Immunoadsorption in Anti-GBM Glomerulonephritis: Case Report in a Child and Literature Review

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Antiglomerular basement membrane glomerulonephritis (anti-GBM GN) is a rare autoimmune disease that is characterized by rapidly progressive glomerulonephritis that may be associated with pulmonary hemorrhage. Anti-GBM GN is caused by autoantibodies (classically type G immunoglobulin) directed against the α3 subunit of type IV collagen. Without any appropriate treatment, the disease is generally fulminant, and patient and kidney survival is poor. The current guidelines recommend the use of plasma exchanges and immunosuppressive drugs. Immunoadsorption (IA) can remove pathogenic IgGs from the circulation and do not require plasma infusions, contrary to plasma exchanges. IA has seldom been used in adult patients with good tolerance and efficiency. We report herein the first pediatric case successfully treated with IA combined with immunosuppressive drugs in a 7-year-old girl who presented acute kidney injury (estimated glomerular filtration rate 38 mL/minute/1.73 m^2). A kidney biopsy revealed numerous >80% glomerular crescents and linear IgG deposits along the glomerular basement membrane. Ten IA sessions led to rapid and sustained clearance of autoantibodies and improvement of kidney function until 21 months after onset (glomerular filtration rate 87 mL/minute/1.73 m^2). No adverse effect was noted. This report adds to the growing body of evidence suggesting IA as a therapeutic alternative to plasma exchanges in anti-GBM GN. The other 27 published pediatric cases of anti-GBM GN are reviewed.

Antiglomerular basement membrane glomerulonephritis (anti-GBM GN) is a rare and generally fulminant autoimmune disorder that is characterized by isolated, rapidly progressive glomerulonephritis (GN) or pulmonary-renal syndrome with alveolar hemorrhage. It is caused by circulating anti-GBM autoantibodies, usually IgGs.[1,2] Anti-GBM GN is estimated to occur in 1 per 1 000 000 adult patients.[3] The diagnosis is made in all racial populations, but the annual incidence is lower in people from African ancestries compared with Caucasian individuals. Most affected cases are adolescents and adults of all ages,[3,4] with a bimodal distribution at 20 to 30 years and 60 to 70 years. However, the pulmonary-renal phenotype is more likely to be diagnosed in younger patients (<30 years) and isolated anti-GBM GN in older patients (>50 years).[4,5] The male-to-female ratio varies from 1:1 to 9:1 according to different series.[6] About one-quarter of patients will also have antineutrophil cytoplasmic antibodies (ANCA), usually with antimyeloperoxidase specificity.[7] The 2012 Kidney Disease Improving Global Outcomes

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Mr Dorval drafted the initial manuscript and reviewed literature; Dr Lion performed kidney biopsies and patient follow-up; Dr Guérin performed pulmonary analyses such as imaging, fibroscopy, and pulmonary function tests; Dr Galmiche-Rolland analyzed and interpreted pulmonary and renal tissue for anatomopathological results; Drs Krid and Salomon were involved in immunoadsorption sessions management and follow-up; Dr Boyer supervised this work, the data collection, and literature review, and she reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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guidelines recommend initiating plasmapheresis as soon as the diagnosis is made to quickly remove anti-GBM autoantibodies from the circulation and corticosteroids (CS) and cyclophosphamide to prevent further antibody production and glomerular injury.[8] Because anti-GBM GN is a rare and fulminant disease, safety and efficacy data concerning alternative treatments are scarce, especially for children. We report herein the first pediatric case of Goodpasture syndrome treated with immunoadsorption (IA) therapy.

