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Interferon-β1a-Induced Thrombotic Microangiopathy: Possible Implication of the Alternative Pathway of the Complement

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INTRODUCTION

Thrombotic microangiopathy (TMA) is a systemic disorder characterized by either thrombotic or nonthrombotic microvascular lesions, leading to microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ involvement.[1] Atypical hemolytic uremic syndrome is characterized by a deficient regulation and therefore an hyperactivation of the alternative pathway of the complement leading to endothelial injury.[1,2] More than 50% of patients with atypical hemolytic uremic syndrome have a proved mutation in the alternative pathway of the complement regulatory genes or other noncomplement related genes.[1,2] Many drugs have been associated with TMA in the literature (Table 1[1,2,S1]). The causal relationship is however uncertain for many drugs because this complication is rare and can appear many years after the initiation of the drug and therefore cannot be accessible for randomized trials.[3] Drug-mediated TMA can be immune mediated or secondary to direct endothelial cell toxicity.[4] The latter mechanism seems to be implicated in interferon beta-1a (IFN β-1a)–associated TMA.[5] Interferon-beta1a is an immune-modulating agent widely used as a first-line treatment for relapsing–remitting multiple sclerosis.[6]

CASE PRESENTATION

A 48-year-old male was admitted to the emergency department for focal epileptic seizure. His medical history included a 13-year history of relapsing–remitting multiple sclerosis, treated with IFN β-1a (Avonex, Biogen, Netherlands) 30 μg weekly at diagnosis time and increased to another IFN β-1a (Rebif, Merck, Europe) at the dose of 44 μg, thrice weekly after a few years because of the persistent activity of the disease. He was also treated with levetiracetam 500 mg twice daily for secondary epilepsy. Blood pressure level was normal and physical examination result was unremarkable. Laboratory findings and urine analysis at the admission and 1 month before admission are found in Table 2. Renal biopsy result revealed severe TMA lesions at light and electron microscopy, with negative immunofluorescence staining (Figure 1a-d and Supplementary Figure S1). *ADAMTS13* activity was normal, and no Shigatoxin was found in the stool and urine. Complement system analysis revealed an elevated factor B and factor Bb with a normal FBb to Fb ratio. SC5b-9 was also elevated (Supplementary Table S1). Genetic workup did not find a mutation for regulators of the ACP.

Because IFN-mediated TMA was highly suspected, its administration was withdrawn and was followed by rapid spontaneous resolution of hemolytic microangiopathic anemia and thrombocytopenia within 2 days. No plasma exchange was required and no eculizumab was administered in the setting of secondary TMA. Renal function continued to decline. After 10 days of admission, the patient developed oliguria with severe hypervolemia requiring initiation of

Table 1. Etiologies of secondary TMA[1,2,S1]

Infectious	HIV
	Hepatitis A, C
	Influenza H1N1
	CMV
	EBV
	Pneumococcus (positive direct Coombs test)
	COVID-19
Neoplasia	Paraneoplastic syndrome (antifactor H antibodies)
Systemic or autoimmune	Systemic lupus erythematous
	Scleroderma
	Antiphospholipid syndrome
	C3 nephropathy
	IgA nephropathy
	Malignant hypertension
Drug induced	Mitomycin
	Gemcitabin
	Calcineurin inhibitor
	Anti-VEGF
	Quinin
	Ticlopidin
	Interferon alpha and beta
	Cocaine
	Estroprogestative
Metabolic disease	Cobalamin C deficiency
Post transplantation	Stem cell transplantation
	Organ transplantation
	Renal transplantation
Pregnancy	HELLP syndrome/pre-eclampsia
	Pregnancy related

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzymes, low platelet count;VEGF, vascular endothelial growth factor.

