Journal of Nephrology & Therapeutics

Davin et al., J Nephrol Therapeutic 2014, S11:008
DOI: 10.4172/2161-0959.S11-008

Case Report Open Access

Hemolytic Uremic Syndrome in Post-Infectious Glomerulonephritis: Possible Pathophysiological Mechanisms

Jean-Claude Davin[1,2], Jaap W. Groothoff[1], Michiel Oosterveld[1], Rixt Schriemer[1], Nicole van de Kar[3], Antonia Bouts[1] and Sandrine Florquin[4]

[1]*Pediatric Nephrology Department, Emma Children's Hospital/Academic Medical Centre, University of Amsterdam, The Netherlands*

[2]*Queen Fabiola Academic Pediatric Hospital, Free University of Brussels, Belgium*

[3]*Pediatric Nephrology Department, Radboud University Nijmegen Medical Centre, The Netherlands*

[4]*Pathology Department, Academic Medical Centre, University of Amsterdam, The Netherlands*

[*]**Corresponding author:** Jean-Claude Davin, Pediatric Nephrology Department, Emma Children's Hospital/Academic Medical Centre Meibergdreef 9, 1105 AZ Amsterdam Zuid Oost, The Netherlands, Fax : 31 20 566 96 83; Tel: 31 20 566 27 27; E-mail: j.c.davin@amc.nl

Rec date: Mar 3, 2014, **Acc date:** Mar 24, 2014, **Pub date:** Mar 27, 2014

Abstract

Malignant hypertension is able to induce glomerular Thrombotic Microangiopathy (TMA) and Hemolytic Uremic Syndrome (HUS) in the absence of Glomerulonephritis (GN). It is therefore commonly admitted that hypertension is the only cause of Glomerular Endothelial Cells (GEC) damage leading to TMA and HUS observed in GN. However, recent literature on TMA in IgA nephropathy calls this hypothesis into question. It is also questionable why so few cases of HUS are reported in association with Post-Infectious GN (PIGN) for which more than 50% of cases necessitate anti-hypertension treatment, we report the case of a 10 years old girl presenting with an extensive cutaneous streptococcal infection, hematuria, nephrotic syndrome, hypertension (146/106) and HUS needing dialysis. The kidney biopsy revealed a severe exudative GN, 30% of crescentic glomeruli and TMA. Immunofluorescence and electron microscopy suggested intense complement activation at the basal level of GEC and podocytes. Genotyping of complement factors was normal. A rapid recovery of a normal renal function was observed after intensive Plasma Exchange (PE) therapy.

We speculate that a high amount of group A streptococcal (GAS) toxins produced in extensive cutaneous lesions might have facilitated TMA initiation by: 1/ a direct damage of endothelial cells; 2/ an intense complement activation induced by the binding of GAS toxins to the complement factor H (CFH), leading to GEC and podocytes' lesions. The favorable effect of PE can be explained by removal of GAS toxins and inactivated CFH on one side and by supply of free CFH on another side. Multicentre studies should be initiated in order to evaluate the frequency and the pathophysiology of TMA and HUS in PIGN.

Keywords: Hemolytic uremic syndrome; Thrombotic microangiopathy; Post-infectious glomerulonephritis; Acute renal failure; Plasma exchange ; Complement

Introduction

Hemolytic Uremic Syndrome (HUS) consists in an association of hemolytic anemia, thrombocytopenia and renal insufficiency. The causal histological lesion is Thrombotic Microangiopathy (TMA) in which the thrombotic process is most of the time induced by a primary lesion of endothelial cells (EC).

Typical HUS results from the toxicity for EC of Shiga toxin (Verotoxin) produced by various types of E. Coli (VTEC) and by Shigella disenteriae. HUS not associated with VTEC infection has been reported with abnormalities of the inhibition of alternative pathway of the complement system (atypical HUS), ADAMTS 13 deficiency, Streptococcus pneumoniae, HIV, malignancy, cobalamin metabolism defect, calcineurin inhibitors, pregnancy, hypertension and various Glomerulonephritis (GN) [1]. Secondary HUS has been reported in post-infectious GN (PIGN) [2-8] but also in other types of GN such as SLE nephritis [9], IgA nephropathy (IgAN) [10], focal and segmental glomerulosclerosis, membranoproliferative GN and vasculitis [11]. This paper reports a case of HUS and TMA associated with a post-streptococcal acute GN and discusses the possible pathophysiological mechanisms involved in this complication.

