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Case Report

Biochemistry for Better Diagnosis and Therapy

Association of non-tuberculosis mycobacterium infection with CRP level and occurrence of type 2 diabetes

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Abstract: Mycobacterium infection is one of the global threats which are responsible for millions of deaths per year around the world. Major pathogen involved in mycobacterium infection is *M. tuberculosis* (MTB) however non- tuberculosis mycobacterium (NTM) infection is also responsible for the mortality in recent years. Most promising tools for the diagnosis of mycobacterium are acid-fast bacilli (AFB), tuberculin skin testing and chest X-ray. However these tools cannot differentiate MTB infection from NTM infection. Inflammation has caused NTM which leads to high concentration of CRP in pleural effusion. High level of CRP has several complications including the chance of development of type 2 diabetes mellitus. In this study, a clinical case of man was studied who was diagnosed with Non-tuberculosis mycobacterium (NTM) infection with symptoms same as reported MTB infection. C-reactive protein (CRP), a marker of inflammation was found high in plural fluid after NTM infection. Though the treatment of NTM was completed in 7 months with no relapse however patients got type II diabetes mellitus (T2DM). Occurrence of T2DM could be because of high CRP in the body for a longer time. Though many reports show the positive diagnosis of NTM infection by RT-qPCR however this platform is not available in commercial diagnostic labs as the confirmatory test Genexpert platform is available for the diagnosis of MTB infection. With this report, author described the occurrence of T2DM because of high CRP level present in NTM infection. Further study has been required to establish the correlation between CRP and T2DM pathogenesis. It is recommended to use anti-inflammatory drugs to reduce the CRP in MTB and NTM infection at the initial stage of infection to avoid occurrence of T2DM in patients.

Keywords: *CRP, Inflammation, Marker, MTB, Non-tuberculosis mycobacterium, Type II diabetes mellitus*

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1. INTRODUCTION

Tuberculosis (TB) is a noteworthy global threat all over the world which is responsible for over one million deaths each year[1]. The pathogen responsible for the occurrence of TB is *Mycobacterium tuberculosis* (MTB), a contagious bacterium [1]. Non-tuberculosis Mycobacterium (NTM) bacteria normally exist in the environment and disease may be caused because of inhalation of these bacteria. NTM can cause infection in lungs in immune compromised people as well as healthy individuals. Person-to-person NTM transmission is rare; in contrast, transmission of MTB is very common. Main species which are responsible for the NTM infection are *M. kansasii*, and *M. abscessus*. Detection of these bacteria's are widely accepted for the diagnosis of NTM infection [2]. The tool available for the diagnosis of pulmonary tuberculosis (PTB) is microscopic examination of acid-fast bacilli (AFB) which is based on the detection of mycolic acids present on cell wall of mycobacterium and resistance of decolorization with acid alcohol, however this tool cannot differentiate between *Mycobacterium tuberculosis* (MTB) and non-tuberculosis mycobacterium (NTM)[3]. The occurrence of pulmonary disorder caused by non-tuberculosis mycobacterium is increasing. However, to make strategy for the treatment, it is required to know the causative agent of disease. In countries like India where the occurrence of pulmonary disorder is very high, clinicians have to rely on microscopic examination of sputum, tuberculin skin testing and chest X ray for confirmation of MTB. But these tests cannot distinguish tuberculosis (TB) from NTM lung disease[4]. NTM may be responsible for both symptomatic and asymptomatic disease in humans. Rates of asymptomatic NTM disease have been incidentally confirmed from skin test studies and antibody test. In locations where *MTB* infections are not common, antibody to another common mycobacterial antigen, lipoarabinomannan (LAM), shows the presence of NTM infection predominantly[5]. The cases of NTM disease are increasing with the cases of cystic fibrosis and bronchiectasis. It is also present with the pathogenesis of MTB and cavitary disease. NTN infection is also reported in persons with deficient immunity and other lung disease [2]. C-reactive protein (CRP) is one of the most promising prognosis markers for inflammation in mycobacterial infection [6]. Concentration of CRP has gone up to a high level in mycobacterium infection including MTB infection and NTM lung disease [4,7]. The median level of CRP was elevated in both patients with pulmonary TB and NTM lung disease as compared to healthy individuals ($p < 0.05$). In NTM, trace element Cu showed positive correlations with CRP along with Alkaline phosphatase (ALP) concentrations. The connection of elicit serum Cu with elevated CRP may imitate a nonspecific increase in the serum level of the Cu-binding protein ceruloplasmin during the acute-phase inflammatory response to infection. In correlation analysis between trace elements and nutritional status-associated parameters, CRP concentration showed the strongest association with Cu concentration and a negative association with Zn concentration[8,9]. Different study levels show that high levels of CRP is associated with the occurrence of type 1 and type 2 diabetes[10,11]. Patients of type 2 diabetes showed low inflammation which is reflected by high plasma concentration of several biomarkers of inflammation including C-reactive protein (CRP). It is also reported that increased CRP level can be used as a risk predictor of developing type 2 diabetes[12].

