Rifampicin-induced disseminated intravascular coagulation: An antibody-mediated side effect

Dear Editor,

Rifampicin (RFM) remains an effective treatment of pulmonary tuberculosis. Gastrointestinal adverse effects and liver toxicity are common. However, more serious reactions such as haemolytic anaemia, acute renal failure, and disseminated intravascular coagulation (DIC) have only been rarely documented. DIC secondary to RFM is a consequence of a rare immunoallergic reaction caused by the intermittent administration of RFM. It is even more uncommon in the absence of neoplastic disease, severe infection or previous exposure to RFM. Clinical features of that reaction include fever, hypotension, abdominal pain, and vomiting within hours of ingestion. Future administration of RFM is life-threatening and is contraindicated.

The aim of this report is to describe a case of RFM-induced DIC and to perform a review of the previous reports of this uncommon finding. The *Pubmed*® database was searched for articles in English that were published between January 1990 and January 2020. We combined search terms RFM and DIC. We also manually searched the reference lists of the eligible studies.

The authors present the case of a 68-year-old man with a history of pulmonary tuberculosis diagnosed in 2007 which was reactivated in 2018. He started the treatment with RFM, isoniazid (IZD), pyrazinamide and ethambutol. Two months later, given the clinical improvement and negative acid-fast bacilli smear, he continued the treatment with RFM and IZD. However, due to gastrointestinal symptoms (nausea and abdominal pain), the patient was following treatment intermittently (on his own initiative).

After one week of interruption, the patient returned to the treatment with RFM and IZD. One hour after, he was admitted to the Emergency Department because of a sudden onset of dyspnoea, nausea, and abdominal pain. He was in respiratory distress, febrile, hypotensive, and tachycardic. The laboratory analysis revealed low platelets (28,000/μL) and d-dimer elevation (43,290 ng/ml) – Table 1.

Six hours after the RFM intake, the patient presented haemorrhagic dyscrasia with hemoptoic sputum, bleeding through the vascular accesses, haematuria, and haematochezia. The analytical study was compatible with DIC, showing low platelets (38,000/μL) and prolonged prothrombin time (PT) 37.8 s; a prolonged activated partial thromboplastin time (APTT) 81.1 s, and a very low fibrinogen level (not measurable) – Table 1. Chest angio-CT scan excluded pulmonary embolism and it revealed a ground-glass opacity infiltrate in the right lower lobe suggestive of inflammatory/infectious process.

DIC secondary to probable septic context, due to community-acquired pneumonia, was assumed. Samples were collected for cultural exams and ceftriaxone was initiated. The patient was admitted to the Intensive Care Unit (ICU).

During his stay in ICU, the patient presented good clinical and analytical recovery. On the 10th day of hospitalization, given the stability, the patient returned RFM. The analytical study (prior to RFM intake) showed no relevant changes – Table 1. Two hours after taking RFM, the patient started having nausea and abdominal pain. Five hours after RFM, a new episode of haemorrhagic dyscrasia was seen with hematemesis, bleeding through the vascular accesses and macroscopic haematuria. Hypotension refractory to fluids and vasopressor support was documented. Six hours after the RFM intake the patient presented cardiorespiratory arrest and death. Analytical study showed acute decrease in haemoglobin level (5.2 g/dL) and DIC criteria with low platelets (21,000/μL), coagulopathy (PT 26.8 s; APTT 79.9 s; low fibrinogen 157 mg/ml) and d-dimers elevation (65236 ng/ml) – Table 1. *Post mortem* study revealed anti-RFM positive antibodies (IgM and IgG) in the patient's serum.

The adverse effects of RFM, include IgE-mediated allergic reactions like rashes, mild gastrointestinal disorders, hepatotoxicity, and drug interactions.[1] In contrast, intermittent intake of RFM can produce more serious adverse effects induced by immunoallergic reactions mediated by IgG and IgM antibodies against erythrocytes, platelets and other target cells expressing blood antigen I, including renal tubular epithelial cells.[2] Clinical manifestations of these reactions begin within hours after the ingestion of RFM and include vomiting, abdominal pain, fever, and hypotension. Diagnostic investigations generally reveal the presence of renal dysfunction, intravascular haemolysis, and DIC. The review of the existing literature identified only 13 previously reported cases of RFM-induced DIC[2–4]; this is the 14th case described (Table 2).

