ORIGINAL RESEARCH PAPER

Medical Science

Endogenous lipoid pneumonia associated with rheumatoid arthritis, Tuberculosis and cytomegalovirus infection

KEY WORDS: Cholesterol (D002784), Pneumonia (D011014), Arthritis Rheumatoid (D001172), Mycobacterium tuberculosis (D009169), Cytomegalovirus (D003587), Tuberculosis (D014376), Lipoid pneumonia

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ABSTRACT

Background: Lipoid pneumonia is a rare disease with presence of lipids in the alveoli from endogenous or exogenous sources. Endogenous Lipoid pneumonia complicated with Rheumatoid arthritis, Cytomegalovirus and Tuberculosis has seldom been documented. Current case of uncommon complicated endogenous lipoid pneumonia adds observational data to previous knowledge about the causes of the disease.

Case Presentation: A woman aged 37 years with eight years of involvement with rheumatoid arthritis developed progressive pleural effusion and semi-turbid exudative lymph dominant fluid. Patient had positive Broncho alveolar lavage fluid for cytomegalovirus and Mycobacterium tuberculosis. Histology of a transbronchial lung biopsy revealed interstitial inflammation and intra alveolar fibrosis associated with lipoid pneumonia. A significantly improvement was achieved by parallel administration of Valgancyclovir, anti TB therapy and steroid therapy by prednisolone.

Conclusions: Rare pathogenesis causes of endogenous lipoid pneumonia in the cases such as described case here, should be better recognized by clinicians to prevent the development of endogenous lipoid pneumonia. The findings highlight that in RA patients suspicious to lipoid pneumonia, RA treatment shift to Adalimumab in combination with MTX, is a fundamental plan.

Background

Lipoid pneumonia (LP) is a rare non-infectious inflammatory pulmonary diseasewhich is characterized by reposition of cholesterol esters in the lung. The involvement can be completely asymptomatic and with no classical radiological features. The diagnosis can be evaluated by CT scan or MRI, based on detecting lipid deposits in the alveoli by endogenous or exogenous sources (1, 2). Moreover, final diagnosis is based on the detecting pulmonary intra-alveolar and interstitial cholesterol granulomas (PICG) in histological examination of the lung biopsy (3,4). LP is categorized as exogenous LP (ExLP) or endogenous LP (EnLP), on the basis of the lipoid source. ExLP is developed by the inhalation or aspiration of lipids. However, EnLP is occasionally found in patients with bacterial or fungal pneumonia (5). Rheumatoid arthritis (RA) is an inflammatory disease associated with many induced pulmonary diseases by RA steroid treatment. There are several pieces of evidence indicating that Rheumatoid arthritis is associated with several infectious diseases agents like Cytomegalovirus (CMV) and Mycobacterium tuberculosis (6). However, to date a case of endogenous LP associated with Rheumatoid arthritis, Cytomegalovirus and Tuberculosis (TB) has not been reported. In the current report, we introduce the first case of endogenous lipoid pneumonia which was associated with rheumatoid arthritis, CMV and TB

General information: A 37-year-old woman admitted to the respiratory hospital of Tehran in January of 2017. Previous clinical signs in Kerman hospital indicated that she had a lung fibrosis with persistent dyspnea, nonproductive cough since the end of November. Documented clinical history revealed that the patient was a known case of rheumatoid arthritis (RA) who received oral prednisolone (10 mg/day) and methotrexate (7.5 mg/w) for the last 8 years.

Pre referral clinical and para clinical documents were studied for further information. Former administered Transbronchial lung biopsy (TBLB) in Kerman indicated that no evidence of RA nodules in the lungs and malignancy changes were recognized. Serology features revealed that HBS antigen; HCV antibody; HIV antibodywere negative. Moreover, immunological examinations for ANA (11<25), anti-ds DNA; anti-LA DNA, anti-Ro-DNA; P-ANCA and C-ANCA were all negative. ESR was 90 and liver enzymes were determined in normal range. Patient also presented with below results for CBC differentiation and blood features:

WBC=2500; HB=9.7 gr/dl; MCV=74; Platelet=511×10^3; Fe=21; TIBC=242; Anisocytosis +1; Poikylocytosis +1; Microcytosis +1; Ovalocytes +1; Hypochromia +2 and no Schistocyte.

Post referral studies: On the same day of referral, she was completely alert and oriented with normal BP (110/70 mm Hg) and low temperature (36.8) and PR=120; RR=30 and O2 saturation of 78% (hypoxemia). The other point in patient was pale conjunctiva, while no cervical LAP was found. A generalized lack of sound in right

lung along with coarse crackles on both lung bases was evident by auscultation. With no murmur, S1 and S2 were heard in cardiac area. No finding was shown in abdominal examination. The patient was immediately admitted in ICU receiving oxygen through the mask. Patient underwent precise clinical examinations.

Echocardiography in terms of cardiac study, revealed normal results. Ultrasound imaging in abdominal and pelvic areas showed normal liver and gallbladder, spleen and kidneys with normal echo. Doppler sonography was also normal in lower extremities. Pulmonary embolism was ruled out by chest computed tomography angiography. Chest radiography (CXR) demonstrated huge pleural effusion at right side. In addition, semi-turbid exudative lymph dominant fluid was revealed with a diagnostic/ therapeutic pleural tap. Ground glass opacity with reticular changes and crazy paving pattern in both lungswas seen in HRCT. Furthermore, right side pleural effusion, patchy consolidation in right lung and cystic changes in both lungs were also recognized. Figure 1 and figure 2 illustrate occurred changes in lungs.

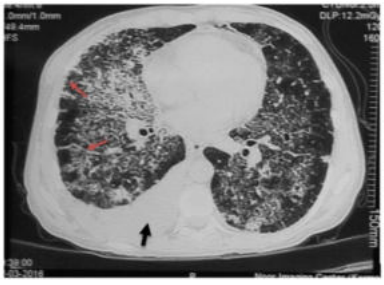

Figure 1: Coarse interstitial networking associated with peri-lymphatic nodules (thin arrow) and peri-bronchial wall thickening is evident for chronic interstitial lung disease. Pleural effusion is present also (black arrow).

Sputum culture growth was negative for Mycobacterium. tuberculosis and fungi. H1N1 influenza virus was also ruled out by PCR conducted on sputum sample. Urinalysis and urine culture were normal. Complementary tests were performed on blood sample and obtained results are mentioned below.

WBC=16500; Hb=8.5; MCV=78; Plt=245000; Creatinine = 0.7; Na=136; K=3.5; Serum Iron=15; TIBC = 267; Ferritin = 2.9; INR=1; ESR=65.

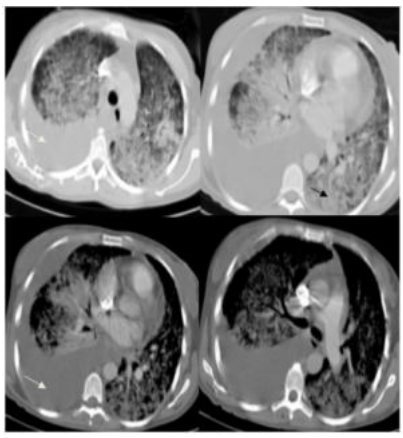

Figure 2: Mixed pattern of alveoli interstitial infiltration revealed the diagnosis of super-added acute infection. Pleura- pericardial effusion is present also. Pleural effusion (white arrow); ground glass opacity (black arrow)

Serum cholesterol showed normalrange results. HB electroph oresis results were: HB-A= 97.1%; HB-F=0.7% and HB-A2=2.2%. Serology tests results are mentioned below:

Wright= Negative; Combs Wright= 1/20; 2ME= Negative; RF= normal; ANA=1/10 homogenous; Anti CCP=4.7(<20).

In spite of an empiric treatment, Meropenem and Vancomycin in addition to Tamiflu (Oseltamivir) and Ciprofloxacin (400 mg IV/bid) were administered (all Bakhtar BehShimi, Iran). Moreover, she also received corticosteroids (1 mg/kg prednisolone) resulting in a transient considerable relief.

