Title: Continuous Rifampicin Therapy Induced Acute Kidney Injury in a Tuberculous Patient: A Case Report and its Literature Review.

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Highlights

- ATT-induced AKI can develop even upon first exposure to rifampicin.

- ATT-induced AKI can develop even when rifampicin is used in a continuous dosing regimen.
- Apart from immune-mediated mechanisms already described in the literature, other pathophysiological mechanisms might also be responsible for ATT-induced AKI.

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ABSTRACT

Background: Tuberculosis (TB) presents with cough, sputum, hemoptysis, chest pain, fever, weight loss, and night sweats. Anti-tuberculosis treatment (ATT) can affect various organs, including the liver and kidneys. ATT-induced acute kidney injury (AKI) presents with fever, rash, nausea, vomiting, diarrhea, and abdominal pain. It occurs due to type 2 or 3 hypersensitivity and affects individuals who have previously used rifampicin or are currently using it intermittently.

Case: An 60-year-old lady was diagnosed with TB and started on ATT. After a few days, she complained of reduced food intake and vomiting, yellow discoloration of the skin, abdominal pain and distention, and limb swelling. She was diagnosed as a case of ATT-induced AKI. She didn't have past exposure to rifampicin and was continuously using it this time.

Conclusion: The key learning point from this case is that ATT-induced AKI can develop even when used in a continuous dosing regimen and even upon first time exposure with no history of past exposure. This prompts vigilance in monitoring renal function of patients being started on ATT regimen with rifampicin as its component as development of this complication poses risk to patient's life and also possibility of developing resistance to anti-tuberculous therapy as a result of discontinuation of treatment. Furthermore, our case suggests that in addition to immune-mediated mechanisms described in literature for ATT-induced AKI, other pathophysiological mechanisms might also be linked to this pathology and need further research for better understanding and optimization of treatment strategies.

Key Words: anti-tuberculosis, rifampicin, isoniazid, acute kidney injury, tuberculosis.

INTRODUCTION

Tuberculosis (TB) has ravaged humankind and has remained endemic and epidemic all over the globe.[1] In 2021, about 10.6 million people, including those living with acquired immune deficiency syndrome (AIDS), were inflicted by TB, and 1.6 million died.[2] With the advent of effective Anti-tuberculosis therapy (ATT) including rifampicin, isoniazid, pyrazinamide, and ethambutol, the future for patients with tuberculosis seemed promising. However, this was cut short as ATT started showing side effects, and the morbidity related to these side effects was significant. Among these side effects, hepatitis, acute kidney injury (AKI), and optic injury are note-worthy, while rash, pyrexia, and gastrointestinal upset are also seen.[3] Rifampicin is a vital player in the treatment of TB. The main side effect of rifampicin is hepatotoxicity, while acute kidney injury is less commonly noted. The pathophysiology that seems to be at play behind this side effect is a type 2 and type 3 hypersensitivity reaction mediated by anti-rifampicin antibodies.[4,5]

Although AKI is a rare complication of ATT, it does delay the treatment of TB and can thus lead to the development of resistance. The same can be said for liver dysfunction caused by these drugs, as it inevitably leads to a halt or change in the treatment regimen.[4] The most common manifestations of renal dysfunction are skin rash, gastrointestinal upset, fever, and hematuria, while common laboratory findings are raised eosinophil count, anemia, and elevated creatinine.[3] Patients inflicted by hepatitis due to ATT complain of general malaise, anorexia, nausea, vomiting, fever, skin rash, and pruritus, while the laboratory results show raised transaminases and serum bilirubin.[6] Despite this, most patients recover following stoppage or change of the treatment regimen.[3]

Our study presents a unique case of ATT-induced AKI, who presented with chief complaints of reduced food intake and vomiting, jaundice, abdominal pain and distention, and limb swelling. Our case proposes that some other pathophysiological mechanisms might also be linked to causing acute kidney injury in setting of exposure to rifampicin as our patient developed AKI with first time exposure to rifampicin and secondary to continuous usage of rifampicin instead of using it intermittently. Liver function tests were also deranged, suggesting the presence of hepatitis due to ATT. She also developed hypertensive urgency and hypoglycemia as well, which were not previously reported.

