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SHORT COMMUNICATION

Rituximab effectively reverses papilledema associated with cerebral venous sinus thrombosis in antiphospholipid antibody syndrome

K.V. CHALAM, S.K. GUPTA, S. AGARWAL

Department of Ophthalmology, School of Medicine, University of Florida, Jacksonville – USA

PURPOSE. *A case of bilateral papilledema secondary to cerebral venous sinus thrombosis treated with Rituximab, an anti-CD20 monoclonal antibody.*

METHODS. *A 23 year old obese female with a one week history of blurred vision, headaches and vomiting presented with bilateral papilledema. Her BCVA was 20/50 in right eye and 20/200 in the left eye with severe reduction of visual fields. Laboratory investigations revealed thrombocytopenia, prolonged prothrombin time (not reversed when mixed with normal plasma) and anticardiolipin antibodies. Besides, cerebral angiogram showed presence of cerebral venous thrombosis. The patient was diagnosed to have anti phospholipid antibody syndrome and treated with rituximab I.V. 375 mg/m 2 weekly x 4 doses, acetazolamide 500 mg BID, methyl prednisolone I. V. QID x 4.*

RESULTS. *At 1-month, her headaches and vision improved to 20/30 in both eyes with partial resolution of papilledema and complete restoration of visual fields. Nine months later, patient had 20/25 vision in right eye and 20/30 in left eye with complete resolution of papilledema and cerebral sinus thrombosis.*

CONCLUSIONS. *Rituximab was effective in reversing papilledema and cerebral sinus thrombosis, while preserving the vision in patient with antiphospholipid antibody syndrome. It is efficacious in treating papilledema in patients refractory to treatment with systemic steroids and immunoglobulin, with better clinical compliance and no side effects. (Eur J Ophthalmol 2007; 17: 867-70)*

KEY WORDS. *Anti phospholipid antibody syndrome, Papillodema, Rituximab, Venous sinus thrombosis*

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INTRODUCTION

Antiphospholipid antibody syndrome (APLAS) is an autoimmune disease, in which antibodies are formed against phospholipids on cell membranes. It classically presents as unexplained spontaneous thrombosis of arteries/veins in any tissue/organ and/or recurrent pregnancy losses, presence of antiphospholipid antibodies, lupus anticoagulant (prolonged aPTT not reversed when mixed with normal plasma), and anticardiolipin antibody of IgG/IgM (1). Common ocular presentation of APLAS includes retinal vascular occlusions, optic neuropathies, transient ischemic attack, amaurosis fugax, isolated retinal hemorrhages and cotton wool spots, and retinal neovascularization (2-4).

Rituximab, a new drug, is a chimeric anti-CD20 monoclonal antibody consisting of human immunoglobulin shown to be effective in treating APLAS (5). We report a patient treated effectively with rituximab who had presented with papilledema secondary to cerebral venous sinus thrombosis and APLAS.

Case report

A 22-year-old woman presented with progressively worsening headache, earache, and blurred vision in both eyes

