Pulmonary-Renal Syndrome in a Newborn With Placental Transmission of ANCAs

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• **Despite clinical and experimental data suggesting a direct relationship between antineutrophil cytoplasmic antibodies (ANCAs) and disease activity in patients with microscopic polyangiitis (MPA), the causal relationship between perinuclear ANCAs specific for myeloperoxidase (MPO-ANCA) and disease manifestations has been controversial. We describe the case of a woman with a history of pulmonary-renal syndrome caused by MPA whose disease became clinically and serologically active during pregnancy. Forty-eight hours after delivery, the newborn developed pulmonary hemorrhage and abnormalities in renal function. The newborn's cord blood showed an immunoglobulin G MPO-ANCA level identical to that of the mother's serum, indicating passive transfer of the antibody to the neonate. Our findings represent the first human model supporting the interpretation that MPO-ANCAs were immunopathogenic.** ***Am J Kidney Dis*** **45:758-761.**

INDEX WORDS: Pulmonary-renal syndrome; vasculitis; microscopic polyangiitis (MPA); antineutrophil cytoplasmic antibodies (ANCAs).

MICROSCOPIC POLYANGIITIS (MPA) is a small-vessel vasculitis that can be manifest as pauci-immune necrotizing glomerulonephritis and pulmonary capillaritis.[1,2] In approximately 70% to 80% of cases, antineutrophil cytoplasmic antibodies (ANCAs) can be shown.[3,4] These most often are in a perinuclear pattern (P-ANCA), with myeloperoxidase (MPO-ANCA) as the target antigen.[4,5] Although there are experimental data to suggest that these antibodies are pathogenic,[6-8] there is no direct evidence of their pathogenic role in human disease.

We describe the case of a woman with a history of pulmonary-renal syndrome caused by MPA whose disease became clinically and serologically active during pregnancy. Forty-eight hours after delivery, the newborn developed pulmonary hemorrhage and had evidence of renal function abnormalities. The newborn's cord blood showed an immunoglobulin G (IgG) MPO-ANCA level virtually identical to that of the mother's serum, indicating passive transfer of the antibody to the neonate. These findings support the notion of the pathogenicity of MPO-ANCA.

CASE REPORT

A 32-year-old woman with a history of MPA was admitted during the 33rd week of her second pregnancy for evaluation of shortness of breath. She had been well throughout this pregnancy; however, 1 week before admission, she developed hypertension, and on admission, she reported a 1-day history of difficulty breathing.

The patient initially presented with pulmonary hemorrhage and glomerulonephritis 8 years before admission. MPO-ANCA level was elevated (42 U/mL; normal, <7 U/mL), and a renal biopsy showed pauci-immune focal segmental necrotizing glomerulonephritis. Clinical and serological remission was attained with a 6-month course of prednisone and cyclophosphamide. The patient remained in remission, and 8 years later became pregnant. At 26 weeks' gestation, MPO-ANCA level again increased to 23 U/mL, but the patient was clinically asymptomatic and had a normal serum creatinine level and urinalysis result. She remained asymptomatic until the day of admission.

On admission, her blood pressure was 140/98 mm Hg, pulse and respiration rates were normal, and oxygen saturation was 98% on room air. Her serum creatinine level was 0.6 mg/dL (53 μmol/L), and urinalysis results were normal. Soon after admission, she became acutely short of breath, with an arterial blood gas showing a partial pressure of oxygen of 75 mm Hg and an oxygen saturation of 96% on 4 L of oxygen by nasal cannula. Her Westergren sedimentation rate was 50 mm/h. Results from a chest roentgenogram, ventilation-perfusion scan, and spiral computed tomography of the lungs with contrast were negative. It was believed her symptoms were caused by a relapse of her vasculitis, and she was administered pulse intravenous methylprednisolone, resulting in improvement in her symptoms, and an urgent

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Table 1. Serological Features

		Days From Delivery				
		0	8	16	90	180
Mother	P-ANCA IgG*	1:640				
	Anti-MPO level†		2.5	0	0	
Infant	P-ANCA IgG	1:640				
	P-ANCA IgM	<1:20				
	P-ANCA IgA	<1:20				
	Anti-MPO level	3.3	1.89	1.55	0	0

*Normal ANCA titer less than 1:20.

†Normal anti-MPO antibody level less than 0.89 cutoff index.

Caesarian section delivery was performed. An apparently healthy 4 lb 5 oz (1.95 kg) female neonate was delivered. At the time of delivery, serum from the mother and neonate (cord blood) were sent for evaluation for ANCA (indirect immunofluorescence; Specialties Laboratories Inc, Santa Monica, CA) and MPO-ANCA (enzyme-linked immunosorbent assay; Trinity Biotech, Jamestown, NY), and both showed the presence of IgG P-ANCA and MPO-ANCA at identical levels (Table 1).