THE CASE

A 60-year-old female patient with the a past medical history of hypertension, uncontrolled with oral anti-hypertensives, and diabetes mellitus, controlled with oral hypoglycemics, presented with reduced food intake and vomiting, yellow discoloration of the skin, diffuse abdominal pain and bilateral upper and lower limb swelling for four days. The patient had a sudden onset of progressive yellow discoloration of the skin. Her urine was yellowish, and she had no pale stools. She had a gradual onset of abdominal pain with no radiation and no aggravating and relieving factors. The patient also complained of abdominal distention and limb swelling. There was no history of facial puffiness, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

For the last two months, she had intermittent, high-grade fever associated with rigors and chills, productive cough with no hemoptysis, and chest pain. She was started on ATT consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol 15 days ago by a local physician as her chest x-ray showed a cavitary lesion and consolidation in the left lung (Figure 1), and the sputum acid-fast bacillus stain was positive.

At the time of admission into the medical unit, her pulse was 92 beats per minute, her blood pressure was 150/90 mm of Hg, her temperature was 98 degrees Fahrenheit, her respiratory rate was 12 per minute, and her random blood sugar was 119 mg/dl. Her weight was recorded to be 95 kilogram. General physical examination revealed yellow sclera, pale conjunctivae, and pitting edema of lower limbs up to mid-shins. Pitting edema of bilateral upper limbs was also seen. Systemic examination revealed abdominal distention with shifting dullness. The rest of the physical examination was unremarkable. After case discussion with senior registrar on-duty, patient was catheterized to measure her urine output and baseline investigations were ordered. Subsequent record of her urine output came to be 380 ml in first 12 hours of admission i.e. she was oliguric (<0.5 ml/kg/hr). Her laboratory investigations are given in Table 1.

Ultrasound of the abdomen and pelvis showed coarse parenchymal echotexture with serrated margins of liver, increased echogenicity in both kidneys, moderate abdominopelvic ascites, and bilateral mild to moderate pleural effusion. A Pleural tap was done, whose findings are given in Table 1. During her stay at the hospital, her blood pressure was once recorded to be 190/120 mm of Hg, and her random blood glucose level was recorded to be 65 mg/dl with both of them being managed appropriately. We followed liver function tests and renal function tests over several days. Values of blood urea nitrogen, serum creatinine, total bilirubin, alanine transaminase, and alkaline phosphatase are given in Table 2.

Our patient lacked a record of baseline serum creatinine value. She had a urine output of less than 0.5 ml/kg/hr for more than 12 hours and a serum creatinine value of 8.8 mg/dl. Based upon this data and the need for hemodialysis in this patient as described later on in this text, she was classified into “Injury” class in RIFLE criteria and Stage 3 of AKIN criteria. (Table 4 and 5). After case discussion with ward seniors and consultant, she was then put on modified ATT regimen (Isoniazid, Ethambutol, and Pyrazinamide) starting from 3rd day of her admission.

Hemodialysis sessions were included in her management plan due to fluid-overload state of the patient and she had her first session on the 4th day of admission followed by six more sessions (one per week) until her renal profile plateaued at serum creatinine value of 3.5 to 4.2 mg/dl (refer to Table

2; serum creatinine values from day 1 to 43 of admission). Remaining inpatient treatment given to the patient is summarized in Table 3.

Given the raised white blood cell count of our patient on arrival (20.35 $X10^3$/ul) with 89.6 % neutrophils (neutrophilic leukocytosis), the patient was commenced on broad spectrum anti-microbial coverage using cefoperazone/sulbactam to provide gram positive and gram negative coverage and moxifloxacin to cover the respiratory microbes including atypical bacteria. The decision to use these specific agents was based on senior consultation keeping in view the availability of agents in the hospital pharmacy

After recording adequate urine output (> 1 ml/kg/hr) and patient becoming clinically and vitally stable, she was discharged with the advice to continue her modified regimen of ATT and follow up in medicine and nephrology outpatient departments follow-up clinical evaluation, urinalysis, and assessment of renal profile and serum electrolytes and optimization of management of her comorbidities in accordance with post-discharge care for AKI patients as proposed by Tsang JY.[7] She was also registered with regional TB center for appropriate and adequate management of her condition.