2. CASE DESCRIPTION

In this study, a case of 37 year old man has been presented who had visited a clinician due to continuous fever and it becomes normal with the effect of antipyretic drug paracetamol. This condition of fever was repeated after every 4-6 h, when the effects of the drug got minimized. He has reported loss of 18 pound weight in the past 6 weeks along with weakness, fatigue, chest pain while breathing and sound from trachea. Other vital sign including blood pressure, 142/82 mmHg, CBC, lipid profile, kidney function test and liver function test was normal, except high value of Serum alkaline phosphate as shown in table 1. The patient had no history of Diabetes. By X-Ray chest report (PA view) and ultrasound report, pleural effusion wasobserved at right pleural cavity with mid mediastinal shift towards right. Rest of the lung field appeared clear and bilateral hila were normal. Left costo-phrenic, cardio-phrenic angles, left dome of diaphragm, bony thoracic cage and soft tissue appeared normal. Tapping was performed by a clinician and fluid examination was performed for different parameters and checked for different tests as shown in table 2.

Table 1. Selected laboratory test: MTB, Chemical examination

Test	Specimen	Reference range	Patient result
***Mycobacterium tuberculosis* detection**			
MTB Detection by GENE XPERT/RIF assay	PF[a]	-	Not detected
Chemical examination			
Blood sugar fasting	Serum	70-110 mg/dl	**142.2 mg/dl**
Blood sugar PP	Serum	<140 mg/dl	**218.40mg/dl**
Sugar fasting	Urine	Present (+++)	Absent
CRP-Quantitative (Imm. Turbidimetry)	Pleural fluid	1-3 mg/L	**21.1 mg/L**
Liver function test			
Total Bilirubin	Serum	0.0-1.0 mg/dl	0.5 mg/dl
Direct Bilirubin	Serum	0.0-0.3 mg/dl	0.3 mg/dl
Indirect Bilirubin	Serum	0.0-0.9 mg/dl	0.2 mg/dl
Total Protein (Biuret)	Serum	6.0-8.5 g/dl	6.8 g/dl
Albumin	Serum	3.5-5.0 g/dl	4.2 g/dl
Globulin	Serum	2.0-3.5 g/dl	2.6 g/dl
A/G ratio	Serum	1-1.8	1.62
AST (SGOT)	Serum	0.1-39 IU/ml	16.6 IU/ml
ALT (SGPT)	Serum	7-35 IU/ml	25.5 IU/ml

ALT/AST ratio	Serum	<1-2	1.54
Alkaline phosphatase	Serum	30-140 IU/L	**181.0 IU/L**
Adenosine deaminase (ADA)	PF	0-30U/L (PF/AF[b])	**40.7 U/L**