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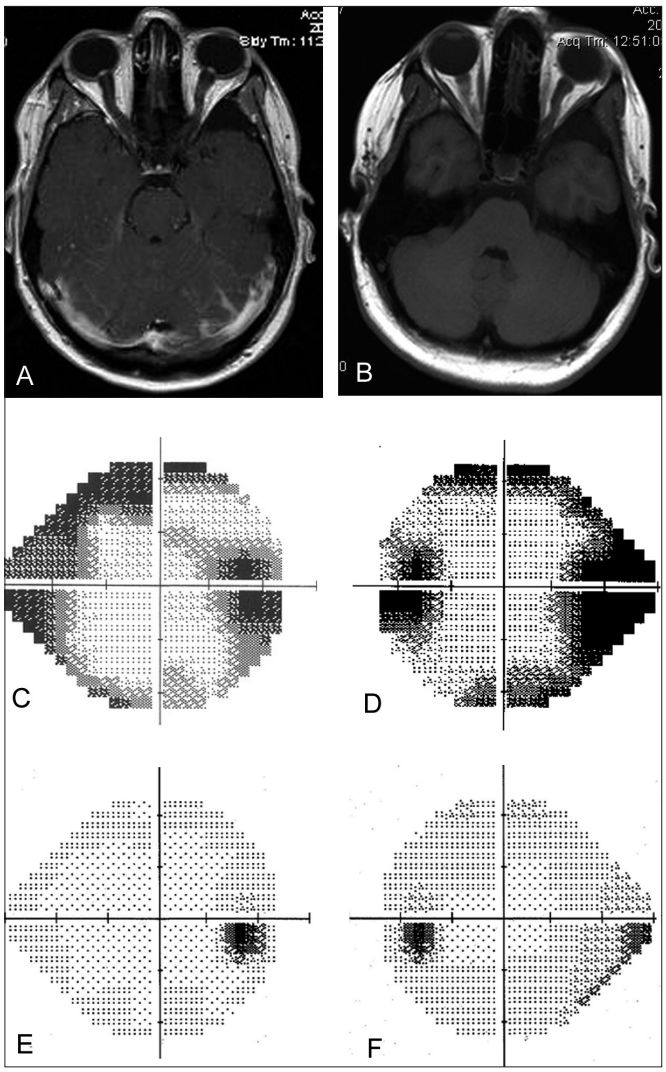

Fig. 1 - (A) *MRI T1-weighted image showing papilledema (bilaterally) with dilated optic nerve sheaths at presentation.* **(B)** *Resolved papilledema after rituximab treatment.* **(C, D)** *Humphrey visual field (HVF) 24-2 of right and left eye showing enlarged blind spot and constricted visual fields at presentation.* **(E, F)** *HVF 24-2 of right and left eye at 9 months showing improved visual fields after treatment with rituximab.*

of 1 week duration associated with vomiting. She had no history of systemic disease, bleeding/clotting disorders, intake of oral contraceptives or estrogen, smoking, or alcohol use. Neurologic examination was normal. Best-corrected visual acuity was 20/50 and 20/200 in the right and left eye, respectively. RAPD was noticed in the left eye. Slit-lamp examination was unremarkable in both eyes. Ophthalmoscopy of both eyes showed no vitreous cells and severe disc edema.

MRI T1-weighted image showed papilledema in both eyes (Fig. 1A). 24-2 Humphrey visual field (HVF) in both eyes revealed enlarged blind spot and constricted fields (Fig. 1, C, D); the mean deviation was –15.47 db in right eye and –15.55 db in the left eye. Lumbar puncture demonstrated an opening pressure of 400 mmH_2O. Laboratory investigations are shown in Figure 2. Cerebral angiogram revealed bilateral filling defects at the junction of transverse and sigmoid sinuses indicative of venous sinus thrombosis (Fig. 3, A, B). Intracerebral venography from right jugular bulb confirmed the presence of sigmoid venous sinus thrombosis (Fig. 3C).

The patient was diagnosed with bilateral sigmoid venous sinus thrombosis, antiphospholipid antibody syndrome, factor V Leiden mutation, and papilledema secondary to raised intracranial pressure. She was treated with rituximab (IV 375 mg/m^2 weekly x 4 doses).

One month after presentation, vision improved to 20/30 in both eyes. At 9 months, BCVA was 20/25 in right eye and 20/30 in left eye. Fundus examination showed resolution of papilledema with secondary optic disc pallor. MRI T1-weighted image showed normal optic disc with no evidence of papilledema in both eyes (Fig. 1B). 24-2 HVF showed restoration of visual fields (Fig. 1, E, F) with mean deviation of –1.56 db in right eye and –4.51 db in left eye (normal <2 db). Cerebral angiography revealed resolution of sinus thrombosis with retained flow (Fig. 3, D, E).

DISCUSSION

In a young, obese female presenting with an acute onset of headache, vomiting, blurred vision, and papilledema, differential diagnosis of raised intracranial pressure includes idiopathic intracranial hypertension (IIH), decreased CSF resorption (venous sinus thrombosis, meningitis, subarachnoid hemorrhage), and intracranial tumors. IIH, a benign condition seen in obese young women, is excluded by the absence of intracranial venous sinus thrombosis. Antiphospholipid antibody syndrome is a diagnosis of exclusion.

