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A CONSEQUENCE OF ANTI-TUBERCULOSIS TREATMENT MAY BE THROMBOCYTOPENIA: A CASE REPORT

Medicine

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ABSTRACT

Thrombocytopenia is considered a rare adverse effect observed post medication for tuberculosis (TB). Antituberculosis treatment or AKT is the preferred combination of medications prescribed to patients with TB. This is a case report of acute and severe thrombocytopenia due to re-administration of antituberculi medication AKT2. The patient, a 51 year old male, who "apparently" had completed an AKT1, 3 years ago, arrived at municipal hospital with clinical suspicion of Pulmonary TB. When the patient was administered the AKT2, he within 7 days, reported to the hospital with severe reactions possibly due to the medication. Considering the high incidence of TB in India and potentially equally high reoccurrence of TB, the use of AKT2 needs to be carefully considered.

KEYWORDS

Tuberculosis, AKT2, thrombocytopenia, rifampicin (RFP)

Introduction

Tuberculosis (TB) remains a global health concern and India accounts for about a quarter of the global TB burden [1]. In 2016 an estimated 28 lakh new cases were reported and 4.5 lakh people died due to TB. It remains one of the top five causes of death in India [1]. WHO has defined India as "ground zero" for TB with 2 to 2.3 million cases per year [2, 3]. Therefore, there is an urgency not only to early detect, monitor but also to improve management of TB.

The treatment of TB has been well defined by WHO which is found to be effective and includes prolonged administration of anti-tuberculosis treatment or AKT [4]. AKT includes rifampicin (RFP) and in most instances the combination of drugs have no or minimal side effects. Having said that, some patients have displayed severe reactions to the drugs [5, 6, 7, 8, 9]. The problem often arises when patients don't complete the whole treatment or not inform the treating physician about the previous history of the treatment [4]. This is a major concern especially in India as relapse rate is almost 10% which is higher than those found in international studies [10]. The implication of this is that the patients are then prone to adverse effects of AKT specifically RFP. RFP has been reported to induce allergic responses, especially when readministered after a treatment interruption and is known to cause thrombocytopenia which is a condition characterized by abnormally low levels of thrombocytes, or platelets, in the blood [11, 12]. Here, we report a case of thrombocytopenia that was observed in a case after he was readministered AKT after 3 years of medication-free interval.

Case report

A 51 year old male presented to the emergency in 2017 with rash over his extremities and trunk region including painful ulcers in the oral cavity. The patient also complained of passage of black-coloured stools. Seven days prior to this emergency admission, patient had been administered AKT2 due to clinical suspicion of pulmonary cox. AKT2 comprises of orally taken Isoniazid hydralazine 300mg, rifampicin 600mg, ethambutol 1200mg, pyrazinamide 1500 mg taken thrice weekly and injected streptomycin 750mg administered twice weekly. At the time of emergency admission patient revealed that in 2014, he had received medication for pulmonary cox for 8 months and also disclosed that he experienced no such symptoms at the time.

Physical examination showed that patient was afebrile. The blood pressure was within limits (140/80). He had no lymphadenopathy and no organomegaly. General examination showed multiple purpuric macules distributed all over chest, arms and thighs (FIGURE 1) and oral hemorrhagic erosions over buccal mucosa and lips bilaterally. On neurological examination the patient was conscious and oriented without any cognitive deficits. Similarly, cranial nerve, and motor and sensory examinations were normal. Cardiovascular and abdominal examination revealed no abnormality. Respiratory examination revealed diminished breath sounds over bilateral lower lung field and bilateral basal crepitations. CT Scan of the thorax region revealed right sided minimal pleural effusion and patchy consolidation in the right lower lobe. Nodular infiltrates noted in postero-basal segment of left lower lobe. Multiple enlarged lymphnodes were noted in pre- and paratracheal as well as prevascular region where the largest lymphnode was noted in the subcarinal region (20 x12 mm). There was no other significant finding within the thorax region.

Peripheral smear revealed normocytic hypochromic red blood cells (RBCs) with markedly reduced platelets (TABLE 1). Dengue serology (NS1 and IGM) was negative. HIV, HCV, HbsAg were nonreactive. Prothrombin time and INR were within normal limits (12 seconds and 1.02 respectively). Activated partial thromoplastin time was 25 s (20-35 s is within normal limits). Finger prick method showed bleeding time was 2 minutes and 10s (normal range is 2-7 minutes). Clotting time using Capillary method showed 4 minutes and 40s (normal range is less than 10 minutes). During the course of investigations, patient developed subconjunctival haemorrhage. C reactive protein was positive indicating acute infection.

