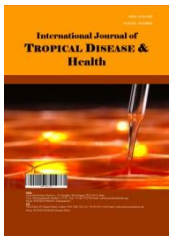

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New Combined Drug Regimen for Complete Cure of Pulmonary Tuberculosis in Patient with Impaired Hepatocellular Functioning – A Case Report

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The research gives new therapeutic regimen to Tuberculosis. Despite of the fact being that the current regimen is a burden on liver functioning; most of these are highly hepatotoxic and increases serum alanine aminotransferase (ALT) manifolds. In the backdrop of such a condition this clinical study has been done. Here 4 drugs has been selected and TB infection of a middle aged female patient was cured rapidly in one month who had hepatocellular changes. The regimen in this research has also showed significant improvement of liver functions post-therapy. This is about the *"Mumbai Protocol"* of tuberculosis management.

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Keywords: Tuberculosis; Mycobacterium tuberculosis; Mumbai protocol; infection therapy.

1. INTRODUCTION

With improvement in medical infrastructure and advent of new drugs in therapeutics, we have been able to win over many epidemics and endemics as well. But few infectious diseases like tuberculosis, caused by *Mycobacterium tuberculosis* are still a burden over the health of world population. Tuberculosis may be localized in different organs of the body, be it the neural meninges or genitalia. But the primary site of infection is the lungs. Currently the recommended drug regimen used to treat Tuberculosis is an intensive therapy with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months and a prolonged phase therapy for 4 months with isoniazid and rifampicin [1]. The Centers for disease control and prevention (CDC) immensely advocates the same. But it is to be noted here that apart from ethambutol, all the other three drugs used in this regimen i.e. isoniazid, rifampicin and pyrazinamide are highly hepatotoxic [2]. It has been pointed out time and again that this anti-TB regimen is major cause for idiosyncratic hepatic injury, worldwide. At the fundamental, these drugs form vicious intermediated compounds in the metabolic pathway after being acted upon by primary microsomal enzymes, thus causing hepatotoxicity [3]. Hence, management of patients with impaired liver function becomes almost next to impossible for clinician by using the current drug regimen. Utilizing the same regimen in such condition blindly may lead to severe complications like drug induced fatty liver, liver cirrhosis and fulminant hepatic failure even. This research deals with utilization of a new regimen of drugs for successful permanent remission of tuberculosis without causing any harm to liver functioning. The regimen has been proven out to be a huge success as the TB was remitted after first month of therapy only, however the 2+4 months regimen was continued to prevent recurrence. The rationality of the experiment is utilization of a combination therapy to cure TB without damaging liver functions. The clinicians involved in this finding are in high hopes that this regimen might be used successfully to cure tuberculosis in patients with liver pathologies.

1.1 Aim of the Study

The aim of this study is to find an alternate and better management regimen for tuberculosis by utilizing drugs that are minimally hepatotoxic or not hepatotoxic at all.

2. CASE PRESENTATION

The experimental therapy and observation was conducted with complete agreement of the patient, safeguarding her physical, psychological and emotional well-being.

2.1 Patient Information

This is taken in two parts – Anamnesis vitae and anamnesis morbi.

2.1.1 Anamnesis vitae

This includes general information past medical history, family history and lifestyle of the patient.

2.1.1.1 General Information and Past Medical History

The patient is a 40 years old female, Indian by nationality. The patient was born on 27th March, 1982 in Kolkata, West Bengal, India with normal post-partum. She is married from the age of 33 years, with normal psychological and sexual functioning but the patient is nulliparous. She works as a professor in a private sector Indian university in Mumbai. No history of drug abuse has been recorded and consumption of alcohol and smoking of cigarette has been denied. The patient has a normal BMI of 21 and no symptoms of metabolic syndrome. In childhood few episodes of acute liver changes have been reported.

