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CASE REPORT

Thrombotic microangiopathy associated with use of interferon-beta

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Abstract: Interferon-beta is widely used for the treatment of relapsing multiple sclerosis. The drug is usually well tolerated, but autoimmune adverse effects, including kidney disease, have been reported. Only a few cases of hemolytic uremic syndrome-thrombotic microangiopathy associated interferon-alpha have been described so far, and even fewer with beta-interferon. We report a patient who developed thrombotic microangiopathy during treatment with interferon-beta and improved after discontinuation and steroid therapy. Complement cascade and antiphospholipid antibodies are investigated. The spectrum of renal diseases associated with interferon-beta treatment is also reviewed.

Keywords: thrombotic microangiopathy hemolytic uremic syndrome, multiple sclerosis, interferon-beta

Introduction

Interferons are well established agents for standard therapy in several malignancies, hepatitis C, idiopathic pulmonary fibrosis, and multiple sclerosis.[1,2] Despite this, adverse autoimmune effects associated with their use have been reported, including minimal change disease in the kidney,[2–5] collapsing focal segmental glomerulosclerosis,[6,7] membranous glomerulonephritis,[8] acute renal failure,[9] lupus nephritis,[10,11] acute renal failure,[12] and thrombotic microangiopathy.[13–18] These side effects are most often associated with interferon-alpha therapy, rather than interferon-beta. The mechanism for this is not clear. Glomerular endothelial cells express and secrete ADAMTS 13.[17] The low activity of ADAMTS 13 has been associated with the presence of an anti-ADAMTS 13 IgG antibody during treatment with interferon-alpha 2a,[16] which could explain these adverse side effects, but no mechanism has been described to explain this with interferon-beta. In the following report, we describe a case of hemolytic uremic syndrome causing thrombotic microangiopathy and chorioretinitis after several months on treatment with interferon-beta which is much rarer. It responded successfully to drug withdrawal and steroid therapy.

Case report

A 37-year-old woman was admitted to our hospital with acute renal failure, hypertension, subnephrotic proteinuria, nausea, and vomiting. She reported a 20-year history of multiple sclerosis, adequately controlled with steroids. She had been treated with interferon-beta due to a sensitive relapse affecting the spinal cord and both legs during the last five months. The patient refused other medications. She had no recent history

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of fever or diarrhea. She reported a two-week history of mild fatigue and arthralgia in the left tarsus, treated with ibuprofen. On admission, the patient had a blood pressure of 205/110 mmHg. She was well hydrated and, apart from pedal edema, physical examination was unremarkable. No skin lesions were detected.

Laboratory test results are shown in Table 1. A possible diagnosis of acute renal injury secondary to thrombotic microangiopathy associated with interferon-beta was suggested. Urinalysis showed no leucocytes, erythrocytes, or nitrites. Proteins were 1.7 g/24 hours. Urine culture showed no pathogens.

Cancer markers were negative. Chest x-ray was unremarkable and renal ultrasound showed kidneys of normal size with a normal echogenic cortex and no hydronephrosis. A kidney biopsy was performed and histological studies showed ischemic changes in 12 of 35 glomeruli studied (Figure 1A). Some other glomeruli showed chronic glomerular microangiopathic lesions with duplication of the glomerular basement membrane (Figure 1B). There was moderate interstitial edema with mild inflammatory cell infiltration and patchy tubular atrophy. The arterioles and intralobular arteries showed marked subintimal fibromucoid edema narrowing the lumen (Figure 1A arrows, Figure 2A). An immunofluorescence study showed only fibrinogen deposits in the arterial wall (Figure 2B).

The patient was finally diagnosed with thrombotic microangiopathy associated with interferon-beta, so the drug was withdrawn and immunosuppressive therapy was started with 1 mg/kg/day of prednisone because leg symptoms of multiple sclerosis had started immediately. Doses of steroids were reduced and finally withdrawn over a period of one month, while glatiramer acetate was started. The leg symptoms of multiple sclerosis disappeared in a few days. Her hypertension was controlled with enalapril and irbesartan. Hematological abnormalities and serum lactate dehydrogenase levels returned to the normal range, and renal function slowly recovered a serum creatinine of 1.0 mg/dL.

