

## CASE REPORT

# Thrombotic Microangiopathy in Interferon-beta-Treated Multiple Sclerosis Patient

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## Abstract

A 43-year-old man who was treated with interferon-beta for multiple sclerosis was presented with hypertension, headache, nausea/vomiting, blurred vision, and renal dysfunction. The treatment with drugs and dialysis relieved the symptoms. Despite plasmapheresis is known to cause improvement in renal function, no such improvement was seen in patient.

## KEYWORDS

interferon-beta, multiple sclerosis, thrombotic microangiopathy

## 1 | INTRODUCTION

Drugs are among the most common causes of primary thrombotic microangiopathy (TMA), previously known as thrombotic thrombocytopenic purpura. It is caused by the formation of thrombi in small vessels, especially arterioles or capillaries. Drug-related TMA might have an immunological or toxicity-related origin. The latter is known as a toxic dose-related TMA.<sup>1</sup> Clinical reports have shown toxic dose-related TMA can be a result of IFN in patients with multiple sclerosis (MS).<sup>2-5</sup> Clinical manifestations include microangiopathic hemolytic anemia and thrombocytopenia due to the accumulation of platelets in microthrombi. Organ injuries, such as that of the kidney, are also reported. Neurologic involvement in IFN- $\beta$ -induced TMA is prevalent, presented by headache,

seizures, and impairment of the vision. Therapeutic plasma exchange, plasmapheresis, is a known treatment for renal dysfunction and hypertension.<sup>6,7</sup>

In this paper, we report first MS patient taking Recigen (an Iranian made IFN- $\beta$ 1) in Iran who was presented with TMA. Despite enough therapeutic measures, no improvement in the renal function was seen.

## 2 | CASE REPORT

A 43-year-old man was referred to the emergency department with a 17-year history of MS, for which he was treated with interferon-beta. The course of the treatment included the intake Avonex for 9 years, followed by Recigen for 8 years.

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TABLE 1 Patient's laboratory data

	On admission to ward (20/1/2016)	At starting dialysis (every other day) (24/1/2016)	At starting plasmapheresis (every other day) (30/1/2016)	At starting plasmapheresis (everyday) (7/2/2016)	After finishing plasmapheresis (13/2/2016)	At discharge (18/2/2016)	First follow-up (17/3/2016)	Second follow-up (9/4/2016)
BP	180/100	200/110	180/100	160/100	150/90	150/90	150/90	150/90
U/O	3500	3200	3200	2100	600	250	100	50
WBC	9300	9300	4700	5100	4400	4000	5400	7700
Hb	6.9	7.2	7.7	7.2	7.7	9	9.1	8.8
MCV	90	89	90.5	91	95	91	89	90
Plt	41 000	118 000	114 000	89 000	93 000	90 000	210 000	236 000
Urea	111	141	74	99	80	75	71	89
Cr	4.94	6.55	5.95	5.46	5.52	5.23	8	11
Retic index	5			2.2		1.3		
LDH	3557	1020	1037	591	558	607	470	530
Bill T(D)		1.1 (0.3)	1.4 (0.4)	1.4 (0.4)	1.38 (0.32)	1.37 (0.32)	1.2 (0.2)	1.3 (0.2)
PTT	30.6	26	25.9	25	27.1	25	24	30
PT	13.4	13.2	13.4	13	13.9	12	13	13.5
INR	1	1.1	1	1.1	1.03	1	1	1.01
PBS	Many schistocytes + echinocyte + anisocytosis			Few schistocytes + echinocyte + anisocytosis				

Abbreviations: Bill T(D), bilirubin total and direct; Cr, creatinine; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PBS, peripheral blood smear; Plt, platelet; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

At the time of referral, he was presented with severe headache, nausea, vomiting, and blurred vision. During the first evaluation, blood pressure (BP) was 230/130; however, both optic disks were sharp, and the remainder of the physical examination was normal. Elevation in the creatinine levels was detected from the laboratory findings along with thrombocytopenia and anemia. Several schistocytes were seen in the peripheral blood smear (Table 1). Renal sonography was unremarkable.

The patient was admitted to the ICU with the diagnosis of drug-induced TMA. Four plasmapheresis sessions were conducted using centrifugal cell separator with 14:1 ratio of whole blood/anticoagulant. The flow rate of plasma was 30 mL/min which was then adjusted to 120 mL/min, and ionized calcium was monitored every 15 minutes. He received 1 plasma volume with 5% albumin and fresh-frozen plasma (FFP) to perform 100% replacement.

