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Title: Rituximab Treatment in Primary Angiitis of the Central Nervous System: Three Case Reports and Literature Review

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Abstract

Primary angiitis of the central nervous system (PACNS) is a rare autoimmune vasculitis affecting the brain and spinal cord. Treatment with biological agents has revolutionised the treatment of many rheumatic conditions but there is scant literature regarding the use of biological agents in PACNS. We present three cases of PACNS treated with rituximab,

including two cases of relapsed disease, and a literature review suggesting a role for rituximab in this condition.

Key words:

Primary angiitis of the central nervous system, vasculitis, rituximab

Figure 1: Imaging findings in PACNS

Figure A & B: Patient 2 - MRI Brain from patient 2 showing multi-territory infarcts; Figure C: Patient 1 - MRA vessel abnormality; D,E & F: Patient 3 - MRI Brain showing ring enhancing lesion from patient 3 with negative DWI signal

Main text

Introduction

Primary angiitis of the central nervous system (PACNS) is a vasculitis characterised by inflammation and destruction of blood vessels isolated to the brain and spinal cord.¹

PACNS is rare, with an annual incidence rate of 2.4 per 1,000,000 person-years.²

Diagnosis can be elusive and only made after all possibilities, ranging from reversible cerebral vasoconstriction syndrome to infection and malignancy have been excluded. Treatment of this condition is based on expert consensus as there are no prospective or randomised trials to guide therapeutic decisions. Data regarding the treatment of refractory or relapsing disease is particularly lacking.

We present three patients who received rituximab for PACNS, two of whom had refractory disease. We also present a review of the literature of the treatment of PACNS.

CASE 1

A 41-year-old man presented with a four-month history of headache, lethargy and 8kg weight loss. Magnetic resonance imaging (MRI) showed a right internal capsule infarct and systemic inflammatory markers were elevated. An autoimmune screen was negative (see Table 1). Analysis of cerebral spinal fluid (CSF) showed a leukocytosis of $25 \times 10^6/L$ and elevated protein level to 0.68g/L (reference range 0.0-0.40g/L). CSF microscopy, culture, viral polymerase chain reaction (PCR) and cytology

were negative (see Table 1). The patient was commenced on prednisolone 25mg daily for a presumed inflammatory central nervous system (CNS) condition with improvement in symptoms. Headache and lethargy returned when prednisolone was weaned to 10mg daily. Follow-up MRI and magnetic resonance angiography (MRA) showed evolution of the previous infarct and new small infarcts involving the thalamus, prominent vessel attenuation and irregularity involving the right middle cerebral artery and left posterior cerebral artery, consistent with vasculitis (see Figure 1). Given the vessel irregularity seen on MRA, dual subtraction angiography was not performed as it was thought unlikely to add further diagnostic information. Repeat CSF analysis showed a persistent leukocytosis and elevated protein level. Investigations for underlying autoimmune disease, malignancy and infection, including causes of bacterial, mycobacterial and viral meningitis and encephalitis, were unrevealing. Multi-disciplinary consensus was that the clinical presentation and investigation findings were consistent with PACNS and in the absence of leptomeningeal enhancement or a peripheral biopsy-accessible brain lesion on MRI, a brain biopsy was not performed. Five doses of 1g intravenous (IV) methylprednisolone followed by high dose oral prednisolone (60mg daily) and monthly IV cyclophosphamide (1g) was commenced. Repeat imaging two-months later revealed further infarcts, prompting a change to oral cyclophosphamide, escalated to a dose of 2mg/kg. Prednisolone was successfully weaned over the next six-months until a recurrence of headache at a prednisolone dose of 15 mg daily. Re-assessment of disease revealed elevated CSF protein (0.66g/L) but no further infarcts on MRI. Two doses of IV Rituximab (1g) were administered with successful wean of prednisolone to 10mg daily and improvement in headache. Oral

cyclophosphamide was weaned over a two-month period and mycophenolate mofetil (MMF) 2g daily commenced.

The patient remained clinically stable with no new neurological symptoms. Routine imaging three months after administration of rituximab revealed foci of acute ischemia in the left internal capsule and right occipital lobe and CSF analysis showed persistently elevated protein (0.48g/L). Use of infliximab was considered, however was unable to be obtained for the patient. MMF was ceased and the patient was recommenced on low dose oral cyclophosphamide (50mg daily) and two further doses of rituximab (1g) were administered. Three months after the second course of rituximab, repeat MRI Brain shows a small new area of T2 hyperintensity but is otherwise stable and the patient remains clinically stable on a weaning course of prednisolone and oral cyclophosphamide.