DISCUSSION.

In this article, we discuss a case of active pulmonary TB in a 60-year-old woman who was tested positive for sputum acid-fast bacillus. She was treated with first line ATT and after 11 days, experienced a reduced food intake and vomiting, progressive yellow discoloration of the skin, abdominal pain and distention and swelling in her limbs for four days. Eventually, she was diagnosed with AKI using the AKIN/RIFLE criteria. Because of acute onset of AKI following initiation of ATT and the absence of any other predisposing factor, it was clinically diagnosed as a case of ATT-induced AKI.

TB, a contagious disease, is caused by a bacteria known as Mycobacterium tuberculosis. Pulmonary TB usually presents with cough, hemoptysis, chest pain, fever, weight loss, and night sweats.[1] First-line ATT consisting of rifampicin, isoniazid (INH), pyrazinamide, and ethambutol is usually the mainstay of treatment.[2] While hepatitis, dyspepsia, joint pain, rash, and vision problems are some common adverse effects of ATT,[3] AKI is a rare adverse effect.[8] Studies have reported this to be caused mostly by rifampicin.[5,9] In a retrospective case series from 2006-2016, Sakashita K et al,[3] Found that 15 out of 1430 patients with active pulmonary TB on ATT developed AKI; 14 of these were rifampin-induced and one INH-induced. Chogtu B et al,[4] in their case report, described a case of ATT associated with AKI whose serological studies revealed the presence of anti-rifampicin antibodies.[4]

Various studies have revealed that patients on ATT develop AKI when they have either an intermittent dosing regimen of rifampicin or a history of exposure to rifampicin.[4,8-10] Muthukumar T et.al,[11] studied twenty five consecutive patients of ATT-induced AKI admitted from July 1990 to June 2000. The most common pattern of rifampicin administration that resulted in acute renal failure was intermittent dosing regimen while anemia and thrombocytopenia was observed in 60% of cases.[11] The proposed pathophysiology is a type 2 or type 3 hypersensitivity reaction mediated by anti-rifampicin antibodies produced upon first-time exposure to rifampicin. Subsequent exposure after a drug-free interval leads to drug-antibody complexes formation, leading to cellular damage causing renal glomerular and tubular injury.[4,5] Also, studies have frequently reported the presence of anemia and thrombocytopenia in ATT-induced AKI cases.[5,10] De Vriese AS et al,[12] proposed that rifampicin-dependent immunoglobulin G and immunoglobulin M exhibit I antigen specificity, expressed on the surface of red blood cells and renal tubular cells, thus explaining hemolytic anemias and renal injury.[12] Emma L Smith et al.[13] demonstrated rifampin-dependent antiplatelet antibodies leading to thrombocytopenia.

Our patient continuously used rifampicin without any past exposure to rifampicin. Yet, she developed AKI on the 11th day of ATT without a laboratory picture of hemolytic anemia or thrombocytopenia, thus proposing that another pathophysiological mechanism might also be linked with ATT-induced AKI.[8] This presentation of our case is very similar to the published case report of Ata F et.al where a 42-year-old Moroccan lady developed AKI secondary to continuous and uninterrupted rifampicin therapy.[14]

Majority of cases of ATT-induced AKI present with fever, rash, and gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) and flu-like syndrome.[5,9] In contrast, our patient experienced only vomiting and abdominal pain. Also, the patient had reduced food intake, yellow discoloration of the skin, abdominal pain with distention, and limb swelling, which can be because of ATT-induced AKI with liver involvement or a different clinical picture of the ATT-induced AKI as described in the literature.[15] This shows that clinical presentation of ATT-induced AKI may vary from

person to person, warranting regular monitoring of renal function tests before and after starting ATT to detect a complication at an earlier stage. Hematuria and proteinuria were documented in our case in the urinalysis report despite our patient presenting an atypical picture of ATT-induced AKI. These findings are also well-documented in literature,[3,5,10] thus suggesting that they can be used as reliable parameters for detecting this etiology of AKI even in patients with the atypical presentation but a clinical history of rifampicin exposure.