Table 2. Blood and urine analysis at admission

Parameters	Admission values	1 mo before the admission	Normal values
Blood analysis			
Hemoglobin (g/dl)	7.0	11.2	13–18
MCV (fl)	90	89	80–100
Thrombocytes/μl	148,000	182,000	150–440,000
Leucocytes/μl	16,060	8000	3500–11,000
CRP (mg/dl)	1.3	10	<5
PT (%)/aPTT (s)	120/23.7	Missing value	70–100/21.6–28.7
Fibrinogen (mg/dl)	486	Missing value	150–400
Urea (mg/dl)	63	19	17–48
Creatinine (mg/dl)	2.94	1.1	0.7–1.2
K/HCO_3 (mmol/l)	4/21	3.7/3.8	3.5–4.5/23–29
LDH (UI/l)	918	199	135–225
Haptoglobin (mg/dl)	<10	Missing value	30–200
Schistocytes (per 1000 erythrocytes)	25/1000	Missing value	<10/1000
Urine analysis			
Proteinuria (g/g de creatinine)	5.6	<0.3	<0.3
Albuminuria (mg/g de creatinine)	3900	<30	<30
Erythrocytes/μl	28	Missing value	<12
Leucocytes/μl	<10	Missing value	<10
Pathologic cylinders	Presence	Missing value	Absence
Urea ER (%)	42.5	Missing value	<35
Sodium ER (%)	2.8	Missing value	<1

aPTT, activated partial thromboplastin time; CRP, C-reactive protein; ER, excretion ratio; HCO_3, bicarbonate; K, potassium; LDH, lactate dehydrogenase; MCV, mean corpuscular volume (femtoliters); PT, prothrombin time.

hemodialysis. Supplementary Figure S2 reveals the evolution of renal function and hemolytic microangiopathic anemia parameters. No relapse of TMA was observed during the next 5 months of follow-up. His renal function slowly recovered, and hemodialysis was stopped after 2 months with persistence of a chronic kidney disease stage G3b (estimated glomerular filtration rate 31 ml/min per 1.73 m^2 according to Chronic Kidney Disease-Epidemiology Collaboration). The patient experienced 2 other episodes of generalized seizures during the follow-up and died because of a pulmonary septic shock.

DISCUSSION

Our patient presented classical biological and histologic TMA. Histologic findings are not specific and therefore cannot help for differential diagnosis.[1] IFN-mediated TMA is a well-known but rare entity, first described with type I alpha-IFN. IFN β-1a–mediated TMA was first described in 1998,[7] and approximately 30 cases have been reported since then. On the basis of limited case reports and case series in literature, IFN β-1a–mediated TMA occurs after several years of a well-tolerated treatment (mean duration of 11 years), as in our patient.[3] It is also more frequent in women and occurs mostly in young adults (mean age of 39 years old). There are no guidelines for the treatment of IFN β-1a–mediated TMA. Withdrawal of the drug is key. Plasma exchange and corticosteroids are often used with poor renal outcome.[3,8] Approximately 20% of patients will recover with normal renal function, approximately one-third will experience chronic kidney disease, and approximately 40% will have end-stage renal disease.[8]

Kavanagh *et al.*[9] investigated the causal relationship between IFN β-1a and TMA. First, in a cohort of patients treated with IFN β-1a for relapsing–remitting multiple sclerosis, there were significantly higher weight-adjusted doses of IFN β-1a in patients with TMA, compared with patients without TMA. Second, among 15 patients with IFN β-1a–induced TMA, none were treated with low doses of IFN β-1a (<50 mcg weekly), 8% were treated with 66 mcg, and 92% with 132 mcg. Finally, they created a transgenic mouse model with mice producing type I interferon either at low levels (IFN^{low}) or high levels (IFN^{high}). In comparison to wild-type mice, they confirmed the dose-dependent relationship on renal microvasculature lesions. They also crossed IFN^{high} mice with mice that