Case 2

A 47-year-old man presented with sudden onset facial droop, slurred speech and confusion with a two-week history of drenching sweats and fatigue. MRI brain and MRA revealed a right pontine infarct with no meningeal enhancement and no large vessel abnormality. CSF analysis showed a leukocytosis ($32 \times 10^6/L$) and normal protein level. CSF microscopy, culture, viral PCR and cytology and an autoimmune screen were negative (see Table 1). He was commenced on prednisolone 50mg daily and broad-spectrum antibiotics to cover possible listeria, bartonella, brucellosis and mycobacterial CNS infection. The patient responded to therapy however following a rapid steroid wean to 12.5mg daily he re-presented with new left arm and leg

weakness, paraesthesia and progressive cognitive impairment. Repeat MRI/MRA brain showed multiple new infarcts in the pons, bilateral frontal lobes and thalamus. CSF leukocyte count and protein were both elevated ($44 \times 10^6/L$ and $0.54g/L$ respectively). Repeat CSF microscopy, culture and viral PCR were negative. Digital subtraction angiography revealed bilateral narrowing of the P1 segment of the posterior cerebral arteries. Prednisolone was increased to 50mg daily with rapid clinical improvement. Oral doxycycline and anti-tuberculous antibiotics were continued. Two-months later, he developed uveitis and retinal vasculitis was seen on fundoscopy. A clinical diagnosis of PACNS was made, antibiotics ceased and azathioprine commenced at 2mg/kg in addition to prednisolone 50mg daily. A brain biopsy was not performed as there was no leptomeningeal enhancement or peripheral lesion amenable to biopsy on MRI.

Progressive cognitive impairment developed as the oral prednisolone dose was reduced and repeat MRI brain showed multiple new infarcts (see Figure 2). The patient was treated with 3 doses of 1g IV methylprednisolone and commenced on oral cyclophosphamide (dose 2mg/kg). He transitioned to MMF following six-months of cyclophosphamide without further neurologic events.

Eight-months after ceasing cyclophosphamide the patient developed a right-sided facial droop. MRI showed areas of cerebral white matter signal abnormality but no new infarcts. CSF protein was elevated at $0.57g/L$. He was treated with 3 doses of 1g IV methylprednisolone, 6 cycles of 500mg IV cyclophosphamide and 2 doses of 1g rituximab without any adverse events. Low dose IV cyclophosphamide was chosen

given the patient's history of oral cyclophosphamide use. Three months after rituximab there were no detectable CD19 positive B-cells. Nine months after treatment with rituximab the patient is stable with no new neurological symptoms and continues on MMF maintenance therapy.

Case 3

A 68-year-old woman was admitted with sudden onset global aphasia on a background of one-week of lethargy and labile mood. A computed tomography (CT) scan with contrast revealed a ring-enhancing irregular mass within the left anterior temporal lobe with associated vasogenic oedema. MRI confirmed a solitary enhancing mass most consistent with a neoplastic lesion. Given the high index of suspicion for malignancy, the patient proceeded directly to surgery (see Figure 1). Histopathological analysis revealed small to medium vessel granulomatous necrotising vasculitis. An autoimmune screen revealed a low titre ANA (1:160) but was otherwise negative and a CT scan of the chest, abdomen and pelvis revealed no malignancy (see Table 1).

The patient received 3 doses of 500mg IV methylprednisolone followed by a weaning course of oral prednisolone and 2 doses of 1g IV rituximab. Maintenance therapy of azathioprine (up titrated to 2mg/kg) was commenced. Rituximab rather than cyclophosphamide was given as induction therapy because of patient concern regarding the possible side effects of cyclophosphamide. There were no complications of rituximab therapy. Six months later the patient was clinically improved with normal speech and mood. The patient has experienced seizures

thought to be complication of her temporal lobectomy. MRI Brain shows no recurrence of vasculitis.

