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Anti-Glomerular Basement Membrane Disease Combined with IgA Nephropathy Complicated with Reversible Posterior Leukoencephalopathy Syndrome: An Unusual Case

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 24
Final Diagnosis: Crescentic glomerulonephritis (type I) with IgA nephropathy
Symptoms: Headache • gross hematuria • nocturia • seizures
Medication: Cyclophosphamide
Clinical Procedure: Dignosis to treatment
Specialty: Nephrology

Objective: Rare co-existance of disease or pathology

Background: Anti-glomerular basement membrane disease (anti-GBM disease) is an autoimmune glomerulonephritis disease that is characterized by IgG linear deposition along the non-collagen domain of α3 chains of type IV collagen on the GBM. Although anti-GBM disease accompanied with IgA linear deposition along GBMs was discussed previously in some papers, anti-GBM disease combined with IgA granular deposition in the mesangial area, especially complicated with reversible posterior leukoencephalopathy syndrome (RPLS), was rarely reported. RPLS is usually caused by hypertensive encephalopathy, renal decompensation, fluid retention, and adverse effects of immunosuppressive drugs.

Case Report: A male patient with the chief complaints of headache, gross hematuria, and nocturia was referred to our hospital. Based on renal biopsy, the diagnosis was finally confirmed as anti-GBM disease combined with IgA nephropathy and, the patient received comprehensive treatment, including cyclophosphamide (CTX), which led to symptom improvement. Two days after the third impulse CTX was given, he suddenly experienced headache and dizziness, which eventually developed into a tonic-clonic seizure. RPLS was identified by cranial magnetic resonance imaging (MRI) with reversible neuroimaging. After diazepam and antihypertension management, seizures were controlled. RPLS, a neurological complication, was found in anti-GBM disease with IgA nephropathy during our immunosuppressants therapy for the first time.

Conclusions: It is worth paying more attention to patients with rapidly progressive glomerulonephritis (RPGN), as they might be complicated with RPLS during intravenous administration of CTX and methylprednisolone. We suggest the neuroimaging be examined as soon as the seizure happens.

MeSH Keywords: Anti-Glomerular Basement Membrane Disease • Glomerulonephritis, IGA • Posterior Leukoencephalopathy Syndrome

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/894619

Background

Rapidly progressive glomerulonephritis (RPGN) can be classified into 3 categories according to immune pathological characteristics: anti-glomerular basement membrane disease (anti-GBM disease), immune complex disease (which refers to IgA nephropathy, Henoch-Schönlein purpura nephritis, and lupus nephritis), and pauci-immune disease (mainly anti-neutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis) [1]. Among these, anti-GBM disease is a rare form of autoimmune glomerulonephritis disease mediated by anti-GBM antibodies [2]. It is characterized by IgG linear deposit along the non-collagen domain of α3 chains of type IV collagen on the GBM. When the condition is accompanied with lung hemorrhage, it is known as Goodpasture's syndrome [3]. IgA nephropathy is an immune complex-mediated glomerulonephritis with the existence of IgA deposits predominantly in the mesangial area, and is accompanied by a variety of histopathologic lesions [4]. As IgA deposition in the mesangial area could also be found in other autoimmune diseases, secondary IgA nephropathy need to be excluded when IgA nephropathy is diagnosed based on immunofluorescence.

Reversible posterior leukoencephalopathy syndrome (RPLS) was described by Hinchey et al. in 1996 for the first time, characterized by a reversible syndrome of headache, altered mental functioning, seizures, and loss of vision associated with white matter edema and signal abnormalities, mostly in the posterior or temporo-parieto-occipital regions of patients with various conditions [5,6]. CT and MRI studies for PRLS have showed extensive bilateral white-matter abnormalities, suggesting edema in the posterior brain regions [6]. A predilection for the posterior brain could be due to a decrease of sympathetic innervation as compared to the anterior circulation [7], thus a reduced ability to self-regulation. With few references discussing RPGN complicated with RPLS, we would like to bring up the issue with this unusual case.