After two weeks of finishing the antibiotics and steroids course of treatment, the patient experienced the shortness of breath and fatigue recurrence again. At the point of diagnosis, fiber optic bronchoscopy with transbronchial lung biopsy were performed (Olympus BF1T; Tokyo, Japan) for diagnostic regards. Multifocal yellowish firm nodules were seen across gross lesions in the lungs. Obtained Pleural effusion sample analysis showed: Sugars=151; Protein = 5; LDH = 665; WBC count = 1150; Lymphocyte = 92%; ADA= 41; Cholesterol=84. BAL was positive for acid fast bacilli (3organisms) and Cytomegalovirus (CMV) (108'704 IU/ml). CMV load in terms of virology study was 12'137 by PCR. On the basis of the BAL histopathology examination, sub epithelial accumulation of cholesterol clefts in respiratory mucosa was evident in TBLB. The pathologic investigation determined interstitial and intra alveolar aggregations of cholesterol clefts which was consistent with the diagnosis of endogenous lipoid pneumonia. IHC staining did not confirmed the presence of pneumonitis. jiroveci (Fig. 3).

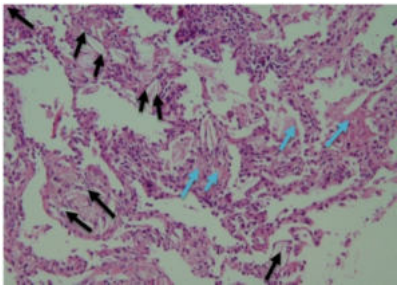

Figure 3: lung parenchyma with patchy interstitial thickening, intra alveolar fibrinous to foamy exudate (blue arrow) associated with interstitial and intra alveolar aggregations of cholesterol clefts (black arrow)

Pathology assessment were obtained as below results: C3=1.6 (normal); C4= 0.24 (normal); CH50=148 (normal); anti-ds DNA= normal and **α**1AT=2.17 (normal range: 0.52-1.69) which the latter was high. At this time Valgancyclovir (900 mg/bd) (Valcyte®) for CMV and anti TB therapy were initiated and steroid therapy was again administered on the sixth day (1 mg/kg/day prednisolone for one week and 0.5 mg/kg/day for another week). A maintenance dose of 10 mg/day prednisolone was administered for next month.

The patient'sphysical capacity improved significantly and was admitted in regular ward. Her O2 saturation also improved to 90%. Following recovery, the patient was discharged and asked to return for follow up clinical observation. She showed no pathological aberrations and disease recurrence during regular visits since May 2017. Adalimumab in combination with MTX was suggested to patient's rheumatologist for her RA further treatment.

Discussion

Lipoid pneumonia is one of the interstitial lung diseases (ILDs) consequences of R.A. In 2016 the first case of endogenous lipoid pneumonia associated with rheumatoid arthritis was described and it was recommended that lipoid pneumonia should be considered in rheumatic patients with lung consolidations (7). Here we introduce a rare and more complex case of endogenous lipoid pneumonia complicated with rheumatoid arthritis, Tuberculosis and cytomegalovirus infection.We also evaluate in charge agents and possible solutions.

Generally, endogenous lipoid pneumonia manifests with the presence of the fat-filled vacuolated macrophages filling the alveoli. Lipoid pneumonia mainly run through primary or secondary mechanisms. Primary mechanismsare usually consequences of

factors like chronic lung inflammation and infection causative agents (2). A variety of causes are related to EnLP such as bronchial obstruction, infection, inhalation of irritating dust particles and lipid metabolism disturbances (5). The mechanisms involved in LP may be linked to increased lipid uptake by alveolar macrophages and presence of modified lipid (8). In general, described EnLP case is suggested to be caused by several different reasons.