Case Report

A 10-year-old Suriname girl presented to another hospital with fatigue, somnolence, gingival and nasal bleeding. She had a 2 week history of abdominal pain, constipation and headache. She had hypertension (146/106 mmHg). The patient was transferred to our department because of blood investigation suggesting HUS (serum creatinine: 8 mg/dl {712 µmol/l}; Hb: 5 gr/dl; platelets: 78 x103/µl).

At admission, the presence of cutaneous ulcerative lesions, some of which with an impetigo-like crusting aspect, widely disseminated on the patient's back and flanks (Figure 1) was remarkable. Apart from renal failure, hemolytic anemia (LDH: 2378 IU/l; N: <450 IU/l, haptoglobin: <20 mg/dl; N: 30-200 mg/dl) with shistocytes (++) and thrombocytopenia, hypoalbuminemia (2.8 g/dl), low C3 (170 µg/ml; N: 900-1800 µg/ml) but normal C4 (190 µg/ml; N: 100-400 µg/ml) were found. Fibrinogen plasma concentration was normal (2.4 g/L) as well as APTT (Activated Partial Thromboplastin Time) (24 sec; N=22-30 sec) whereas PT (Prothrombin test) (11.9 sec; N 9.7 to 11.6 sec) was slightly prolonged. Urinalysis revealed microscopic hematuria and gross proteinuria (7.26 g/l). A biopsy of an ulcerative skin lesion

displayed a leucocytoclastic vasculitis with a negative immunofluorescence (data not shown). A feces sample was negative for VTEC infection (bacteriological culture, Shiga toxin PCR). ADAMTS 13 activity was normal (68%).

Methylprednisolone pulses therapy followed by prednisone was initiated. Plasma exchange (PE) sessions were also started immediately in the same time as hemodialysis.

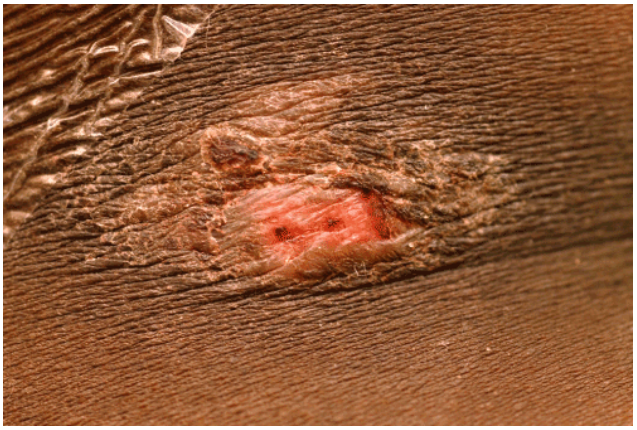

Figure 1: Ulcerative cutaneous lesion situated on the back of the patient.

Investigation for ANA, double strand anti-DNA and ANCA was negative. A kidney biopsy performed on day 4 of admission revealed a massive neutrophils influx in glomerular capillaries, highly swollen EC and crescents in 30% of glomeruli (Figure 2A). In some glomeruli, erythrocytes were trapped in partially occluded capillaries with fibrin deposits (Figure 2B). Obliteration of some arterioles with fibrinous thrombi was found (Figure 2C). On immunofluorescence microscopy (IM), ribbon- like and coarse granular intense C3c deposits along capillary walls (Figure 2D) were accompanied by moderate IgG and IgM deposits (data not shown). Deposits of C5b-9 (Membrane Attack Complex:MAC) were found in the same distribution and intensity as those of C3c (data not shown). A delicate meshwork of fibrin was observed in the glomeruli (Figure 2E). On electron-microscopy (EM), large subepithelial (humps) and tiny subendothelial electron-dense deposits were present (Figure 2F). Effacement of podocytes foot processes was also obvious on EM. Altogether, these findings were compatible with the diagnosis of post-streptococcal GN with a TMA component. Microbial culture of a skin lesion grew Streptococcus pyogenes and plasma levels of anti-streptodornase B antibodies were found to be elevated (600 IU/ml; N<300 IU/ml), confirming the diagnosis, upon which antibiotic therapy was commenced.

Genotyping of CFH, CFI, CFB, MCP and C3 as well as detection of anti-FH circulating antibodies and C3 nephritic factor did not reveal any abnormality.