Case Report

A 24-year-old HBV-infected man (without the specific process of infection) was referred to our department on April 19, 2014, who had been suffered from sudden headache, gross hematuria, proteinuria and nocturia for one month. He had no habit of drinking or smoking, nor had contacted with organic solvents and hydrocarbons. General examination showed a blood pressure of 194/120mmHg, bilateral lower extremity edema. No positive results in neurologic examination. Laboratory studies revealed anemia (a hemoglobin level of 8.2g/dl), hypoalbuminemia (a total protein of 25.8g/dl, a serum albumin of 3.09 g/dl) and hyperlipidemia. Urinary sediment showed 25–30 red blood cells/HPF, and urinary protein excretion was 7.04g/24h. His urine output dropped significantly, and plasma creatinine rose rapidly from April 18 to 30 (serum creatinine from 3.7mg/dl to 15.7mg/dl). The valuation for RPGN showed that the test for anti-GBM antibody was positive. Other parameters showed: IgA 5.07g/l, HBV-DNA 3.07E+08IU/ml. C-reactive protein (CRP) 8.24mg/l. Antinuclear, anti-dsDNA, antineutrophil cytoplasmic antibodies, antibody of HIV and hepatitis C were all negative. Serum C3 and C4 fraction levels of complement were within the normal range. The chest radiograph and cranial computed tomography (CT) were normal. An ultrasound revealed normal-sized kidneys and healthy liver. With the guidance of ultrasonography, renal biopsy was carried out to ascertain the cause. It contained two cores of renal parenchyma with 31 glomeruli, two of which were globally sclerotic and 18 of were crescents. Tubuli were atrophic with interstitial edema and lymphocyte infiltration was noted. There were two glomeruli immunofluorescent staining. A strong linear staining of GBMs for IgG and C3 (Figure 1B, 1D), along with mesangial granular deposition for IgA (Figure 1C) and no staining was observed for IgM, C1q, HBcAg or HBsAg. Electron-dense deposits in GBM and mesangium were demonstrated by electron microscopy (Figure 1A). Based on these pathologic findings, the patient was diagnosed as crescentic glomerulonephritis (type I) with IgA nephropathy. Accordingly, the patient received conventional dialysis three times a week, plasma exchange (PE) for six sessions. He was treated with pulse dose of intravenous methylprednisolone 500mg/day for three days followed by maintenance oral prednisolone at 1mg/kg/day and intravenous cyclophosphamide (10 mg/kg) every two weeks. As a result, his anti-GBM antibody titers turned negative on Day 35. The third cyclophosphamide (CTX) therapy was one week delayed because of a respiratory tract infection. The patient was coughing and spitting, so tests were carried for bacterium sputum culture and viral serology, with fungal spores identified by smears. After oral fluconazole for 1 week, his cough and expectoration improved and fungal smears were negative. Two days after the third CTX infusion (on day 56), the patient suddenly experienced headache and dizziness, and then had 4 tonic-clonic seizures. After 1 therapy session, his blood pressure rose to 180/120 mmHg. Biochemical evaluation showed slight hypokalemia (k 2.95 mmol/l) and hypocalcemia (Ca 1.86 mmol/l). His blood glucose was normal and serum creatinine was 5.9 mg/dl (post-dialysis). With the application of diazepam and antihypertension, seizures were controlled.

The cranial magnetic resonance imaging (MRI) without contrast on day 61 revealed multiple abnormal cerebral signals, which were considered to be a cerebral white-matter lesion (Figure 2A). The second MRI, on day 72, without contrast, showed patchy abnormal spots restricted to the occipital lobe (bilateral) and posterior parietal lobe (left), but scopes of the lesion were improved compared with 12 days before. Therefore, brain vasogenic edema was considered (Figure 2B). A follow-up cranial MRI, which showed the almost complete resolution of the brain lesions,

