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Rituximab for eosinophilic granulomatosis with polyangiitis with severe vasculitic neuropathy: Case report and review of current clinical evidence

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ABSTRACT

Objective: Rituximab is approved for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis. Our objective was to review published clinical evidence on the efficacy of rituximab in the treatment of eosinophilic granulomatosis and polyangiitis (EGPA).

Methods: We describe a case of refractory EGPA with severe vasculitic neuropathy, which responded impressively to B-cell-depleting therapy. A systematic search of the English literature was also performed to capture all available clinical evidence on the use of rituximab in EGPA.

Results: We identified a total of 73 EGPA patients who have been treated with rituximab, all data coming from case series or isolated case reports. The majority of patients (85.1%) were treated for refractory or relapsing disease; a mean (SD) of 2.1 (0.9) different immunosuppressive agents were used prior to rituximab administration. Efficacy of RTX therapy was significant in the majority of cases and in a wide variety of disease manifestations; however, a lack of standardized assessment of disease activity before and after treatment was observed in many reports. Overall, 54.0% of patients were treated with a single cycle of rituximab and only 10.8% experienced relapses of the disease. Few significant side effects were observed during a highly variable period of follow-up (3 months to 5 years), mainly severe infections and allergic reactions.

Conclusions: RTX seems to be effective in cases of severe EGPA refractory to standard of care immunosuppressive treatment, although support comes from case reports and non-controlled studies.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome) is a small-vessel, antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. Although it shares common features with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), EGPA also displays some unique characteristics, including the striking correlation with asthma, the abundance of circulating and tissue eosinophils, and the frequent heart involvement, which confer a distinct clinical phenotype [1]. The lung, skin, and peripheral nervous system (PNS) are commonly involved, but EGPA can affect any organ system, including the cardiovascular, gastrointestinal, renal, and central nervous system (CNS).

Rituximab (RTX), a chimeric monoclonal antibody against the CD20 molecule on B-lymphocytes, has been successfully used and is now officially approved for treatment of patients with GPA and MPA [2,3]. However, its efficacy in EGPA has been tested in a very limited number of case reports and small case series. Here, we report a case of severe vasculitic neuropathy and glomerulonephritis associated with EGPA, which responded impressively to RTX. We accompany it with a literature review of published EGPA cases treated with B-cell depletion and discuss relevant issues.

Methods

A case of EGPA treated with RTX is presented. We also searched the English language literature using the PubMed database from January 1966 to December 2014, using the following index terms: (“rituximab” OR “B-cell depletion” OR “anti-CD20”) AND (“eosinophilic granulomatosis with polyangiitis” OR “Churg–Strauss

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syndrome"). Original articles, case series, and case reports were included in the search. Pertinent articles identified by manual search within the reference list of the originally retrieved publications were also included. Only cases with adequate demographic and clinical information were eligible for inclusion.

We recorded the following variables: baseline demographic and clinical characteristics of patients, prior immunosuppressive treatments, RTX regimen, number of RTX cycles and concomitant medications, disease outcome and relapses, and duration of follow-up. Due to the striking response of vasculitic neuropathy to RTX in our patient, we also performed a more detailed assessment of the specific response of EGPA-associated vasculitic neuropathy to B-cell depletion in previously published studies. We also reviewed the efficacy of RTX in neuropathy in the context of vasculitides other than EGPA [ie. GPA, MPA, and mixed cryoglobulinemia syndrome (MC)].

Results

Case presentation

The patient, a 51-year-old man with a past medical history of recurrent nasal polyposis but no known asthma, presented with a 10-day history of arthralgias and progressive numbness of the upper and lower extremities. Two weeks prior to onset of symptoms, he had been treated for a possible viral respiratory tract infection with oral antibiotics and inhaled β -agonists.

Physical examination on admission revealed tachycardia (120 bpm), widespread bilateral wheezing, and symmetrical polyarthritis of small joints of the hands. A detailed neurologic examination was remarkable for reduced muscle strength in left wrist extension and left foot dorsiflexion and loss of pinprick sensation in the same areas. Hypoxemia was evident on arterial blood gas examination (pO_2 , 58.3 mmHg and pCO_2 , 37.3 mmHg).