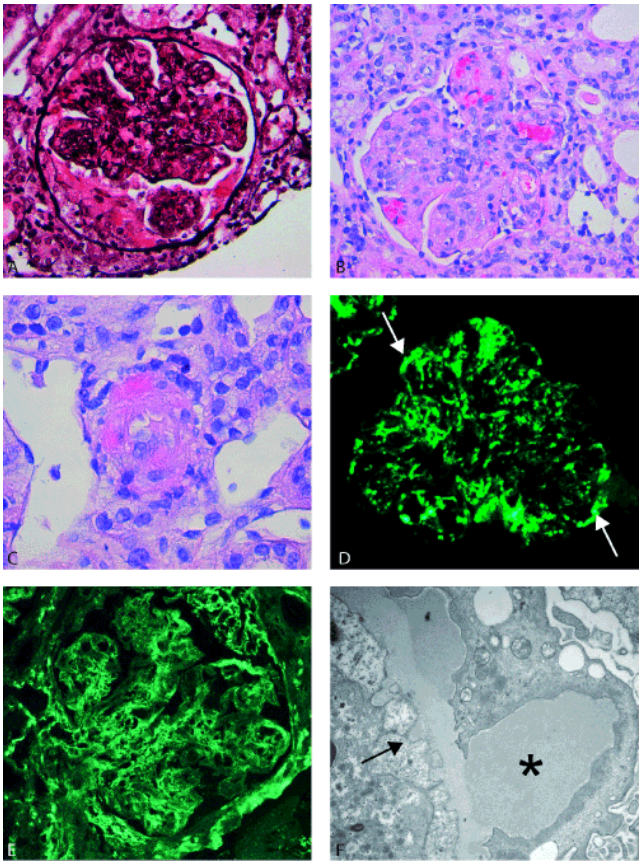

Figure 2: A: Acute exsudative glomerulonephritis with crescent formation (silver staining, magnification x20). **B:** Erythrocytes trapped inside glomerular capillaries (H&E staining, magnification x20). **C:** Arteriolar obliteration by a fibrinous thrombus (H&E staining, magnification x40). **D:** Immunofluorescent staining for C3c showing coarse granular C3c deposits and ribbon-like (subendothelial) deposits along capillary walls (arrow) (magnification x20). **E:** Immunofluorescent staining for fibrinogen showing a delicate meshwork along the glomerular capillary walls (magnification x20). **F:** Electron-microscopy: a large subepithelial electron dense deposit (hump, star) and tiny subendothelial deposit (arrow)

The patient was dialyzed for 10 days and received PE sessions once daily for two weeks and on alternate day for another week. Blood pressure normalized on the day of admission under anti-hypertensive drugs. C3 normalized two weeks after admission. Serum creatinine values and proteinuria were normalized 60 days after admission. Microhematuria persisted until 10 months after admission. At last control, 17 months after admission, serum creatinine was 0.67 mg/dl (59 µicromol/L); hematuria was not found but the urinary albumin/creatinine ratio was increased (10 mg/mmol; N<3.5) under enalapril 2.5 mg daily.

Discussion

Although several other cases with the association HUS-PIGN have been reported [2-8], this complication of PIGN remains exceptional considering the relative high commonness of the latter disease.

In the present case, we postulate that the glomerular EC (GEC) damage leading to TMA and HUS might result from the combination of different factors: 1/ a shear stress due to hypertension; 2/ a direct effect of streptococcal toxins; 3/ complement activation damaging GEC either directly or through an impairment of vascular endothelial growth factor (VEGF) production by damaged podocytes. 1/ TMA due to isolated hypertension (absence of glomerulonephritis and of any other possible cause) has been reported by Zhang et al. [12] in 21 patients with biopsy proven isolated TMA, hemolytic anemia and malignant hypertension (200 to 280 / 100 to 180 mm Hg). In that study, LDH plasma levels were moderately increased (285-425 U/L; N: 110-250) and the majority of patients had no thrombocytopenia in contrast to what was observed in our patient.

From the 10 patients with HUS and PIGN previously reported [2-8], two [4,5] did not have hypertension at presentation. In a report of TMA in IgAN (10), 29% of patients presenting with TMA had controlled hypertension or no hypertension at all.

