International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Case Report .

A Case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) in Granulomatosis with Polyangitis (GPA)

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ABSTRACT

A 14 years old boy from Saudi Arabia arrived to emergency room with diffuse abdominal pain, nausea and frequent non bloody, non-bilious vomiting. On examination, he had pale conjunctiva, some erythematous purpuric rash which appeared over his cheeks and both arms, not painful or itchy with mild epigastric tenderness, no signs of volume overload. Urine dipstick showed ++++ blood and + protein. High-resolution computed tomography (HRCT) showed small peripheral infiltrations at the base of the right lung and bilateral pleural effusion. Based on clinical, histopathological (kidney and skin biopsies) along with high C ANCA titer the patient diagnosed as having GPA. After we started him on treatment he developed status epilepticus and MRI brain showed classical findings of RPLS, which later resolved completely. Final diagnosis was reversible posterior leukoencephalopathy syndrome (RPLS) in GPA. In conclusion, RPLS is an important, rare entity to be recognized in patients with GPA and other connective tissue diseases. It is important to differentiate RPLS from other common CNS disorders found in patients with autoimmune diseases.

Keywords: Posterior Leukoencephalopathy Syndrome, Granulomatosis With Polyangitis, Children, High-Resolution Computed Tomography.

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Article History:

Received: 05-01-2017, **Revised:** 18-01-2017, **Accepted:** 29-01-2017

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2017.3.1.041	

INTRODUCTION

Reversible posterior leukoencephalopathy syndrome (RPLS) is a recently reported disorder present with characteristic findings in magnetic resonance imaging (MRI) exhibiting bilateral gray and white matter abnormalities in the posterior regions of the cerebral hemispheres and cerebellum.[1]

This syndrome is characterized by acute to subacute onset of headache, nausea, dizziness, changes in consciousness (lethargy, coma, diminished spontaneity of speech, convulsions and transient visual disturbances.[2]

RPLS is caused by various heterogeneous factors and has been described in numerous medical disorders.[3] Hypertension and immunosuppressive or cytotoxic drugs have been observed to be the most significant causes of RPLS in pediatric and adult patients.[4,5]

RPLS has been previously reported to affect adults mainly. However, it has been recently recognized that RPLS is also prevalent among children,[6] particularly in those with autoimmune disease, acute leukemia, sickle cell anemia and nephrotic syndrome, in patients mainly taking glucocorticoids, immunosuppressant medications, cytotoxic drugs or had severe hypertension.

Granulomatosis with polyangitis (GPA) or Wegener's granulomatosis (WG) is one of the systematic vasculitides involved in various organs and characterized pathologically by necrotizing granulomatous inflammation.[7] It is particularly difficult due to its various presentations; from isolated dermatologic, to respiratory, to ophthalmologic manifestations, which may be mistaken for an isolated complaint.[8]

We report here a 14 years old boy diagnosed with both disorders (RPLS and GPA).

CASE REPORT

A 14 years old boy from Saudi Arabia who had been well until 6 days before arrival to emergency room where he was complaining of diffuse abdominal pain, nausea and frequent non bloody, non-bilious vomiting.

Two weeks prior to his presentation, he had symptoms of common cold in form of sore throat and runny nose along with epistaxis. The epistaxis was intermittently occurred since six months of small amount of fresh blood which always stopped spontaneously without difficulty in breathing or previous facial trauma.

He denied hemoptysis, hematuria, gingival bleeding, genital or oral ulcers. There was no history of fever or joint pain. There were no episodes of sinusitis or respiratory symptoms like wheezes or chronic cough. In addition, he denied dysuria, presence of stone or frothy urine.