A complete blood count showed prominent peripheral blood eosinophilia 10,300/ μ l or 47% of total white blood cells [upper limit normal (ULN) 700/ μ l or 10%, respectively]. Serum creatinine (Scr) was 1.1 mg/dl (GFR, 71 ml/min) and urinalysis showed an active urine sediment (glomerular hematuria and cellular casts). Immunologic testing revealed positive p-ANCA antibodies (1:80 perinuclear pattern—normally negative at dilutions $\leq$ 1:20) and high anti-MPO titers 89.8 U/ml (ULN, 20 U/ml). Rheumatoid factor and anti-CCP antibodies were negative. Chest X-ray was normal, while high-resolution computed tomography of the chest revealed bilateral bronchiectasis without other specific findings. An upper and lower limb asymmetric sensorimotor axonal mononeuritis multiplex, indicative of a vasculitic neuropathy, was confirmed on nerve conduction studies (NCS). A heart echocardiogram was normal. A kidney biopsy demonstrated evidence of a pauci-immune focal segmental necrotizing glomerulonephritis, with cellular crescents occupying approximately 40% of glomeruli. An abundance of eosinophils was also observed within the dense inflammatory infiltrates of the renal interstitium and glomeruli. We selected to perform a kidney over a sural nerve biopsy, due to the risk of the latter for permanent neurologic damage, but mainly in order to stratify the severity of renal involvement and choose appropriate immunosuppressive therapy.

The diagnosis of EGPA was established based on the presence of nasal polyposis, peripheral eosinophilia, mononeuritis multiplex, and histological proof of vasculitis with extravascular eosinophils (four of six 1990 ACR criteria for EGPA), with a total Birmingham Vasculitis Activity Score (BVAS) of 22. Other causes of eosinophilia, eg, parasitic infections, were excluded based on the history (absence of recent travel) and physical examination, which was suggestive of a systemic disorder. Hypereosinophilic syndrome

(HES) was considered in the differential diagnosis; the fulfillment of criteria for EGPA precluded further workup for a myeloproliferative HES, as EGPA is currently considered a HES associated with a specific condition [4]. Moreover, since glomerulonephritis was a prominent clinical manifestation, we decided to perform renal biopsy in order to establish the diagnosis.

Therapy was promptly initiated with three daily pulses of intravenous (IV) methylprednisolone (MP) 1000 mg, followed by PO glucocorticoids (prednisolone, 0.5 mg/kg/d), together with monthly IV pulses of cyclophosphamide (CYC) 0.75 mg/m², and resulted in a rapid normalization in peripheral blood eosinophil number.

At 10 days after the 1st dose of CYC, the patient's neurologic symptoms significantly deteriorated with ultimate complete loss of motor function in the left hand (Video 1) and gait difficulty. Lab tests showed rebound prominent peripheral blood eosinophilia, and repeat nerve conduction studies demonstrated significant axonal degeneration compared with baseline examination. Although a primary failure of CYC could not be established due to the very short duration of follow-up, a decision to administer RTX (2×1000 mg in 14 days) as a "rescue therapy" was made and the patient received RTX 3 weeks after the 1st CYC pulse, accompanied by two additional pulses of IV MP.

Six months after the RTX cycle, the patient's neurologic status had significantly improved with the addition of physiotherapy, and laboratory values had returned to normal. A 2nd course of RTX 2×1000 mg was preemptively administered at that time, and the patient was subsequently started on maintenance therapy with methotrexate (MTX) and a tapering steroid dose. Currently, 20 months after initial presentation, he has regained full strength in upper and lower limbs (Video 2), while on MTX at 25 mg/wk. Renal function at last follow-up remained normal (Scr 1.0 mg/dl—GFR 78 ml/min). Oral steroids were administered during the whole period of follow-up and were finally discontinued 18 months after initial presentation. Disease is in full-remission with a BVAS of 0. No significant adverse events were observed during the whole period of follow-up.