Discussion

The three cases above demonstrate the varied presentations of PACNS and summarise the diagnostic modalities used, including brain MRI/MRA, DSA and CSF analysis. In situations where MRA or DSA do not show typical features of vasculitis, tissue diagnosis may be contemplated via brain biopsy. Biopsy remains the gold standard diagnostic test, however this is obtained in only 35-60% of patients in published series.^{3,4} Brain biopsy for this indication has a reported sensitivity ranging from 0% for untargeted biopsies to 78% for targeted biopsies.⁵ If the procedure is being contemplated, a targeted open wedge resection including the overlying leptomeninges is recommended to increase the diagnostic yield of the test.^{5,6}

Initial treatment of PACNS involves induction therapy with high dose corticosteroids, with or without cyclophosphamide, which has a success rate of up to 85%.^{3,4} This treatment regimen was extrapolated from the successful treatment of ANCA-associated vasculitides (AAV) with cyclophosphamide and cohort data confirm its successful use for PACNS.^{3,4} Despite currently available treatments, the relapse rate for PACNS remains up to 25%, and mortality between 6-15% with treatment.^{2-4,7}

Poor prognostic factors include older age at diagnosis, large vessel abnormalities on angiogram, presentation with infarction and focal neurological deficits,^{2,3,8} and higher disability scores at baseline⁸. Granulomatous or necrotising histopathological

subtypes in association with a rapid clinical onset of disease are thought to be less responsive to treatment.⁶

Treatment options for refractory or relapsed disease are limited. Individual cases and small case series have reported the successful use of biological therapy with rituximab (anti-CD20 targeted monoclonal antibody) and infliximab (anti-TNF α targeted monoclonal antibody) for this condition.⁹⁻¹² Much of the experience of treating vasculitis with rituximab comes from use in AAV, where in randomised controlled trials rituximab is as effective as cyclophosphamide for induction therapy and possibly superior for treatment of relapsed disease.^{13, 14} Whilst the mechanism of action of rituximab is incompletely understood, the rationale for use in vasculitis is that the induced selective B-cell death inhibits the production of pathogenic autoantibodies, reduces pro-inflammatory cytokine production, halts presentation of antigen to T-cells, and inhibits the co-stimulation between B- and T-cells.¹⁵ Four previous case reports have shown rituximab can be an effective treatment for PACNS (see Table 1). Rituximab therapy was successful in cases of failed cyclophosphamide therapy in two cases of PACNS^{10, 12} as well as induction therapy.^{9, 10} A variety of histopathological subtypes of PACNS have been reported to respond to rituximab, including a patient with a T-lymphocyte infiltrate¹², reflecting the variety of mechanisms through which rituximab can alter pathological processes. No adverse events have been reported with the use of rituximab for this indication and no disease recurrence has been reported at up to twelve-months of follow-up.

There is limited literature regarding the use of rituximab for other inflammatory CNS conditions. A series of ten patients with confirmed neuropsychiatric lupus demonstrated effectiveness of rituximab with improvement in clinical symptoms in all ten patients and improvement of CNS imaging in six of nine patients. Duration of remission ranged from four to twenty-three months, suggesting that consideration be given to re-treatment in some patients as persistent remission is not universal.¹⁶ The role of monitoring peripheral B-cell populations to predict disease relapse remains controversial as there is not a clear relationship between B-cell reconstitution and clinical relapse and it is hypothesised that peripheral circulating B-cell populations may not reflect the cellular milieu of the inflamed tissue.¹⁷⁻¹⁹

The successful use of tumour necrosis factor (TNF) α inhibitors in refractory PACNS has been documented.¹¹ The use of TNF α inhibitors in this patient population is controversial as there is a suggestion that exposure to high dose corticosteroids, cyclophosphamide and infliximab in SLE results in a higher risk of lymphoma.²⁰ Given the significant background cyclophosphamide exposure of both patients with refractory PACNS reported here and a greater body of literature to support the use of rituximab, we elected to proceed with rituximab therapy.

Conclusion

We have presented three cases of the use of rituximab in PACNS, two in patients with refractory disease and one as induction therapy. To our knowledge, this is the largest case series of patients treated with rituximab for this indication, including the

first report of re-treatment of relapsed disease, and adds further evidence supporting the use of rituximab to treat PACNS.

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Table 1: Patient characteristics

	Patient 1	Patient 2	Patient 3
Patient characteristics of current case series			
Age	41 years	47 years	68 years
Sex	Male	Male	Female
Clinical symptoms	Headache	Facial droop	Aphasia
	Lethargy	Fever	Confusion
	Weight loss	Drenching sweats	Emotional lability
ESR (ULN 20mm/hr)	40	56	Not done
CRP (ULN 5mg/L)	86	148	< 5
MRI/angiography findings	Multi-territory infarcts	Pontine infarct	Solitary enhancing mass
	Vascular abnormalities	No vascular abnormalities	
CSF analysis			