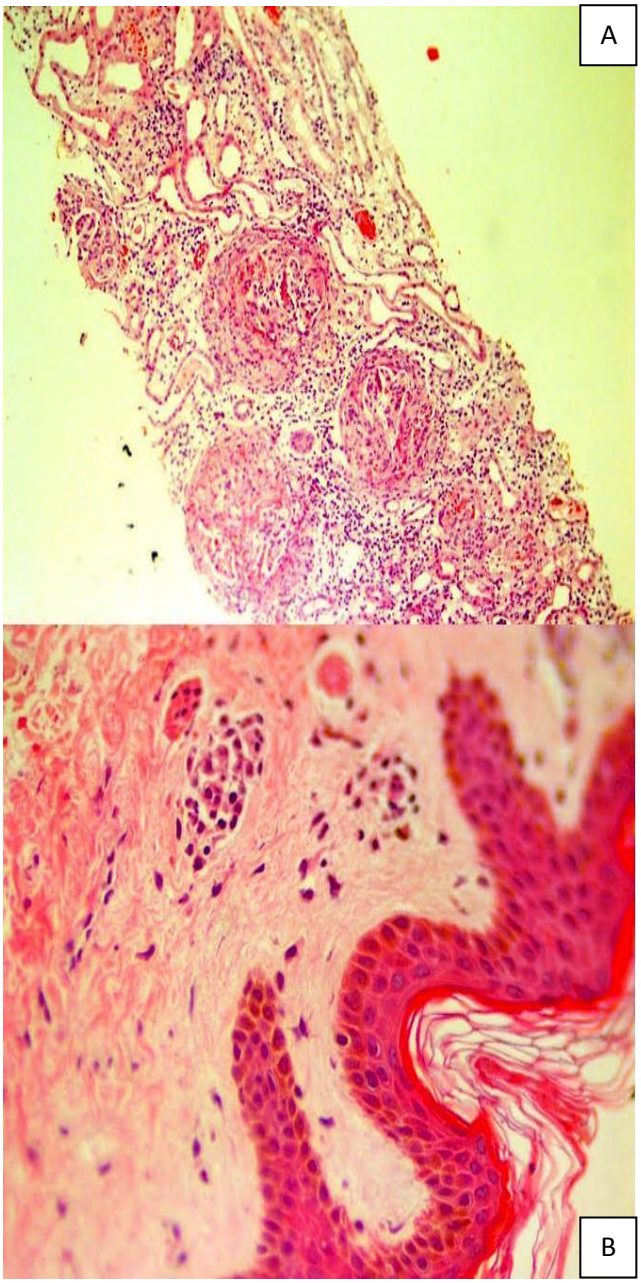

Fig A,B: (A) Renal biopsy showing crescent glomerulonephritis with necrotizing proliferative and sclerotic lesions involving almost 100% of glomeruli. Vasculitis with fibroid necrosis. (B): Skin biopsy showing leuckocytoclastic vasculitis.

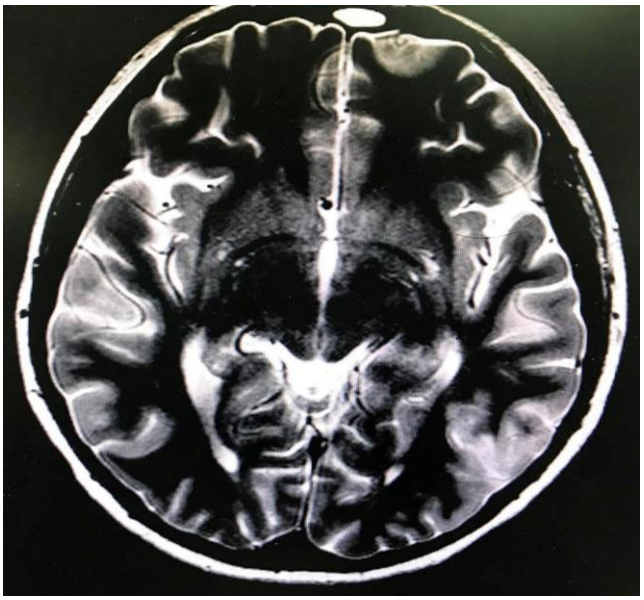

Fig C: MRI: Bilateral cortical patches of altered signal intensity are seen distributed in the parka to-occipital lobes. It is hypo intense on T1-weighted image &hyper intense on T2 and FLAIR images, water restriction in DWI posterior reversible encephalopathy syndrome is the first differential. Intracranial Venus sinuses are patent.