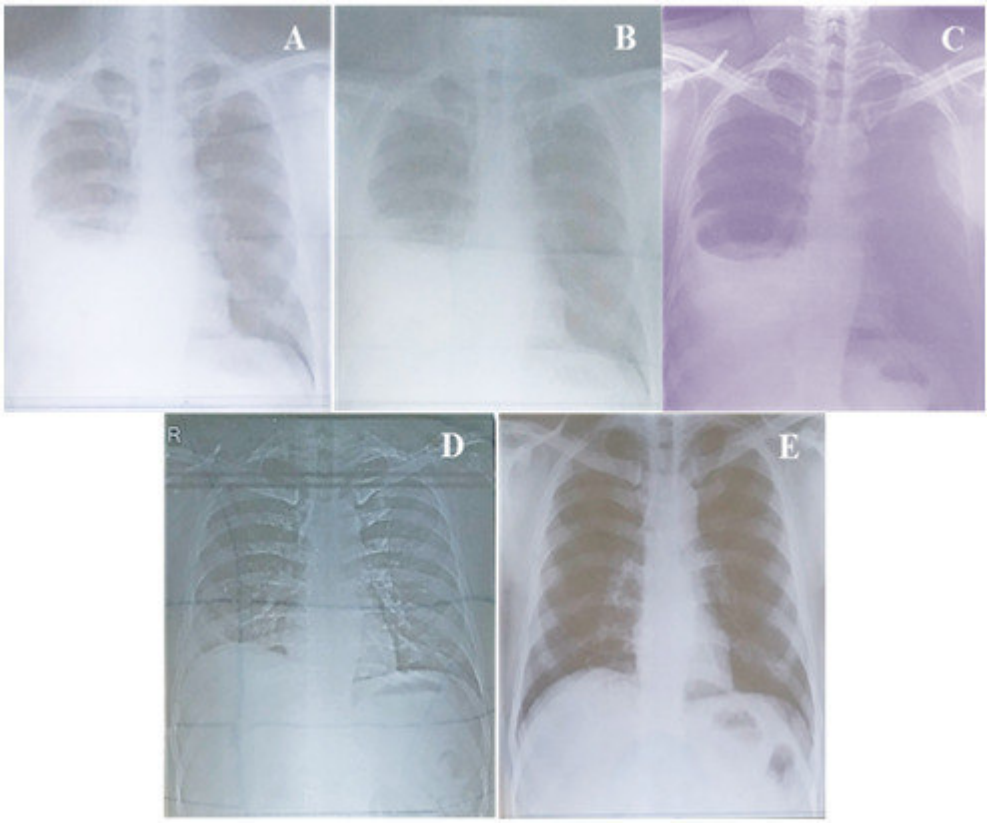
[a]Pleural Fluid (PF); [b] Ascitic fluid (AF)

Table 2. Selected laboratory result: Physical and microscopic examination

Physical examination		Microscopic Examination	
Specimen	Pleural fluid	Total White blood cells	930 cell per cmm
Colour	Pale yellow	Polymorph	14 %
Appearance	Slightly hazy	Lymphocytes	81 %
Quantity	3 ml	Other	05 %
Coagulum	Absent	ZN stain	No AFB seen
Sediment	Absent	Gram Stain	No Organism seen

3. PATIENT FOLLOW-UP

Clinician further did the tapping while hospitalization, removed 1 L of pleural fluid and sent it for analysis. CRP level was 32 mg/L and again it was negative for MTB infection detected by GENE XPERT/RIF assay. Even after removal of 1L pleural fluid, X-ray showed no or minor reduction in volume of pleural fluid (PF). Though the result was negative for *Mycobacterium tuberculosis* infection but on the basis of other symptoms including sudden weight loss, excessive sweating after the effect of antipyretic drug, sound from trachea and pleural effusion, clinician suspected non-tuberculosis mycobacterium (NTM) infection. He prescribed Akurit 4 (Lupin Ltd.), 5 tablets in each morning along with Razo 20 to reduce acidity. Akurit 4 is the recommended drugs for the treatment of MTB. After one week, volume of pleural effusion was not reduced so that additional Metformin (500 mg), twice a day was prescribed for type II diabetes with Akurit 4 (Lupin Ltd.), 4 tablets each morning. After one month of treatment, volume of PF has gone down to base line and X-Ray confirmed that there was no residual PF. Liver function tests including Alkaline phosphatase and Adenosine deaminase (ADA) have reported normal. However Metformin is prescribed to control the sugar level. After 3 months, the HbA1c level was 7.2 % (Estimated blood glucose: 159.94) which indicates permanent occurrence of type II diabetes and prescribed for the continuation of Metformin (500 mg). Lost weight was recovered in 3 months. After 4 months of treatment with Akurit 4, the clinician prescribed Akurit 3 for the next 3 months. After 5 months of treatment with Akurit, X-ray was found to be fully clear (Fig. 1) and hence treatment was stopped after 7 months. No relapse of disease was reported further. However Metformin was recommended to control sugar level.