Review of the literature

We identified 73 cases of EGPA treated with RTX, for which sufficient information regarding patient characteristics and efficacy of RTX was provided by the authors [5–22]. We did not include patients who were incorporated within large cohorts of patients with ANCA-vasculitis [23] or EGPA [24,25] from specialized vasculitis centers due to lack of adequate detailed individual data. We also did not include one patient with EGPA and rheumatoid arthritis, in whom RTX was administered for treatment of the latter [26]. The purpose of one study was the report of an unusual severe side-effect in two patients in whom the drug was discontinued and efficacy could not be assessed [5]; nevertheless, we included this study due to the severity of the adverse event.

Demographic and clinical characteristics of patients are shown in Table 1. The largest case series was recently reported, including 41 patients from four different centers [22]; the remaining are case reports and case series of $\leq$ 9 subjects. As expected, RTX was mainly given as $\geq$ 2nd line therapy in the majority of cases, although in some it was administered as 1st line (Table 2, including our patient). Interestingly, the regimen most commonly used was 2×1000 mg ("RA regimen") in more than half of cases, although randomized controlled trials of RTX in ANCA-vasculitis have used the 4×375 mg/m² protocol ("lymphoma regimen"). Patients had received a wide variety of immunosuppressive medications prior to RTX administration (CYC in 63.5%) and nearly

Table 1
Summary of EGPA patients treated with RTX in the English literature review

Study	Gender	Age (years)	Disease duration (months)	ANCA status	Clinical manifestations	Prior therapies	RTX regimen	Baseline BVAS	Outcome ^a	Relapses	RTX cycles	Duration of follow-up (months)
Mohammad et al. [22] ^b	20 M 21 F	Median, 54	Median, 46	Anti-MPO (+) 9/41 Anti-PR3 4/41	Asthma/lung 40/41, ENT 35/41, Skin 20/41, PNS 12/41, Renal 10/41, Heart 9/41, GI 9/41, Eyes 5/41, and CNS 1/41	27/41 CYC 21/41 AZA 20/41 MMF 11/41 MTX 7/41 IVIG 5/41 1st line	2 × 1000 mg 30/41 4 × 375 mg 10/41 2 × 800 mg 1/41	Median, 11	14/41 CR - 20/41 PR at 6 months 20/41 CR - 16/41 PR at 12 months Drop in median BVAS from 11 to 1 at 12 months	1 relapse in 4 pts at 12 months	1 19/41 2 5/41 3 17/41	12
Thiel et al. [19]	6 M	Mean, 45	24	Anti-MPO (+)	ENT, asthma, and heart ^c	1st line	2 × 1000 mg	10	1 CR - 8 PR at 3 months	0	1	19
Thiel et al. [19]			12	(-)	ENT, asthma, PNS, and heart ^c	AZA	2 × 1000 mg	18		0	1	6
Thiel et al. [19]			66	Anti-MPO (+)	ENT, asthma PNS, and CNS ^c	AZA and MTX	2 × 1000 mg	14		0	1	6
Thiel et al. [19]			5	(-)	ENT, asthma, PNS, heart, and skin ^c	1st line	2 × 1000 mg	16		0	2	32
Thiel et al. [19]			16	(-)	ENT, asthma, and heart ^c	AZA and MMF	2 × 1000 mg	19	Drop in median BVAS from 14 to 3 at 9 months	0	4	34
Thiel et al. [19]	3 F		184	Anti-MPO (+)	ENT, asthma, PNS, renal, and skin ^c	CYC, AZA, and MTX	2 × 1000 mg	13		0	6	36
Thiel et al. [19]			35	(-)	ENT, asthma, PNS, renal, heart, skin, and CNS ^c	CYC and MTX	2 × 1000 mg	23		0	1	13
Thiel et al. [19]			7	Anti-MPO (+)	Asthma, PNS, and renal ^c	AZA	2 × 1000 mg	9		0	1	6
Thiel et al. [19]			8	Anti-MPO (+)	ENT, asthma, and PNS ^c	MTX	2 × 1000 mg	10		0	1	6
Cartin-Ceba et al. [6]	M	54	48	Anti-MPO (+)	PNS and renal	CYC and MTX	4 × 37 mg	6	CR at 12 months	1 (at 6 months)	2	12
Cartin-Ceba et al. [6]	F	54	0	Anti-MPO (+)	Lung, PNS, and renal	1st line	4 × 375 mg	6	CR at 12 months	0	1	12
Cartin-Ceba et al. [6]	F	64	0	Anti-MPO (+)	PNS and renal	1st line	4 × 375 mg	8	CR at 12 months	0	1	12
Roccatello et al. [17]	M	64	12	NS	PNS, heart, and skin	CYC	6 × 375 mg	28	BVAS 6 at 12 months	0	1	35
Roccatello et al. [17]	M	35	10	NS	ENT and lung	1st line	6 × 375 mg	26	BVAS 3 at 12 months	1	2	36
Donvik et al. [9]	M	50	72	(-)	ENT, asthma, lung, and skin	AZA, MTX	2 × 1000 mg	NS	17% rise in FEV1 1% rise in FEV1/ FVC	0	5	19
Donvik et al. [9]	F	35	58	(-)	ENT, asthma, and lung	AZA	2 × 1000 mg	NS	15% rise in FEV1 18% rise in FEV1/ FVC	0	2	6
Bouldouyre et al. [5]	F	44	24	(-)	ENT, asthma, lung, and PNS	CYC, AZA, and MTX	4 × 375 mg	NS	NA	NA	1	NA
Bouldouyre et al. [5]	F	33	88	(-)	Asthma and lung	CYC, AZA, and MMF	4 × 375 mg	NS	NA	NA	1	NA
Pepper et al. [15]	M	40	2	Anti-PR3 (+)	Asthma, lung, renal, and skin	CYC and PE	2 × 1000 mg	NS	Remission	0	2	9
Pepper et al. [15]	M	66	NS	Anti-MPO (+)	ENT, asthma, PNS, and skin	CYC and IVIG	4 × 375 mg	NS	Remission	0	1	3
Koukoulaki et al. [12] ^b	F	37	NS	(-)	ENT, asthma, lung, PNS, heart, and skin	CYC, MMF, IVIG, and alemtuzumab	4 × 375 mg	9	BVAS 0 at 18 months	2 (at 7 and at 16 months)	3	18
Koukoulaki et al. [12] ^b	F	35	48	NS	Asthma, PNS, and skin	CYC, MMF, AZA, and alemtuzumab	2 × 1000 mg	9	BVAS 0 at 15 months	0	1	15
Smith et al. [21] ^b	F	36	36	NS	ENT, asthma, skin, PNS, and heart	CYC ^d	4 × 375 mg at 1st dose 2 × 1000 at relapses	NS	NS	3	3	22
Saech et al. [18]	M	46	NS	Anti-MPO (+)	ENT, asthma, PNS, skin, and CNS	CYC and MMF	2 × 1000 mg	NS	Improvement of symptoms	0	1	4
Kaushik et al. [11]	M	49	5	Anti-PR3 (+)	ENT, lung, and skin	CYC and AZA	4 × 375 mg	NS	PR	0	1	3

