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Microscopic polyangiitis complicated by intracerebral hemorrhage and pulmonary hemorrhage in a pediatric patient

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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: Female, 10
Final Diagnosis: Polyangiitis
Symptoms: Intracranial hemorrhage • swelling • oliguria
Medication: Cyclophosphamide • prednisolone
Clinical Procedure: Plasmapheresis
Specialty: Paediatric nephrology • nephrology • paediatrics





Objective: Rare disease
Background: MPO ANCA-associated vasculitis is very rare in children. Renal disease is almost universally present but lung and central nervous system involvement are not commonly reported.

Case Report: We present a pediatric case of microscopic polyangiitis with the unusual presentation of pauci-immune glomerulonephritis, intracerebral hemorrhage and pulmonary hemorrhage. The neurological and pulmonary symptoms settled after treatment with cyclophosphamide and plasmapheresis. However, there was no renal recovery and the patient was rendered dialysis-dependent.

Conclusions: We believe that this is the first reported case of pediatric microscopic polyangiitis with central nervous system involvement. The disease may have a subclinical presentation resulting in chronic damage to different organs. Prompt treatment of acute disease with immunosuppression and plasmapheresis can halt disease progression in these patients.

Key words: microscopic polyangiitis • ANCA • intracerebral haemorrhage • pulmonary haemorrhage • paediatric

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Background

MPO ANCA-associated vasculitis is very rare in children. A recent case series of patients from ARCHiVe (A Registry for Childhood Vasculitis) in the USA and Canada only yielded 17 MPA patients over a study period of 5 years [1]. Another recent childhood vasculitis case series from the United Kingdom reported only 6 MPA cases over a 13-year period in a tertiary pediatric nephrology unit [2]. Yu F et al. [3] reported 19 MPA cases of Chinese pediatric patients from their tertiary center in Beijing over a 7-year period in the largest case series to date. Studies in experimental animals suggest a pathogenic role for MPO-ANCA in activating primed neutrophils to release oxygen species and lytic enzymes that can damage and lyse endothelial cells of blood vessels of targeted organs, leading to a wide array of clinical presentations [4]. Common organ involvements include kidneys (acute kidney injury and hemoproteinuria), lungs (hemorrhage, nodules, and infiltrates), skin (purpura and petechia), bowels (abdominal pain and nausea) and joints (arthritis and arthralgia) [1]. There are also recent anecdotal reports on unexplained anemia [5–7].

We present a pediatric case of microscopic polyangiitis with the unusual presentation of pauci-immune glomerulonephritis, intracerebral hemorrhage and pulmonary hemorrhage.

Case Report

A 10-year-old girl was admitted with a 2-week history of generalized swelling, oliguria, and frothy urine. There was no antecedent history to suggest any potential causes of these symptoms. Her deceased maternal aunt and grandmother had both been on dialysis. Initial examination revealed a blood pressure of 180/120 and generalized peripheral edema. Routine investigations showed evidence of nephrotic syndrome (serum albumin 23 g/L, cholesterol 7.4 mmol/L, urine albumin creatinine ratio 520 mg/mol), and kidney injury (serum urea 30.1 mmol/L, creatinine 354 mmol/L, potassium 5.0 mmol/l). She also had normocytic, normochromic anemia (hemoglobin 6.4 g/dl), hyperphosphatemia (2.5 mmol/L), and hyperparathyroidism (33 pmol/L). Immunological investigations showed p-ANCA positivity with a raised MPO titre (>300 u/ml). Other immunological markers were negative. Ultrasonic imaging revealed kidneys measuring 8.4 and 9.3 cm with poor corticomedullary differentiation. Chest X-ray showed a left-sided pleural effusion.

Due to progressive renal impairment and hyperkalemia, she was started on acute peritoneal dialysis 4 days into her admission. She was also immediately treated with pulsed methylprednisolone therapy for presumed pauci-immune glomerulonephritis. A renal biopsy later showed evidence of crescentic glomerulonephritis, with most glomeruli showing changes ranging

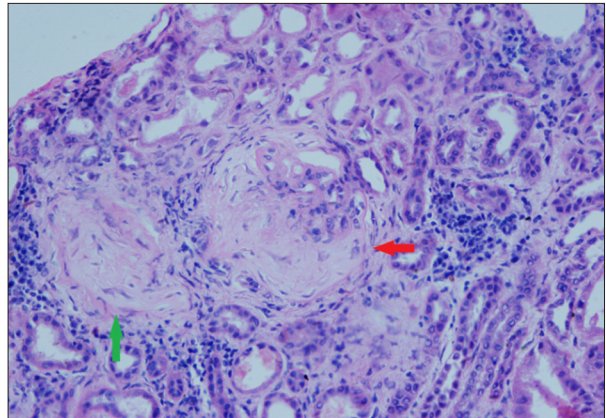


Figure 1. Renal histology. Collapsed glomerular tuft with fibrous crescent obliterating Bowman's space (red arrow). Adjacent globally sclerosed glomerulus (green arrow).

from fibrous crescents to complete sclerosis, indicating chronicity of the disease. In addition, there was focal tubular atrophy, interstitial edema, a mononuclear cell infiltration, and focal fibrosis within the interstitium. There was minimal staining for immunoglobulins by immunofluorescence, apart from IgM, which showed probable non-specific staining. Fibrinoid necrosis was noted in the small vessels. There was no evidence of granulomatous inflammation (Figure 1). In light of the histological findings, she was commenced on oral cyclophosphamide and high-dose oral prednisolone therapy. Despite renal replacement therapy, her blood pressure remained difficult to control, necessitating the use of multiple antihypertensive agents, including methyldopa, hydralazine, atenolol, isosorbide mononitrate, and furosemide. Ten days into her admission, she was converted from automated peritoneal dialysis to continuous ambulatory peritoneal dialysis due to poor ultrafiltration.

