

## Congestive cardiac failure induced by antitubercular therapy in a child: A case report

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### ABSTRACT

Tuberculosis is a significant public health concern affecting people of all age groups in developing countries. Agranulocytosis and pancytopenia occurring in adult tuberculosis patients taking antitubercular therapy (ATT) are well known. In contrast, only a couple of reports are available in the literature documenting pancytopenia in children with tuberculosis receiving ATT. These have reported pancytopenia secondary to disseminated tuberculosis presenting as hemophagocytosis or due to drug-induced systemic lupus erythematosus. However, clinically significant pancytopenia in the absence of hemophagocytosis and secondary lupus along with concurrent hepatitis leading to congestive cardiac failure in pediatric age group as witnessed in the index patient occurring due to ATT has not been reported previously. This child developed severe anemia presenting as congestive cardiac failure requiring multiple packed red blood cell transfusions. This case reinforces the need for regular hematological and liver function test monitoring in children receiving ATT so as to prevent the development of complications such as congestive cardiac failure.

**Key words:** *Antitubercular therapy, congestive cardiac failure, hepatitis, pancytopenia, severe anemia*

**W**e report a 6-year-old female child who was diagnosed as abdominal tuberculosis and started on first-line four drug antitubercular therapies (ATT). She developed symptomatic pancytopenia 2 months after the start of ATT in the form of congestive cardiac failure due to severe anemia in addition to concurrent hepatitis. She required multiple packed red blood cells (RBC) transfusions and was transiently shifted to second-line ATT. She recovered completely and was restarted on first-line ATT under strict hematological and liver function test monitoring. She has been under follow-up for the past 3 months and has remained asymptomatic thereafter. The case report has been framed using the CARE Guidelines [1].

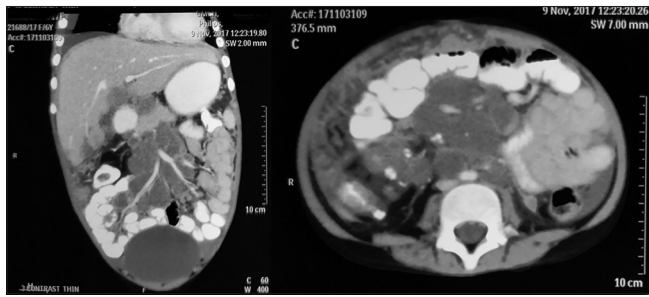
### CASE REPORT

A 6-year-old female child presented to the emergency department with difficulty in breathing for 1 day associated with increased rate of breathing and chest indrawing. There was no history of cough, fever, abdominal pain, bluish discoloration, altered sensorium, or loss of consciousness. Examination revealed tachycardia (heart rate 132/min), tachypnea (respiratory rate 30/min), severe pallor, and knuckle hyperpigmentation. Grade II systolic murmur was heard on auscultation. The liver was palpable 4 cm below the right subcostal margin while spleen was not palpable. Investigations showed hemoglobin (Hb) 1.9 mg/dL, total leukocyte count (TLC) 2500/mm<sup>3</sup>, and platelet count 39,000/mm<sup>3</sup>. She had hyperbilirubinemia (bilirubin total/conjugated 2.1/1 mg/dL),

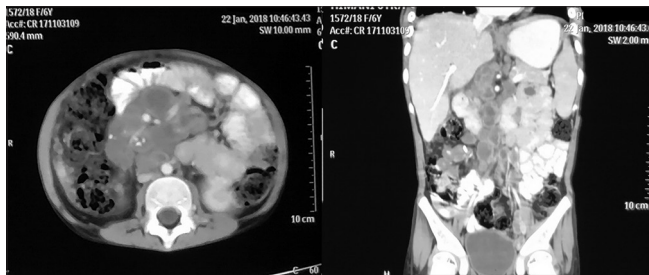
elevated aminotransferases (aspartate transaminase [AST]/alanine transaminase [ALT] 650/398 IU/L), and raised lactate dehydrogenase (1150 U/L). Coagulation profile was deranged with prothrombin time (PT) 22 s (control: 15 s), activated partial thromboplastin time 44 s (control: 30 s), PT index 64%, and International Normalized Ratio (INR) 1.8. The patient was managed with non-invasive ventilation and packed red blood cell transfusions. First-line ATT was stopped and second-line ATT started.

2 months before admission, she was hospitalized with the complaints of intermittent fever for 1 month and abdominal distension for 1 week before admission. On abdominal computed tomography (CT), there were necrotic and conglomerated abdominal, pelvic and epiphrenic lymphadenopathy, hepatosplenomegaly, and diffuse mental thickening suggestive of abdominal tuberculosis (Fig. 1). She was started on daily ATT (isoniazid at 10 mg/kg/day, rifampicin at 15 mg/kg/day, ethambutol at 20 mg/kg/day, and pyrazinamide at 30 mg/kg/day) for the same. As per the parents, adherence to the treatment regime was good.