The patient has no chronic systemic disorder. Menarche was at normal age range of 12-13 years. Psychiatric modalities were satisfactory. At the age of 26 years stress induced gastritis was diagnosed which subsequently subsided with proper sleep and use of pantoprazole 40mg and drotaverine 40mg for a small period of time. Recently she was treated for moderate infection COVID19 and salmeterol inhaler was started on diagnosis of asthma.

2.1.1.2 Family History

The patient's father, mother and younger brother are of Indian nationality and origin. Her father was diagnosed with papillary carcinoma of the thyroid gland and a complete thyroidectomy was

performed. Both parents have diabetes mellitus type 2 and arterial hypertension stage 1. The patient's younger brother is a patient of mild Schizophrenia and is on selective serotonin reuptake inhibitor drugs.

2.2 Anamnesis Morbi

It includes, present condition, complaints, general observation, systemic observation and clinical observation of the patient.

2.2.1 Primary complaint

Her main complaint was that of dyspnea, fatigue, persistent cough, loss of appetite and night sweat. Breathlessness increases at night and on mild physical excursion.

2.2.2 General observation

The patient was suffering from breathlessness, there was immense fatigue and the skin was pale. All neurological symptoms like Shchetkin Blumberg sign was negative. No tremor was noticed. Pulse was 77 beats per minute. There was persistent coughing of non-productive type.

2.2.3 Cardiac system

Borders of heart on percussion were found to be in normal position. The left apex impulse was heard at normal position. The heart sounds were normal on auscultation. The pulse was 77 beats per minute.

2.2.4 Respiratory system

Breathing was exacerbated. Thoracic breathing with paroxysm was noticed. Deflections of right and left scapula were equal. On auscultation, wheezing and crackling sounds were heard prominently.

2.2.5 Digestive system

Normal position of stomach in the left hypochondrium, diaphragm was situated without any changes. Slightly increased size of liver was felt on palpation of right hypochondrium and it was slightly painful to palpate as well. Couvier's sign was negative. No pain was felt on palpation along the intestine. Bowel sounds were normal on auscultation.

2.2.6 Other organs systems

All findings in other organs systems were absolutely normals.

2.2 Initial Diagnostics and Assessment

Based on the clinical signs and symptoms, pulmonary tuberculosis was suspected with pathological changes of the hepatocytes. Hence a Montoux test and IGRA were done to assess presence of *Mycobacterium tuberculosis* and a liver function test was carried out to assess the functionality of liver.

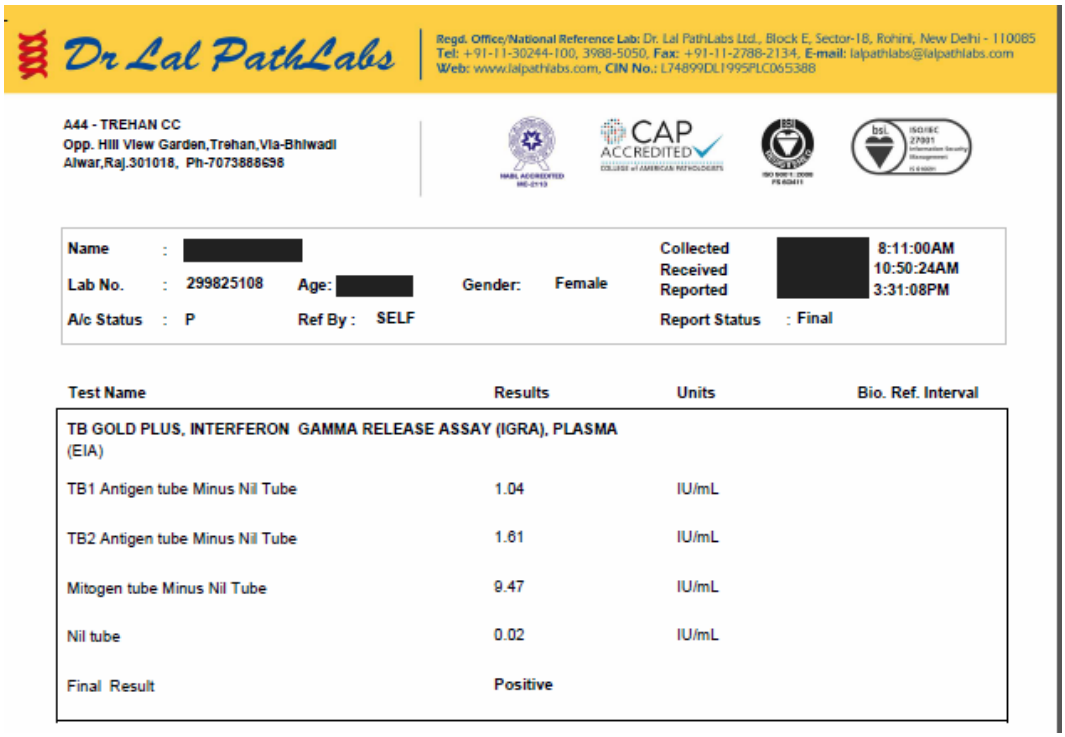
The result of Montoux test is hereby attached below, showing positive tuberculin.