In our patient, presence of cerebral venous sinus thrombosis, thrombocytopenia, prolonged prothrombin time (not reversed when mixed with normal plasma), and anticardiolipin antibodies points to classical features of APLAS (1). Absence of anti-double stranded antibodies rules out systemic lupus erythematosus, which is present in up to 50% of patients with antibodies to phospholipids, making it a primary APLAS.

Fig. 2 - *Laboratory test values in the patient with antiphospholipid antibody syndrome (APLAS) before and after rituximab treatment.*

Laboratory tests	Before rituximab	After 3 injections of rituximab	Normal range
White blood cells	12.8	3.9	4.5-11.0 (thou/mm$^{3)}$
Red blood cells	4.46	4.11	4.2-5.5 (mill/cumm)
Platelets	94	216	140-440 (thou/mm$^{3)}$
Mean Platelet Volume	12.8	11.9	7.4-10.4 (u/cum)
Prothrombin Time	13.9	13.4	10-13 (seconds)
Dilute Russell Viper Venom Screen (DRVVT)	49.7		< 41 (seconds)
PTT mixing study	52.9		20-36 (seconds)
Patient plasma + normal plasma	38.5		
Control (seconds)	26.3		
Anticardiolipin antibodies Ig G	17		0-10 GPL u/ml
Lupus anticoagulant	positive		
Protein C functional	171 %		74-151 %
Factor V Leiden mutation(Heterozygous)	positive		

Other tests done were within normal range: Hemoglobin, hematocrit, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) Mean Corpuscular Volume (MCV), Red cell distribution width (RDW), Erythrocyte sedimentation rate (ESR), Thrombin time, Anti DNA double strand Antibody, Beta Human chorionic gonadotrophin (B-HCG), Rheumatoid factor, Antinuclear Antibody, Rapid plasma reagin (RPR), Protein S functional, Factor V assay, serum electrolytes.

