Thrombotic microangiopathy due to acquired complement factor I deficiency in a male receiving interferon-beta treatment for multiple sclerosis

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Abstract

Interferon-beta, the most widely prescribed medication for multiple sclerosis, is generally considered safe. Nevertheless, rarely serious and/or life-threatening side effects have been reported such as thrombotic microangiopathy. A few mechanisms have been proposed to explain how interferon causes thrombotic microangiopathy, but insufficient immunological studies have been unable to pin this phenomenon down to a single pathophysiologic pathway. We report thrombotic microangiopathy due to acquired complement factor I deficiency in a male receiving interferon-beta treatment for multiple sclerosis. After three years of starting the therapy, the 28-year-old patient presented with malignant hypertension causing seizures, rapidly progressive renal failure requiring hemodialysis, and hemolytic anemia. Corticosteroid and plasma exchange sessions permitted hemolysis control. Nonetheless, the patient remained hemodialysis-dependent. Exploration of the complement system found a complement factor I deficiency whose activity normalized at the control carried out after two years. We concluded that IFNβ treatment may cause complement factor I deficit, which can lead to thrombotic microangiopathy and severe renal failure.

Introduction

For patients with relapsing-remitting multiple sclerosis (RRMS), interferon-beta (IFN) is a well-established first-line therapy that is still commonly administered.

Thrombotic microangiopathy (TMA), a group of microvascular disorders with diminished organ perfusion and hemolytic anemia, is a rare yet serious side effect that can arise years after starting IFN therapy [1].

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are the two most common diseases associated with TMA. Ischemia in the brain and other organs is caused by systemic microvascular aggregation of platelets in TTP. In HUS, platelet-fibrin thrombi mostly occlude the renal circulation [2].

TTP is specifically caused by a severe deficiency in ADAMTS13 while HUS is mostly due to a Shiga toxin producing-Escherichia Coli infection. In 10% of the cases, excessive complement activation and membrane attack complex deposits contribute to atypical HUS (aHUS) when one or more regulators of the alterna-

tive route of the complement (factor H, factor I, C4b-binding protein, complement receptor 1, CD46) are dysregulated [3,4].

We report herein, a TMA case due to acquired complement factor I deficiency in a patient receiving interferon-beta (IFNβ) for multiple sclerosis.

It's worth mentioning that there's relatively little experience with TMA associated with interferon. Particularly those involving immunological testing and complement system study, underscoring the need of reporting such cases today.

Case report

A 28-year-old man was diagnosed with RRMS in 2007. Subcutaneous IFNβ 44 µg was commenced three times a week in 2017. He had no other medical conditions and received no other treatment.

In July 2020, he was admitted to the intensive care unit for a status epilepticus associated with severe arterial hypertension and then transferred to the Nephrology department for management of malignant arterial hypertension with acute renal failure. On examination, he did not present any neurological disorder but had very unbalanced blood pressure under triple therapy. Urine dipstick showed proteinuria +++ and hematuria +++. Biological investigations showed hemolytic anemia (hemoglobin at 9.7 g/dL, elevated LDH level at 3N, low haptoglobin level < 58.3, elevated reticulocyte count, and presence of schistocytes at 4%), normal platelet count at 165 G/L, renal failure (creatininemia at 146 µmol/L, and urea at 9.1 mmol/L) and hypokalemia at 3 mmol/L. Urinary analysis revealed proteinuria of glomerular origin (7g/day).

Initial immunological investigations showed no complement activation (C3 at 1.08g/l and C4 at 0.32 g/l), undetectable antiphospholipid antibodies (assays for anti-b2-glycoprotein 1 and anticardiolipin antibodies were negative and there was no lupus anticoagulant), negative antinuclear antibodies, negative anti-glomerular basement membrane and positive anti-neutrophil cytoplasmic antibodies (40, N< 20) with no specificity.

This clinical-biological presentation strongly evoked aHUS complicating IFNβ. In addition to treatment discontinuation, the patient received methylprednisolone of 10 mg/kg intravenous for 3 consecutive days switched to oral corticosteroid therapy of 0.5 mg / Kg/day and received supportive treatment including plasma exchange.

Despite the achievement of seven sessions of plasma exchange, the renal failure rapidly worsened and the patient required hemodialysis. A kidney biopsy was therefore indicated and was performed three days after stopping the plasma exchange sessions with a normal hemostasis assessment.