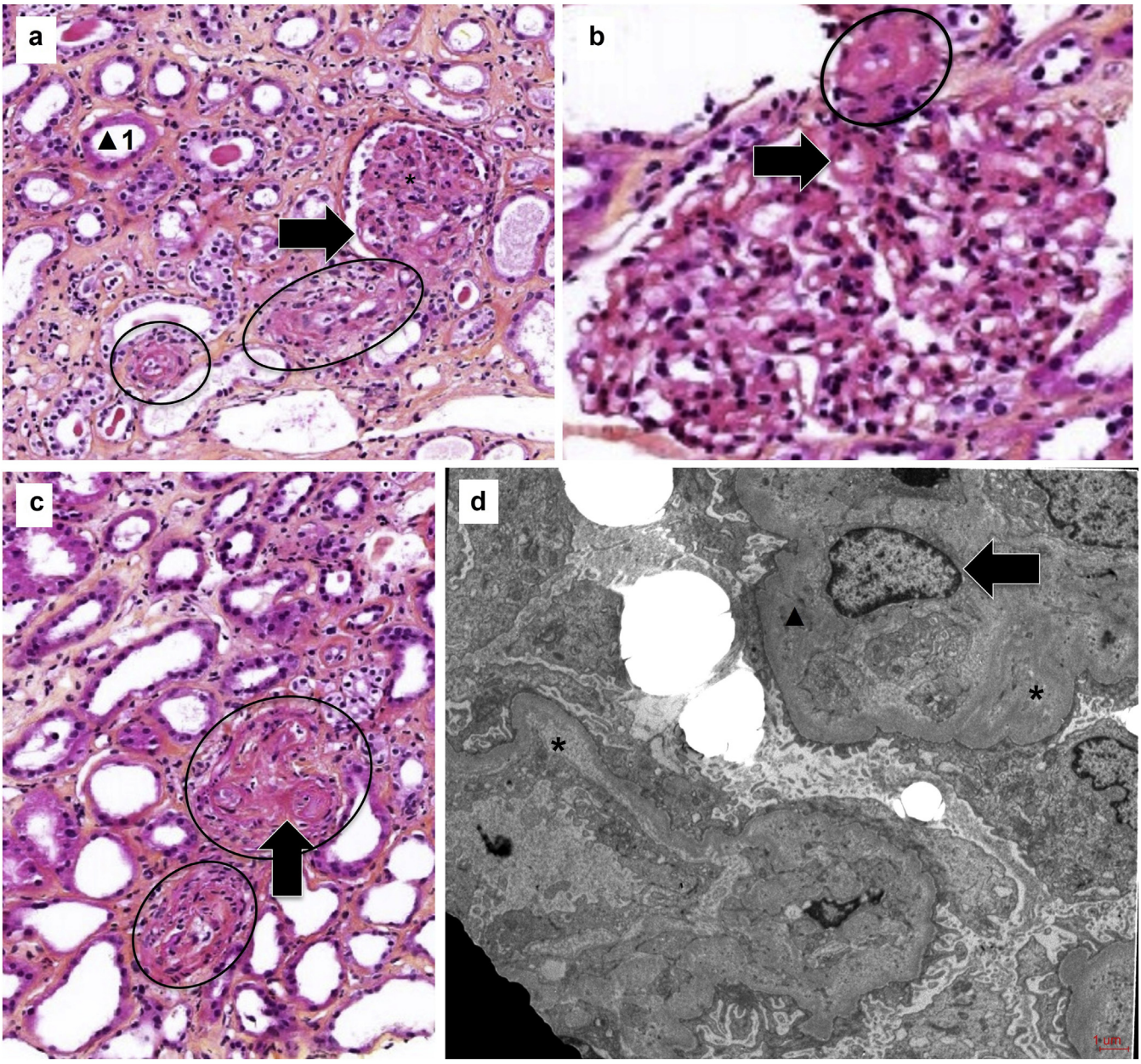

Figure 1. Renal biopsy images of the patient. (a) Hematoxylin/eosin staining illustrating 2 sections of the same afferent arteriole (surrounded) revealing endothelial cell swelling with intimal hyperplasia and severe narrowing of the lumen. Left arteriole is even occluded. Glomerular changes are found: dense flocculus where only few capillary lumens are found (black arrow) and double contour with swollen basal membrane. Interstitial fibrosis and edema are also found in the left upper part of picture 1. Tubular atrophy with loss of the nuclei (▲1). (b) Hematoxylin/eosin staining illustrating double contours and thickened glomerular basement membrane (black arrow). (c) Hematoxylin/eosin staining illustrating 2 occluded arterioles with fibrin necrosis (arrow). (d) Electron microscopy illustrating subendothelial space widening and expansion of lamina rara interna (*) with duplication of the glomerular basement membrane (▲). The arrow illustrates the swollen endothelial cell's nuclei.

were null for the type I interferon receptor ($IFNAR^{-/-}$), confirming the implication of the latter receptor in up-regulation of interferon response genes and histologic lesions. Indeed, $IFN^{high} \times IFNAR^{-/-}$ mice did not have any microvascular histologic lesion. Jia *et al.*[5] revealed that IFN β-1a was associated with endothelial cell dysfunction and lower survival by the inhibition of fibrinolysis and vascular endothelial growth factor-dependent angiogenesis in an *in vitro* study using human umbilical vein endothelial cells. These findings are also consistent with the association of vasulopathy and TMA in rare interferonopathic diseases, such as Aicardy-Goutière syndrome.[9,S1,S2]

Is there a relationship between IFN β-1a and ACP activation? Parisi *et al.*[3] reported 25 cases of TMA in patients treated with IFN. Among these patients, 18 were treated with IFN β-1a and 6 had atypical hemolytic uremic syndrome (defined as the absence of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or other secondary TMA except of IFN).