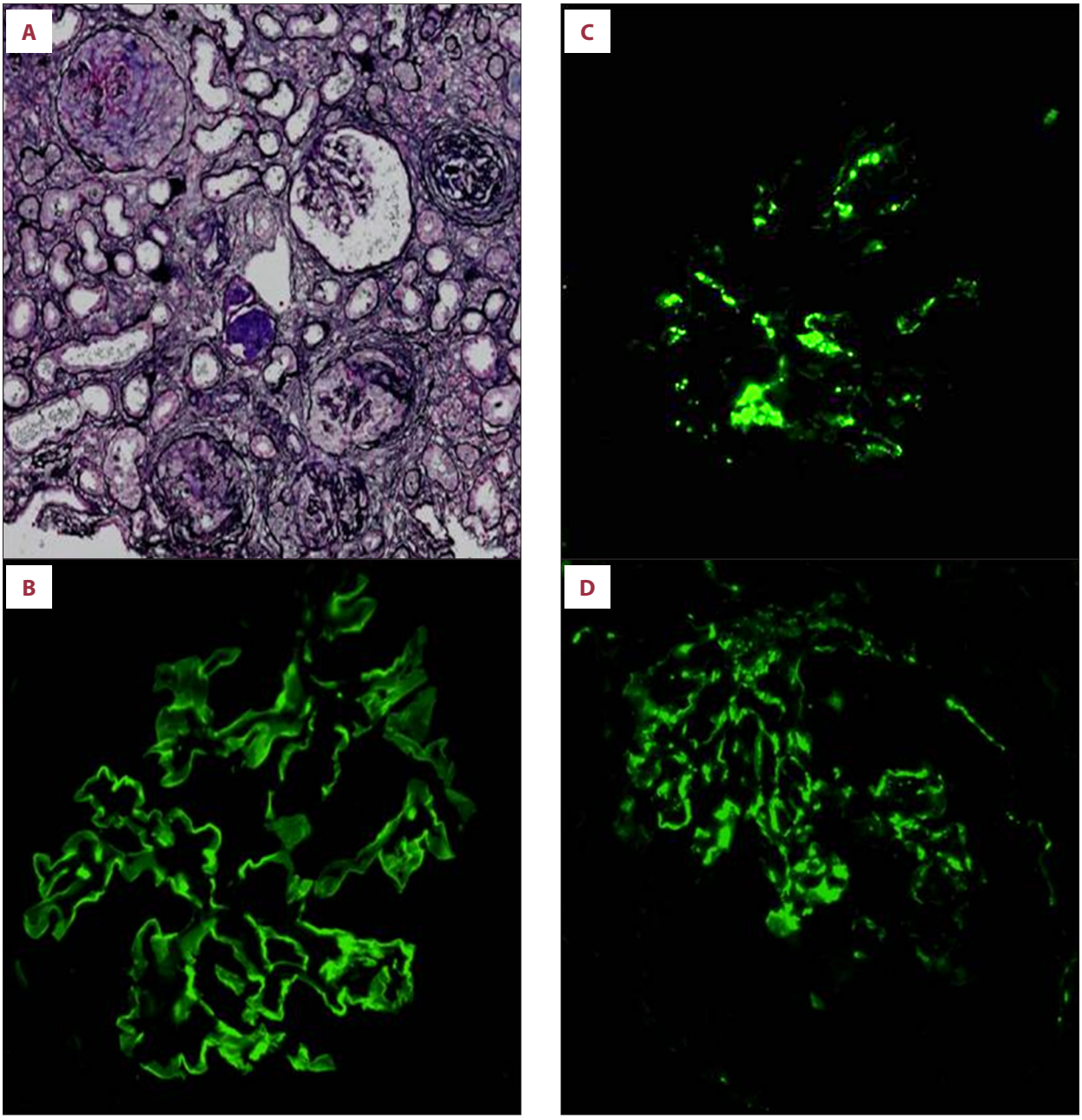

Figure 1. Active crescentic glomerulonephritis was present in the renal biopsy by Masson's trichrome covering with silver staining. Large crescents direct immunofluorescence was shown in the renal biopsy specimen (**A**). Linear fixation of IgG was shown along the GBM (**B**), while the deposition of IgA was exhibited (**C**), predominantly within the mesangial regions of glomeruli. C3 granular deposits in the mesangium area and glomerular capillary wall (**D**).

was conducted on day 86. However, the serum creatinine was around 7.9 mg/dl and the patient remained on hemodialysis.