The renal puncture biopsy showed acute and chronic vascular and glomerular TMA (mesangiolysis, reduction of the lumen of the glomerular capillaries, fibrinoid necrosis, mesangial fibrosis, and onion bulb appearance of vessels) with IgG and fibrinogen deposits in the immunofluorescence study (Fig 1, 2&3). The biopsy was complicated by the progressive constitution of a perirenal hematoma leading to a state of hemorrhagic shock which required embolization of two distal arteries.

The patient subsequently benefited from five other plasma exchange sessions permitting the regression of the hemolytic process. However, there was no renal recovery and the patient remained hemodialysis-dependent.

Far from plasma exchanges, we explored the complement system. The results were received lately while the hemolytic process was controlled by standard treatment and showed a decrease in complement factor I: 26,83 mg/l (32,3-87,5). The other proteins of the alternate complement pathway (factor B, factor H, and MCP) as well as the ADAMTS13 activity were within the normal range.

Given the absence of recurrence of hemolysis, no other treatment with rituximab, initially mentioned, was initiated.

At follow-up 6 months later, the patient had not regained kidney function and the complement factor I rate was still low. He remained on hemodialysis and was still taking three antihypertensive treatments.

Two years after the initial diagnosis, he did not experience hematological relapse and remained dependent on hemodialysis. His blood pressure has normalized without antihypertensive treatment and he was desiring cadaveric kidney transplantation. The exploration of the complement system was therefore redone and the activity of factor I was this time normal at 70% (70-100%).

Discussion

Herein, we described a case of TMA due to acquired complement factor I deficiency in a male receiving interferon-beta treatment for multiple sclerosis.

The immunomodulatory effect of interferon therapy has been recorded in the literature to generate autoimmune disorders, particularly with interferon-alpha, including examples of TMA in chronic myelogenous leukemia patients where high-dose treatment for a long period has been advised [5].

With IFNβ, only a few autoimmune signs have been documented even though it can cause flu-like symptoms, temporary laboratory abnormalities, menstrual problems, and local dermal injection site responses. IFNβ-induced TMA has been rarely reported [6].

A few mechanisms have been proposed to explain how interferon causes TMA, but insufficient immunological studies have been unable to pin this phenomenon down to a single pathophysiologic pathway [5, 7].

Some authors inferred that complement-mediated TMA was excluded due to normal complement levels [7]. However, serum complement factor C3 and C4 measurements have poor predictive value in determining the underlying pathophysiology of TMA [9]. Indeed, during most aHUS presentations, serum C3 and C4 levels are generally within reference values [10, 11].

Published literature identified 25 patients who developed TMA with renal impairment after receiving IFNβ as a disease-modifying treatment [1].

Orvain et al. [12] described a 52-year-old man who got TMA-associated severe renal failure due to severe ADAMTS13 insufficiency as a result of an anti-ADAMTS13 IgG antibody generated during IFN treatment for multiple sclerosis. Treatment included IFNβ discontinuation, immediate plasma exchange therapy, corticosteroids, and hemodialysis. Rituximab was introduced in face of hemolysis relapse.

The patient did not experience hematological relapse but remained dependent on hemodialysis.

Our case is very similar to that of Orvain et al. except that the clinical presentation of our patient was compatible with aHUS while the underlying pathophysiological mechanism was an acquired factor I deficiency in the context of IFNβ treatment for multiple sclerosis.

Due to its ability to destroy activated complement proteins C3b and C4b in the presence of cofactors, factor I is a critical inhibitor governing all complement pathways. Complete lack of factor I, which is mostly generated in the liver, is uncommon and results in excessive complement consumption, which can lead to repeated severe infections, glomerulonephritis, or autoimmune disorders. The incomplete factor I deficiency, as noted with our patient, is in turn associated with aHUS [13].

The factor I deficiency in the reported patient doesn't seem important, this could be explained by the complement investigation after the instauration of the treatment but far from the plasma exchange sessions so as not to distort the result. unfortunately, exploration of the complement system was not done at the start of support.

In this report, two arguments support the hypothesis of an acquired incomplete deficiency of factor I due to antibodies generated by IFNβ. The first is the subsequent normalization of factor I level and the second is immunoglobulin deposition on kidney biopsy which indicates an underlying antibody-mediated process.

The state of autoimmunity secondary to IFNβ treatment is on another hand attested by the presence of anti-neutrophil cytoplasmic antibodies without specificity in our patient while Orvain et al. found antinuclear antibodies positivity [12].