- Leucocyte count	25 x 10 ⁶ /L	32 x 10 ⁶ /L	Not done
- Leucocyte subsets	92% mononuclear	100% lymphocytes	
- Protein (ULN 0.40g/L)	0.68 g/L	0.38 g/L	
- Viral PCR†	Negative	Negative	
Autoimmune testing			
- ANA	Negative	Negative	1:160 (homogeneous)
- ENA	Negative	Negative	Negative
- dsDNA	Negative	Negative	Negative
- ANCA	Negative	Negative	Negative
- Rheumatoid factor	Negative	Negative	Negative
- Antiphospholipid antibodies	Negative	Negative	Negative
- Serum ACE (20-70 U/L)	Not done	14	13

Histopathology	No biopsy	No biopsy	Small to medium granulomatous necrotising vasculitis
Treatment prior to rituximab	IV & oral corticosteroid IV & oral cyclophosphamide Mycophenolate mofetil	IV & oral corticosteroid Oral cyclophosphamide Azathioprine	IV & oral corticosteroid
Duration of cyclophosphamide	11 months	6 months	Nil
Rituximab dose	Two treatments of 2 x 1g rituximab	2 x 1g rituximab	2 x 1g rituximab
Adjunct treatment to rituximab	Cyclophosphamide (oral)	Mycophenolate mofetil	Azathioprine
Treatment response	Improved neurological status New foci of infarction and	No new neurological symptoms No deterioration in neurocognitive dysfunction	Post-operative non- epileptiform seizure activity

	evidence of active vessel inflammation on MRI	No new lesions or evidence of vasculitis on MRI		
Duration of follow up to date following initial rituximab	Ten months	Ten months	Eight months	
Previous use of rituximab in PACNS				
	Patient 1	Patient 2	Patient 3	Patient 4
Age at onset	68 years	42 years	57 years	3 years
Sex	Female	Male	Female	Female
Clinical symptoms	Headache	Progressive cerebellar ataxia	Balance disorder	Headache
	Transient paraesthesia		Dysarthria	Speech disturbance
	Fever	Left hemiparesis	Focal motor deficit	Limb hypotonia
		Binocular diplopia	Cognitive decline	

MRI/angiography findings	Multi-territory infarcts Multiple deep white matter lesions Leptomeningeal enhancement	Multiple, enhancing white matter lesions, including of cervical spine Meningeal enhancement	Multi-territory infarcts Multiple small vessel stenoses	Bilateral supratentorial lesions Optic nerve involvement
CSF analysis				
- Leukocyte count	587 μL	60/ mm^3	17/ mm^3	Normal
- Protein	1.07 g/L	0.6 g/L	0.7 g/L	0.63 g/d
Histopathology	Granulomatous vasculitis of leptomeningeal vessels	Lymphocytic infiltrate of vessel walls	No biopsy	T-lymphocytes infiltrating vessel walls & surrounding white matter
Treatment prior to rituximab	Oral corticosteroids	Oral corticosteroids IV cyclophosphamide	Oral corticosteroids	IV & oral corticosteroids Azathioprine IV cyclophosphamide

Duration of cyclophosphamide	Nil	5 months	Nil	6 months
Rituximab dose	2 x 1g rituximab	4 x 375mg/m ² rituximab	4 x 375mg/m ² rituximab	2 x 350mg/m ² rituximab
Adjunct treatment to rituximab	5 months IM methotrexate	Azathioprine	Nil	Nil
Treatment response	Neurological deficits resolved Reduced white matter & contrast-enhancing abnormalities	Reduced paraesthesias & ataxia Reduced number of MRI lesions	Improved neurological status Reduced size & number of MRI lesions	No new neurological symptoms No deterioration in cognition
Duration of response	7 months	12 months	20 months	11 months

†Viral PCR testing for herpes simplex virus type 1 & 2 DNA, varicella zoster virus DNA, cytomegalovirus DNA, enterovirus RNA

Abbreviations: ANA: anti-nuclear antibodies; ACE: angiotensin converting enzyme; ANCA: anti-neutrophil cytoplasmic antibody; CRP: C-reactive protein; CSF: cerebral spinal fluid; dsDNA: anti-double stranded DNA antibodies; ENA: extractable nuclear antigens; ESR: erythrocyte sedimentation rate; MRI: magnetic resonance imaging; PCR: polymerase chain reaction; ULN: upper limit of normal

List of abbreviations

AAV: ANCA-associated vasculitis
ANCA: anti-neutrophil cytoplasmic antibody
CNS: central nervous system
CSF: cerebral spinal fluid
CT: computed tomography
GPA: granulomatosis with polyangiitis
IV: intravenous
MMF: mycophenolate mofetil
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
PACNS: primary angiitis of the central nervous system
PCR: polymerase chain reaction
TNF: tumour necrosis factor

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