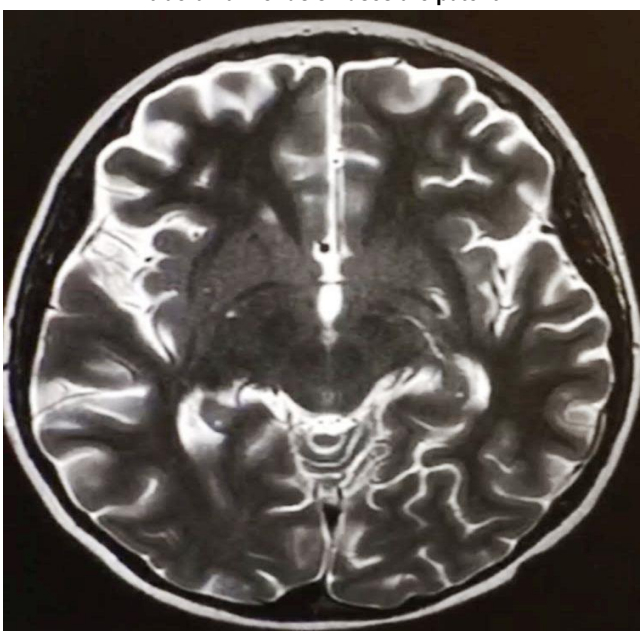

Fig D: MRI after 3 weeks

However, he noticed decrease in the urine volume per day in the last week. He was unaware to have any genitourinary congenital anomaly and both of his parents are healthy. He never smoke or snuff as well as he denied intake of herbal therapies or recent analgesic medications. On examination, his vital signs were stable with temperature of 36.6˚c, Blood pressure of 109/72, heart rate of 102/minute and O_2 saturation of 95%. He had pale conjunctiva, some erythematous purpuric rash which appeared over his cheeks and both arms, not painful or itchy. Mild epigastric tenderness, no signs of volume overload.

Laboratory investigations showed that hemoglobin level was 9.1 g/dL, mean corpuscular volume (MCV) was 79 liters/cell, mean corpuscular hemoglobin (MCH) was 27 grams/cell, white cell count was14.5 per mm^3, platelet count was 470 x 10^9/L, urea was 255 mg/dl, creatinine was 12.8 mg/dl, potassium was 5.4 mEq/L, sodium 128 mEq/L, Erythrocyte sedimentation rate (ESR) was 150. Normal coagulation profile and Anti streptolysin O titerwas negative. Anti-nuclear antibody was 1:40. Perinuclear Antineutrophilic cytoplasmic antibodies was negative. Cytoplasmic Antineutrophil cytoplasmic antibodies were > 100, Complements 3 and 4 were at normal levels, Hepatitis C and B were negative and Human immunodeficiency virus was negative.

Urine dipstick showed ++++ blood and + protein. Urine analysis showed Specific Gravity of1.020, Albumin +1, RBC 40-50, epithelial cells Nil, pus cells 2-3 and blood +4.

Kidney/bladder ultrasound (US) showed that both kidneys were in average size with bilateral increase of cortical echogenicity and decreased cortical medullary differentiation grade II/III medical renal disease, no stone or back pressure changes were noted. 24 hours urine collection revealed that patient was oligouric.

Chest x-ray was unremarkable. Echocardiogram showed normal ventricular systolic function and ejection fraction (EF) was 55%, with mild pericardial effusion. High-resolution computed tomography (HRCT) showed small peripheral infiltrations at the base of the right lung and bilateral pleural effusion.

Nerve conduction study was done and reported as normal study. Otolaryngeal evaluation revealed presence of sinusitis, but no evidence of nasal obstruction, bleeding, masses or crusts. Biopsies from the kidney and skin lesion had been taken early and the results are shown in Figures A and B.

Based on clinical, histopathological (kidney and skin biopsies) along with high C ANCA titer the patient diagnosed as having granulomatosis with polyangitis (GPA, formerly called Wegner disease).

He received intravenous (IV) methylprednisolone 500mg immediately after admission for 5 days, first cycle of intravenous cyclophosphamide 1gm was given plus prophylactic Trimethoprim/sulfamethoxazole adjusted dose every other day and prednisolone 1mg/Kg/day. All beside regular hemodialysis through jugular permacath.

Later on, he had new onset of cough, dyspnea and small amount of hemoptysis, he was tachypnic and tachycardiac, blood pressure was 121/62, temperature was 37.3 ˚c and O_2 saturation was 86-88%. There were bilateral lung crackles, normal CV examination, JVP not raised and no lower limb edema.

Chest x-ray showed bilateral fluffy infiltrations and hemoglobin level dropped from 9.6 to 8.3 to 7.5 g/dL in 24hours period. Patient was managed for pulmonary hemorrhage. Prednisolone increased to 1.5mg/kg/day and two sessions of plasmapheresis (two days apart) accompanied with two units of blood transfusion and antibiotics. Hemoptysis subsided after the third day of onset. Patient was discharged after he improved and given an appointment for the next cycle of cyclophosphamide.

After 5 days from discharge, patient presented to ER with status epilepticus of generalized tonic-clonic type, he received IV diazepam and phenytoin infusion but it was aborted after sedative agents. Prior to that, he was intubated and admitted in ICU.

As the history was taken from his father, the convulsion happened suddenly, but he vomited one time before he convulsed. He did not complain of precipitant headache, fever or upper respiratory tract infection. His last dialysis session was in the previous day and it ran completely for 3hours without shivering or documented fever.

By examination: Intubated on SIMV-MV, under sedation (propanol 75mg & midazolam 7mg/hr infusion) and CRRT (CVVHD mode). Temperature was 37˚c pulse was 81/minutes, blood pressure was118/88 and O_2 saturation was 99%. No jerky movements, pupils were 2mm reactive and symmetrical. No meningeal signs. Motor, sensory and plantar reflexes were unable to examine (deeply sedated).