To confirm the diagnosis and rule out false negative results, an IGRA or interferon gamma releasing assay was performed. The result of IGRA also showed positive for TB antigens. The result has been attached below.

To assess the extent of hepato-cellular functions a liver function test was done too. Since, on palpation, right hypochondrium was painful. The test results showed increased ALT and globulin with decreased total protein and albumin. The findings were suggestive of progression towards mild grade Non-Alcoholic Fatty Liver Disease (NAFLD).

Chart 1. The result of Montoux test

Immunology - Serology	
Montoux Test (A)	
Tuberculin is Given Intradermally. Report after 72 Hours	
Result	POSITIVE
Induration	18 x 20 MM



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A44 - TREHAN CC
Opp. Hill View Garden,Trehan,Via-Bhiwadi
Alwar,Raj.301018, Ph-7073888698

CAP ACCREDITED

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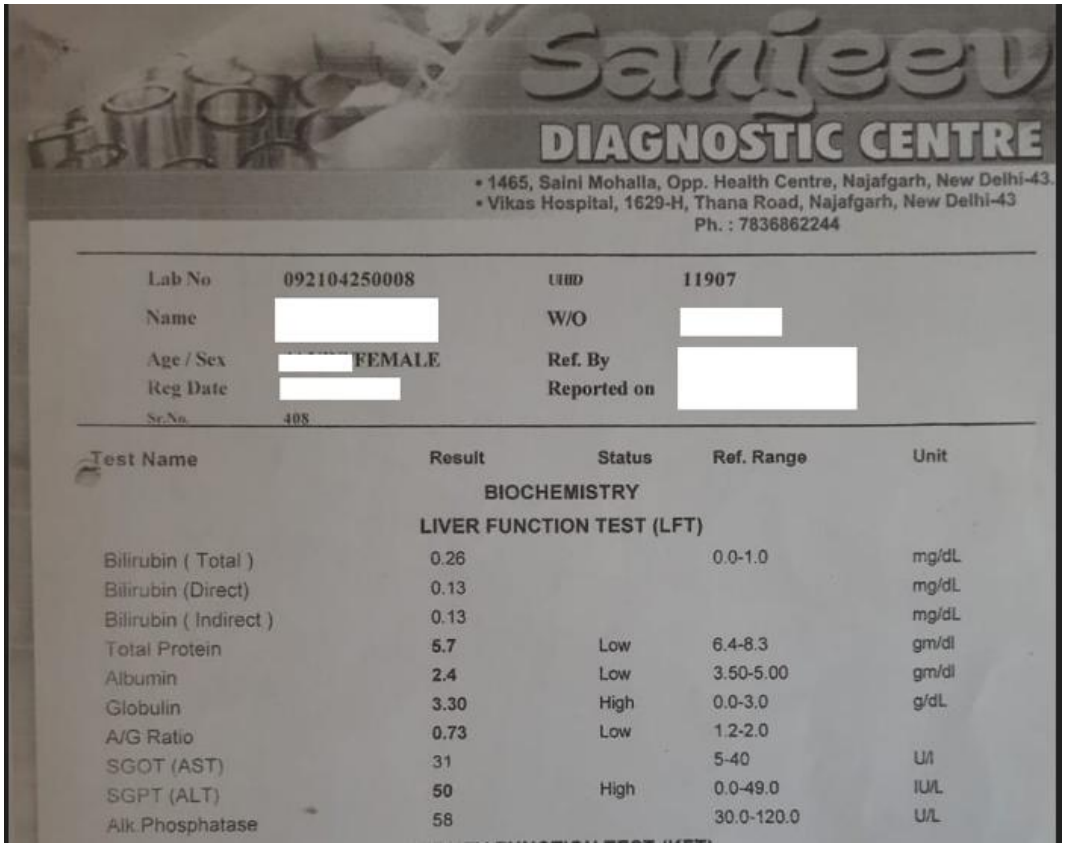
A/c Status	: P	Ref By : SELF		Reported	3:31:08PM
				Report Status	: Final