On further investigations during the current hospitalization, hepatitis B surface antigen, anti-hepatitis C antibody, serologies for hepatitis A, hepatitis E, human immunodeficiency virus, and autoantibodies (antinuclear, anti-smooth muscle, antimitochondrial, anti-liver kidney muscle, and anti-parietal cell) were negative. Peripheral blood smear, indirect bilirubin, and G6PD levels were within normal limits. Urine for Hb, direct



**Figure 1: Contrast enhanced CT (CECT) of abdomen showing multiple enlarged necrotic lymph nodes in mesentery, retroperitoneum and encasing common iliac vessels. Hepatomegaly and right pleural effusion also seen**



**Figure 2: Contrast enhanced CT abdomen showing multiple conglomerated lymph nodes with central necrosis in mesentery, retroperitoneum, peri-pancreatic region and along the iliac vessels**

Coombs test, and sputum-for-hemosiderin laden-macrophage was negative. Given the temporal correlation, absence of other etiologies and a score of 6 on Naranjo Probability, a possibility of drug-induced pancytopenia, and hepatitis were considered [2]. The concurrent antitubercular medications were withheld and the child was started on modified regimen consisting of ofloxacin, ethambutol, and streptomycin. The liver function tests subsequently improved with total serum bilirubin 0.7 mg/dL, AST/ALT, 46/72 IU/L, and hematological parameters recovered with Hb 8.1 mg/dL, TLC 7700/mm<sup>3</sup>, and platelet count 175,000/mm<sup>3</sup>. A repeat abdominal CT scan showed multiple large conglomerated mesenteric and retroperitoneal lymphadenopathy and hepatosplenomegaly (Fig. 2). Radiologically, there was neither deterioration nor improvement. First-line ATT was reintroduced starting with Isoniazid at 50 mg/day which was gradually increased to 150 mg/day over 3 days followed by Rifampicin at 75 mg/day increased to 250 mg/day over 3 days. Complete blood counts and liver function tests (LFTs) were regularly monitored during this period. The child was discharged in stable condition after 4 weeks of hospitalization. The child was asymptomatic when he came for follow-up after 3 months, and his hematological parameters and LFTs were normal.

## DISCUSSION

Tuberculosis is a significant public health concern affecting people of all age groups in developing countries. From the earlier thrice a week regimen, a daily drug regimen using fixed-dose combinations is now the preferred strategy [3]. For abdominal tuberculosis, an intensive phase of 2 months with isoniazid,

rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of 4 months with isoniazid and rifampicin is recommended.

Drug-induced hematological disorders can affect red cells, white cells, platelets, and the coagulation system, causing hemolytic anemia, red cell aplasia, sideroblastic anemia, megaloblastic anemia, polycythemia, aplastic anemia, and leukocytosis. It has been seen that agranulocytosis can occur in tuberculosis patients taking isoniazid and rifampicin [4]. However, all the patients in this case series were adults, and similar reactions in children have not been reported. Leukopenia and thrombocytopenia with ATT have also been observed [5,6]. Pancytopenia following ATT in adults has been attributed to idiosyncratic reaction to streptomycin and hemophagocytosis in two separate reports [7,8]. Idiosyncratic reaction, malabsorption, and interference with iron metabolism or hemolysis can also cause hematological abnormalities in patients on ATT [9]. However, clinically significant pancytopenia leading to congestive cardiac failure requiring multiple packed RBC transfusions occurring in pediatric age group due to ATT has not been reported previously.

Pancytopenia can be a manifestation of disseminated tuberculosis in children. Disseminated tuberculosis complicated by macrophage activation syndrome can also present as pancytopenia. Hemophagocytic lymphohistiocytosis (HLH) has also been diagnosed in patients with tuberculosis who present with cytopenias, organomegaly, and coagulopathy [10]. In our case, there were no clinical or radiological signs of dissemination, the 2004 diagnostic criteria for HLH was not fulfilled, and there was an improvement in symptoms after ATT was withheld. Drug-induced lupus erythematosus due to isoniazid presenting as pancytopenia has been reported, with positive antinuclear, anti-dsDNA and anti-histone antibodies [11]. However, ANA and anti-dsDNA were negative in our patient.

Drug-induced liver injury (DILI) is defined as an increase in ALT  $\geq 5$  times the upper limit of normal (ULN) or ALP  $\geq 2$  times ULN or ALT  $\geq 3$  times ULN with bilirubin  $\geq 2$  times ULN following drug exposure [12]. Pediatric acute liver failure (ALF) is defined as evidence of liver dysfunction within 8 weeks of onset of symptoms, correctable coagulopathy with INR  $>1.5$  in patients with hepatic encephalopathy, or INR  $>2.0$  in patients without encephalopathy and no evidence of chronic liver disease either at presentation or in the past. Antibiotics and ATT are a common cause of DILI-LF. In our case, the laboratory values were consistent with DILI not progressing into ALF. Animal studies for investigation of the mechanism of rifampicin-induced liver injury have identified the involvement of PPAR $\gamma$  signaling pathway and cytochrome P450 [13]. A population study done on isoniazid-induced liver injury in Singapore showed that association between single nucleotide polymorphisms in NAT2 slow acetylators and isoniazid-DILI was significant and could be used for the prediction of DILI [14].

Transaminitis with concurrent pancytopenia commonly occurs due to viral hepatitis, but a drug-induced event must also be kept as a differential diagnosis. It has been reported previously

with drugs like terbinafine [15]. The mechanism is uncertain but likely due to an idiosyncratic reaction or immunologically mediated hypersensitivity, involving immunoglobulin E, G, M, or antigen-antibody complexes. In our case, the pancytopenia with concurrent hepatitis points to an allergic reaction to first-line ATT or an idiosyncratic reaction. It is therefore advised that a complete hemogram along with LFTs must be done at regular intervals in children taking ATT. This could detect any drug-related side effect promptly and prevent the development of pancytopenia-induced complications such as congestive cardiac failure as seen in our patient.

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