Thrombotic microangiopathy associated with use of interferon-beta

Teresa Olea1
Raquel Díaz-Mancebo1
Maria-Luz Picazo2
Jorge Martínez-Ara1
Angel Robles3
Rafael Selgas1

1Departments of Nephrology, 2Pathology, 3Internal Medicine, Hospital Universitario La Paz, Madrid, Spain

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...
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.

**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. The drug is usually well tolerated, but constitutional side effects and autoimmune adverse events have been reported. The similarities between some manifestations of systemic lupus erythematosus, those of viral infections, and side effects of immunotherapy with recombinant interferons,

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**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.*

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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 autoantibodies, 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.22

Renal side effects including minimal change disease,2–4 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 nephritic 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 find 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.

### Table 2 Spectrum of renal diseases induced by interferon-beta

| Authors            | Year | Gender | Age | Disease          | Clinical | Kidney biopsy               | Treatment     | Evolution |
|---------------------|------|--------|-----|------------------|----------|-----------------------------|---------------|-----------|
| Ubara et al19       | 1998 | Female | 66  | CHC              | NS       | Thrombotic microangiopathy  | SB            | Remission |
| Farkas et al20      | 1998 | Female | 52  | MS               | NS       | Focal segmental glomerulosclerosis | SB            | HUS       |
| Nakao et al21       | 2002 | Male   | 64  | Melanoma         | NS       | Minimal change disease      | SB            | Remission NS |
| Tola et al22        | 2003 | Male   | 39  | MS               | NS       | Minimal change disease      | SB            | Remission NS |
| Aury and Saleh23    | 2005 | Male   | 28  | MS               | NS       | Membranous nephropathy      | SB            | Remission NS |
| Kamasaka et al24    | 2006 | Female | 43  | MS               | NS       | Minimal change disease      | SB            | Remission NS |
| Hansen et al25      | 2009 | Male   | 41  | MS               | RF       | Thrombotic microangiopathy, antiphospholipid, SLE | SB            | CKD |
| Aravindan et al26   | 2010 | Female | 44  | MS               | NS       | Minimal change disease      | SB            | Remission NS |
| Markowitz et al27   | 2010 | Female | 27  | MS               | NS       | Collapsing focal segmental glomerulosclerosis | SB            | CKD |
| Broughton et al28   | 2011 | Female | 53  | MS               | RF-Pro   | Membranous nephropathy      | SB            | CKD |

**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.
Disclosure

The authors report no conflicts of interest in this work.

References

1. Walther EU, Hohlfeld R. Multiple sclerosis: side effects of interferon beta therapy and their management. Neurology. 1999;53:1622–1627.
2. Aravindan A, Yong J, Killingsworth M, Suranyi M, Wong J. Minimal change disease with interferon-beta therapy for relapsing remitting multiple sclerosis. NDT Plus. 2010;3:132–134.
3. Kamasaka R, Nakamura N, Shirato K, et al. Nephrotic syndrome associated with interferon beta-1b therapy for multiple sclerosis. Clin Exp Nephrol. 2006;10:222–225.
4. Tola MR, Caniatti LM, Gogonniello D, et al. Recurrent nephrotic syndrome in a patient with multiple sclerosis treated with interferon beta 1a. J Neuro. 2003;250:768–769.
5. Nakao K, Sugiyma H, Makino E, et al. Minimal change nephrotic syndrome developing during postoperative interferon-beta therapy for malignant melanoma. Nephron. 2002;90:498–500.
6. Gotsman I, Elhalel-Darnitski M, Friedlander Z, et al. Beta-interferon-induced nephrotic syndrome in a patient with multiple sclerosis. Clin Nephrol. 2000;54:425–426.
7. Markowitz GS, Nasr SH, Stokes MB, D’Agati VD. Treatment with INF-α, -β or -γ is associated with collapsing focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2010;5:607–615.
8. Bremer CT, Lastrapes A, Alper AB Jr, et al. Interferon-alpha-induced focal segmental glomerulosclerosis in chronic myelogenous leukemia: a case report and review of the literature. Am J Clin Oncol. 2003;26:262–264.
9. Auty A, Saleh A. Nephrotic syndrome in a multiple sclerosis patient treated with interferon beta 1a. Can J Neurol Sci. 2005;32:366–368.
10. Abbott IJ, Chang CC, Skinner MI, et al. Development and management of systemic lupus erythematosus in an HIV-infected man with hepatitis C and B co-infection following interferon therapy: a case report. J Med Case Reports. 2009;3:7289.
11. Hansen T, New D, Reeve R, Donne R, Stephens W. Acute renal failure, systemic lupus erythematos and thrombotic microangiopathy following treatment with beta-interferon for multiple sclerosis: case report and review of the literature. NDT Plus. 2009;2:466–468.
12. Fahal IH, Murry N, Chu P, Bell GM. Acute renal failure during interferon therapy. Br Med J. 1993;306:973.
13. Jadoul M, Pissevaux H, Ferrant A, Cosyns JP, van Ypersele de Striou C. Renal thrombotic microangiopathy in patients with chronic myelogenous leukaemia treated with interferon alpha 2b. Nephrol Dial Transplant. 1995;10:111–113.
14. Badid C, McGregor B, Faire JM, et al. Renal thrombotic microangiopathy induced by interferon α. Nephrol Dial Transplant. 2001;16:846–848.
15. Magee CC. Renal thrombotic microangiopathy induced by interferon-alpha. Nephrol Dial Transplant. 2001;16:2111–2112.
16. Kitano K, Gibo Y, Kamiyo J, et al. Thrombotic thrombocytopenic purpura associated with pegylated-interferon alpha-2a by ADAMTS 13 inhibitor in a patient with chronic hepatitis C. Haematologica. 2006;91:E3C4.
17. Tati R, Kristofferson AC, Stahl AL, et al. Phenotypic expression of ADAMTS 13 in glomerular endothelial cells. PLoS One. 2011;6:e21587.
18. Stepianan A, Cohen-Moatti M, Sanglier T, et al; ECLAXIR Study Group. Von Willebrand factor and ADAMTS13: a candidate couple for preeclampsia pathophysiology. Arterioscler Thromb Vasc Biol. 2011;31:1703–1709.
19. Alanoglu G, Kilbas S, Arslan C, Senol A, Kuthuhan S. Autoimmune hemolytic anemia during interferon-beta-1b treatment for multiple sclerosis. Mult Scler. 2007;13:683–685.
20. Garg N, Weinstock-Guttman B, Bhasi K, Locke J, Ramanathan M. An association between autoreactive antibodies and anti-interferon-beta antibodies in multiple sclerosis. Mult Scler. 2007;13:895–899.
21. Broughton A, Cosyns JP, Jadoul M. Thrombotic microangiopathy induced by long-term interferon-β therapy for multiple sclerosis: a case report. Clin Nephrol. 2011;5:396–400.
22. Ubara Y, Hara S, Takedatu H, et al. Hemolytic uremic syndrome associated with beta-interferon therapy for chronic hepatitis C. Nephron. 1998;80:107–108.
23. Herrera WG, Balizet LB, Harberts SW, Brown ST. Occurrence of a TTP-like syndrome in two women receiving beta interferon therapy for relapsing multiple sclerosis. Neurology. 1999;Supp 2:A153.
24. Anders HJ, Lichnekert J, Allam R. Interferon-β therapy for relapsing remitting multiple sclerosis. Mult Scler. 2007;13:895–899.
25. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009;362:1676–1679.