Test Name	Results	Units	Bio. Ref. Interval
TB GOLD PLUS, INTERFERON GAMMA RELEASE ASSAY (IGRA), PLASMA (EIA)			
TB1 Antigen tube Minus Nil Tube	1.04	IU/mL	
TB2 Antigen tube Minus Nil Tube	1.61	IU/mL	
Mitogen tube Minus Nil Tube	9.47	IU/mL	
Nil tube	0.02	IU/mL	
Final Result	Positive		

Fig. 1. The result of IGRA before therapy



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Lab No	092104250008	UHID	11907
Name	[redacted]	W/O	[redacted]
Age / Sex	[redacted] FEMALE	Ref. By	[redacted]
Reg Date	[redacted]	Reported on	[redacted]
Sr.No	408		

Test Name	Result	Status	Ref. Range	Unit
BIOCHEMISTRY				
LIVER FUNCTION TEST (LFT)				
Bilirubin (Total)	0.26		0.0-1.0	mg/dL
Bilirubin (Direct)	0.13			mg/dL
Bilirubin (Indirect)	0.13			mg/dL
Total Protein	5.7	Low	6.4-8.3	gm/dl
Albumin	2.4	Low	3.50-5.00	gm/dl
Globulin	3.30	High	0.0-3.0	g/dL
A/G Ratio	0.73	Low	1.2-2.0	
SGOT (AST)	31		5-40	U/l
SGPT (ALT)	50	High	0.0-49.0	IU/L
Alk Phosphatase	58		30.0-120.0	U/L

Fig. 2. The result of LFT before therapy

From the patient's condition, it was not suitable to use the usual anti-tuberculosis drug regimen comprising of isoniazid, pyrazinamide, rifampicin and ethambutol, because of their hepatotoxicity. Hence, an experimental approach was taken and a new regimen was formulated with drugs which have shown to be having somewhat anti-tuberculosis properties.