In the case reported, as in 3 cases before, the fact that sepsis is a common source of DIC made diagnosis difficult.[2] This led to the re-exposure to RFM with a new episode of DIC and a fatal outcome. 3 other fatal cases have already been documented.[2] The prior treatment with RFM, the temporal association between the two episodes of DIC and the RFM intake, as well as the absence of new episodes after its interruption, pointed to the causal role of the drug in the case described. The suspicion was confirmed post mortem by the detection of anti-RFM IgG and IgM antibodies in the patient's serum. However, DIC due to RFM is a clinical diagnosis and it has been confirmed by antibodies in only two cases before.[5,6] The present case is intended to draw attention to a rare side effect of a commonly used drug.

Table 1 Laboratory data. Evolution of two DIC episodes.

Variable	Reference range, adults, this hospital[a]		1st episode of DIC					10th day (ICU)		2nd episode of DIC		
			1 h		6 h					2 h	5 h	
Haemoglobin (g/dL)	14.0–18.0	RFM	Sudden onset dyspnoea, nausea, and abdominal pain	13.7	Haemorrhagic dyscrasia	11.6	Recovery	8.5	RFM	Non-specific malaise, nausea, and abdominal pain	Haemorrhagic dyscrasia	5.2	Death
Platelets (/μL)	150–400,000			28,000		38,000		573,000				21,000	
PT (s)	9.4–13.4			11.9		37.8		15.3				26.8	
APTT (s)	24.0–37.0			28.8		8.1		30.2				79.9	
Fibrinogen (mg/mL)	200–400			–		Very low (not measurable)		981				157	
D-dimers (ng/mL)	0–250			43,290		-		1403				65,236	

[a] Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used in Hospital do Divino Espírito Santo, Ponta Delgada; are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Table 2 Cases of RFM-induced DIC previously described in the literature.

Author	Study design	Case no. Author	Age (years)/gender	Diagnosis	Dosage	Prior exposure	Time to development of DIC	Clinical features	Outcome
Havey et al.[2]	Case report and review	1. Brasil et al.[2]	NA/M	L	600 mg/month	Yes	3 doses	NA	Death
		2. Denis et al.[2]	48/F	T	600 mg/day	NA	5 months	Fever, jaundice, vomiting, diarrhoea	Recovery
		3. Fujita et al.[2]	43/M	T	450 mg/day	NA	7 days	Bleeding	Recovery
		4. Ip at al.[2,5]	29/F	T	600 mg, three times a week	Yes	6 months	Fever, hypotension, vomiting, oliguria, pruritis	Recovery
		5. Luzzati et al.[2,6]	35/M	T	600 mg/day	Yes	1 dose	Fever, rash, hypotension, abdominal pain, vomiting, myalgias	Recovery
		6. Namisato and Ogawa[2]	64/M	L	600 mg/month	Yes	3 doses	Fever, hypotension, facial oedema, vomiting, abdominal pain	Recovery
		7. Nowicka et al.[2]	53/F	T	450 mg; dosing schedule unclear	Yes	3 doses	Lumbar and abdominal pain, anuria	Death
		8. Souza et al.[2]	46/F	L	600 mg/month	Yes	3 doses	Fever, haematuria	Death
		9. Havey et al.[2]	66/F	B	600 mg/month	Yes	6 doses	Fever, hypotension, vomiting, abdominal pain, oliguria	Recovery
Sadanshiv et al.[3]	Case report and review	10. Costiniuk et al.[3]	20/F	T	600 mg/day	Yes	3 weeks	Renal failure, non-bloody diarrhoea, hypotension, vomiting, decreased urine output, haemolysis	Recovery
		11. Soltani et al.[3]	71/F	B	600 mg/day	No	7 days	Renal failure, haemolysis, abdominal pain, vomiting, jaundice, decreased urine output	Recovery
		12. Sadanshiv et al.[3]	50/F	L	600 mg, single dose	Yes	1 day	Renal failure, haemolysis, dark-coloured urine, jaundice, fever, vomiting, decreased urine output	Recovery
Chen et al.[4]	Case report	13. Chen et al.[4]	22/M	T	450 mg/day	Yes	7 days	Epistaxis, haematochezia, haematuria, purpura, jaundice	Recovery
14. Present case			68/M	T	600 mg/day	Yes	3 months	Fever, hypotension, abdominal pain, haemolysis, hemoptoic sputum, bleeding through the vascular accesses, haematuria, haematochezia	Death

T – tuberculosis; B – brucellosis; L – leprosy; NA – not available.