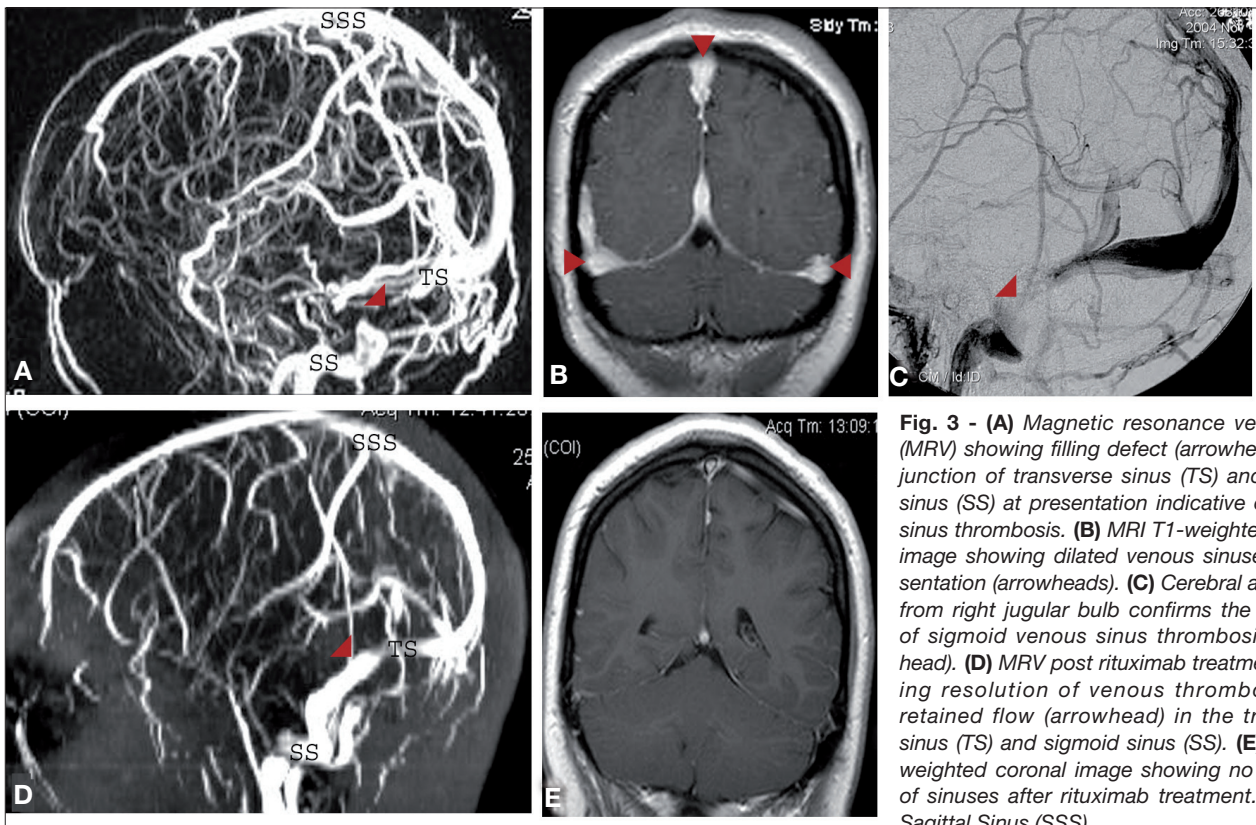

Fig. 3 - (A) *Magnetic resonance venography (MRV) showing filling defect (arrowhead) at the junction of transverse sinus (TS) and sigmoid sinus (SS) at presentation indicative of venous sinus thrombosis.* **(B)** *MRI T1-weighted coronal image showing dilated venous sinuses at presentation (arrowheads).* **(C)** *Cerebral angiogram from right jugular bulb confirms the presence of sigmoid venous sinus thrombosis (arrowhead).* **(D)** *MRV post rituximab treatment showing resolution of venous thrombosis with retained flow (arrowhead) in the transverse sinus (TS) and sigmoid sinus (SS).* **(E)** *MRI T1-weighted coronal image showing no dilatation of sinuses after rituximab treatment. Superior Sagittal Sinus (SSS).*

The most common ocular presentation in patients with APLAS is retinal vascular thrombosis and optic neuropathies (2-4).

Corticosteroids, immunosuppressive, and anticoagulant drugs are the mainstay therapy in patients with APLAS. Rituximab, an anti-CD20 monoclonal antibody, has been shown to be successful for both oncologic and autoimmune diseases of the hematopoietic system with no side effects (5). It interferes with the production of autoantibodies and induces B-cell depletion. Our patient responded dramatically with rituximab (IV 375 mg/m ^{2} weekly x 4 doses) with no side effects and complete resolution of papilledema and cerebral venous thrombosis with complete visual recovery.

Rituximab is a promising and safe drug in the treating patients with raised intracranial pressure secondary to antiphospholipid antibody syndrome. Its major advantage is the fact that it does not have the severe side effects that can be associated with steroids or immunosuppressive agents.

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Reprint requests to:
K.V. Chalam, MD
580 West 8th Street
Tower 2, 3rd Floor
Jacksonville, FL 32209, USA
kchalam@jax.ufl.edu

REFERENCES

1. Sammaritano LR. Antiphospholipid syndrome: review. South Med J 2005; 98: 617-25.
2. Smirnova TV, Kozlovskaia NL, Kiseleva TN, et al. Anterior ischemic neuropathy associated with antiphospholipid syndrome. Vestn Oftalmol 2006; 122: 46-7.
3. Giorgi D, Balacco Gabrieli C. Optic neuropathy in systemic lupus erythematosus and antiphospholipid syndrome (APS): clinical features, pathogenesis, review of the literature and proposed ophthalmological criteria for APS diagnosis. Clin Rheumatol. 1999; 18: 124-31.
4. Giorgi D, Balacco Gabrieli C, Bonomo L. The clinico-ophthalmological spectrum of antiphospholipid syndrome. Ocul Immunol Inflamm 1998; 6: 269-73.
5. Erdozain JG, Ruiz-Irastorza G, Egurbide MV, Aguirre C. Sustained response to rituximab of autoimmune hemolytic anemia associated with antiphospholipid syndrome. Haematologica 2004; 89: ECR34.