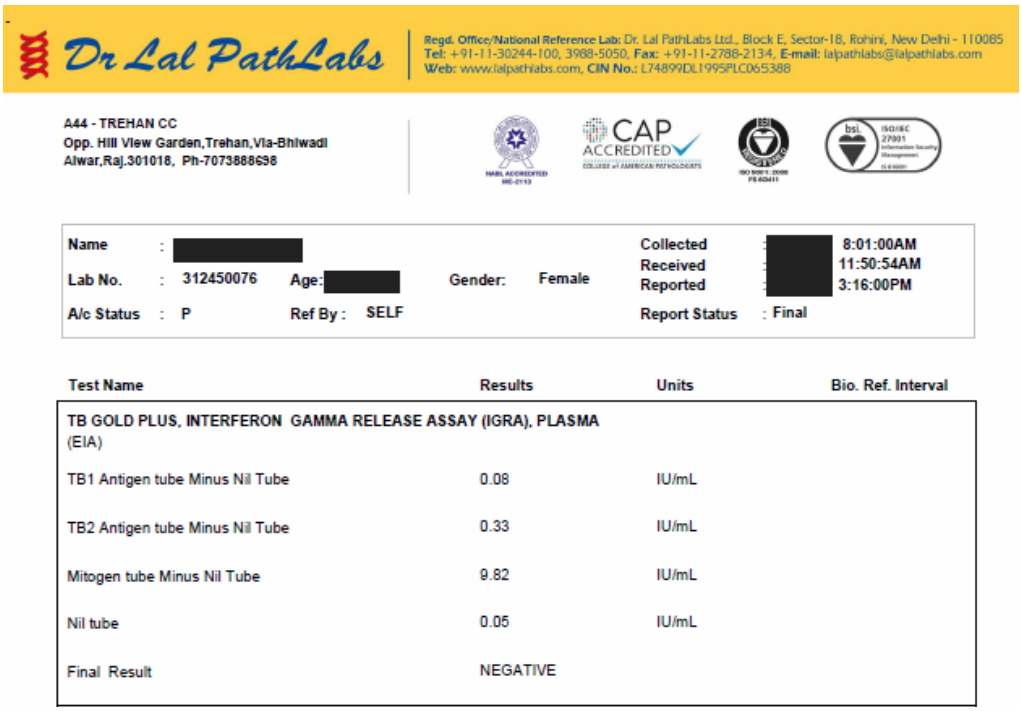
2.3 The Experimental Therapy

The drugs selected are Streptomycin, cycloserine, p-amino salicylic acid and ethambutol. The first 2 months regimen of intensive therapy included all the four drugs. Streptomycin 1g intramuscular injection was given twice a week in a gap of three days, cycloserine 500mg PO was given twice daily, p-amino salicylic acid 4g PO was given once daily by sprinkling on slightly acid food diet and ethambutol 400mg PO was given once daily.

In the continuation phase of 4 months, only cycloserine 500mg PO once daily and ethambutol 400mg PO once daily were used.

2.4 Follow-up and Outcome

It is a known fact for clinicians that after 2 weeks of intensive therapy phase, the tuberculosis becomes latent in most of the cases but for test report to be negative, at least the first 2 months of therapy has to be completed. Test for IGRA was done after 1 month of intensive therapy phase since symptoms were markedly reduced. The IGRA result was negative for tuberculosis. Such fast recovery was unexpectedly surprising for the clinicians involved as well. The patient was unwilling to conduct another Montoux test and hence it was avoided, neither was any necessity for it felt from clinicians point of view. The IGRA test report after 1 month of intensive phase therapy has been attached below.



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Name : [redacted]
Lab No. : 312450076 Age: [redacted] Gender: Female
A/c Status : P Ref By : SELF