Tentative diagnosis of thrombocytopenia was made based on platelet count of 5000/µl and haemoglobin count of 7.15gm/dl. It was suspected that the cause of these adverse events i.e., purpura and melena was a result of one of the AKT drugs i.e., Rifampicin (RFP). RFP has been reported to induce allergic responses, especially when readministered after a treatment interruption (12), hence RFP was withdrawn. Within 7 days of withdrawal of RFP, there was improvement in platelet counts as shown in Table 1.

Discussion

RFP remains a drug of choice in treating TB [2]. RFP as part of AKT is known to induce thrombocytopenia, renal failure and similar other adverse effects as noted by a number of case reports from various quarters [5-9, 14].

There are two main aspects that are notable in the current case report. First that there was no reported reaction from the first administration of the AKT; and second that within 7 days of RFP ingestion led to an acute reaction even though RFP was readministered after 3 years of medication-free interval. We can only assume that patient completed the course of AKT from the first TB episode but it is not uncommon for patients to stop the medication when they feel better [2]. Previous literature has reported adverse reaction when the RFP was administered the first time and that re-administration after a few months led to more severe reaction within a few hours [12]. There is

one paper similar to the current case study that found a 71 year old had similarly reacted when RFP was readministered 2 years after the first treatment [14]. These findings are of relevance as reoccurrence of TB is close to 10% and therefore an absence of reaction in the first instance may not be a true indication of what the reaction maybe after re-administration of RFP even if it is a few years later. In vitro assessments to detect presence of antibodies is neither easy nor sensitive [9]. Therefore, it is imperative to be aware of the previous history prior to commencing medical intervention in cases of TB and assume adverse reaction unless proven otherwise [13]. In such cases Chen et al (2017) recommend immediate drug discontinuation, supportive management and regular monitoring [7].

The question that needs to be addressed is why should there be a reaction to the drug. Researchers hypothesize that RFP with antiplatelet antibodies form an antigenic complex that interacts with blood-cell membrane proteins specifically glycoprotein Ib/IX which leads to low platelet count [14, 12, 15]. The mechanism identified here is not unique to RFP but also known with other drugs such as quinine [15].

The next question that needs to be discussed is if a causal relationship between RFP and thrombocytopenia can be verified. Literature suggests that withdrawal of the drug along with observation and platelet count is often enough to determine the association [9]. As this case developed severe purpura, the RFP had to be stopped and similar to this case, platelet infusion is possible supportive management.

In conclusion, this case report highlights the importance of the RFP-induced adverse reaction such as thrombocytopenia. TB is one of the major health concerns in India and reoccurrence of TB is equally problematic. Additionally, non-compliance to treatment regime is high, therefore, re-initiation of AKT even after a significant time lapse can increase the chances of the patient experiencing adverse reaction.

FIGURE 1. Purpura on the patient's back (A), chest (B) and leg (C)

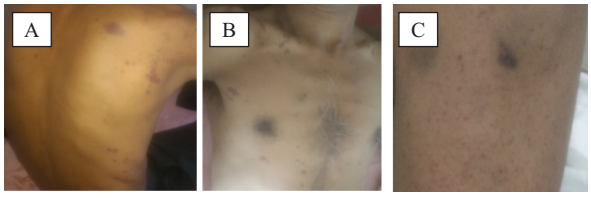

TABLE 1. Complete blood count on the day of admission to emergency (day 1) and following day RFP was withdrawn. Blood count on day 3 and then day 7 after the RFP was withdrawn

	Day 1	Day 3	Day 7
Hb % (g/dl)	6	9.08*	9.18
Erythrocyte Count (million/µl)	4.28	2.20	4.48
TLC (K/µl)	9.20	10.5	13.0
DC	N70L24M4 E2	N70L24M3 E3	N69L26M4 E1
Platelet Count (K/µl)	5,000	34,000	2,86,000
PCV %	37.3	32.4	32.5
MCV (fl)	87.2	87.7	89.4
MCH (pg)	26.7	28.5	29.7
MCHC (g/dl)	30.6	32.5	33.2
RDW (%)	15.7	13.3	16.7
Se.B12 (pg/ml)	291		
Ferritin (ng/ml)	221.94		

**2 units of packed cell volume and 4 units of platelet-rich concentrate*

HB Haemoglobin; TLC total leucocyte count; DC differential leucocyte count; PCV packed cell volume; MCV mean corpuscular volume; MCH mean corpuscular haemoglobin; MCHC mean corpuscular haemoglobin concentrate; RDW-CV Red cell distribution width

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