Literature review of ATT-induced AKI revealed rifampicin to be the likely cause in most cases.[16] Based on this review and after case discussion with ward seniors and consultants, she was started on modified ATT regimen that included isoniazid, ethambutol and pyrazinamide. Considering the signs and symptoms of fluid overloaded state (abdominal distention, bilateral upper and lower limb edema), consensus in round discussion was to start renal replacement therapy in form of hemodialysis.

Our patient was managed by temporarily stopping ATT regimen and arranging hemodialysis sessions until adequate urine output (> 1 ml/kg/hr) and plateaued serum creatinine values were obtained after six weeks. This is in contrast with the case of Ata F et.al[14] and their literature review where kidney functions were observed to normalize within three weeks after discontinuation of culprit agents. However, Ata F et.al also mention the use of steroids along with hemodialysis sessions that was not utilized in our case thereby suggesting potential benefit of steroid therapy in speeding recovery in such cases. However, it is important to note that use of steroids for ATT-induced AKI remains a topic of controversy.[14]

During her stay, our patient developed hypertensive urgency (blood pressure was recorded to be 190/120 without the progression of her abnormalities), for which she was managed with anti-hypertensives. This can be because either the potency of antihypertensive medications is decreased in patients who are on ATT or ATT-AKI induced,[17] warranting regular monitoring of blood pressure. Even though our patient was diabetic, she developed an episode of hypoglycemia managed with intravenous 25% dextrose. This can be due to hypoglycemic agents or decreased caloric intake as well.[18] Apart from that, hypoglycemia has been reported due to kidney injury.[19] Therefore, regular monitoring of blood glucose levels should be done.

Limitations:

Key limitations of this case report that warrant mention are:

1. Lack of Renal biopsy and histopathological studies to support our evidence of drug-induced acute kidney injury/acute interstitial nephritis. In our case report, due to a lack of easy availability and affordability, AKI was not confirmed to be secondary to rifampicin exposure by histopathological (renal biopsy) and serological (rifampicin dependent antibodies) means. However, the literature review suggests that even without serological and histopathological studies, a diagnosis of ATT/-induced AKI can be made based on clinical grounds (suggestive history and time course) and by excluding other causes.[20] Renal biopsy can provide information about whether Acute tubulointerstitial nephritis (ATIN) or Acute Tubular Necrosis (ATN) is the underlying cause of ATT induced- AKI.[21] Knowing this is beneficial as the management differs between them; ATIN is usually treated with discontinuation of offending agent along with immunosuppressive therapy while ATN has no specific therapy.[22] Long term

complications like kidney fibrosis and progression to chronic kidney disease can arise if ATIN is not identified and managed promptly.[22] Furthermore, knowing the underlying mechanism behind ATT induced AKI can also help to determine prognosis as ATIN is associated with better renal recovery than ATN.[21]

2. Lack of baseline serum creatinine level before initiation of ATT.
3. Lack of patient follow-up after discharge from the hospital. Post-discharge care and follow-up is essential in cases of AKI because lack of follow-up can result in re-hospitalization and progression to end stage renal disease (ESRD). It is essential to monitor patient's renal function parameters and assess for development of comorbidities like diabetes and hypertension.

Hypothetical expectations and way forward:

From the knowledge we have gathered from our literature review of this case, our hypothetical expectations and the way forward are:

1. The pathophysiological mechanism of ATT-induced AKI proposed and discussed in the literature is an immune-mediated phenomenon usually related to previous exposure or intermittent dosing regimen of rifampicin (the most common culprit medicine in ATT-induced AKI) that leads to the formation of Anti-rifampicin antibodies formation and subsequent deposition of rifampicin-antibody complexes upon next time exposure leading to cellular injury.[4,5] A similar mechanism has also been linked to hemolytic anemia and thrombocytopenia, seen as an association in these cases.[12,13] However, in our case report, a patient with no history of previous exposure to rifampicin was put on a continuous dosing regimen of rifampicin and also lacked association of anemia and thrombocytopenia. Thus, our hypothetical expectation is that there might also be some other pathophysiological mechanism responsible for ATT-induced AKI besides the widely reported immune-mediated pathophysiology. A better understanding of its pathophysiology can lead to better treatment modalities and management guidelines that can significantly impact the long-term outcome and burden of ATT associated with AKI.
2. The literature review showed a lack of agreement on the use of corticosteroids in cases of Drug-induced AKI or acute interstitial nephritis. While some state no significant benefit with corticosteroids in these settings,[6] others recommend its use due to facilitation in both short and long-term recovery.[23] Even those who recommend their use report that the dosing regimens tailored to this condition vary widely and are not standardized.[23] Further work is required in this field to develop standardized guidelines discussing whether or not and when and how to use steroids in cases of ATT associated with AKI.
3. In developing countries like Pakistan, where it becomes difficult to accurately diagnose and treat a complication once it develops and keep appropriate follow-up, the resources can be utilized better if they are focused on preventing a complication. Given the high prevalence of Tuberculosis in our region, the use of ATT is widespread, and thus, preventing the development of ATT associated with AKI will be far more effective than treating it once it develops. However, the literature needs a discussion on how to prevent the development of this complication. Further work and study into this topic are required to create detailed guidelines.

SUMMARY - ACCELERATING TRANSLATION

Acute kidney injury is a rare side effect of anti-tuberculosis therapy, usually caused by either intermittent use of rifampicin or a history of previous exposure to rifampicin. The pathophysiological mechanism responsible for this is reported to be a type 2 or type 3 hypersensitivity reaction resulting from anti-rifampicin antibodies. Acute kidney injury resulting from anti-tuberculosis therapy usually presents with fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain), and flu-like symptoms. We present a unique case of anti-tuberculosis therapy-induced acute kidney injury that had a concomitant anti-tuberculosis-induced liver injury as well and presented with the clinical features of reduced food intake and vomiting, yellow discoloration of the skin, abdominal pain and distention, and limb swelling suggesting that clinical suspension of this side effect should be high as signs and symptoms might vary. Rifampicin was used continuously, and this patient had no reported history of rifampicin use, which suggests that another pathophysiological mechanism might be responsible for anti-tuberculosis therapy-induced acute kidney injury instead of type 2 or type 3 hypersensitivity. She developed hypertensive urgency and hypoglycemia during her stay in the hospital, suggesting that vital monitoring should be done in these patients to prevent life-threatening emergency.

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FIGURES AND TABLES.

Figure 1. Chest X-ray Showing Cavitary Lesion (shown by a Circle) and Consolidation in the Left Lung (shown by an Arrow).

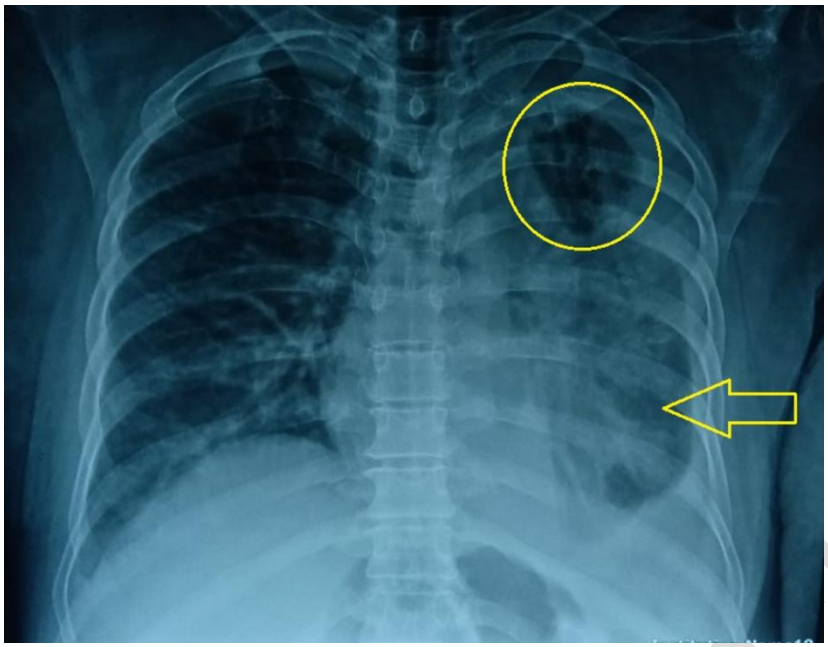

Table 1: Laboratory Investigations of the Patient at the time of admission.