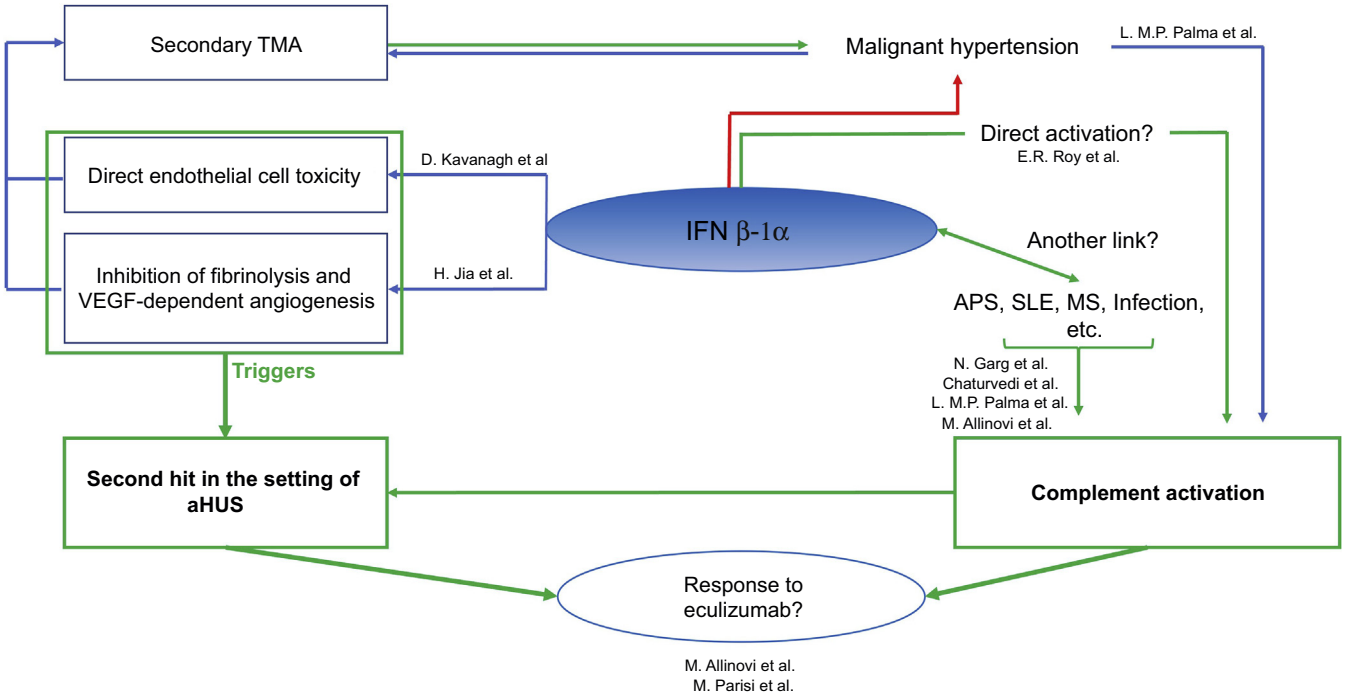

Figure 2. Pathophysiological hypotheses of IFN β-1a–mediated TMA. Blue lines represent data from literature whereas green arrows represent pathophysiological hypotheses. The red arrow represents the absence of data revealing a link between type I IFN and hypertension in literature. IFN, interferon; TMA, thrombotic microangiopathy.