Hypertension is very common in PIGN (60 to 80% of cases) and is severe enough to need a treatment in 50% of cases [13]. The range of blood pressure presented by our patient is not uncommon in PIGN and she did not present with major symptoms of other target organs for malignant hypertension (convulsions, vision changes, heart failur). Therefore, it is doubtful that hypertension should have been the only cause of TMA and HUS in the present case 2/ several group A Streptococcus (GAS) proteins have been detected in glomeruli of patients with post-streptococcal GN [14]. The binding of fibrinogen to GAS fibrinogen receptor M1 facilitates adherence to and the invasion of EC [15]. It is therefore possible that GEC lesions resulted at least partly from a direct effect of GAS toxin.

3/ The intense linear and coarse distribution of complement factors along capillary walls and the subendothelial and subepithelial electron dense deposits suggest a damaging process of GEC and of podocytes by complement activation. The cellular lesions were characterized by a swollen aspect of GEC and by the effacement of podocytes foot processes. Nephrotic proteinuria presented by the patient pleads also for a damage of podocytes. Several observations suggest that podocyte damaging might result in endothelial lesions leading to TMA and HUS. a) VEGF is an endothelial-specific growth factor that promotes endothelial cell proliferation, differentiation and survival. In the kidney, VEGF expression is most prominent in glomerular podocytes and in tubular epithelial cells, while VEGF receptors are mainly found on preglomerular, glomerular, and peritubular endothelial cells [16] b/ It has been recently shown that the activation of the alternate pathway of the complement induces podocyte injury [17] c/ Patients treatment with bevacizumab, a humanized anti-VEGF antibodies results in TMA and HUS [18], d/ Mice with a genetic deletion of VEGF from glomeruli develop podocytes damaging, TMA and HUS [18]. Even if speculative, those observations suggest that podocytes damaging by complement activation might have played a role in the pathophysiology of TMA and HUS observed in our patient.

One heterozygote mutation of CFH and at risk polymorphism of CFH and MCP has been recently shown in 5 from a series of 6 adult patients presenting a GN complicated by HUS [11]. Although the investigation on genetic and immunological anomalies of the alternate pathway of the complement system in our patient was negative this does not completely exclude the diagnosis of atypical HUS since no genetic abnormality can be found in about 30% of aHUS up to now and that we did not look for the recombinant gene CFH-CFHR3. However, other mechanisms might be involved in the activation of the alternate pathway of the complement system in post-streptoccal GN. Some data suggest that it can result from a binding of complement factor H (CFH: co-inhibitor of the C3 convertase of the alternate pathway of the complement system) by several group A Streptococcus (GAS) proteins [19-21]. This binding might induce on one side a GAS escapement to opsonisation and on the other side a defect of inhibition of the alternative pathway at systemic and glomerular levels. The high intensity of glomerular complement activation observed in our patient could be related to a great amount of GAS proteins produced by the extensive streptococcal cutaneous lesions of the patient.

Although a spontaneous healing cannot be excluded, the intensive PE therapy might have been responsible for the rapid recovery of our patient by removing GAS toxins and inactivated CFH on one side and on the other side by providing free and active CFH in order to restore the physiological inhibition of the alternate pathway of the complement system.

In conclusion, this observation confirms that PIGN may be complicated by TMA and HUS which constitutes a higher risk of CKD. The extreme rarity of TMA and HUS in PIGN despite the commonness of hypertension in that disease, suggests the involvement of other pathophysiological mechanisms, for example the toxicity of GAS proteins for GEC and their ability to activate the alternative pathway of the complement system. PE therapy used in this complication may play an important role in the recovery of a normal renal function and in the prevention of CKD.

Contrarily to what was commonly admitted in the past PIGN may be frequently complicated by CKD [22]. Multicentre prospective studies should bet set up in order to evaluate the frequency and pathophysiology of TMA and HUS in this GN since the latter might enhance the risk of acute renal failure which increases the risk of CKD at long-term [23].

Funding Source

No funding was secured for this study.

Financial Disclosure

No financial relationship is to disclose.

Conflict of interest

No conflict of interest to disclose.

Acknowledgement

Dr Mitra Telbe, dermatologist provided the picture of a skin lesion and reviewed the manuscript.

References

1. Besbas N, Karpman D, Landau D Loirat C, Proesmans W, et al. (2006) European Paediatric Research Group for HUS. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int 70: 423-431.