Table 1 (continued)

Study	Gender	Age (years)	Disease duration (months)	ANCA status	Clinical manifestations	Prior therapies	RTX regimen	Baseline BVAS	Outcome ^a	Relapses	RTX cycles	Duration of follow-up (months)
Martinez-Villaescusa et al. [14]	M	70	4	Anti-MPO (+)	Asthma, lung, and renal	CYC and PE	4 × 375 mg	NS	Remission	0	1	60
Umezawa et al. [20]	F	44	5	Anti-MPO (+)	Asthma and PNS	CYC and IVIG	4 × 375 mg	NS	Remission	0	1	6
Rees et al. [16]	M	59	24	Anti-PR3 (+)	PNS and renal	CYC and AZA	2 × 1000 mg	11	Remission	0	1	16
Lovic et al. [13]	F	72	11.5	(-)	NS	CYC and AZA	4 × 375 mg	9	BVAS 3 at 10 months	1	1	10
Grigoriou et al. [10]	F	22	10	Atypical pattern	ENT, asthma, liver, and skin	CYC	2 × 1000 mg	NS	Remission	0	1	NS
Chao et al. [7]	F	29	0.5	NS	ENT and skin	CYC and PE	4 × 375 mg	NS	Remission	0	1	2
Diamanti et al. [8]	F	31	4	Anti-MPO (+)	ENT, asthma, PNS, and CNS	1st line	4 × 500 mg	NS	Remission	0	3	12