CASE REPORT

A 7-year-old girl was admitted to the pneumology unit for a 2-week history of fever, abdominal pain, cough, and headache. She had no relevant personal or familial medical history. A clinical examination upon arrival revealed tachycardia (129 per minute) and hypertension (115/71 mmHg) with clear lungs to auscultation bilaterally. Blood laboratory tests showed the following: anemia (Hg 8.2 g/dL); thrombocytosis (655 000/μL); leukocytosis (16 980/μL) with 86% neutrophils; elevated fibrinogen (750 mg/dL); C-reactive protein 235 mg/L; ferritin 671 ng/mL; and acute kidney injury (creatinine 0.85 mg/dL, serum urea nitrogen 17.6 mg/dL, estimated glomerular filtration rate [eGFR] 63 mL/minute/1.73 m^2). Plasma C3 and C4 levels were normal. Antinuclear and anti-DNA antibodies were negative. Initially, urine sediment was remarkable for isolated microscopic hematuria; then, non-nephrotic-range proteinuria developed on day 5 of hospitalization (up to 80 mg/mmol of creatinine). A chest radiograph revealed pulmonary interstitial infiltration, and computed tomography showed peripheral micronodular infiltration compatible with pulmonary hemorrhage (Fig 1A). Bronchial fibroscopy and bronchoalveolar lavage were performed. There was no siderophage, and the Golde score based on the hemosiderin content of alveolar macrophages stained with Prussian blue was 16, which is below the accepted threshold for pulmonary hemorrhage diagnosis (>20).[9] At day 5, she was referred to our pediatric nephrology unit for worsening acute kidney injury (creatinine 1.4 mg/dL; eGFR 38 mL/minute/1.73 m^2). A kidney biopsy was performed the same day and revealed glomerular circular crescents with fibrinoid necrosis associated with Bowman's capsule rupture in more than 80% of the glomeruli (out of 19 glomeruli), inflammation of the tubulointerstitial space on optic microscopy, and massive linear anti-GBM staining on immunofluorescence (Fig 1 B and C). The circulating anti-GBM autoantibody titer was 180UI/L (enzyme-linked immunosorbent assay; Bio-Advance, Philadelphia, PA). Serum ANCAs were negative. The girl was treated with 2 methylprednisolone pulses (500 mg/m^2) followed by prolonged oral prednisone (1 mg/kg per day) and oral cyclophosphamide (2 mg/kg per day for 3 months). IA sessions were started immediately after pulses and anti-GBM results. Blood was drawn via a central venous line at a flow rate of 50 to 90 mL per minute and anticoagulated by continuous infusion of citrate (citrate-to-whole-blood ratio of 1:22). Plasma was separated with a rotating membrane (Life 18 - Disk Separator; Miltenyi Biotec, Bergisch Gladbach, Germany), and antibodies were filtered using an adsorber containing 2 Ig columns (TheraSorb-Ig flex; Miltenvi Biotec). Plasma passed alternately through 1 of 2 columns filled with sepharose-coupled polyclonal sheep antibodies to human immunoglobulins, whereas the other column was regenerated by elution of the adsorbed proteins with HCl-Glycine buffer. The plasma was then mixed with the separated blood cells and reinfused into the patient. Calcium gluconate was infused at a mean rate of 5 mmol per hour to avoid citrate-induced hypocalcaemia. In a single treatment session, 21 cycles were performed, and 2600 mL of plasma was processed over a period of 4 hours (plasma volume was calculated by Life 18 software according to the child weight [27 kg], and 2 plasma volumes were treated by session). Sessions were initially scheduled on a daily basis and then on alternating days for a total of 10 sessions (Fig 1D). Each session was followed by intravenous immunoglobulin (0.2 g/kg BW). This treatment led to a rapid and sustained clearance of autoantibodies that became undetectable from the eighth session on day 18 to the last follow-up, 21 months after onset. Similarly, kidney function quickly improved and remained stable at last follow-up (eGFR 87 mL/minute/1.73 m^2) as well as pulmonary examination (spirometry, carbon monoxide diffusing capacity). Steroids were withdrawn 12 months after onset. No adverse effect was noted.

DISCUSSION AND REVIEW OF THE LITERATURE

We report herein the first pediatric case of anti-GBM GN treated by the association of IA and immunosuppressive drugs, with an immediate and sustainable improvement during the patient's 21 months' follow-up.