2. Proesmans W, Baten E, Van Damme B (1995) A boy with acute renal failure. Pediatr Nephrol 9: 389-391.
3. Medani CR, Pearl PL, Hall-Craggs M (1987) Acute renal failure, hemolytic anemia, and thrombocytopenia in poststreptococcal glomerulonephritis. South Med J 80: 370-373.
4. De Chadarévian JP, Goodyer PR, Kaplan BS (1980) Acute glomerulonephritis and hemolytic uremic syndrome. Can Med Assoc J 123: 391-394.
5. Tan PH, Yadin O, Kleinman KS, Gura V, Cohen AH (1998) Simultaneous postinfectious glomerulonephritis and thrombotic microangiopathy: a renal biopsy study. Am J Kidney Dis 31: 513-520.
6. Duvic C, Desramé J, Hérody M, Nédélec G (2000) Acute poststreptococcal glomerulonephritis associated with thrombotic microangiopathy in an adult. Clin Nephrol 54: 169-173.
7. Laube G, Sarkissian A, Hailemariam S, Neuhaus TJ, Leumann E (2001) Simultaneous occurrence of the haemolytic uraemic syndrome and acute post-infectious glomerulonephritis. Eur J Pediatr 160: 173-176.
8. Siebels M, Andrassy K, Waldherr R, Ritz E (1995) Hemolytic uremic syndrome complicating postinfectious glomerulonephritis in the adult. Am J Kidney Dis 25: 336-339.
9. Song D, Wu LH, Wang FM, Yang XW, Zhu D, et al. (2013) The spectrum of renal thrombotic microangiopathy in lupus nephritis. Arthritis Res Ther 15: R12.
10. El Karoui K, Hill GS, Karras A, Jacquot C, Moulonguet L, et al. (2012) A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy. J Am Soc Nephrol 23: 137-148.
11. Manenti L, Gnappi E, Vaglio A, Allegri L, Noris M, et al. (2013) Atypical haemolytic uraemic syndrome with underlying glomerulopathies. A case series and a review of the literature. Nephrol Dial Transplant 28: 2246-2259.
12. Zhang B, Xing C, Yu X, Sun B, Zhao X, et al. (2008) Renal thrombotic microangiopathies induced by severe hypertension. Hypertens Res 31: 479-483.
13. Rodrigez-Iturbe B, Mezzano S (2009) Acute post infectious glomerulonephritis. In: Ellis D Avner,William E Harmon, Patrick Niaudet, Norishige Yoshikawa, Eds. Pediatric Nephrology. Springer-Verlag Berlin Heidelberg 743-755.
14. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ (2011) Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol 26: 165-180.
15. Uchiyama S, Andreoni F, Zürcher C, Schilcher K, Ender M, et al. (2013) Coiled-coil irregularities of the M1 protein structure promote M1-fibrinogen interaction and influence group A Streptococcus host cell interactions and virulence. J Mol Med (Berl) 91: 861-869.
16. Schrijvers BF, Flyvbjerg A, De Vriese AS (2004) The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. Kidney Int 65: 2003-2017.
17. Locatelli M, Buelli S, Pezzotta A, Corna D, Perico L et al. (2014) Shiga Toxin Promotes Podocyte Injury in Experimental Hemolytic Uremic Syndrome via Activation of the Alternative Pathway of Complement. J Am Soc Nephrol. 2014 Feb 27 [Epub ahead of print].
18. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, et al. (2008) VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 358: 1129-1136.
19. Pandiripally V, Gregory E, Cue D (2002) Acquisition of regulators of complement activation by Streptococcus pyogenes serotype M1. Infect Immun 70: 6206-6214.
20. Pandiripally V, Wei L, Skerka C, Zipfel PF, Cue D (2003) Recruitment of complement factor H-like protein 1 promotes intracellular invasion by group A streptococci. Infect Immun 71: 7119-7128.
21. Wei L, Pandiripally V, Gregory E, Clymer M, Cue D (2005) Impact of the SpeB protease on binding of the complement regulatory proteins factor H and factor H-like protein 1 by Streptococcus pyogenes. Infect Immun 73: 2040-2050.
22. Hoy WE, White AV, Dowling A, Sharma SK, Bloomfield H, et al. (2012) Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. Kidney Int 81: 1026-1032.
23. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, et al. (2013) Acute kidney injury: an increasing global concern. Lancet 382: 170-179.

This article was originally published in a special issue, entitled: **"Pediatric Nephrology"**, Edited by Dr. Moazzam Hossain, Bangabandhu Sheikh Mujib Medical University, Bangladesh