Unfortunately, 2 weeks into her admission she started having seizures, which were controlled by phenytoin and sodium valproate. A computed tomography (CT) scan of her head showed hemorrhage with surrounding edema in her right parietal lobe. There were also non-specific white matter changes in the brain (Figure 2). At around the same time, she started having frequent hemoptysis episodes. A chest x-ray confirmed the previously seen left-sided pleural effusion and new radiological evidence of pulmonary hemorrhage. Pleural aspiration later gave a transudate picture, probably associated with her hypoalbuminemic state. Due to the presence of these acute extra-renal features, she was started immediately on plasmapheresis. After 7 cycles of plasmapheresis, her pulmonary and cerebral symptoms resolved and her repeat ANCA and MPO titre normalized. She was discharged 4 weeks later on CAPD, maintenance cyclophosphamide, and steroid therapy.

A subsequent biopsy performed 3 months after discharge revealed progressive sclerosis affecting nearly 90% of her kidney

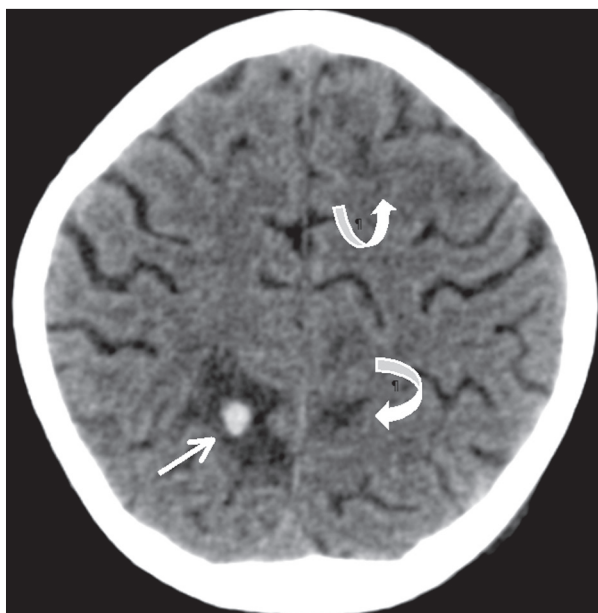


Figure 2. CT brain. Unenhanced axial CT brain image shows a haemorrhagic focus with surrounding oedema in the right parietal lobe (straight arrow) and scattered subcortical white matter hypodense lesions in the left frontal and parietal lobes (curved arrows).

specimen, indicating the non-reversible nature of her kidney disease. Her disease remained in remittance and ANCA levels were persistently negative with maintenance immunosuppression.

Discussion

Renal disease is present in almost 100% of MPA cases [8]. Renal involvement is usually characterized by crescentic glomerulonephritis with a rapid decline in renal function. Compared to Wegener's granulomatosis, chronic and severe renal damage is significantly higher in MPA [2,9]. Serum creatinine, sclerotic lesions, and number of normal glomeruli on renal biopsy are the best predictors of renal outcome [8]. Fibrous crescents are also associated with a worse outcome than fibrocellular crescents [10].

Neurological involvements in the MPA pediatric population are rare and mainly limited to the peripheral nervous system

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[11,12]. However, in the adult population there are reports on central nervous involvement, including presentations with subarachnoid hemorrhage [13], pontine infarction [14], intracerebral hemorrhage [15,16], and reversible posterior leukoencephalopathy syndrome (RPLS) [17]. These hemorrhagic and ischemic neurological complications are thought to be secondary to weakening of blood vessel walls by means of an inflammatory vasculitis, resulting in vessel rupture and bleeding [18].

Our patient had intracerebral hemorrhage and non-specific ischemic changes on CT scan. The intracerebral hemorrhage may be the result of a combination of difficult hypertension and intrinsic bleeding tendency of vasculitic blood vessels within the brain. The non-specific chronic white matter changes in the brain were in keeping with infarcts associated with chronic vasculitic insults. Murphy et al. [18] reported similar non-specific white matter changes in 10 patients with Wegener's granulomatosis. Our patient's renal histology (crescentic glomerulonephritis with features ranging from fibrous crescents to complete sclerosis, and focal interstitial sclerosis) and chronic renal blood parameters (high PTH and severe anaemia) indicated that she may also have had chronic kidney damage from previously undetected low-grade immunological injuries. Her chronic renal damage may explain the failure of complete renal recovery despite prompt aggressive treatment. We also believe her acute presentation was the result of reaching a symptomatic threshold from the culmination of progressive multi-organ damages.

Conclusions

We would like to highlight that ANCA-associated disease can affect the central nervous system and the pediatric population. Based on clinical, histological, radiographic, and immunological findings, our patient fulfilled most vasculitis criteria for microscopic polyangiitis (MPA). The disease may have a subclinical presentation resulting in chronic damages to different organs. Prompt treatment of acute disease with immunosuppression and plasmapheresis can halt disease progression in these patients.

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