Contrary to adults, very few pediatric cases of anti-GBM GN (also known as Goodpasture syndrome when associated with pulmonary hemorrhage)[10] are reported in the literature. We identified 27 pediatric cases whose clinical characteristics are detailed in Table 1. Mean age at diagnosis was 8.76 ± 4.6 years. Although some studies reported equal sex prevalence in the adult population,[11] others outline a male prevalence[6] (n = 85; mean age 44 years old) and a female

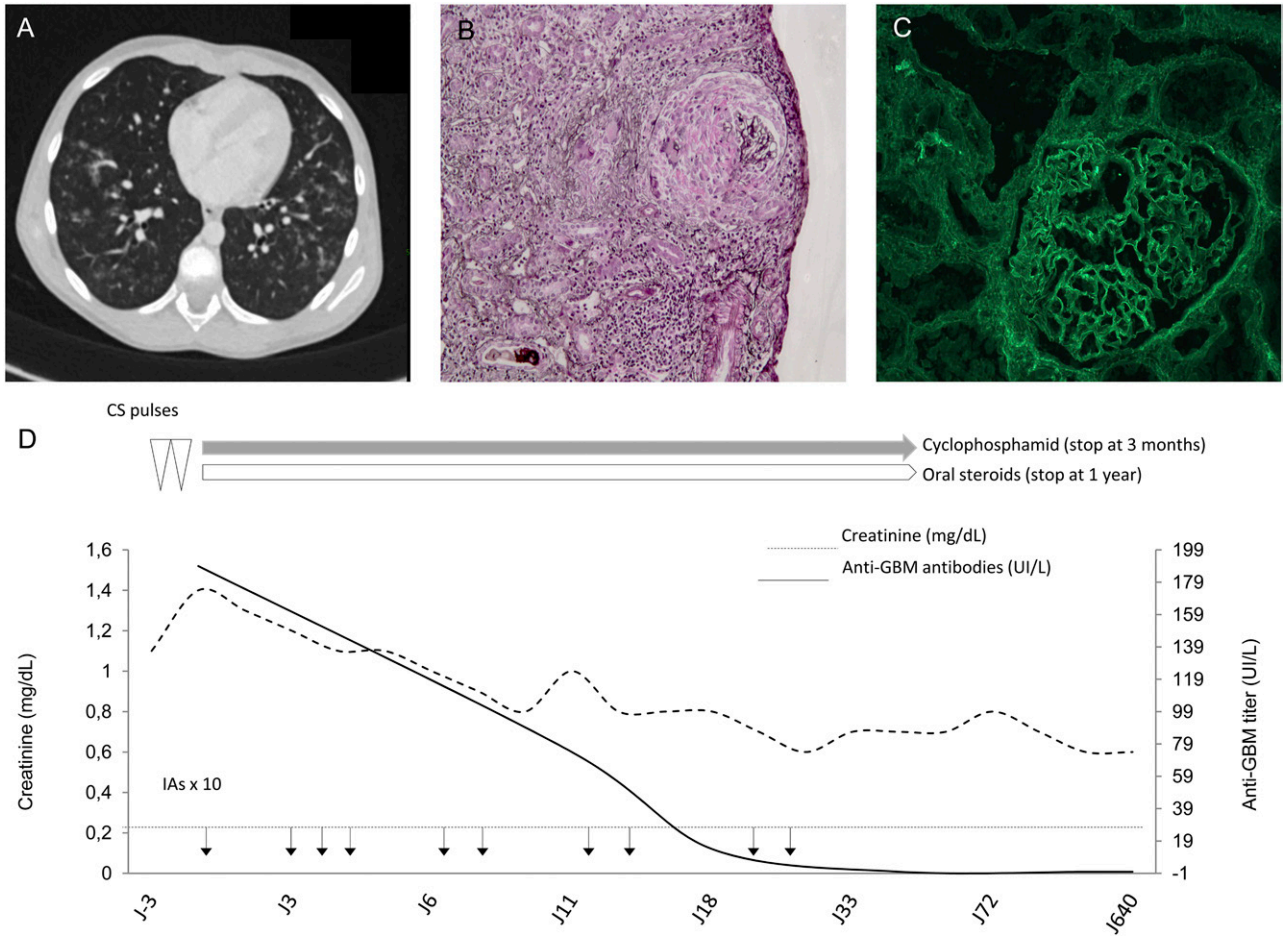

FIGURE 1

(A) A thoracic CT scan shows peripheral micronodules evoking intra-alveolar hemorrhages; (B) Kidney optic microscopy reveals crescentic glomerular formation with tubulointerstitial inflammation; (C) Immunofluorescence microscopy shows a pathognomonic, linear IgG staining along the GBM; and (D) plasma creatinine and anti-GBM antibodies titer during follow-up show a durable reduction in anti-GBM antibodies titer with independent renal function.