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References

1. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5:231–49.
2. Havey TC, Cserti-Gazdewich C, Sholzberg M, Keystone JS, Gold WL. Recurrent disseminated intravascular coagulation caused by intermittent dosing of rifampicin. Am J Trop Med Hyg. 2012;86:264–7.
3. Sadanshiv M, George AA, Mishra AK, Ajay Kuriakose CK. Rifampicin-induced immune allergic reaction. Trop Doctor. 2017;48:156–9.
4. Chen G, He J. Rifampicin-induced disseminated intravascular coagulation in pulmonary tuberculosis treatment. Medicine. 2017;96:6135.
5. Ip M, Cheng K, Cheung W. Disseminated intravascular coagulopathy associated with rifampicin. Tubercle. 1991;72:291–3.
6. Luzzati R, Giacomazzi D, Franchi F, Barcobello M, Vento S. Life-threatening. Multiple hypersensitivity reactions induced by rifampicin in one patient with pulmonary tuberculosis. Southern Med J. 2007;100:854–6.

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A PI*MS is not always a PI*MS. An example of when genotyping for alpha-1 antitrypsin deficiency is necessary

Dear Editor,

Alpha-1 antitrypsin (AAT) is a serum glycoprotein with functions which include neutrophil elastase inhibition in the lung (protecting it from destruction and emphysema), and antioxidant, anti-inflammatory, anti-infectious and immunomodulation effects. Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant disease and is considered one of the most frequent hereditary disorders; however, its epidemiology remains partially unknown owing to underdiagnosis.[1] At least 60 deficient proteinase inhibitor* (PI*) alleles have been described, the most common being PI*S (5%–10% in Caucasians) and PI*Z (1%–3%), which are associated with reduced serum AAT levels of 40 an escalation plan and ceilings care and 10%–20%, respectively. PI*ZZ is the most frequent genotype (95%) among individuals with severe deficiency.[2] Previous studies suggest that some areas of Portugal may have a very high frequency of deficient variants.[3] Other deficient variants (non-S, non-Z) are considered as ''rare'' because of their low frequency, they cannot be identified by the usual allele-specific genotyping methods and cannot always be characterized by isoelectrofocusing (IEF) for phenotyping; therefore they can only be detected by molecular biology techniques, such as genome sequencing.[4] Consequently, in cases with discordant plasma and phenotype results, it is important to continue diagnostic assessment since the identification of a severely deficient genotype supports the possible indication of augmentation therapy and the need for family screening.[1]

The PI*M_{Malton} variant is a rare deficient variant that differs from the normal M allele by deletion of the entire codon (TTC) for the residue Phe at position 51/52 (exon II). It is associated with severely reduced plasma AAT levels and hepatic inclusions by polymers and is characterized by a normal isoelectrophoretic pattern, which may be confounded with a normal M protein on IEF.[4]

Information about the frequency of rare alleles in Portugal is scarce. In a previous study including 1864 subjects, 9.5% of the AATD cases were related to a rare allele and null variants.[2] The majority of rare alleles (n = 64; 15.3%) corresponded to PI*M_{Malton} and PI*$M_{Palermo}$, including n = 16 PI*SM_{Malton} (3.8% of the individuals with AATD). However, the study sample might not be representative of the whole country, because most of the samples had been collected in the North and Central regions of Portugal.

Similarly, the PI*M_{Malton} variant is considered to be the second cause of severe AATD in Spain. A study including 3511 subjects over 12 years showed 1.6% of rare AAT variants, with PI*I (34%) and PI*M_{Malton} (20%) being the most frequent, accounting for 54% of all rare variants.[5] PI*M_{Malton} allele was also very common among the rare variants in other countries: 60% in Tunisia, 35% in Italy (particularly in Sardinia), and 8% in Switzerland. However, it has not been found in Finland, and is rare in Ireland.[4,5]

Augmentation therapy is indicated in severely deficient patients (AAT serum levels < 57 mg/dL) associated with deficient genotypes, including PI*SZ.[1] Since M_{Malton} is associated with levels similar to the Z variant, patients with genotypes such as PI*$M_{Malton}M_{Malton}$, PI*ZM_{Malton}, PI*SM_{Malton} and PI*NullM_{Malton} may be candidates for augmentation therapy. Therefore, it is crucial to identify these genotypes in patients with clinical manifestations, low AAT serum levels and inconsistent phenotypes on IEF.

We had the opportunity to treat the case of a 57-year-old man, ex-smoker of 40 pack-years, with severe chronic obstructive pulmonary disease (COPD) and extensive emphysema on computed tomography scan. He was diagnosed with severe AATD due to a serum AAT level of 46 mg/dL and ful-