Name of Investigation	Result	Normal range	Unit
Sodium	122 (↓)	135-150	mmol/L
Potassium	4.64	3.5-5.1	mmol/L
Chloride	81 (↓)	96-112	mmol/L
Blood Urea	186 (↑)	18-45	mg/dl
Creatinine	8.8 (↑)	0.42-1.06	mg/dl
Total Bilirubin	1.3 (↑)	0.1-1.0	mg/dl
Alanine Transaminase	208 (↑)	10-50	IU/L
Alkaline Phosphatase	222 (↑)	35-104	IU/L
Serum Albumin	2 (↓)	3.4-5.4	g/dl
PT	21.3 (↑)	12	seconds
APTT	39.8 (↑)	28	seconds
White Blood Cells	20.35 (↑)	4-11	$X10^3$/ul
Red blood Cells	4.86	4-6	$X10^3$/ul
Hemoglobin	11.2 (↓)	11.5-17.5	g/dl
Hematocrit	32.2 (↓)	36-54	%
Mean Corpuscular Volume	66.3 (↓)	76-96	fL
Mean Corpuscular Hemoglobin	23 (↓)	27-33	pg
Mean Corpuscular Hemoglobin Concentration	34.8	33-35	g/dl
%Red Blood Cell Distribution width	14.6 (↑)	11.5-14.5	%
Platelets	628 (↑)	150-450	$X10^3$/ul
%Neutrophils	89.6 (↑)	40-75	%
%Lymphocytes	6 (↓)	20-45	%
%Monocytes	4	2-10	%
%Eosinophils	0.3	0-6	%
#Neutrophils	18.23 (↑)	1.9-8	$X10^3$/ul
#Lymphocytes	1.22	0.9-5.2	$X10^3$/ul
#Monocytes	0.82	0.16-1	$X10^3$/ul
#Eosinophils	0.06	0-0.8	$X10^3$/ul
C Reactive Protein	10.708 (↑)	<0.5	mg/dl
Virology			
Hepatitis B surface antigen (By ICT)	Negative		
Anti-Hepatitis C Virus (By ICT)	Negative		

Anti-Human immunodeficiency Virus (By ICT)	Negative		
pH (arterial blood)	7.216 (↓)	7.35-7.45	
pCO2	51.0 (↑)	35-45	mmHg
pO2	48 (↓)	75-100	mmHg
HCO3	20.7 (↓)	24-27	mmol/L
Lactate Dehydrogenase	777 (↑)	80-235	IU/L
Creatine Kinase-MB	28 (↑)	<25	IU/L
Troponin I	0.1	<0.6	ng/ml
Hemoglobin A1c	14.5 (↑)	4.6-6.56	%
Physical Examination of Urine			
Color	Yellow		
Appearance	Clear		
Chemical Examination of Urine			
Glucose	Nil	Negative	
Bilirubin	Nil	Negative	
Ketones	Nil	Negative	
Bile Salt/Pigment	Nil		
pH	6	4.5-8.0	
Protein	++ (↑)	Negative	
Urobilinogen	Nil	Normal	
Microscopic Examination of Urine			
Pus/White Blood Cells	6-8 (↑)	0-5/Hpf	
Red Blood Cells	Numerous (↑)	0-5/Hpf	
Epithelial Cells	Few	0-10/Hpf	
Hyaline Casts	Nil	0-4/Hpf	
Cellular Casts	Nil	0/Hpf	
Granular Casts	Nil	0/Hpf	
Bacteria	Nil	Negative	
Mucous	Nil	Negative	
Yeast cells	+ (↑)	Negative	
Physical Examination of Pleural Fluid			
Volume	2 millilitre		
Turbidity	Slight		
Clot	Nil		
Color	Straw		
Chemical Examination of Pleural Fluid			
Protein	1.6		
Microscopic Examination of Pleural Fluid			

Cell Count	15/cubic millimeter		
Red Blood Cells Count	3200/cubic millimeter		
Differential Leukocyte Count of Pleural Fluid			
Neutrophils	10%		
Lymphocytes	90%		
Gram Stain	No Micro-Organisms seen		
Ziehl Neelsen Stain	No AFB seen		

