Case Report

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Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in relapsing-remitting multiple sclerosis patients on high-dose interferon β

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Abstract

Three women aged 34–47 years old, on high dose interferon beta-1a for relapsing–remitting multiple sclerosis, were hospitalized between 2009–2012 for thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Patients sought medical attention for neurological symptoms including cephalalgia, blurred vision, confusion, focal deficits and seizures. All patients presented thrombocytopenia, hemolytic anemia and arterial hypertension. Despite plasma exchanges, corticosteroids and anti-CD20 treatments, all patients progressed towards severe renal insufficiency and one patient died of hemorrhagic shock. In this report we identify a rare but morbid complication of interferon beta-1a treatment associated with female gender, Caucasian background and low body mass index.

Keywords

Multiple sclerosis, interferon beta, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, thrombocytopenia, hemolytic anemia, renal insufficiency

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Introduction:

Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal insufficiency, neurologic impairment and fever.[1] Treatment of TTP-HUS involves immediate initiation of plasma exchange (PLEX),[2] combined with corticosteroids. For refractory TTP-HUS, anti-CD20 therapy (rituximab), cyclophosphamide, vincristine or cyclosporine may be considered.[1]

Acquired TTP-HUS has been associated with bloody diarrhea, pregnancy, autoimmune disorders, complement dysregulation, drug toxicity, or with the presence of autoantibodies against ADAMTS-13,[1,3,4] but not with multiple sclerosis (MS). Here we report three cases of TTP-HUS in relapsing–remitting (RR) MS patients undergoing interferon beta-1 (IFNβ1a) therapy.

Patient 1: A 34-year-old woman was evaluated for recent onset of confusion and left hemiparesis/hemineglect. She reported decreased energy, global weakness and frontal headache for the last few days. Fever, arterial hypertension, tachycardia and mild desaturation were noted on admission. Chest X-ray was compatible with acute respiratory distress syndrome (ARDS), and cerebral computed tomography (CT) showed diffuse white matter vasogenic edema in the right hemisphere and a left parietal white matter hypodensity. Thrombocytopenia and hemolytic anemia

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Table 1. Patient baseline characteristics and symptoms at presentation.

	Patient 1	Patient 2	Patient 3
Gender	Female	Female	Female
Ethnic background	Caucasian	Caucasian	Caucasian
Age (years)	34	47	41
Height (cm)	147	163	152
Weight (kg)	40.8	54	44
BMI	18.9	20.3	19.0
RRMS duration (years)	9	13	12
EDSS prior to hospitalization	3.0	2.0	4.0
Other medical conditions	Amblyopia, anxiety	Asthma, minor depression	Nasal polyps, migraine
Previous RRMS medication	Glatiramer acetate	None	IFNβ1a 22 µg tiw
Active RRMS medication	IFNβ1a 44 µg tiw	IFNβ1a 44 µg tiw	IFNβ1a 44 µg tiw
IFNβ1a treatment duration (months)	14	132	60
Other concurrent medication	Venlafaxine	Oral contraceptive, multivitamin	Nabilone, gabapentin, baclofen, celecoxib
Symptoms/signs at presentation			
Cephalalgia	Yes	Yes	Yes
Blurred vision	Not documented	Yes	Not documented
Confusion	Yes	No	Yes
Focal deficits	Left hemiparesis	No	Right UE > LE paresis
Seizures	No	No	Yes
Body temperature	Transient fever (38.5°C)	Normal	Transient fever (38.8°C)
Blood pressure (mm Hg)	195/120	187/107	170/80
Others	Fatigue, weakness, cervicalgia, dyspnea	Left otalgia, papillary edema	GI complaints, nausea, vomiting, cough
Laboratory data on admission			
Platelet count (per mm³) *Ref: 140000–450000*	71000	112000	66000
Hemoglobin (g/l) *Ref: 120–160*	100	93	112
Schistocytes *Ref: none*	2+	2+	3+
LDH (U/l) *Ref: 104–205*	3709	995	1806
Creatinine (µmol/l) *Ref: 42–89*	79	350	87

BMI: body mass index; IFNβ1a: interferon beta-1a; ref: reference values; RRMS: relapsing–remitting multiple sclerosis; EDSS: expanded disability status scale; tiw: three times in a week; GI: gastrointestinal; UE: upper extremity; LE: lower extremity; LDH: lactate dehydrogenase.

(Table 1), but normal coagulogram and creatininemia were found. Patient was intubated, PLEX, intravenous (IV) corticosteroid treatments and broad-spectrum antibiotic therapy were initiated. All previous medications including IFNβ1a were discontinued. The fever abated rapidly and blood pressure remained around 160/100. After seven days the cerebral CT scan showed improvement of edema and better definition of hypodense lesions in the right corona radiata and the centrum semi-ovale. The patient was able to follow simple commands. However, fluctuating thrombocytopenia (nadir 35000) and hemolytic anemia persisted, while creatininemia steadily increased to 332 µmol/l. In addition to twice daily PLEX and IV corticosteroids, the patient received two courses of vincristine and one of rituximab during the first 14 days. Improvement of platelet count and hemolytic anemia were finally observed on day 14. Drainage of a pleural effusion on day 14 led to hemorrhagic complication, ultimately leading to fatal hemorrhagic shock.