predominance in the older age group (>50 years old).[12] On the opposite, the overall male-to-female ratio is 1:3 in the present review. These differences may be due to sample bias. Fourteen of 26 patients (54%) had pulmonary hemorrhages at disease onset (unknown status for one). At diagnosis, mean serum creatinine was 6.26 ± 4 mg/dL (n = 25), and 15 children were dialyzed. Patient and renal survival rate vary from 67% to 94% and 15% to 58%, respectively, at 6 to 12 months in the adult population.[13] In our pediatric review, results seem to be similar. Five children died within the first 2 months (patient survival rate: 81.5%). Twelve (44.5%) had an independent renal function after a mean follow-up of 2 years (1 day to 10 years). Among dialyzed patients (n = 14), only 3 recovered an independent renal function (maximum duration of dialysis before discontinuation: 1 year). Four patients underwent renal transplantation (14.8%), compared with 12% in a recent adult study.[6]

Adult studies demonstrated that serum creatinine >5.7 mg/dL and dialysis requirement at diagnosis are linked to long-term renal failure and end-stage kidney disease (ESKD).[37,38] Furthermore, crescentic glomeruli >85% seems to represent a poor prognosis factor.[39] In the pediatric literature, all but 2 patients with a serum creatinine above 5.0 mg/dL (n = 13 of 27) were dialyzed during the disease course. None recovered normal renal function. As reported in previous adult study,[12] the proportion of crescentic glomeruli correlated well with serum creatinine at diagnosis (P= 0.67; 95% Confidence Interval, 0.30–0.86). Serum creatinine at diagnosis seems to be linked to a poor long-term prognosis in children. In children, the glomerular filtration rate would be more accurate to define a threshold of risk. Unfortunately, this parameter is not available in most published cases. Among the 27 children from the literature, 13 of 20 (65%) had >80% crescents, and all died or reached ESKD, contrary to

TABLE 1 Pediatric Anti-GBM Disease Reported Since 1980s (n = 27)