The neonate developed tachypnea, with increasing oxygen requirements 24 hours after delivery requiring intubation. Twenty-four hours later (48 hours after delivery), copious amounts of bright red blood were noted in the endotracheal tube. A chest roentgenogram showed homogenous diffuse bilateral infiltrates associated with air bronchograms (Fig 1A). Because of the severity of the pulmonary hemorrhage, continuous suctioning of blood and positive pressure ventilation were required to maintain oxygenation. Renal function studies performed at the time of pulmonary hemorrhage showed evidence of active renal disease, with an elevated blood urea nitrogen level of 17 mg/dL (6 mmol/L; normal in a neonate, <10 mg/dL [<3.5 mmol/L]), serum creatinine level of 0.8 mg/dL (77 μmol/L; normal in a neonate, <0.4 mg/dL [<35 μmol/L]), urinalysis with 1^+ proteinuria and 3^+ hematuria, and urine protein-creatinine ratio of 1.3. Pulse intravenous hydrocortisone was administered at 3 mg/kg (60 mg/m^2) and continued every 8 hours, and exchange transfusion with packed red blood cells was performed. During the next 12 hours, the newborn's pulmonary function improved. The pulmonary hemorrhage resolved and was associated with marked improvement in the air space opacities on chest roentgenogram (Fig 1B). The newborn was extubated successfully 24 hours later. Renal function improved (blood urea nitrogen, 11 mg/dL [3.9 mmol/L]; serum creatinine, 0.4 mg/dL [35 μmol/L]; and normal urinalysis results) during the 5 days after initiation of steroid therapy and remained stable thereafter. The newborn remained asymptomatic without recurrence of respiratory compromise, and hydrocortisone therapy was discontinued after a 3-week course. Serial measurements of P-ANCA and MPO-ANCA showed continued improvement (Table 1). During 6 months of follow-up, the infant remained asymptomatic, with no recurrence of ANCA or MPO-ANCA.

DISCUSSION

MPA is a systemic disease characterized by vasculitis involving small blood vessels, particularly the glomerular and pulmonary capillaries. Clinical manifestations include necrotizing pauci-immune glomerulonephritis and pulmonary hemorrhage.[2-5] Despite clinical data suggesting a direct relationship between ANCAs and disease activity in patients with MPA,[9-12] the causal relationship between P-ANCAs specific for myeloperoxidase (MPO-ANCA) and disease manifestation has been controversial. MPO-ANCAs may not be present in all patients with active small-vessel vasculitis.[13] Additionally, MPO-ANCAs are described frequently in association with other disorders, such as rheumatoid arthri-

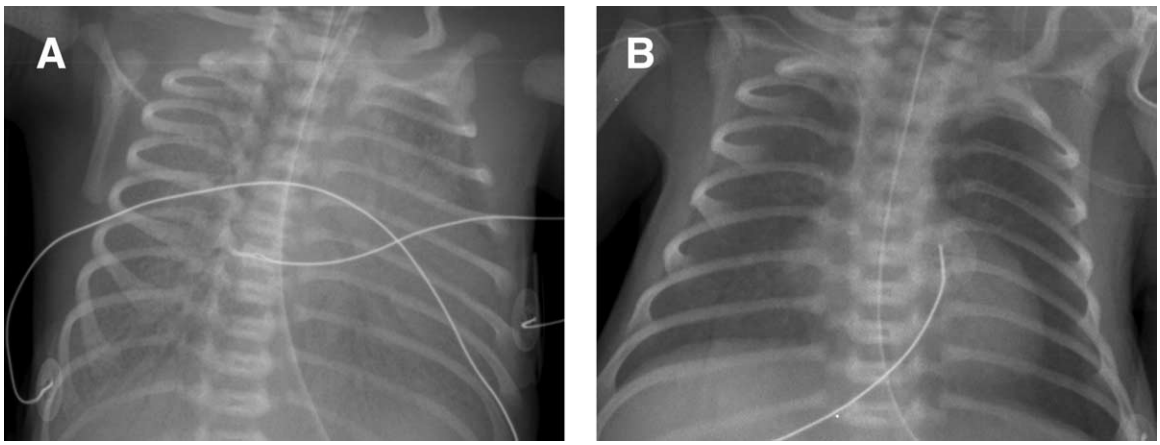

Fig 1. Chest roentgenograms of the neonate showing (A) severe, diffuse, bilateral alveolar infiltrates with air bronchograms, which (B) markedly improved within 12 hours of hydrocortisone administration.