PT: prothrombin time; APTT: activated partial thromboplastin time; pCO2: partial pressure of carbon dioxide; HCO3: bicarbonate; mmol/L: millimoles per liter; mg/dl: milligrams per deciliter; ng/ml: nanograms per milliliter; Hpf: high power field; AFB: acid fast bacillus; mmHg: millimeters of mercury; IU/L: international units per liter; ul: microliter; g/dl: grams per deciliter; fL: femtoliter; pg: picogram; ICT: immunochromatographic test: ↓; decreased: ↑; increased

Table 2: Showing Values of Blood Urea Nitrogen, Serum Creatinine, Total Bilirubin, Alanine Transaminase, and Alkaline Phosphatase over the Course of Several Days starting from the day of admission.

Days	Blood Urea Nitrogen (milligrams per deciliter)	Creatinine (milligrams per deciliter)	Total Bilirubin (milligrams per deciliter)	Alanine Transaminase(milligrams per deciliter)	Alkaline Phosphatase (milligrams per deciliter)
1	186	8.8	1.3	208	222
8	78	7.6	0.5	17	217
15	53	5.6	1.6	12	159
22	50	4.5	1.5	7	154
29	80	5.9	1.1	15	153
36	92	6.3	1.8	5	256
37	74	4.9	n/a	n/a	n/a
38	64	4.8	n/a	n/a	n/a
39	80	4.8	n/a	n/a	n/a
41	71	4.2	0.7	12	218
42	75	3.8	0.8	10	227
43	64	3.5	n/a	n/a	n/a

n/a: data not available

Table 3: Treatment Given to the Patient in the Hospital.

DRUG	ROUTE	DOSE	FREQUENCY
Alprazolam (ALP)	Oral	0.25 mg	Once a day
Amlodipine (Lodopin)	Oral	5 mg	Once a day
Cefoperazone (Sulzon)	Intra Venous	2 g	Twice a day
Dialysis			6 sessions were done during her stay in the hospital
Ethambutol	Oral	400 mg	Once a day
Hypertonic Dextrose 25%	Intra Venous	2 ampules	
Insulin Glargine (Lantus)	Subcutaneous	10 unit	Once a day
Insulin Regular (Humulin R)	Subcutaneous	8 unit	Three times a day
Metoclopramide (Maxolon)	Intra Venous	10 mg	Three times a day
Moxifloxacin (Moxiget)	Oral	400 mg	Once a day
Omeprazole (Risek)	Intra Venous	40 mg	Once a day
Isoniazid	Oral	300 mg	Once a day
Pyrazinamide	Oral	1200 mg	Once a day
Salt Free Albumin	Intra Venous	100 ml	Twice a day

mg: milligram; g: gram; L: liter

Table 4: Rifle criteria for Acute Kidney Injury[24]

Stage	GFR Criteria	UO Criteria
Risk	SCr increased 1.5-2 times baseline or GFR decreased >25%	UO < 0.5 mL/kg/h < 6 h
Injury	SCr increased 2-3 times baseline or GFR decreased >50%	UO < 0.5 mL/kg/h >12 h
Failure	SCr increased >3 times baseline or GFR decreased 75% or SCr ≥4 mg/dL; acute rise ≥0.5 mg/dL	UO < 0.3 mL/kg/h 24 h (oliguria) or anuria 12 h
Loss of Function	Persistent acute renal failure: complete loss of kidney function >4 weeks (requiring dialysis)	
ESRD	Complete loss of kidney function >3 months (requiring dialysis)	

GFR: glomerular filtration rate; UO: urine output; SCr: serum creatinine; ESRD: end-stage renal disease

Table: 5 The AKIN classification/staging system of Acute Kidney Injury.[25]

Stage	SCr	UO
1	↑ SCr ≥26.5 µmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5 a 2×)	<0.5 mL/kg/h (>6 h)
2	↑ SCr >200 a 300% (>2 a 3×)	<0.5 mL/kg/h (≥12 h)
3[b]	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑SCr ≥44.2 µmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

SCr: serum creatinine; UO: urine output.

[a]Stage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.