MPO: myeloperoxidase; PR3: proteinase 3; ENT: ear, nose and throat; PNS: peripheral nervous system; CNS: central nervous system; CYC: cyclophosphamide; MMF: mycophenolate mofetil; AZA: azathioprine; IVIG: intravenous immunoglobulin; PE: plasmapheresis; MTX: methotrexate; BVAS: Birmingham Vasculitis Activity Score; CR: complete remission; PR: partial remission; NS: not specified; NA: not applicable.

^a In studies that reported BVAS after RTX treatment, this is used as the outcome measure. In the remaining studies, the terms "remission," "quiescent disease," and "improvement" were used by the authors without objective documentation of disease activity.

^b The three patients in the reports of Koukoulaki et al and Smith et al are possibly included in the case series of Mohammad et al.

^c Seven of nine patients had nonfixed lung infiltrates without further specification.

^d A total of five immunosuppressive therapies were administered to this patient prior to RTX, but only CYC is specified.

half of the patients were not administered concomitant immunosuppressives along with B-cell depletion.

Overall efficacy of RTX

Efficacy of RTX therapy was significant in the majority of cases, as shown in Table 1. Objective documentation of baseline disease activity (baseline BVAS) was recorded in 59 patients [12,13,16,17,19,22] and at last follow-up in 55 [17,19,22]. In the largest case series of 41 patients, median BVAS dropped from 11 to 1 at 12 months [22], while in the nine patients reported by Thiel et al. [19], median BVAS dropped from 14 to 3 at 9 months. In studies not reporting BVAS values, authors defined response as "disease remission," "quiescent disease," and "improvement of symptoms," and a study reported improvements in pulmonary function test values [9]. Withstanding this heterogeneity, RTX showed efficacy in a wide variety of disease manifestations, including cutaneous vasculitis, glomerulonephritis, lung disease including asthmatic symptoms, and occasional severe indications, ie, liver and heart involvement (Table 1). In the majority of cases (54%), a single cycle of RTX was adequate to produce symptom alleviation; retreatment in the remaining 46% of patients was given preemptively in the vast majority (88.2%) and only four patients had to be retreated due to a relapse (Table 2, our patient included). Moreover, duration of follow-up after RTX was highly variable among studies, ranging from 3 months to 5 years.

In terms of safety, severe allergic reactions or bronchospasm during RTX administration occurred in four patients [5,22] and severe infections necessitating hospitalization in seven patients [11,22]. The remaining studies did not report severe reactions or infection; nevertheless, one has to keep in mind that efficacy rather than safety was their main objective (publication bias).

Efficacy of RTX in EGPA vasculitic neuropathy

We scrutinized published EGPA cases to investigate whether any data on specific response of neuropathic symptoms to RTX are available. Including our patient, a total of 33/74 patients had PNS involvement at the time of RTX administration (Table 1), with a median (IQR) duration of symptoms of 12 (21) months before administration of RTX. Of the patients, 12 were characterized as peripheral neuropathy and six as mononeuritis multiplex (no details were provided in 15 patients, including the 12 patients in the largest multicenter case series). In the latter study, at the end of follow-up, 8/12 patients were in complete remission (BVAS 0) and three in partial remission [22]. Although the authors do not specify whether ongoing disease activity in partial responders was attributed to PNS disease, complete response in 8/12 patients indicates significant efficacy of RTX in EGPA neuropathy. Similarly, the three patients with peripheral neuropathy in the report by Cartin-Ceba et al. [6] experienced symptom improvement 12 months after B-cell depletion. On the contrary, in the study of Thiel et al. [19], all patients who had PNS manifestations at baseline (seven of nine, all with peripheral neuropathy and not mononeuritis multiplex) had persistent neurologic symptoms 3 months after the administration of RTX (unfortunately not further clarified at 9 months or at last follow-up). In general, patients with documented mononeuritis multiplex had good responses to RTX, as four of six cases showed improvement (no details were provided in the remaining two). Objective measurements of response to therapy (ie, repeat nerve conduction studies) or peripheral nerve biopsy were not performed in any patient, and "improvement" was determined by physician judgment.

