Central nervous system vasculitis in pediatric microscopic polyangiitis

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ACTA REUMATOL PORT. 2016;41:372-375

ABSTRACT

Central nervous system involvement in childhood microscopic polyangiitis (MPA) is a very rare entity. Here we report a 14 year Indian female child, diagnosed case of MPA, presented with seizure. Magnetic resonance imaging (MRI) of brain showed diffuse involvement of brain parenchyma. Repeat MRI brain after 6 months revealed complete resolution of the earlier lesions but with development of foci of microhemorrhages in different stages of evolution, reminiscent of vasculitis.

Keywords: Microscopic polyangiitis; Leukocytoclastic vasculitis; Pauci immune glomerulonephritis; Central nervous system vasculitis

INTRODUCTION

Microscopic polyangiitis (MPA) is a small vessel vasculitis, associated with myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA). It usually affects males of middle age with a predilection to involve kidney, lung and peripheral nervous system[1]. MPA is extremely rare in children; it has been reported that girls have slightly more predilection as compared to boys[2-4]. Central nervous system (CNS) involvement in pediatric microscopic polyangiitis is not a well-known entity with perhaps only five cases till date reported[2,3,5]. We hereby present a 14-year-old Indian girl with arthralgia, leukocytoclastic vasculitis, interstitial lung disease secondary to recurrent pulmonary hemorrhage, pauci-immune glomerulonephritis and central nervous system vasculitis, having high titers of MPO-ANCA, hence diagnostic of microscopic polyangiitis.

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CASE REPORT

A 14-year Indian girl, with intermittent polyarthralgia of 6 years duration and being treated for interstitial lung disease (ILD) for the last 3 years, presented with acute exacerbation of joint pains. She had an history of recurrent anemia with serum hemoglobin documented as low as 6g/dl (11- 14g/dl) at 6 and 7 years of age. She had an history of receiving category-I antitubercular drugs, at 9 years of age, for suspected pulmonary tuberculosis based on infiltrates in chest X-ray, without significant benefit. Evaluation for acute exacerbation of dyspnea in 2011 revealed diffuse ground-glass opacities in computed tomography (CT) of the chest. She never had hemoptysis. She was diagnosed as ILD and received oral methylprednisolone 16 mg/day and azathioprine 25 mg/day, and was subsequently referred to our department. Examination was significant for pan-digital grade III clubbing, maculopapular skin lesions on both legs and diffuse fine crepitations on chest auscultation. High resolution chest CT showed diffuse areas of ground glassing and reticular thickening in both lung fields with paraseptal emphysematous changes (Figure 1). Bronchoalveolar lavage showed hemosiderin laden macrophages suggestive of alveolar hemorrhage and the pulmonary function test showed restrictive pattern with low diffusion capacity of carbon monoxide. Skin biopsy revealed leukocytoclastic vasculitis with evidence of fibrinoid necrosis in few blood vessels (Figure 2). She had high erythrocyte sedimentation rate (80 mm/1st hour) and positive MPO-ANCA in high titers 123 RU/ml (normal <20). Antinuclear antibody, extractable nuclear antibody profile and anti proteinase 3 antibody were negative. Urine examination showed significant albuminuria and active sediments comprising red blood cells (RBC) 120-140/hpf, white blood cells (WBC) 15-20/hpf and frequent granular casts. 24 hour urinary protein was of 3 grams.