Investigations revealed hemoglobin of 8 gm/dl, white blood cells 12 mm^3, platelet count 113x10^9/L, creatinine 8 mg/dl, urea 106 mg/dL, sodium 133 mEq/L, potassium 5.6 mEq/L, phosphorus 6.8 mg/dl, and calcium 8.3mg/dl.

Initial CT brain without contrast was unremarkable. Lumber puncture showed CSF with the following; white blood cells Nil, protein 45 mg/dl and glucose 60 mg/dl. Portable electroencephalogram (EEG) revealed no epileptic discharges. Brain MRI study with MRV as shown below.(Figure C)

The patient received acyclovir 200mg IV TID, ceftazidime 500mg OD, Moxifluxacilline 200mg BD, linezolid 600mg BD and intravenous Methylprednisolone 40mg IV, Valproate sodium200mg IV BD. After 48hours, he was extubated with no recurrent convulsions or residual weakness.

Lumber puncture was repeated and showed no WBC, protein 105mg/dl and glucose 50mg/dl. After few days in the hospital, patient had fever and pulmonary hemorrhage and required ventilatory support. He was managed by pulse steroid of methyl prednisone 1gm intravenous for 3days then changed to 40mg intravenously along with antibiotics and a total of 5 IVIG doses. No convulsion episode was documented thereafter.

Patient became stable and MRI was repeated after about 3 weeks which showed marked improvement and resolution of the previous edema as shown in the Figure D. Patient then discharged in stable condition on prednisone 40mg,phenytoin 200mg, Topiramate 25 mg OD, Trimethoprim/sulfamethoxazole 480mg every other day and regular hemodialysis.

Final diagnosis was reversible posterior leukoencephalopathy syndrome (RPLS) in Granulomatosis with polyangitis (GPA).

DISCUSSION

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical radiographic syndrome of heterogeneous etiologies that are grouped together because of similar findings on neuroimaging studies.[9]

It is a clinical syndrome of insidious onset of headache, confusion or decreased level of consciousness, visual changes, and seizures associated with characteristic neuroimaging findings of posterior cerebral white matter edema[9] but gray matter and other regions including the brainstem and cerebellum may be involved.[10]

Clinical conditions such as end-stage renal disease, immunosuppressive drug use, eclampsia, and autoimmune diseases had been found to be risk factors for this syndrome.[10]

Endothelial dysfunction, altered cerebral vasoregulation and vasospasm have all been implicated in the theory of its development. Vasculitides, such as Takayasu's Arteritis, Lupus vasculitis and Eosinophilic Granulomatosis with Polyangiitis share many of these mechanisms and they may also be complicated by renal failure and or hypertension, thus, they are ideal conditions for the development of PRES.[11,12]

Among all cases which had been documented with thepresence of autoimmune disorders, PRES had been reported only in 5 cases with GPA.[13]

It's very critical to exclude other disorders which have similar clinical and radiological picture, in particular CNS infection and CNS involvement in GPA.

Central nervous system involvement is an uncommon manifestation of WG, it was reported in 7%-11% of patients. The mechanism would be one of the following: contiguous invasion of granuloma from extracranial sites, remote intracranial granuloma, and CNS vasculitis,[14] which either can cause cerebral ischemia or hemorrhage.

In our patient, who is recently diagnosed to have GPA, the presence of renal impairment and acute status epilepticus along with rapidly resolved partial occipital edema found in the MRI, and after the exclusion of underlying infectious cause, this clinical picture go in favor of PRES. Although his blood pressure was

persistently normal, however, normal blood pressure in PRES have been reported in 20-30% of cases.[15]

Unfortunately, clinical reports are limited to case reports and small series that reseed treatment recommendations.[9] However, cyclophosphamide is the key drug to control the activity of Wegener's granulomatosis and was the most frequently used therapy for RPLS with rheumatologic disease in the reported cases[16], so we decided to continue cyclophosphamide therapy in addition to high dose corticosteroid and antiepileptic medication. His symptoms and radiological findings were completely resolved as the majority of reported cases although, there are some cases had recurrence or permanent neurological dysfunction.[17]

In conclusion, RPLS is an important, rare entity to be recognized in patients with GPA and other connective tissue diseases. It is important to differentiate RPLS from other common CNS disorders found in patients with autoimmune diseases.[9]

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Source of Support: Nil.

Conflict of Interest: None Declared.

Cite this article as: Hana Alahmari, Mansour Somaily. A Case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) in Granulomatosis with Polyangitis (GPA). Int J Med Res Prof. 2017; 3(1):203-06. DOI:10.21276/ijmrp.2017.3.1.041