Efficacy of RTX in non-EGPA vasculitic neuropathy

RTX has been widely used in cases of MC, in which neuropathy represents a common manifestation. A retrospective multicenter

Table 2

Baseline characteristics, prior and concomitant therapies, relapses, and retreatment with RTX of patients with EGPA treated with B-cell depletion

Gender, male/female, n (%)	37/37 (50/50)
Age in years, median (IQR)	45 (10)
Disease duration, months, median (IQR)	14 (42)
Baseline BVAS, median (IQR)	12 (11)
Choice of RTX treatment, n (%)	
1st line	11 (14.9)
≥ 2nd line	63 (85.1)
Prior therapies before RTX administration, n (%)	
CYC	47 (63.5)
AZA	34 (45.9)
MTX	18 (24.3)
MMF	25 (33.8)
IVIG	11 (14.9)
RTX regimen, n (%)	
2 × 1000 mg	47 (63.5)
4 × 375 mg/m ²	23 (31.1)
6 × 375 mg/m ²	2 (2.7)
4 × 500 mg	1 (1.3)
2 × 800 mg	1 (1.3)
Concomitant therapies with RTX treatment, n (%)	
None	36 (48.7)
AZA	12 (16.2)
MMF	9 (12.2)
CYC	6 (8.1)
MTX	4 (5.4)
Duration of follow-up, months, median (IQR)	13 (24)
Relapses, n (%)	
None	66 (89.2)
1	6 (8.1)
2	1 (1.3)
3	1 (1.3)
RTX cycles, n (%)	
1	40 (54.0)
> 1	34 (46.0)
Preemptively	30 (88.2)
On relapse	4 (11.8)

BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil; IVIG: intravenous immunoglobulin.

Italian study showed complete and partial response rates of 44% and 26%, respectively, in 69 patients with neuropathy in the context of MC (92% hepatitis C virus-related) [27]. An accompanying literature review of older observational studies found very high rates of response in neuropathic symptoms (85/89 patients, 95%), albeit with significant heterogeneity among reports regarding definition of response [27]. A more recent randomized trial comparing RTX to standard immunosuppression in severe MC confirmed a beneficial effect on neuropathy (11/16 patients improved at 6 months); however, loss of response beyond 6 months led to RTX retreatment in six patients [28].

The large controlled trials of RTX in GPA and MPA did not provide specific data on the response of the neuropathic component to B-cell depletion. Nevertheless, smaller observational studies have reported efficacy of RTX in ANCA-vasculitis with a special regard on neurological manifestations [29–31]. This data was recently reviewed and, similarly to EGPA and MC, response rates were high, approaching 90% in 22 patients [32].

Discussion

EGPA is the least common among the three ANCA-vasculitides. Left untreated, EGPA has a reported 5-year survival of 25%;

however, implementation of aggressive treatment has led to a substantial improvement, with 10-year survival rates reaching 90% in recent cohorts [24,25]. We herein reported a case of successful use of RTX in a case of EGPA with severe vasculitic neuropathy and glomerulonephritis and reviewed the quality of current clinical evidence to support its use in this rare disease.

We identified a significant number of EGPA patients who have received RTX mostly for relapsing or resistant disease. A major drawback of several individual studies was the lack of formal assessment of disease activity with a validated instrument like the BVAS, when evaluating efficacy of treatment. Indeed, if we applied strict criteria for the inclusion of studies from the literature review, we would probably have to exclude such reports. Nevertheless, given the rarity of the disease and the paucity of high-quality data, we chose to apply a more lenient approach, in order to capture all published experience regarding this novel therapeutic approach for EGPA. With this limitation in mind, available data suggest that RTX is able to induce at least partial remission in most patients and in a wide variety of manifestations, including glomerulonephritis, CNS involvement, and lung infiltrates, typically accompanied by a robust decline in eosinophil counts.