Kidney biopsy revealed numerous cellular and fibrocellular crescents along with foci of fibrinoid necro-

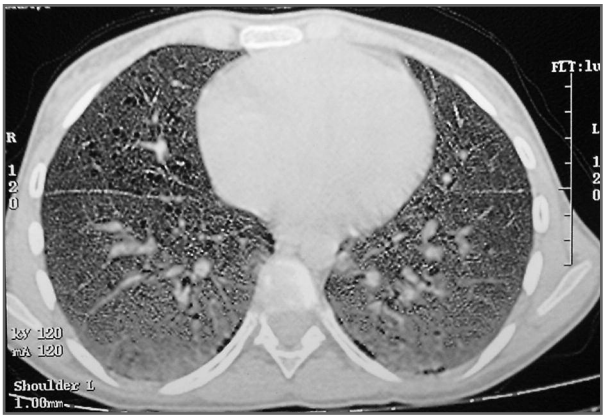

FIGURE 1. Chest HRCT showing diffuse area of ground glassing and reticular thickening in both lung fields with paraseptal emphysematous changes

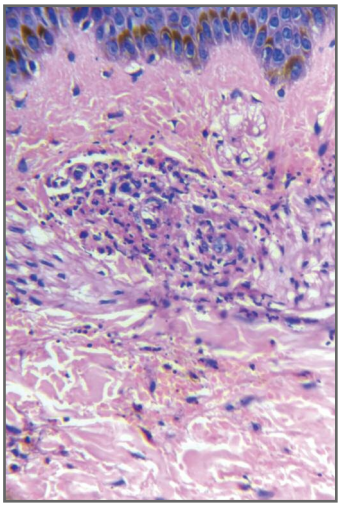

FIGURE 2. Skin biopsy shows leukocytoclastic vasculitis with evidence of fibrinoid necrosis in few blood vessels (40x)

sis and segments of sclerosis in several glomeruli (Figure 3). Immunofluorescence study was significant for absence of immune deposits. Hence she was diagnosed as MPO-ANCA associated vasculitis (microscopic polyangiitis) based on clinical, immunological, histological and radiological findings. Cyclophosphamide pulse (15 mg/kg IV) was initiated and oral prednisolone was increased to 1mg/kg/day (European Vasculitis Study Group- protocol). She presented 12 days later with an episode of seizure not associated with any focal neurological deficit. Magnetic resonance imaging of brain revealed multiple cortical and subcortical lesions in bilateral frontal, parietal, occipital and cerebellar regions, whereby a possibility of central nervous

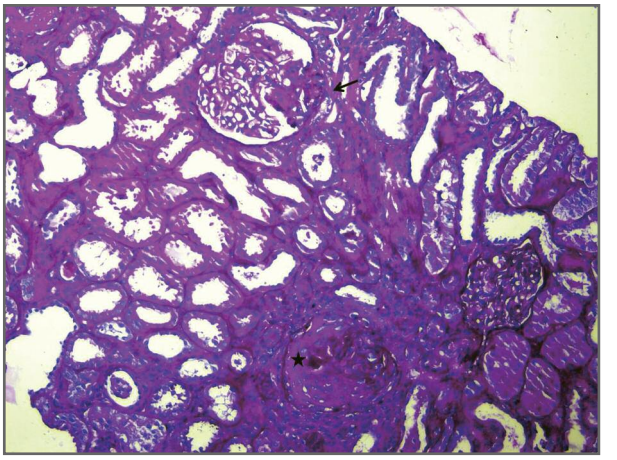

FIGURE 3. Renal biopsy shows a segment of fibrinoid necrosis (arrow) and a fibrocellular crescent (asterix). (PAS, x200)