Standard treatment with corticosteroids and plasma exchange was sufficient to control the hemolytic process in the reported case. Rituximab was necessary to control the situation in some cases reported in the literature [12, 14].

Conclusion

IFNβ treatment can cause complement factor I deficit, which can lead to a life-threatening TMA and severe renal failure. Hence, IFNβ should be stopped and corticosteroids and plasma exchange therapy began promptly. Exploration of the complement system should be considered in the face of a clinical-biological presentation of IFNβ-induced TMA to clarify the diagnosis.

In cases of the resistant or relapsing disease, rituximab should be investigated.

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Data availability

Data are available on request from the corresponding author.

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Conflict of interest disclosure

The authors have no conflict of interest to declare.

Ethical approval

Given the nature of the article, a case report, no ethical approval was required.

Consent

Written informed consent was obtained from the patient for publication of this case and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Clinical trial registration

This does not apply as it is a case report of a patient who has given written consent and has been de-identified. It is therefore not prospective research involving human participants.

References

1. Parisi M, Manni A, Caputo F, Trojano M, Paolicelli D. A case report of late-onset atypical Hemolytic Uremic Syndrome during interferon-beta in multiple sclerosis: Open issues in literature review. *Brain Behav* . 2021 ; 11(1) :e01930.
2. Caprioli J, Remuzzi G, Noris M. Thrombotic microangiopathies: from animal models to human disease and cure. *Contrib Nephrol* . 2011 ; 169:337-350.
3. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura.*Blood* . 2017 ; 129(21) :2836-2846.
4. Jlajla H, Denman F, Jallouli M, et al. Molecular basis of complement factor I deficiency in Tunisian atypical hemolytic and uraemic syndrome patients. *Nephrology (Carlton)* . 2019 ; 24(3) :357-364.

5. Zuber J, Martinez F, Droz D, Oksenhendler E, Legendre C ; Groupe D'stude Des Nephrologues D'ile-de-France (GENIF). Alpha-interferon-associated thrombotic microangiopathy: a clinicopathologic study of 8 patients and review of the literature.*Medicine (Baltimore)* . 2002 ; 81(4) :321-331.
6. Walther EU, Hohlfeld R. Multiple sclerosis : side effects of interferon-beta therapy and their management. *Neurology* . 1999 ; 53(8) :1622-1627.
7. Broughton A, Cosyns JP, Jadoul M. Thrombotic microangiopathy induced by long-term interferon-β therapy for multiple sclerosis: a case report. *Clin Nephrol* . 2011 ; 76(5) :396-400.
8. Yam C, Fok A, Mclean C, Butler E, Kempster P. Interferon-beta in multiple sclerosis causing thrombotic microangiopathy. *Intern Med J* . 2019 ; 49(2) :274-276.
9. Fox LC, Coney SJ, Kausman JY, Shortt J, Hughes PD, Wood EM, et al. Consensus opinion on diagnosis and management of thrombotic microangiopathy in Australia and New Zealand. *Intern Med J* . 2018 ; 48:624-36.
10. Loirat C, FréOrganicBacchi V. Atypical hemolytic uremic syndrome.*Orphanet J Rare Dis* .2011 ; 6: 60.
11. de Malmanche T. Routine complement blood tests are insensitive for alternative complement activation. *Intern Med J* . 2019 ; 49(8) :1057-1058.
12. Orvain C, Augusto JF, Besson V, et al. Thrombotic microangiopathy due to acquired ADAMTS13 deficiency in a patient receiving interferon-beta treatment for multiple sclerosis. *Int Urol Nephrol* . 2014 ; 46(1) :239-242.
13. Nilsson SC, Sim RB, Lea SM, Fremeaux-Bacchi V, Blom AM. Complement factor I in health and disease. *Mol Immunol* . 2011 ; 48(14) :1611-1620.
14. Gerischer, L. M., Siebert, E., Janke, O., Jungehuelsing, G. J., & Ruprecht, K. (2016). Favorable outcome of interferon-beta associated thrombotic microangiopathy following treatment with corticosteroids, plasma exchange and rituximab: A case report. *Multiple sclerosis and related disorders* , *10* , 63–65.

Figure legends :

Figure 1 : Mesangial fibrosis with mesangiolysis and reduction of the lumen of glomerular capillaries (Trichrome stainingx40).

Figure 2 : Segmental fibrinoid necrosis in a glomerulus (Trichrome stainingx40).

Figure 3 : Onion bulb appearance in medium-caliber vessels (Trichrome stainingx40)

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