The first cause of endogenous lipoid pneumonia in current patient is developed airways obstruction due to rheumatoid arthritis. The airway blockage is ordinarily caused by persistent broncho pneumonia. When infection is added to the airway blockage, the consequences are restrictive pulmonary function and hypoxia. It has been demonstrated that this tissue injury stimulates phospholipases and mono-oxygenases enzymes, which in turn modify low-density lipoprotein within the lung tissue. Lipid uptake by alveolar macrophages is enhance by the modified low-density lipoprotein, which is held responsible for EnLP (5).

Overall, rheumatoid arthritis patients are prone to repeated respiratory infections such as EnLP. In RA, high-density lipoprotein (HDL) constituents are altered due to induced inflammation. Increased oxidative processes, lipid profiles changes and increased lipid uptake are also observed in RA (9, 10). These facts describe how RA is responsible in EnLP involvement. As a solution to this problem, lipid lowering intensive treatment with Statins in patients with RA is today considered in the management of RA (10). Indeed, rheumatoid arthritis is the second cause of endogenous lipoid pneumonia in described case.

On the other hand, obstruction of the airways and glucocorticoids receiving immune compromised body, provide appropriate conditions for opportunistic infections. Opportunistic infections in the respiratory tract can lead to excess production of the mucous (11). Reabsorption of mucous in macrophages due to mycobacterium tuberculosis and cytomegalovirus opportunistic infections in current patient, is suggested to be the third mechanism lead to endogenous lipoid pneumonia.

Atypical rapid growing *Mycobacterium. chelonei* coexistence with lipid pneumonia, was previously reported in some cases (12). As described earlier, current patient was involved with Tuberculosis disease that can be a RA induced opportunistic infection. In *mycobacterium tuberculosis,* the mce4 gene cluster encodes a cholesterol import system to consume host cholesterol as carbon and energy sources. Mentioned cholesterol import occurs within the IFN-**γ**-activated macrophages and results in a persistent endogenous lipoid pneumonia (13). Explained pattern is a reliable clue to suppose *M.tuberculosis* as the fourth cause of endogenous lipoid pneumonia in current patient.

Another complexity in current patient was CMV infection as the second RA induced opportunistic infection. There are some evidences that show CMV infection inhibits the development of the foam cell formation and lipid accumulation upon the increased uptake of LDL in permissive macrophages (14,15). These features make CMV suggested to be the fifth involved cause of endogenous lipoid pneumonia in current patient.

Methotrexate is currently the first line of RA treatment in Iran. Anti-inflammatory action induced by methotrexate (MTX) is the main target of RA treatment. Some known side effects of MTX are serum lipoprotein function affecting and foam cell formation (16). Respective effects of MTX on macrophages cholesterol handling, provide the sixth responsible cause of endogenous lipoid pneumonia in current patient. Similarly, rituximab which is an alternative administered drug in RA treatment, is a case of controversy to improve or develop ILD in RA patients (7). Recently, Adalimumab which is a recombinant human monoclonal antibody to TNF alpha administered in RA, showed to result in much lower effects on macrophage cholesterol uptake. However administering Adalimumab in combination with MTX in RA treatment programs, demonstrated higher beneficial efficacy on RA achieved remission with a less incidence of pulmonary complications especially endogenous lipoid pneumonia (16).

We suggest, therefore, that RA treatment programs in Iran should consider shift of treatment to Adalimumab in combination with MTX instead of MTX separately administration.

Conclusions:

Rare pathogenesis causes of endogenous lipoid pneumonia in the cases such as described case here, should be better recognized by clinicians to prevent the development of endogenous lipoid pneumonia.The findings highlight that in RA patients suspicious to lipoid pneumonia, RA treatment shift to Adalimumab in combination with MTX, is a fundamental plan.

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Author declaration

The authors certify that the manuscript represents a valid work and neither this manuscript nor one with substantially similar content under named authorship has been published or is being considered for publication elsewhere. The study was performed at the Masih Daneshvari referral respiratory hospital of Tehran, Iran. The authors have participated in the research and the shaping of the manuscript.

Conflict of interests

Authors have no conflicts of interest to declare. Authors give consent to submission and publication on the work. Authors disclose no relationship with any organization or industrial manufacture in any material discussed.

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