Interestingly, mutations for regulators of the ACP were assessed in 5 of these patients. One patient had a heterozygous mutation of the *MCP* of unknown significance. Another patient had a nonpathogenic heterozygous deletion of *CFHR1/R3*.[8] *CFHR1/3* is known to be associated with antifactor H antibodies, but that was not the case in this patient. Genetic workup was negative in 3 patients and missing in 1 case report.[3] Interestingly, among these 6 patients, 4 were treated with eculizumab, an anticomplement C5 monoclonal antibody. IFN was withdrawn in all patients, and all were treated with plasma exchange (8–18 sessions). One patient was treated with corticosteroid because of worsening of renal function requiring the initiation of hemodialysis. Despite the absence of proven mutation for regulators of the ACP, eculizumab was associated with a significant improvement of renal function, with persistence of chronic kidney disease stages 2 to 4. Hemodialysis was stopped 5 months after the initiation of eculizumab in the most severe case.[3,8] These data suggest a potential efficacy of eculizumab but are not a proof for a causal relationship. Our patient did not receive eculizumab despite a potential alternative complement pathway activation (Supplementary Table S1). Indeed, these analyses were performed 4 days after cefuroxime was started for a pyelonephritis, and therefore their interpretation remains uncertain. Moreover, TMA resolved rapidly and spontaneously, and the reimbursement policies of social security in Belgium do not allow prescription of eculizumab in a patient with secondary TMA.

Pathophysiological Hypotheses of IFN β-1a–Mediated TMA

1. IFN β-1a could act as a trigger in patients with yet undiscovered mutation for regulators of the ACP. Indeed, complement-mediated TMA is usually triggered by a second hit such as infection, pregnancy, or the initiation of a new drug.[S3,S4] IFN β-1a may act as a second hit, by its direct toxicity on endothelial cells[9] and indirect action on fibrinolysis and angiogenesis.[5]
2. IFN β-1a may activate the complement system:
   - A direct activation of the complement cascade by IFN β-1a has been described,[S5] suggesting a potential direct crosstalk between IFN and complement cascade.
   - An indirect activation of the complement cascade can also be hypothesized. Malignant hypertension may activate complement pathway,[S6] but IFN β-1a is not associated with such complication in literature. Antiphospholipid antibodies may also be a potential factor. The latter has been associated with IFN β therapy,[S7] is a well-known cause of TMA,[1] and is known to activate the complement pathway.[S8] Our patient had 1 antiphospholipid positive assay at the time IFN β-1a was started. Control result was

negative at 12 weeks, and since then, several antiphospholipid assay results were negative.

- Complement cascade activation has been described in some drugs, in the setting of secondary TMA (e.g., gemcitabine or cisplatin).[S9]
- Complement system dysregulation seems to be implicated in the pathogenesis of multiple sclerosis.[S10] Classical pathway seems to be activated and patients with multiple sclerosis may experience plasma elevation of C3, C4, C4a, C5b-9/MAC, and factor H.[S11] Our patient had elevated factor B, factor Bb, and serum C5b-9, suggesting an activation of the alternative pathway of the complement. Plasma C3 level was normal. These data could be associated with multiple sclerosis itself. Indeed, experimental studies have revealed that factor B could be implicated in the pathogenesis of multiple sclerosis.[S12] Our patient's neurologic assessment revealed no active lesion at magnetic resonance imaging and no worsening of neurologic status that were consistent with a nonactive disease. Complement activation could also be associated with the episode of pyelonephritis that our patient presented. Finally, as discussed previously, the complement activation has been associated with IFN β-1a treatment in the setting of TMA (summary illustrated in Supplementary Figures S2, S3, and S4).

Figure 2 summarizes the pathophysiological hypotheses of IFN β-1a–mediated TMA.

CONCLUSION

Prescribers of IFN β-1a should be aware of IFN β-1a–mediated TMA. Weight-adjusted doses should be evaluated on a regular basis and adjusted according to the disease activity because this complication is dose dependent. Treatment mainly consists in withdrawal of IFN, corticosteroids, and plasma exchange with poor renal outcome. Eculizumab seems to be promising, because it has been associated with a better renal prognosis in case series even in the absence of a demonstrated abnormality in the regulatory factors of the ACP. These data may suggest that either IFN β-1a activates the complement cascade or that TMA occurs as a second hit in a patient with atypical hemolytic uremic syndrome and yet undiscovered mutations for regulators of the ACP. These data need to be confirmed by further studies with a higher level of evidence.

DISCLOSURE

P.S. reports personal fees from Sanofi Genzyme, outside the submitted work. All the other authors declared no competing interests.

PATIENT CONSENT

The patient's next of kin provided consent to publish this case study.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Figure S1. Kidney biopsy.

Figure S2. Evolution of renal function and hemolytic microangiopathic anemia parameters.

Figure S3. Pathophysiologic algorithm.

Figure S4. Alterative diagram of the pathophysiologic hypotheses of IFN β-1a–mediated TMA.

Table S1. Patient's complement pathway analysis.

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