Patient 2: A 47-year-old woman was evaluated for headache, blurred vision and left otalgia. Ophthalmological examination demonstrated optic nerves edema and hypertensive retinopathy. Blood pressure was 187/107. Patient was hospitalized for diagnostic workup, which revealed elevated creatininemia, mild proteinuria, low platelet count and hemolytic anemia (Table 1). The coagulogram was normal. Antihypertensive therapy, PLEX and methylprednisolone were started. Ultrasound study ruled out renal artery stenosis

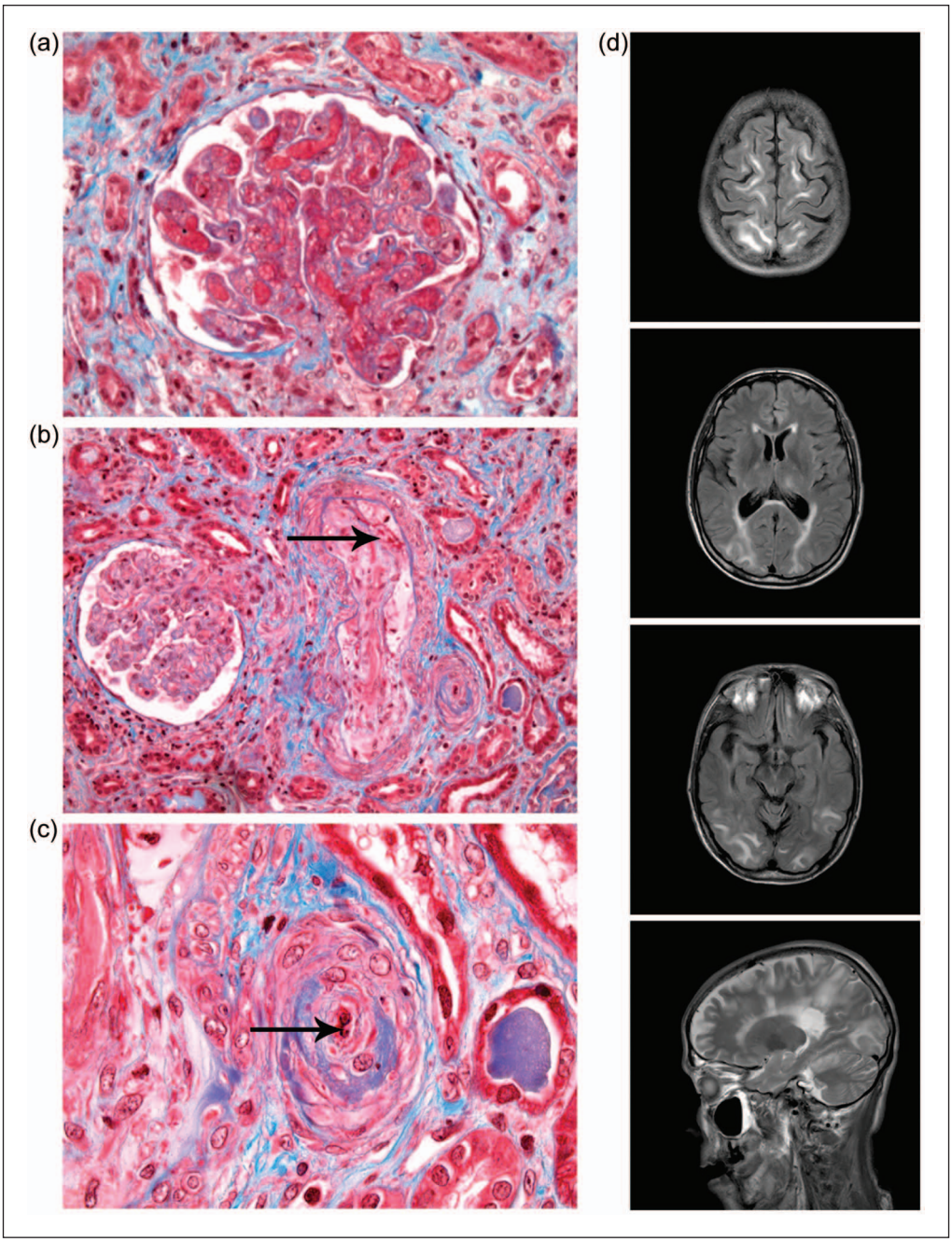

Figure 1. Masson's trichrome stain of material from renal biopsy specimen (patient 2). (a) Thrombotic microangiopathic glomerulopathy with remodeled glomerular basement membrane and highly congested capillary lumen with possible microthrombi, magnification 400×; (b) striking intimal mucous edema with scattered extravasation of fragmented red blood cells, arrow: fibrinoid material, magnification 100×; (c) typical "onion skin" aspect of the vascular wall leading to vascular occlusion with the presence of intraluminal fibrinoid material (arrow), magnification 400×; (d) fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (patient 3). Axial (top three) and sagittal (bottom) images demonstrating typical chronic multiple sclerosis (MS) lesions and confluent multiple bilateral hyperintense subcortical white matter lesions in a predominantly posterior distribution (occipito-parietal), compatible with vasogenic edema, suggesting a diagnosis of posterior reversible encephalopathy syndrome (PRES) in this relapsing–remitting (RR) MS patient.