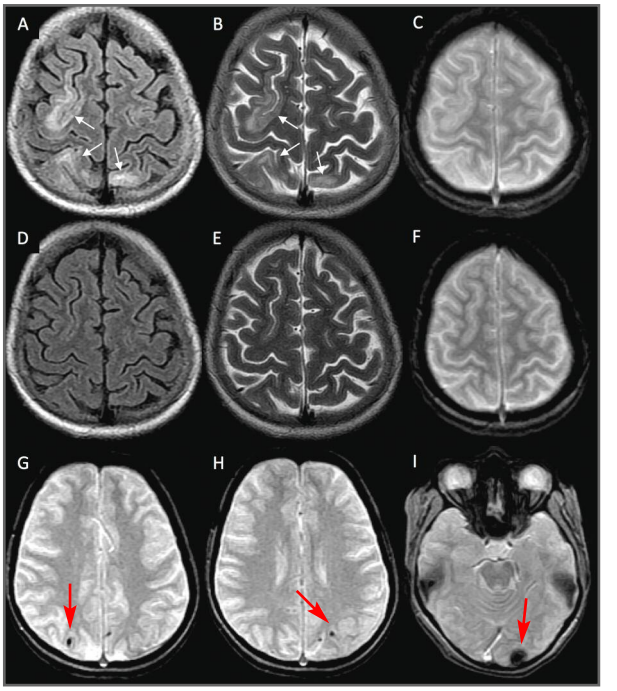

FIGURE 4. FLAIR and T2-weighted sequences of MRI (Brain) depict hyperintense lesions involving the frontoparietal cortices (A and B, arrows), which show complete resolution at 6 months (D and E). Initial T2* (C) and follow-up (F) sequences of the involved regions did not reveal any hemorrhagic foci. T2* images (G-I) reveal the presence of multiple hemorrhagic foci (blooming) spread across the brain parenchyma

system vasculitis was considered (Figure 4 A-C). Cerebrospinal fluid examination was normal. The patient was managed with antiepileptic medication and pulse

methylprednisolone. Routine cyclophophamide pulse was given. Interestingly, MRI of the brain after six months revealed complete resolution of the earlier lesions (Figure 4 D-F) but with development of foci of microhemorrhages in different stages of evolution (Figure 4 G-I), reminiscent of vasculitis. At 8 months, she is in complete remission. Twenty-four hour proteinuria is <300 mg/day and cellular casts in urine disappeared completely, with no recurrence of seizure and no skin lesions. Currently she is on azathioprine (2 mg/kg/day) and tapering dose of steroid (prednisolone 7.5 mg/day) as per European Vasculitis Study Group- protocol after completion of 10 doses of pulse cyclophosphamide (first three doses at two weeks interval and remaining seven doses at 3 weeks interval).

DISCUSSION

MPA is predominantly a disease of middle-aged males[1], affecting primarily small vessels such as capillaries, arterioles, or venules with the basic pathology finding being fibrinoid necrotizing vasculitis with few or no immune complex deposition[6]. MPA is the most common ANCA associated vasculitis of childhood in Asian population[2,3]. Pediatric MPA reports from Japan[2] and China[3] show a female predominance. A recent case series in the USA and Canada yielded only 17 MPA patients over a period of 5 years from ARCHiVe (A Registry for Childhood Vasculitis) study[4]. In this case series 67% patients were girls and the mean age of presentation was 13 years. The most common involved organ was kidney. None of them had central nervous system involvement. Hattori et al[2] found CNS involvement in one patient out of 21 childhood-MPA and Sun et al[3] found three patients out of twenty. All four patients from both the studies had convulsion. Within contrast Tan et al[5] reported a case of pediatric MPA complicated by intracerebral hemorrhage. Our patient had ILD secondary to recurrent alveolar hemorrhage, pauci immune glomerulonephritis, leukocytoclastic vasculitis and multiple cortical and subcortical lesions in brain due to CNS vasculitis.

The renal biopsy findings were significant since an admixture of acute necrotizing lesions and segments of sclerosis and fibrous crescents, suggestive of chronicity were noted. This indicates that the lesions were long standing but still active. Renal involvement was found to have present in all patients of pediatric MPA by Sun et al[3]. Lung involvement was the second most common (15% of patients) presentation in this study. The most common presentation of lung involvement was cough and hemoptysis.

Wang et al[7] conducted a retrospective analysis of pediatric MPA patients with pulmonary lesions. Nine patients (2 boys and 7 girls) were enrolled in this study. Seven out of nine had cough and hemoptysis. The most common finding on pulmonary imaging was ground glass or patchy shadows, which were observed in 6 cases. Renal involvement was observed in seven patients in this study.