Table 1 Results of laboratory investigations

	May 21, 2008	June 13, 2008	August 8, 2008
Creatinine (mg/dL)	2.4	1.0	0.8
Urea (mg/dL)	86	42	24
Proteinuria (g/24 hours)	1.7	0.28	0.03
Hemoglobin (g/dL)	9.3	10.3	11.2
Platelets (mm^3)	108,000	229,000	265,000
Lactate dehydrogenase (IU/L)	491	348	257
Schistocytes	Positive	Negative	Negative
ANCA	Negative	Negative	Negative
ANA	Negative	Negative	Negative
Anti DNA	Negative	Negative	Negative
Anti Ro	Negative	Negative	Negative
Anti La	Negative	Negative	Negative
Factor H, I	Normal range	–	–
Antiphospholipid (*)	Negative	Negative	Negative

Note: *Antiphospholipids included anticardiolipin, lupus anticoagulant and anti β2GP1.
Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies.

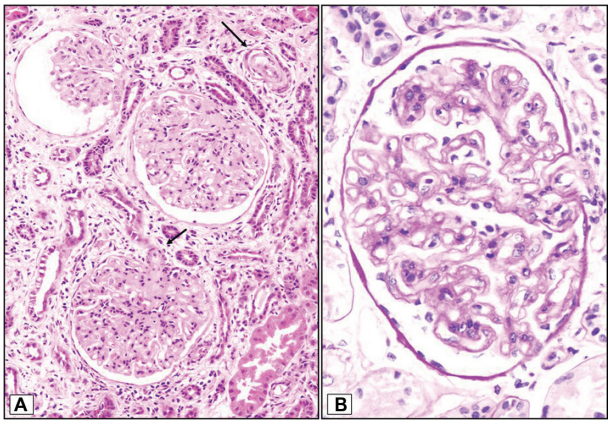

Figure 1 (**A**) Ischemic changes in the upper glomeruli (arrow). Marked subintimal fibromucoid edema narrowing the lumen in the intralobular arterioles (arrows) and (**B**) duplication of glomerular basement membrane.

Discussion

Interferon-beta is widely used for the treatment of relapsing multiple sclerosis. It is postulated that interferon-beta acts in this disease by inhibiting activation and proliferation of T cells.[1,2] The drug is usually well tolerated, but constitutional side effects and autoimmune adverse events have been reported.[19,20]

The similarities between some manifestations of systemic lupus erythematosus, those of viral infections, and side effects of immunotherapy with recombinant interferons,

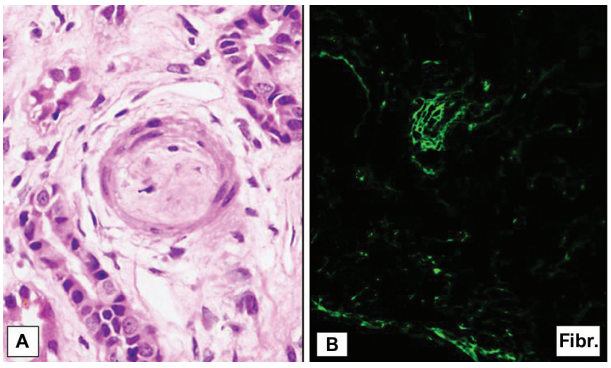

Figure 2 (**A**) Moderate interstitial edema with mild inflammatory cell infiltration and patched tubular atrophy with (**B**) fibrinogen deposits in the arterial wall in the immunofluorescence study.