Discussion

The pathology of anti-GBM disease reveals linear immunoglobulin deposition for IgG and C3, whereas IgA and IgM are deposited less commonly [2]. We have found some cases reporting anti-GBM disease with IgA linear deposition along GBMs [8], but anti-GBM disease combined with IgA granular deposition in the mesangial area is rarely discussed. After excluding some differential diseases that could reveal IgA granular deposited in the mesangium under immunofluorescence, such as IgA-dominant acute postinfectious glomerulonephritis, Henoch-Schönlein purpura, and HBV-glomerulonephritis [9], we

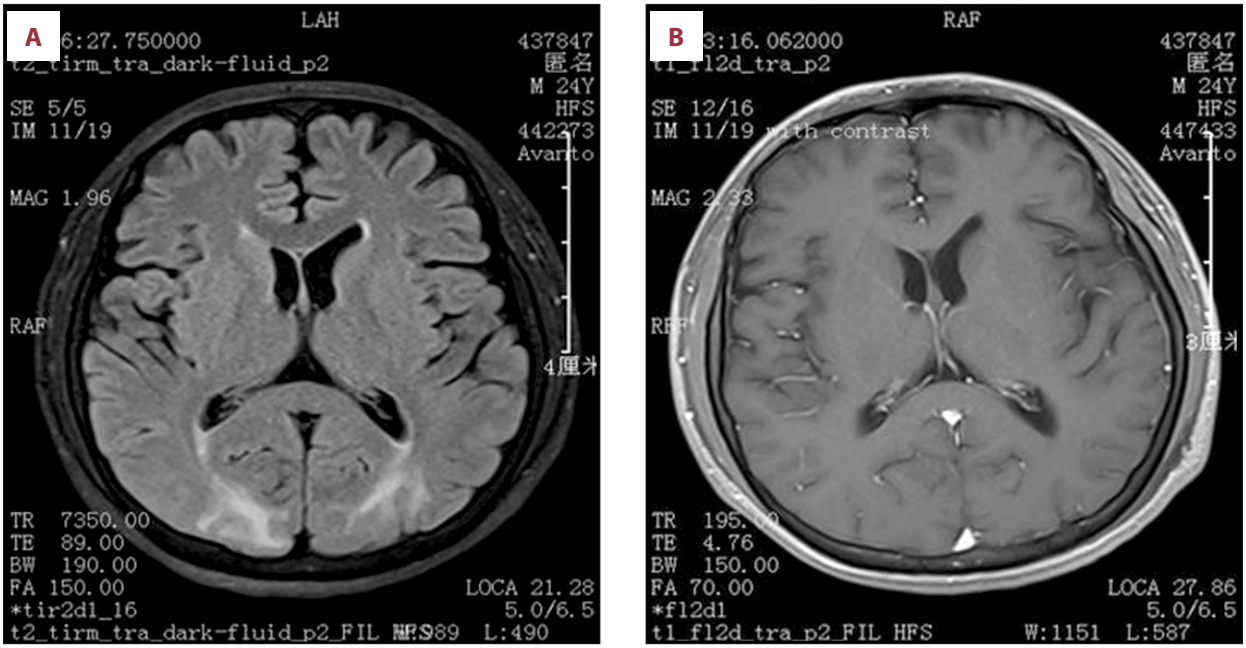

Figure 2. Axial FLAIR image, obtained 5 days after the patient's seizures, reveals high-signal-intensity lesions at many points in the bilateral occipital cortex and posterior parietal cortex (**A**). Follow-up axial FLAIR image MRI on day 72 shows high signal range reduced compared with the image on day 61 (**B**).