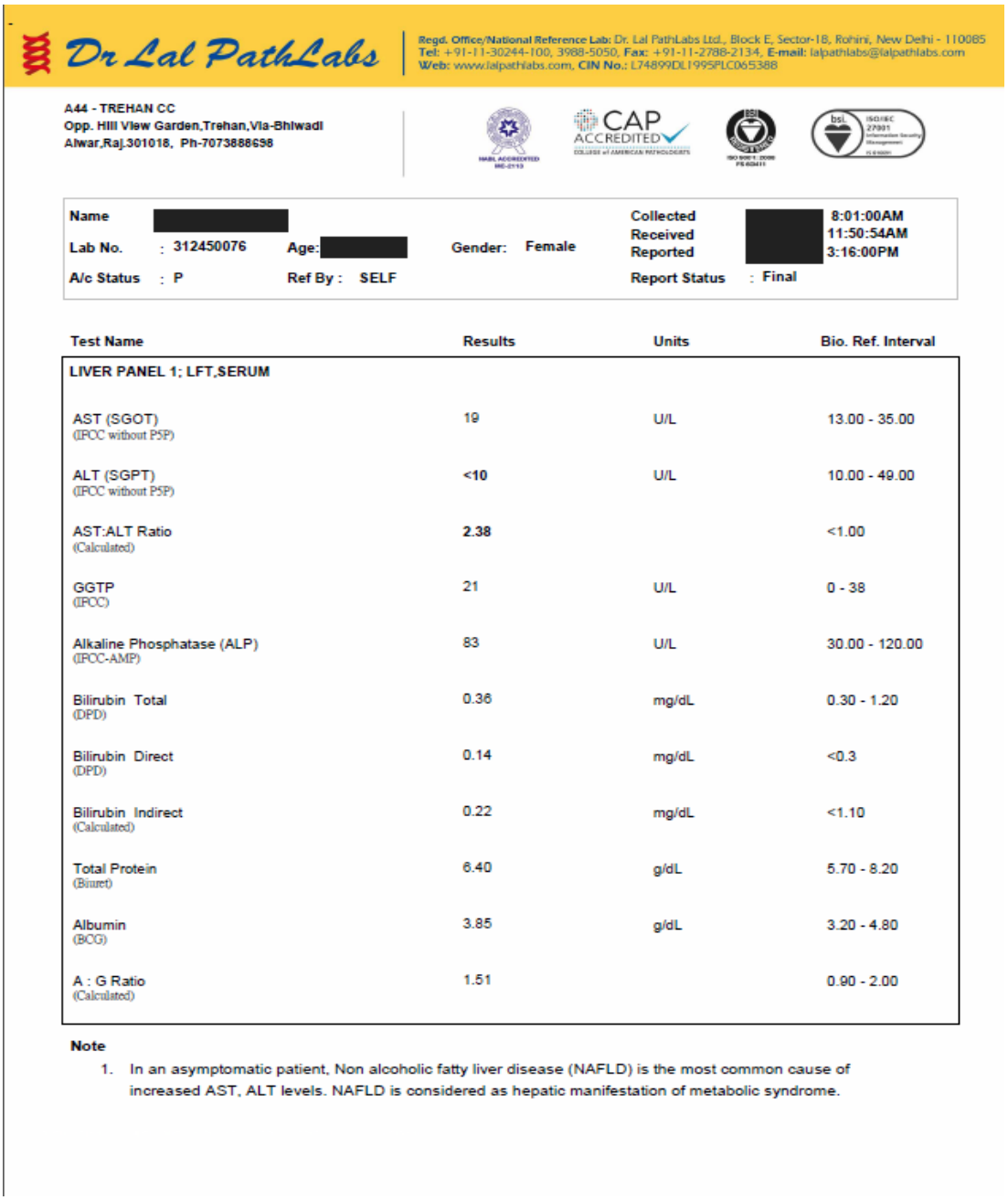
Collected : [redacted] 8:01:00AM
Received : 11:50:54AM
Reported : 3:16:00PM
Report Status : Final

Test Name	Results	Units	Bio. Ref. Interval
TB GOLD PLUS, INTERFERON GAMMA RELEASE ASSAY (IGRA), PLASMA (EIA)			
TB1 Antigen tube Minus Nil Tube	0.08	IU/mL	
TB2 Antigen tube Minus Nil Tube	0.33	IU/mL	
Mitogen tube Minus Nil Tube	9.82	IU/mL	
Nil tube	0.05	IU/mL	
Final Result	NEGATIVE		

Fig. 3. The result of IGRA after therapy

Thus the patient was cured of tuberculosis, no TB antigen were present anymore.

