvement, was present in our patient’s biopsy.

The presence of hilar adenopathy and chest CT findings of a perilymphatic nodular pattern, with the aforementioned histopathologic findings makes hypersensitivity pneumonitis unlikely.

If one considers a diagnosis of Sarcoidosis, Baughman (6) in a recent review suggested the presence of multisystem involvement (at least one additional organ) and exclusion of an alternative diagnosis, which was not the case in our patient.

Lacasse, et al. (7), concluded that in Sarcoidosis, mild inflammation is usually found in the vicinity of the granulomas. Another distinctive feature is that granulomas have a Lymphangitic distribution in Sarcoidosis, whereas they are seen along the airways in hypersensitivity pneumonitis.

Several clinical characteristics distinguish hypersensitivity pneumonitis from Sarcoidosis. The two main distinctive features were from physical examination and chest radiograph (HP Study Group, unpublished data, 2003). Compared with Sarcoidosis, patients with hypersensitivity pneumonitis presented more often with inspiratory crackles (87% vs. 15%). Hilar and or mediastinal lymphadenopathy was seen more often in Sarcoidosis than in hypersensitivity pneumonitis (46% vs. 2%) (7).

Regarding the exposure latency, though many of these disorders require long-term exposure, the type, extent, and genetic susceptibility of the patient, dictates the early vs. late appearance. Data from World Trade Center disaster showed that after the WTC disaster, the incidence of Sarcoidosis or SLGPD (Sarcoid-Like Granulomatous Pulmonary Disease) was increased among FDNY rescue workers (8).

The finding of reversible obstructive on PFT is seen not infrequently in Sarcoidosis (in literature 10-18%) , some experts use the term endobronchial hyper reactivity in such instances, and extrapolating data from occupational lung diseases, such as post-exposure reactive airways disease can explain the finding in our patient, who per history denied any previous history of reactive lung disease.
Pathologic evidence consistent with new-onset Sarcoidosis was found in 26 patients: all had intrathoracic adenopathy, and 6 patients (23%) had extrathoracic disease. Thirteen patients were identified during the first year after WTC dust exposure (incidence rate, 86/100,000), and 13 patients were identified during the next 4 years (average annual incidence rate, 22/100,000; as compared to 15/100,000 during the 15 years before the WTC disaster). Half these patients developed the disease within the first year of exposure, highlighting the dose response relationship (high, unusual type of exposure as seen in our case), however in their study the inclusion required pathologic findings of non-caseating granulomas without evidence of foreign body reaction or malignancy by light microscopy, or fungus or mycobacterium by culture.(8).

The presence of polarized foreign body may represent only exposure thus a surrogate of the exposure, however the pathophysiologic abnormality here is related to the granuloma formation that is centered on this foreign body.

An approach to diagnosis of pulmonary Sarcoidosis (6):

**Teaching points:**
1) Though chronic cough in a non-smoker below the age of 40 is mostly caused by post nasal drip, bronchial asthma, gastro-esophageal reflux or a combination of these, a detailed and thorough environmental, work place exposure history is mandatory.
2) The diagnosis of Sarcoidosis should be only made after such detailed history has been taken.
3) The use of polarized microscopy should be an integral part in the histopathologic evaluation of granulomatous diseases.
4) Three types of parenchymal responses have been identified with occupational inhalational dust exposure: Interstitial fibrosis, nodular fibrosis and macule formation with emphysema.
5) Occasionally Sarcoid like reaction can accompany foreign body granuloma.
6) The most important step in caring of these patients is to avoid future exposure.
7) Sarcoidosis and hypersensitivity pneumonitis should always be considered in such presentations.

References:

4) Sarcoid Like Foreign Body Granulomatosis, Ghazala T. Farooqui, MBBS*, Judy King, MD and Ronald Allison, MD, University of South Alabama, Mobile, AL, chest meeting 2003.
7) Recent Advances in Hypersensitivity Pneumonitis, Yves Lacasse, MD; Mélissa Girard, PhD; Yvon Cormier, MD. CHEST.2012;142(1):208-217. doi:10.1378/chest.11-2479.

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Figure 1: Chest X-ray (PA).

Figure 2: Chest CT: Enlarged hilar lymph nodes.
Figure 3: Chest CT: Diffuse lymphatic and hematogenous micronodular infiltrate.

Figure 4: Chest CT: Diffuse lymphatic and hematogenous micronodular infiltrate. Notice the nodularity along the minor fissure.
Figure 5: (LUL Transbronchial Biopsy) Epithelioid cells are noted associated with giant cells.

Figure 6: (LUL Transbronchial Biopsy) - Polarized microscopy Epithelioid cells are noted associated with giant cells containing foreign polarizable material (arrow).