Reference	Sex	Age	Anti-GBM Abs	ANCA	IgG IF	S-cr at Diagnosis (mg/dL) and/or eGFR mL/min/1.73 m^2	Crescents (%)	Pulmonary Hemorrhages	Medical Therapy	Physical Treatment	Dialysis	F/U	Status at Last F/U (S-Cr mg/dL, eGFR mL/min/1.73 m^2)
Williamson et al[14]	F	8 y	–	+	+	7.7	83	+	—	—	—	1 d	Deceased
	M	10 y	+	–	+	11.5	87	–	CS/CP	12 PEs	PD	3.5 y	RTx (0.8)
	M	17 y	+	–	+	13.9	100	+	CS/CP/AZA	11 PEs	HD-PD (1 y)	1 y	CKD (2.1)
Bjerre et al[15]	M	19 mo	+	–	+	1.70	76	–	CS/CP/MMF	13 PEs	—	3 y	NI R fn (0.37)
Bakkaloglu et al[16]	F	5.5 y	+	–	+	3.2	Diffuse	–	CS/CP/MMF	9 PEs	PD (8 wk)	15 mo	CKD (0.9)
Poddar et al[17]	M	9 y	+	+	+	8.8	NA	+	CS/CP	21 PEs	HD	2 mo	Deceased
Bayat et al[18]	F	14 y	+	–	–	eGFR 60	+	+	CS/CP	4 PEs	—	1 y	NI R fn (eGFR 90)
Bogdanovic et al[19]	F	10 y	+	+	+	0.53 eGFR 116	16	+	CS/CP/MMF	—	—	10 mo	NI R fn (0.67)
Jiao et al[20]	F	15 y	+	–	–	11 eGFR 5	92	+	CS/CP	9 PEs	HD	11 d	AKI
Gilvarry et al[21]	M	6 y	+	NA	+	3.82	70	–	CS/CP	14 PEs	PD (3 d)	2.5 y	NI R fn (eGFR 104)
Hijosa et al[22]	M	12 y	+	+	+	7.4 eGFR 16	60	+	CS/CP/MMF	10 PEs	—	1.5 y	CKD (eGFR 58.8)
Boven et al[23]	F	2.5 y	+	–	+	4.5	90	NA	CS/CP	18 PEs	PD	2 y	ESKD
Naidoo and Waller[24]	F	4 y	+	+	+	2.68	50	–	CS/CP	11 PEs	—	>9 mo	CKD (0.8)
Brito et al[25]	F	5 y	+	–	+	1.72 eGFR 39	+	–	CS/CP	8 PEs	—	18 mo	NI R fn (eGFR 112)
Hecht et al[26]	F	9 y	+	NA	+	3.7	60	–	CS/CP	13 PEs	—	1 y	NI R fn
Levin et al[27]	F	4 y	+	NA	+	5.27	100	–	CS/CP	2 PEs	—	6 wk	Deceased
	F	10 y	+	NA	+	4.5	80	–	CS/AZA/DPD	4 PEs	HD	>1 y	ESKD
	F	7 y	+	NA	+	14.7	100	+	CS/CP	24 PEs	PD	13 mo	ESKD
Upshaw et al[28]	F	16 y	NA	–	NA	4 eGFR 20	NA	+	NA	NA	NA	NA	NA
Scully et al[29]	F	17 y	+	+	+	11.7	NA	+	—	—	—	1 d	Deceased
McCarthy et al[30]	M	10 y	+	NA	NA	6.2	100	+	CS/CP	6 PEs	PD	12 y	RTx
Bigler et al[31]	F	11 mo	+	–	+	4.92	100	–	CS/CP	1 PE	HD	1.5 y	RTx
Blanco Filho et al[32]	F	10 y	+	+	+	6.13 eGFR 9.3	NA	+	—	—	PD	0	Deceased
Harrity et al[33]	F	13 y	+	NA	NA	Normal	NA	+	NA	NA	—	NA	NI R fn
Martini et al[34]	F	8 y	+	NA	+	8.26 eGFR 14	90	+	CS/CP	PE	HD	>8 mo	ESKD
Nagano et al[35]	F	8 y	+	–	+	0.4	0	–	CS/CP	3 PEs	—	NA	NI R fn
Hibbs et al[36]	M	4 y	+	+	+	8.3	100	–	CS/CP	—	PD	10 y	RTx

TABLE 1 Continued

The 27 reported pediatric cases had a mean age at diagnosis of 8.76 ± 4.6 y and a sex ratio of 1:3 male to female. Fifty-four percent had pulmonary hemorrhages at disease onset. Mean serum creatinine at diagnosis was 6.26 ± 4 mg/dL. Twenty-five of 26 (96%) had positive anti-GBM autoantibodies in the serum and 8 of 19 (42%) had positive ANCAs. The median proportion of crescents on kidney biopsies was 87% (0%–100%). Twenty-two of 25 (88%) received immunosuppressive drugs and 20 of 25 (80%) had plasma exchanges (2–24 sessions). Five died within 2 months after diagnosis because of pulmonary hemorrhage (n = 2), cardiovascular failure (n = 1), or vascular access complications in dialysis (n = 2). At last follow-up (mean follow-up of 2 years), 5 were deceased, 9 were in ESKD or transplanted, and 12 had recovered independent renal function that was normal in 7 children. One 15-year-old girl also presented Turner syndrome. Conversion factors for units: serum creatinine in mg/dL to μmol/L × 88.4. Abs, antibodies; AKI, acute kidney injury; AZA, Azathioprine; CKD, chronic kidney disease; CP, cyclophosphamide; DPD, Dipyridamole; F/U, follow-up; HD, hemodialysis; IF, immunofluorescence; MMF, Mycophenolate Mofetil; NA, not available; NI R fn, normal renal function; PD, peritoneal dialysis; PEs, plasmatic exchanges; RTx, renal transplantation; S-Cr, serum creatinine.

the 7 patients with <80% crescents who were alive with independent renal function at last follow-up. In the present case, although >80% of glomeruli bore crescentic lesions, serum creatinine at onset was low (0.85 mg/dL), and the outcome was rapidly favorable and sustainable during 21 months. However, a sampling bias cannot be excluded.