The intracranial parenchymal activity of the disease in our patient was manifested by an episode of seizure and lesions suggestive of vasculitis on imaging. The resolution of initial lesions suggests the occurrence of reversible posterior leukoencephalopathy. The second MRI of the brain, done at 6 months, lends more credence to the diagnosis of cerebral vasculitis owing to the presence of microbleeds in different stages of evolution. Only five cases of central nervous system involvement in childhood MPA has been previously reported[2,3,5] and probably this is the sixth case in the literature. Guillevin et al[8] in a series of 85 patients with adult MPA observed CNS involvement in 10 [11.8%] patients. CNS involvement in MPA can be hemorrhagic infarct[9], nonhemorrhegic multiple infarcts[10] and reversible posterior leukoencephalopathy syndrome[11]. Patient with CNS involvement are said to have a poor prognosis[12]. The effective rate and complete remission rate of cyclophosphamide therapy in children with MPA are 71.4% and 28.5%, respectively[13]. Though our case is not a biopsy proven CNS vasculitis, but the pattern of CNS involvement on MRI of the brain, normal CSF examination, and response to immunosuppressive therapy favor diagnosis of CNS vasculitis. We emphasize the importance of considering MPA as a possibility in children of adolescent age with suggestive clinical features. Renal biopsies with acute on chronic lesions in such patients should alert the treating physician for other impending vasculitic episodes, especially in the central nervous system.

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REFERENCES

1. Villiger PM, Guillevin L. Microscopic polyangiitis: clinical presentation. Autoimmun Rev. 2010;9(12):812–819
2. Hattori M, Kurayama H, Koitabashi Y; Japanese Society for Pediatric Nephrology. Antineutrophil cytoplasmic autoantibody-

associated glomerulonephritis in children. J Am Soc Nephrol. 2001;12:1493–1500
3. Sun L, Wang H, Jiang X, et al. Clinical and pathological features of microscopic polyangiitis in 20 children. The Journal of rheumatology 2014;41(8), 1712-1719.
4. Uribe AG, Huber AM, Kim S, et al. Increased Sensitivity of the European Medicines Agency Algorithm for Classification of Childhood Granulomatosis with Polyangiitis. J Rheumatol. 2012;39(8):1687
5. Tan J, Hussain A, Daiwajna R, et al. Microscopic polyangiitis complicated by intracerebral hemorrhage and pulmonary hemorrhage in a pediatric patient. Am J Case Rep. 2013; 14: 276–279
6. Ferraro A, Hassan B, Savage COS: Pathogenic mechanisms of antineutrophil antibody-associated vasculitis, Exp Rev ClinImmunol3:543–555, 2007.
7. Wang H, Sun L, Tan W. Clinical Features of Children with Pulmonary Microscopic Polyangiitis: Report of 9 Cases. PLoS One. 2015; 10(4)
8. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis, clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42:421–430.
9. Sasaki A, Hirato J, Nakazato Y, Tanaka T, Takeuchi H. An autopsy case of P-ANCA-positive microscopic polyangiitis with multiple cerebral hemorrhagic infarction. No To Shinkei. 1998;50:56–60.
10. Ku BD, Shin HY. Multiple bilateral non-hemorrhagic cerebral infarctions associated with microscopic polyangiitis. Clin. Neurol. Neurosurg. 2009;111:904–906.
11. Tajima Y, Matsumoto A. Reversible posterior leukoencephalopathy syndrome in p-ANCA-associated vasculitis. Intern Med. 2006;45(20):1169–1171.
12. Bourgarit A, Le Toumelin P, Pagnoux C, et al. French Vasculitis Study Group. Deaths occurring during the first year after treatment onset for polyarteritisnodosa; microscopic polyangiitis; and Churg- Strauss syndrome, a retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine (Baltimore) 2005;84:323–330.
13. Peco-Antic A, Bonaci-Nikolic B, Basta-Jovanovic G, et al. Childhood microscopic polyangiitis associated with MPO-ANCA. Pediatr Nephrol. 2006; 21: 46–53.