A) One day before hospitalization. B) After tapping at the hospital. C) One week after medication. D) One month after medication. E) 5 months after medication

Fig 1. Status of pleural effusion seen by X-Ray

4. DISCUSSION

In case of non-tuberculous mycobacteria (NTM), most of the patients show abnormal chest roentgenograms with sporadic infiltrations, nodular abscesses, and cavities resembling TB radiological evidence[13]. The differentiation of *Mycobacterium tuberculosis* (MTB) from non-tuberculosis mycobacteria (NTM) infection is of primary importance for infection control and choice of antimicrobial therapy. Real-time PCR assay with melting curve analysis consistently accurately detected and differentiated *M. tuberculosis* from NTM however this diagnostic platform is not common in pathology labs [14]. Hence there is a need for an RT-PCR commercial platform for the diagnosis of NTM. CRP is one of the inflammatory markers present in NTM [15-17]. Various cohort studies reported the association of elevated CRP as a risk factor for the development of T2DM[18,19]. The association between elevated CRP and type 2 diabetes mellitus (T2DM) is independent of insulin resistance and BMI [18, 20]. In this case, the value of CRP has gone high in NTM infection. Though this NTM infection was assumed, based on the experience of the doctor and treated with medicines for MTB. CRP level is directly associated with the pathogenesis of type 2 diabetes (T2DM) hence patients got T2DM and it was not reversed even after completion of 7 months of medication for NTM. Authors suggested that, after detection of NTM or MTB infection, clinician should prescribe the anti-inflammatory drug to rapidly reduce CRP along with medicines for MTB in the first month of infection to avoid occurrence of T2DM in patients suffering with NTM infection.

QUESTION TO CONSIDER

1. What is the commercial diagnostic platform for NTM infection?
2. What is the diagnostic platform available to differentiate NTM to MTB infection?
3. What anti-inflammatory drug can be prescribed to reduce the CRP in MTB and NTM infection?
4. What drug can reverse T2DM caused in MTB/NTM infection?

ABBREVIATIONS USED

AF, Ascitic fluid; ALP, Alkaline phosphate; CRP, C-reactive protein; MTB, *Mycobacterium tuberculosis*; NTM, non-tuberculous mycobacterium; PF, Pleural fluid; T2DM, type 2 diabetes mellitus;

5. CONCLUSION

In the present study, a case of pathogenesis of non-tuberculosis mycobacterium (NTM) has been described. Patients have symptoms similar to *Mycobacterium tuberculosis* (MTB) and disease was treated with MTB medicines combination (Akurit 3 and Akurit 4). At the time of initial diagnosis, CRP level was very high and this could lead to the pathogenesis of type 2 diabetesmellitus (T2DM). This association was published in many studies. To manage these clinical complications, there is a need of commercial diagnostic platform for NTM infection which can diagnose NTM infection at initial stage and hence treatment can be initiated immediately. It is also suggested to prescribe anti-inflammatory drug to reduce the CRP in NTM infection at initial stage to avoid occurrence of T2DM.

6. AUTHOR CONTRIBUTION STATEMENT

Ms. Parvinder Kaur conceptualized and gathered the data with regard to this work. Dr. Anuj Kumar Gupta analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

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8. CONFLICTS OF INTEREST

Conflict of interest declared none.

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