After the partial improvement in the symptoms and recovery from the malignant hypertension, the patient was transferred to the general ward. His was 110/180, whereas headache and blurred vision had substantially improved. The patient underwent corticosteroid plus triple antihypertensive therapy. After 4 days, due to no improvement in serum creatinine levels and persistent hypertension, dialysis (thrice per week) was started. Owing to persistent hemolysis and evidence of disease activity, plasmapheresis for an alternate day was restarted where, after 7 days of continuous plasmapheresis, hypertension was controlled, lactate dehydrogenase (LDH) and retic index decreased, and anemia and thrombocytopenia improved substantially. Additionally, schistocyte count was also reduced in a peripheral blood smear. Also, rituximab was prescribed for the patient according to the standard protocol. The patient was discharged with a plan of dialysis, thrice a week, since there was no improvement in the serum creatinine levels. During the 2 months of follow-up, there was no evidence of hemolysis, but kidney function showed no significant improvement (Table 1).

### 3 | DISCUSSION

Here, we reported a patient with MS who was under a long-term interferon-beta treatment and was presented with thrombotic microangiopathy. A large number of studies have reported adverse effects of interferon-alpha,<sup>8-10</sup> but only a few number of cases are reported concerning interferon-beta.<sup>2-5,11</sup> Allinovi et al<sup>12</sup> reviewed three cases of long-term interferon-beta-induced TMA. They reported that these patients were presented with chronic kidney disease and malignant hypertension that were successfully treated with eculizumab. Similarly, a case report of a 41-year-old man who was taking interferon-beta for 10 years has also been reported. He

was also presented with headache, nausea, hypertension, vision dysfunction, and kidney dysregulation. Moreover, he was also diagnosed with posterior reversible encephalopathy syndrome.<sup>13</sup> Some of the significant findings in these patients include severe hypertension, hematological anomalies, and renal dysfunction.<sup>14</sup> To it, high blood pressure has also been reported to be accompanied by Raynaud phenomenon in some cases.<sup>15</sup> The patient reported in this study was also presented with the similar symptoms but Raynaud syndrome. To it, renal toxicity can be serious and irreversible complication.<sup>15</sup> Plasma exchange, corticosteroids, and monoclonal antibody-based treatment are known to produce favorable outcomes in these patients.<sup>16</sup> The underlying mechanisms of this reaction are not fully understood, but there are some proposed hypotheses, such as low ADAMTS 13 activity or background mutations in complement regulatory factors (Factor H, Factor I, etc), in patients receiving interferon. Endothelial injury caused by dysregulation of complement activity or inhibition of vascular endothelial growth factor, induced by interferon, also can be related to TMA.<sup>2-3,5,11</sup> The renal outcomes in these patients vary from complete recovery to end-stage renal disease.<sup>3,5,11</sup> Unfortunately, our case did not show any improvement in the kidney function, 2 months following the regular dialysis. The differential diagnosis included TMA and malignant hypertension. Due to TMA, the patient was not the potential candidate for a kidney transplant, owing to the odds of the dysregulation of the complement system. To our knowledge, this is the first report of thrombotic microangiopathy due to interferon-beta usage in Iran. The notable late onset of TMA, in this case, is the indicator of the cumulative effect of the drug on the renal vessels. However, we did not carry out genetic testing to determine any mutations. Furthermore, biopsy was also not ordered due to severe thrombocytopenia. The case has been reported to the drug manufacturing company and is going to be mentioned in the drug pamphlet.

### 4 | CONCLUSION

Since TMA can occur after long-term drug tolerance, symptoms such as headache and hypertension should be carefully monitored. This case, in addition to the previous reports, confirms the effects of interferon-beta on thrombotic microangiopathy and heralds more attention to the serious adverse effects of this drug, such as on renal system, which can be subsided by early measures like plasmapheresis and corticosteroid therapy.

### CONFLICT OF INTEREST

The authors deny any conflict of interest in any terms or by any means during the study. All the fees provided by research center fund and deployed accordingly.

## AUTHOR CONTRIBUTIONS

MMM and ZA: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; RA: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript; MAS: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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