Table 2 Spectrum of renal diseases induced by interferon-beta

Authors	Year	Gender	Age	Disease	Clinical	Kidney biopsy	Treatment	Evolution
Ubara et al[22]	1998	Female	66	CHC	HUS	Thrombotic microangiopathy	SB	Remission HUS
Gostman et al[6]	2000	Female	52	MS	NS	Focal segmental glomerulosclerosis	SB	Remission NS
Nakao et al[5]	2002	Male	64	Melanoma	NS	Minimal change disease	SB	Remission NS
Tola et al[4]	2003	Male	39	MS	NS	Minimal change disease	SB – Steroids – azathioprine	Remission NS
Auty and Saleh[9]	2005	Male	28	MS	NS	Membranous nephropathy	SB – Steroids CsA – MMF	Remission NS
Kamasaka et al[3]	2006	Female	43	MS	NS	Minimal change disease	SB – Steroids	Remission NS
Hansen et al[11]	2009	Male	41	MS	RF	Thrombotic microangiopathy, antiphospholipid, SLE	SB – Steroids – CFM – MMF	CKD
Aravindan et al[2]	2010	Female	44	MS	NS	Minimal change disease	SB – Steroids – ACEI	Remission NS
Markowitz et al[7]	2010	Female	27	MS	NS	Collapsing focal segmental	NA	NA
		Female	33	MS	RF-Prot	SLE and Glomerulosclerosis	SB – Steroids	CKD
		Female	37	MS	RF-Prot		SB – Steroids – CFM	Proteinuria
Broughton et al[21]	2011	Female	53	MS	RF-Prot Mhem	Thrombotic microangiopathy	SB – ACEI	CKD Mhem

Abbreviations: CHC, chronic hepatitis C; HUS, hemolytic uremic syndrome; MS, multiple sclerosis; NS, nephrotic syndrome; SB, stopped interferon-beta; CsA, cyclosporin; MMF, mycophenolate mofetil; RF, renal failure; NA, not available; CKD, chronic kidney disease; Prot, proteinuria; Mhem, microhematuria; CFM, cyclophosphamide; ACEI, angiotensin-converting enzyme inhibitors; SLE, systemic lupus erythematosus.

such as fever, arthralgia, myalgia, and fatigue, are evident. In fact, interferon-alpha is a central mediator in systemic lupus erythematosus, and specific neutralizing antibodies are now in clinical trials for the treatment of this disease.[21] Our case can be immediately catalogued as a thrombotic microangiopathy-hemolytic uremic syndrome, which would explain the acute kidney injury. The absence of diarrhea made atypical hemolytic uremic syndrome very unlikely. She had no symptoms or serological findings suggestive of systemic sclerosis, malignancy, malignant hypertension, or antiphospholipid syndrome. The presence of autoreactive antibodies, particularly antiphospholipid antibodies and antithyroid antibodies, are associated with an increased risk of interferon-beta antibodies in patients with multiple sclerosis on long-term therapy.[22] However, we did not find any of these antibodies in our patient. Kidney complications have not been directly attributed to multiple sclerosis.[2]

Renal side effects including minimal change disease,[2–5] collapsing focal segmental glomerulosclerosis,[6–8] membranous nephropathy,[9] lupus nephritis,[10,11] acute renal failure,[12] and thrombotic microangiopathy,[13–23] are most often associated with interferon therapy rather than with interferon-beta. The incidence of transient proteinuria during interferon-beta therapy is around 20%. To our knowledge, this is the fourth case of hemolytic uremic syndrome induced by interferon-beta. Two of these patients were treated with corticosteroids and plasmapheresis, and another was only treated with supportive antihypertensive and antiproteinuric therapies. The fourth patient was diagnosed also with pseudo-SLE and treated with immunosuppressants. In all of them interferon-beta was withdrawn. The spectrum of kidney disease related to interferon-beta is shown in Table 2.

The mechanism by which interferon could induce thrombotic microangiopathy lesions and nephrotic syndrome remains unclear.[14] Pleiotropic drugs such as interferon might disrupt complex pathways of complement regulation and play a role in endothelial damage.[21] In recent years, mutation of complement system regulators (factors H and I, and membrane cofactor protein) have been directly implicated in the induction of atypical hemolytic uremic syndrome.[24,25] However, we did not found any of these alterations in our case. Furthermore, a recent publication described a case of low ADAMTS 13 activity associated with the presence of an anti-ADAMTS 13 IgG antibody during treatment with interferon-alpha 2a.[16] Glomerular endothelial cells express and secrete ADAMTS 13.[17] It has been suggested that pre-eclampsia is also associated with decreased levels of ADAMTS 13.[18]

The delayed appearance of thrombotic microangiopathy observed in our case and others suggest that the development of renal lesions may be the result of cumulative effects.[14,22] In conclusion, thrombotic microangiopathy-hemolytic uremic syndrome induced by interferon-beta is an unusual side effect manifested as acute or subacute kidney injury. Attempts should be made to detect it as soon as possible, and to clarify the mechanism of microangiopathy lesions.

Disclosure

The authors report no conflicts of interest in this work.

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