The limited role and risky profile of Rituximab in nephritis associated with Henoch-Schönlein purpura

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ABSTRACT

Adult-onset IgA vasculitis or Henoch-Schönlein purpura (HSP) is a systemic vasculitis characterized by IgA1-dominant deposits [1]. The symptoms include cutaneous purpura, ankle arthritis, enteritis and nephritis [2]. Contrary to children the disease is rare and is characterized by frequent and prolonged relapses as well as progressive nephritis [3]. HSP nephritis (HSPN) can be severe and refractory to corticosteroids with/without immunosuppressive agents [4]. The role of B cells in HSPN is not clearly defined with few case reports and studies showing high rates of remission and preservation of glomerular function with Rituximab therapy [5, 6]. The concept of depletion of antibody producing B cell with Rituximab is appealing despite the uncertainty of HSP pathogenesis. In the present case report; we describe our experience with Rituximab treatment in a patient with this disease. Our patient had different triggering factors for her relapses and lately Rituximab itself. Review of the literature indicates that autoantibodies to Gd-IgA1 did not decrease with Rituximab therapy and others indicated an inherited predisposition for higher levels in patients with progressive disease. Our findings confirm the limited role and risky profile of Rituximab in treatment of HSP.

Keywords: HSP, IgA, Rituximab, vasculitis.

INTRODUCTION

Adult-onset IgA vasculitis or Henoch-Schönlein purpura (HSP) is a systemic vasculitis characterized by IgA1-dominant deposits [1]. The symptoms include cutaneous purpura, ankle arthritis, enteritis and nephritis [2]. Contrary to children the disease is rare and is characterized by frequent and prolonged relapses as well as progressive nephritis [3]. HSP nephritis (HSPN) can be severe and refractory to corticosteroids with/without immunosuppressive agents [4]. The role of B cells in HSPN is not clearly defined with few case reports and studies showing high rates of remission and preservation of glomerular function with Rituximab therapy [5, 6]. The concept of depletion of antibody producing B cell with Rituximab is appealing despite the uncertainty of HSP pathogenesis. In the present case report; we describe our experience with Rituximab treatment in a patient with this disease.

THE CASE:

A 30-year-old woman presented with purpuric skin rash at lower extremities and buttocks. She also had ankle arthritis, abdominal pain and abnormal urine analysis. The latter showed microscopic hematuria and proteinuria (2 g/day). Systemic examination did not show abnormality. Serum sugar, urea, creatinine, electrolytes and liver functions were normal. Serum complements (C3 & C4), IgA level and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM-antibodies, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Kidney biopsy showed focal proliferative glomerulonephritis with immunoflorescent stains positive only for IgA and C3 in the mesangium (Fig. 1A). Since she had severe abdominal pain and ankle arthritis she had received Prednisone 20 mg/day, for 2 weeks, and felt better. For her proteinuria she received Lisinopril 20 mg/day and it decreased to < 500 mg/day. Two years later, she presented with the severe abdominal pains and the purpuric rash reappeared. She was pregnant at 12 weeks. At that time, her blood tests, liver and renal functions were normal except for hematuria and proteinuria again. She had discontinued Lisinopril months ago and planned for her current pregnancy. Upon assessment, her fetus was dead and evacuation was done. She was pregnant at 12 weeks. At that time, her blood tests, liver and renal functions were normal except for hematuria and proteinuria again. She had discontinued Lisinopril months ago and planned for her current pregnancy. Upon assessment, her fetus was dead and evacuation was done. However, in next few days she did not improve, even with high-dose Corticosteroids, and her rash became worse. She was re-evaluated by her gynecologist and found to have placental remnants. After proper evacuation, she felt better and the rash disappeared. Subsequently, she lost follow up and presented for management during 2 more successful pregnancies without complications except for increment of
her proteinuria to 3 g/day and decrease creatinine clearance to 50 ml/minute. In an attempt to improve her IgA disease, Rituximab was tried at a dose of 1 g to be followed by another 1 g 2 weeks later. However, after the first Rituximab infusion, she developed the purpuric rash again (Fig. 2). Skin biopsy showed non-necrotizing subepidermal leukocytoclastic vasculitis (Fig. 3). Moreover, she had abdominal pain, ankle arthritis and serum creatinine had increased from normal to 250 umol/L. Biopsy of the skin rash showed leukocytoclastic vasculitis (Fig. 3). Kidney biopsy; showed focal proliferative glomerulonephritis with IgA deposits yet with cellular crescent formation > 50% (Fig. 1B). She was treated with Solumedrol 1 g daily for 3 days followed by Prednisone 60 mg/day for 1 month. The latter was tapered down and was discontinued 2 more months later. She felt better and her serum creatinine decreased to 165 umol/L. Repeat kidney biopsy 6 months later showed that 60% of her glomeruli have global sclerosis with fibrous crescents and mesangial fibrosis (Fig. 1C). In the past 2 years; she is being treated with Lisinopril 20 mg daily with Spironolactone 25 mg twice weekly. Moreover, she was instructed to avoid further pregnancies. She did not have subsequent relapse and her creatinine clearance is 30 ml/minute with proteinuria at 800 mg/day.