An interesting observation from the present case is the dramatic response of peripheral neuropathy to B-cell depletion with a full recovery of motor strength following initial paralysis. Review of available literature data showed favorable outcomes in neuropathic symptoms both in EGPA and other systemic vasculitides [32]. Vasculitic neuropathy due to inflammation and ultimate occlusion of the vasa nervorum is very common in EGPA (present in about 80% of patients) and frequently results in permanent neurologic sequelae and limitations in daily activities and quality of life, even when active inflammation has subsided [33]. Indeed, a *post-hoc* analysis from the European Vasculitis Study (EUVAS) Group trials in 40 patients with GPA and MPA (but not EGPA) showed that, although active vasculitic neuropathy was responsive to immunosuppressive treatment, the majority of patients (65%) experienced chronic neuropathic symptoms due to nerve damage at 9 months [34]. Accordingly, it is difficult to interpret response of neuropathy to RTX in the published EGPA cases, only based on physician judgment of improvement and without objective validation (eg, with NCS). Acute mononeuritis multiplex generally responds better to immunosuppressive treatment than pure sensory polyneuropathy and an improvement was indeed observed in our case and the few cases in the literature. Response of peripheral neuropathy was more heterogeneous [6,19]; however, persistence of (mainly sensory) neuropathic symptoms could well indicate axonal irreversible damage due to axonal degeneration rather than ongoing inflammation.

Long-standing asthma is considered a *sine qua non* for the diagnosis of EGPA and typically precedes the diagnosis of the disease for years. Our patient did not have a diagnosis of asthma prior to his current presentation. Nevertheless, clinical presentation and physical examination upon admission were highly suggestive of an asthmatic exacerbation. It would be of interest to evaluate any role of RTX in the asthmatic symptoms, as this clinical feature is unique to EGPA. Our patient has not re-experienced respiratory symptoms during the 20 months of follow-up after B-cell depletion. Three additional studies have provided data on response of asthmatic symptoms to RTX. Six of nine patients in the study of Thiel et al. [19] experienced an improvement in their asthma at 3 months, but the remaining three were unable to taper steroids due to symptom persistence. Conversely, the two patients in the report of Donvik et al. [9] were administered RTX due to severe asthma, and they both showed a significant subjective and objective response. One final patient experienced a relapse in asthmatic symptoms after initial response to RTX, following B-cell reconstitution at 7 and 16 months [12].

From a pathophysiologic point of view, it is interesting that RTX shows efficacy in EGPA, similarly to the other ANCA-vasculitides. The role of B-cells in EGPA, a disease traditionally viewed as a T helper-2-driven disease with eosinophils acting as the main effectors, may be suggested by the frequent presence of ANCA, although a clear pathogenetic role for the latter has not been firmly established. Notably, ANCA-positive patients tend to present more often with vasculitic manifestations of the disease (eg, purpura, glomerulonephritis, and neuropathy), while eosinophilic manifestations due to infiltration of tissue by eosinophils (eg, pulmonary infiltrates and cardiomyopathy) are more common in ANCA-negative patients [1,35]. A similar categorization in GPA dissects disease manifestations into pure vasculitic and granulomatous (eg, orbital masses and pachymeningitis), and it is intriguing that observational studies suggest that RTX may have differential effects on these different manifestations, with higher remission rates in the former and more refractory or relapsing course in the latter, especially for orbital masses [30,36]. The presumed crucial role of T-cells—spared by B-cell-depleting therapy—in granuloma formation may theoretically account for this discrepancy, although this therapeutic predilection has not been replicated in all studies [37,38] and is questioned [39]. By the same token, it would be tempting to examine potential dissimilar efficacy of B-cell depletion in EGPA, since T-cells and eosinophils are involved in tissue injury [40,41]. Our patient had a typical vasculitic appearance; however, available data from the literature review suggest that RTX is also efficacious in “infiltrative” manifestations (heart, lungs, CNS, one case with liver involvement, etc.) with the limitation of a lack of detailed outcome descriptions.

In summary, RTX seems to be effective in cases of severe EGPA, with both renal and PNS manifestations, refractory to standard of care immunosuppressive treatment, although support comes from isolated case reports and non-controlled studies. Prospective, controlled studies are now needed to document RTX short- and long-term efficacy and assess its safety.

Appendix A. Supporting Information

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.semarthrit.2015.03.004>.

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