In the literature, 14 of 26 children had pulmonary hemorrhages (54%) as well as our patient. Prevalence in the adult series varies from 22% to 84%,[6,39–41] and the largest series reported 45.5% among 221 adult cases.[39] Rare cases with isolated pulmonary involvement related to circulating anti-GBM have been reported.[41,42] Among the 30 cases published to date, only 2 were children, diagnosed at 11 and 17 years of age, respectively. This difference could be explained by the smoking status, which is a major risk factor of pulmonary hemorrhages in anti-GBM disease.[6,40]

Some patients with acute GN, with or without pulmonary hemorrhage, also may have other autoimmune disorders linked to the ANCA positivity,[43] which is known to lead to more systemic manifestations and inflammation[44,45] but does not correlate with a poor long-term outcome or a relapsing risk, according to many studies.[41,46] However, in the adult population, anti-GBM antibody titers and presence of ANCAs in serum are independent predictors for death.[47] In the review presented herein, 4 of the 5 children who died had positive ANCAs (unknown status for 1). Our patient presented no systemic signs and complaints that would orient us to other vasculitis, and ANCAs were negative. All children were treated with plasma exchanges associated with immunosuppressive drugs.

Without any appropriate and rapid treatment, the outcome is poor, and natural evolution leads to ESKD and/or death. Classic therapeutics in the pediatric population are extrapolated from adult guidelines and mostly consist of plasma exchanges associated with immunosuppressive drugs (steroids and cyclophosphamide). The largest evidence of plasma exchange efficiency was offered by Johnson et al[48] in a small, randomized control trial (n = 17). Only 25% of patients who received both plasmapheresis and immunosuppressive therapy developed ESKD compared to 66% of patients in the immunosuppressive-alone group.

To date, no data are available regarding IA therapy and anti-GBM GN in children. In 2014, Biesenbach et al[37] reported 10 adult patients treated by IA since 1997. Anti-GBM antibodies became undetectable after the first 9 IA sessions in all patients, and dialysis was able to be stopped in 3 of 6 patients. In 2014, Zhang et al[49] compared double filtration plasmapheresis (DFPP) (n = 16) to IA (n = 12) between 2003 and 2013. Efficacy of anti-GBM antibody clearance was similar in the 2 groups (59.0% vs 71.2%, P = 1.00), although fewer patients in the DFPP group experienced reduced IgG (62.7% vs 83.5%, P = .002). Patient and renal survival were similar in the DFPP and IA groups at the end of follow-up. IA is a blood-purification technique that enables the selective and near-complete clearance of Ig from separated plasma through high-affinity adsorbers. In the present report, IA was chosen because of its availability in our center, the absence of a blood product substitution requirement, and the above-mentioned recent results obtained in adult populations. We used a TheraSorb-Ig flex IA because of its high capacity to filter IgGs. Indeed, anti-GBM antibodies are known to be IgGs directed against the noncollagenous domain of the α3 chain of type IV collagen,[50] as observed in our patient. The outcome was good: anti-GBM antibodies were found to be negative after the seventh IA session, with prolonged remission and no adverse effect.

Since 2002, rituximab has been used within 3 months after diagnosis in 14 patients with a classic therapeutic failure.[51,52] Anti-GBM antibodies became undetectable in all cases, and disease activity stopped. However, in all but 1 patient,[51] rituximab did not improve renal function.

CONCLUSIONS

Anti-GBM GN is a rare and severe condition in which the promptness of immunosuppressive therapy is fundamental to improving the outcome. IA was reported as noninferior to plasma exchange with regard to renal and patient survival in adults.[37] We report herein the first pediatric case treated with a combination of IA and immunosuppressive drugs that led to a sustainable disappearance of anti-GBM antibodies 21 months after onset. Hence, if IA is now considered a valuable option for anti-GBM antibody removal in the adult population, larger studies are necessary to validate this therapy as an efficient alternative to plasmapheresis in children.

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ABBREVIATIONS

ANCA: antineutrophil cytoplasmic antibodies
anti-GBM GN: antiglomerular basement membrane glomerulonephritis
CS: corticosteroids
DFPP: double filtration plasmapheresis
eGFR: estimated glomerular filtration rate
ESKD: end-stage kidney disease
GN: glomerulonephritis
IA: immunoadsorption

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