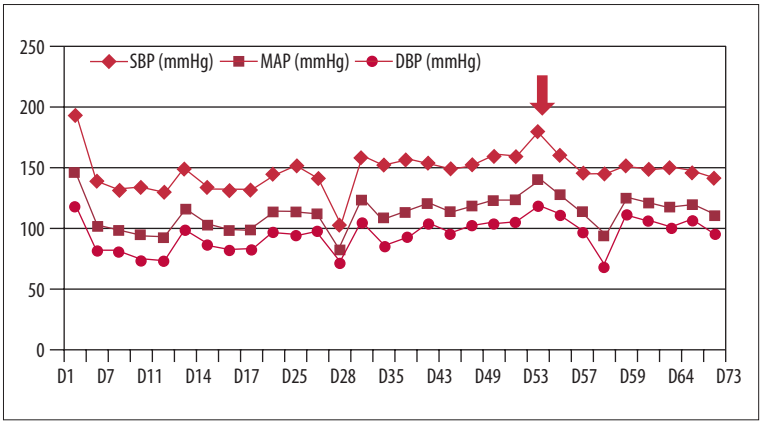

Figure 3. The tendency of diastolic and systolic blood pressure and mean arterial pressure showed in the graph. The mean arterial pressure (MAP) was 147 mmHg on day 1, which is higher than when he had a sudden seizure on day 56 (140 mmHg).

diagnosed it as primary IgA nephropathy. The patient started plasmapheresis and pulse steroid and cyclophosphamide therapy; as a result, the anti-GBM antibody turned negative, but the patient had to rely on hemodialysis. RPLS was complicated by anti-GBM crescentic glomerulonephritis and IgA nephropathy during treatment. So far, the pathogenesis of RPLS is still vague [10].

Two possible causes were summarized for our case. On the one hand, it can be seen clearly from the following graph (Figure 3) that the mean arterial pressure (MAP) of the patient when he was referred to our hospital was higher than when the seizures happened. The abrupt rise of blood pressure above the cerebral auto-regulation limit could lead to disturbance of the blood-brain barrier (BBB) and vasogenic cerebral edema [11]. Given the MAP data, we could not completely exclude the possibility of hypertensive encephalopathy. On the other hand, during the treatment, the patient received 3 sessions of intravenous pulse methylprednisolone therapy constantly, the most common adverse effect of is fluid retention [12]. Moreover, triple CTX therapy in this case contributed to endothelial dysfunction and injury of the BBB. Both of these 2 drugs are able to decrease cerebral vessel resistance by myogenic response changes of brain blood vessels. Thus, as the cerebral blood flow increases, it might result in vasogenic cerebral edema, which is characterized by seizures in clinical features. During the process of remission, we stopped CTX, but never ceased the steroids management (methylprednisolone 40 mg/day). Therefore, the possibility that methylprednisolone caused RPLS was excluded.

We are still unable to clearly define the cause of the underlying disease, anti-GBM disease, which revealed the high titer of anti-GBM antibody. In 1919, Rydel et al. reported the case of an 18-year-old boy who was diagnosed with Goodpasture's syndrome and ANCA-negative central nervous system vasculitis. They speculated on the role of anti-GBM antibodies in CNS vasculitis in Goodpasture's syndrome [13].

Because the clinical manifestations of this syndrome are not specific, it is necessary to distinguish it from other causes of headache, confusion, and seizure [14]. More specifically, in order to identify the above diseases, it is important to pay attention to the range of electrolytes, serum creatinine, and timely neuroimaging.

In summary, it is not unusual to deliver large doses of methylprednisolone and CTX therapy during the treatment of RPGN, a common and severe nephropathy. If central nervous system symptoms occur, MRI should be conducted to exclusively diagnose RPLS [15].

Conclusions

When anti-GBM disease combined with IgA deposited in the mesangium occurs, we should suspect IgA nephropathy. Treatment of RPGN with intravenous administration of CTX and methylprednisolone might be complicated with RPLS. In our case, the main cause of RPLS could be CTX adverse effects and hypertensive encephalopathy. Neuroimaging is needed after a seizure.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publishing of this paper.

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