To assess the liver condition post-therapy, a liver function test was conducted again. The LFT test report was highly satisfactory. All parameters were normal; ALT which was increased in earlier report is now slightly decreased along with rationally slightly increased ALT/AST ratio. The result of LFT has been attached below thus.



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A/c Status : P Ref By : SELF

Collected [redacted] 8:01:00AM
Received 11:50:54AM
Reported 3:16:00PM
Report Status : Final

Test Name	Results	Units	Bio. Ref. Interval
LIVER PANEL 1; LFT,SERUM			
AST (SGOT) (IFCC without P5P)	19	U/L	13.00 - 35.00
ALT (SGPT) (IFCC without P5P)	<10	U/L	10.00 - 49.00
AST:ALT Ratio (Calculated)	2.38		<1.00
GGTP (IFCC)	21	U/L	0 - 38
Alkaline Phosphatase (ALP) (IFCC-AMP)	83	U/L	30.00 - 120.00
Bilirubin Total (DPD)	0.36	mg/dL	0.30 - 1.20
Bilirubin Direct (DPD)	0.14	mg/dL	<0.3
Bilirubin Indirect (Calculated)	0.22	mg/dL	<1.10
Total Protein (Biuret)	6.40	g/dL	5.70 - 8.20
Albumin (BCG)	3.85	g/dL	3.20 - 4.80
A : G Ratio (Calculated)	1.51		0.90 - 2.00

Note

1. In an asymptomatic patient, Non alcoholic fatty liver disease (NAFLD) is the most common cause of increased AST, ALT levels. NAFLD is considered as hepatic manifestation of metabolic syndrome.

Fig. 4. The result of LFT after therapy

3. DISCUSSION

The rationale of the drugs selected was such that the drugs should be efficiently anti-TB and at the same time not hepatotoxic or mildly hepatotoxic. Streptomycin is now being used quiet frequently to treat multi-drug resistant tuberculosis It has shown high efficacy in this regard [4]. But at the same time it is not hepatotoxic. Although, earlier it was doubted to be but recent findings have suggested that no concrete evidence of streptomycin being hepatotoxic could be identified [5]. Likewise cycloserine is also utilized in multi-drug resistant tuberculosis with good efficacy. But no strong evidence of hepatotoxicity could have been identified [6]. P-amino salicylic acid is now used as a second-line anti-tuberculin drug. But it was frequently and efficaciously used in 1940s. With passing time this drug was replaced by other newer drugs [7]. The drug acts as a pro-drug which generates a toxic dehydrofolate analogue when incorporated in

folate pathway [8]. IN this patient, during the therapy no gastric related anomaly was noticed as a side effect. It might be that incorporation of the four drugs has some interaction present between them. The primary cause behind replacing it was gastrointestinal irritation. Thus, it was prescribed only for the first 2 months of intensive therapy and was not prescribed for the 4 month prolonged phase therapy. Finally, ethambutol being a drug of regular choice in treatment of tuberculosis has never shown hepatotoxic property [9]. Another reason for adding ethambutol to the regimen is to prevent multi-drug resistance [10]. Thus the candidate was selected for the 4 month prolonged phase therapy as well. It is widely known that the current regimen of treatment for tuberculosis is a not very good variant taking hepatological aspect into considerations. Drug Induced Liver Injury (DILI) after treatment has been widely noted around the world. Cohort study also proves the same, with 1st to 3rd grades of DILI being noticed in approximately 50% patients [11].

4. CONCLUSION

Mycobacterium tuberculosis, the causative agent of tuberculosis is still a health issue with strangulating livelihood of people all around the world [(11)]. Successful treatment of patients with changed liver function becomes almost impossible with the current regimen as all the drugs in it apart from ethambutol become contraindicated. Moreover the current regimen prescribes such drugs which causes immense hepatic injury even in individuals with no liver complaints. The authors would like to name this regimen in memory of the patient as the *"Mumbai protocol"*. Thus, this study brings a drastic change in clinical science of combination therapy.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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