and rheumatologic workup was entirely negative. Cerebral CT scan demonstrated no acute lesion. Over the next days platelet count, anemia, blood pressure and ophthalmologic findings improved, however creatininemia continued to rise up to 566 µmol/l. A renal biopsy was performed (Figure 1(a)–(c)). The final pathologic diagnosis was HUS. After more than a

year of dialysis, the serum creatinine has improved and stabilized to 230 μmol/l (stage 4 chronic kidney disease). The patient is now neurologically stable on glatiramer acetate.

Patient 3: A 41-year-old woman was admitted for a generalized tonic-clonic seizure. The patient was complaining of worsening headache, mild cough with clear secretions and gastrointestinal discomfort for the previous week, without diarrhea. Family also noted recent mild confusion and worsening of upper extremity weakness. The patient was intubated and received acyclovir, vancomycin, ceftriaxone and phenytoin. All previous medication including IFNβ1a was discontinued. The lumbar puncture and cerebral CT scan were normal. Blood analysis demonstrated thrombocytopenia, microangiopathic hemolytic anemia and mildly elevated creatininemia (Table 1), in the context of a normal coagulogram and fibrinogen. Rheumatologic workup was negative. A cerebral magnetic resonance imaging (MRI) was compatible with a posterior reversible encephalopathy syndrome (PRES) (Figure 1(d)). An echocardiogram showed an adrenergic stress cardiomyopathy. Platelet count and hemolytic anemia parameters improved over two weeks of daily PLEX. By day 14, MRI was markedly improved and cardiac left ventricular dysfunction had resolved. Creatininemia levels steadily increased up to 350 μmol/l over a month, despite the addition of prednisone and rituximab. Renal biopsy demonstrated changes compatible with thrombotic microangiopathy. The patient subsequently started hemodialysis for chronic renal insufficiency. The patient has now resumed her usual activities but is still hemodialyzed. ADAMTS-13 functional dosage, performed after two days of PLEX, was within the reference range at 0.8 U/ml.

Discussion

Case reports of multiple sclerosis patients developing TTP-HUS are few in the literature (four cases retrieved from Pubmed and ISI Web of Knowledge), and all were on IFNβ therapy.[5–8] Taking into consideration the three patients reported herein and the four patients reported in published case-reports, all seven cases of TTP-HUS seen in MS patients seem to have occurred in women (7 of 7) receiving IFNβ1a therapy (6 of 6, one not specified) and of Caucasian origin (4 of 4, three not specified). Up to now, TTP-HUS has not been reported in males affected by MS, nor in untreated MS females or in females taking MS medication other than IFNβ. Although the sample size is limited, female gender and IFNβ therapy seem to be the only risk factors associated with the development of TTP-HUS in MS patients. This is not surprising given that TTP-HUS is more frequent (a) in women, (b) in patients affected with autoimmune diseases and (c) that IFNβ has been associated with onset or exacerbation of other antibody-mediated autoimmune disorders, especially in women.[1,8–10] ADAMTS-13 levels were normal in the only patient tested, similar to cases of drug-induced TTP-HUS from the Oklahoma registry.[3] Complement factor H autoantibodies[4] were not measured in our cohort.

We can only speculate why our patients developed TTP-HUS more than one year following IFNβ1a initiation. Abnormal von Willebrand factor (vWF) release or emergence of autoantibodies against ADAMST-13 or Complement H could have been triggered by environmental factors in combination with IFNβ treatment. Interestingly, the body mass index of our three patients was low. Although speculative, this could suggest a form of dose-related toxicity of IFNβ in women of low body mass index. We cannot exclude a role of cumulative IFNβ1a toxicity on endothelium on the development of TTP-HUS and this observation raises questions about the concept of a single dose approach for the treatment of MS.

Finally, IFNβ-induced TTP-HUS is associated with severe renal involvement (7 of 7) frequently progressing toward renal failure (4 of 6 survivors requiring dialysis). Neurological involvement was frequently seen (5 of 7) and hemorrhagic complications occurred in 2 of 7 patients, leading to fatal hemorrhagic shock in one case.

Conclusion

As prompt diagnosis and treatment initiation are crucial, it should be recognized that although rare, TTP-HUS with severe renal insufficiency and frequent neurological involvement can be a life-threatening complication of IFNβ therapy in Caucasian female MS patients of small stature. The medical consequences of this under recognized complication of IFNβ therapy are important, especially as the currently accepted treatment for TTP-HUS was only partially effective and did not prevent terminal renal failure.

Conflicts of interest

The authors declares that there are no conflicts of interest.

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