Figure 1. Photomicrograph of kidney biopsy: (A) initially showing just segmental mesangial proliferation. (B) Immediately after Rituximab therapy showing extensive cellular crescents. (C) 6 months after Rituximab therapy. H&E X 100

Figure 2. Showing extensive purpura after Rituximab therapy.
DISCUSSION

Patients with HSP have an underlying IgA disease with persistent hematuria [7]. The prognosis of HSP depends on: (a) frequency of relapses of the systemic disease and (b) outcome of its nephritis [8]. Hence, management of HSPN entails: (a) control of relapses and (b) prevention of its progressive IgA disease. The triggering factors for relapses are difficult to ascertain yet infections and drugs are common culprits. Moreover, relapses are usually associated with crescent formation on top of a focal proliferative IgA disease [9]. Naturally; frequent and poorly-treated relapses has poor prognosis since associated progressive crescentic glomerular loss as seen in our patient. Our patient experienced her first relapse with intra-uterine fetal death then concealed placental remnants. The second relapse was timely related to Rituximab therapy. The latter was used to slow the progression of her chronic IgAN yet was immunogenic. Unless contraindicated by infections; Corticosteroids and immunosuppressive agents are indicated in crescentic IgAN [10]. On the other hand; halting the progression of the chronic disease i.e. IgAN should be include safe and efficacious measures. Unfortunately, Rituximab-use in such prophylaxis was not safe and had induced a relapse of HSPN. Recent large randomized multicenter trials questioned the role of Corticosteroids, immunosuppression and even Rituximab in halting the progression of chronic IgAN [11]. Interestingly, IgAN is the most common primary glomerular disease in the world [12]. Among patients with reduced renal function and proteinuria >1 g/24 h, outcomes remain poor with up to 50% of such patients can progress to ESRD over 10 years [13]. The concept of an underlying immunological disorder stemmed from the discovery of galactose deficient-IgA1 phenomenon. The extent of Mesangial Gd-IgA1 deposition and its serum levels was associated with disease progression [14, 15]. However, in a recent multicentric study; there was no favorable effect of rituximab on the level of Gd-IgA1 [16]. Moreover, a recent study questioned the role of autoimmunity in the development of aggressive disease in IgAN and indicated that a higher level of Gd-IgA1 is a hereditary predisposition [17]. Our findings indicate that Rituximab is not useful in IgAN and can trigger flare of HSP with further crescent formation and progressive disease. At present, the established benefit in halting the progressive nature of IgAN in predisposed patients with high autoantibodies to Gd-IgA1 is limited to decrease intraglomerular pressure via: (a) limiting pregnancies in females and (b) agents that antagonize the renin-angiotensin-aldosterone system (RAAS) [18].

REFERENCES: