

CASE REPORT

Nagoya J. Med. Sci. 76. 361 ~ 368, 2014

LIMBIC ENCEPHALITIS ASSOCIATED WITH RELAPSING POLYCHONDritis RESPONDED TO INFlixIMAB AND MAINTAINED ITS CONDITION WITHOUT RECURRENCE AFTER DISCONTINUATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Central nervous system (CNS) manifestations are rare complications of relapsing polychondritis (RP). The majority of patients respond well to glucocorticoid therapy, but need to maintain it. Some patients are refractory to initial glucocorticoid therapy and to additional immunosuppressants, and end up with an outcome worse than at therapy initiation. The standardized therapeutic protocol for this condition has not been established. The effects of anti-tumor necrosis factor (TNF) - α agents have been reported recently. We experienced a patient with RP and limbic encephalitis who was refractory to initial high-dose glucocorticoid, but subsequently responded to infliximab and did not show deterioration of signs and symptoms after stopping therapy. We report this case together with a systematic literature review. This is the first case report of RP with CNS manifestations successfully treated by an anti-TNF- α agent without recurrence after discontinuation.

Key Words: relapsing polychondritis, limbic encephalitis, infliximab, anti-tumor necrosis factor-alpha agent, therapy discontinuation

INTRODUCTION

Relapsing polychondritis (RP) is an uncommon disorder of unknown etiology that is characterized by recurrent and progressive inflammation of cartilaginous structures. A minority of patients with RP develop central nervous system (CNS) manifestations,¹⁾ and limbic encephalitis has also been reported.¹⁻⁵⁾ Glucocorticoid has been used as the first-line therapeutic agent,¹⁻²²⁾ but a standardized second-line therapeutic protocol for RP with CNS manifestations has not

Received: April 3, 2014; accepted: July 14, 2014

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been established. The effects of anti-tumor necrosis factor (TNF) - α agents have been reported recently.^{5,9)} We report a patient with limbic encephalitis associated with RP who was refractory to initial high-dose glucocorticoid therapy, but subsequently responded to infliximab and discontinued therapy without recurrence. We also reviewed cases of RP with CNS manifestations using PubMed with regard to clinical manifestations and treatment.

CASE PRESENTATION

A 58-year-old Japanese male architect was brought to our institution by his wife, presenting with amnesia, disorientation, emotional lability and urinary incontinence. One year prior to admission, he had bilateral ear pain with swelling and erythema which improved without any treatment over a 4-week period. Nine months prior to admission, he experienced iritis and scleritis in addition to recurrent pain in bilateral auricles. Subsequent biopsy of the left auricle revealed infiltration of inflammatory cells in the perichondrium (Fig. 1). Diagnosis of RP was made based on McAdam's criteria, modified by Damiani and Levine.^{23,24)} No other organs were affected. Inflammation of bilateral auricles disappeared without any treatment, while iritis and scleritis were controlled by topical glucocorticoid therapy. Around 2 months prior to admission, he showed amnesia with gradual progression. One month prior to admission, he developed difficulty with drawing architectural drafts and finding his way home, together with emotional lability and urinary incontinence. Past medical history revealed well-controlled diabetes mellitus by diet and dipeptidyl peptidase-4 inhibitor (HbA1c was 6.4 to 6.7%).

On admission, his body temperature was 36.7°C, blood pressure was 112/66 mmHg and heart rate was 68 beats per minute. Physical examination revealed flared ears. Head, eye, ear, nose, chest and abdominal examinations were unremarkable. Neurological examination revealed poor tandem gait and poor finger-nose-finger test, but other examinations such as the cranial nerve, sensory and motor systems were unremarkable. He was euphoric and disoriented. His Mini-Mental States Examination (MMSE) result was 16 out of 30. Complete blood cell count, serum chemistry screening and endocrine function were unremarkable. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, urinalysis and serological tests for human immunodeficiency virus (HIV)

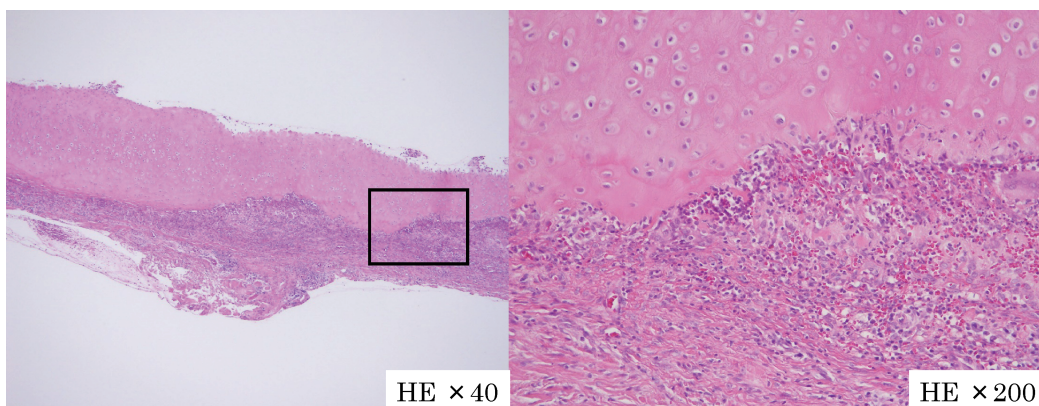


Fig. 1 Histopathological examination of ear biopsy (hematoxylin-eosin stain) showed infiltration of inflammatory cells (histiocytes, lymphocytes, neutrophils and eosinophils) in perichondrium and chondrium.

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and *treponema pallidum* were all normal or negative. Cerebrospinal fluid (CSF) analysis showed 33 cells/ μ l with 32 polymorphonuclear leukocytes, glucose 81 mg/dl and protein 92 mg/dl. CSF smear for Gram stain and acid-fast organisms stain were negative. CSF cultures for bacteria and *Mycobacterium tuberculosis* and polymerase chain reaction of *Herpes simplex virus* and cytology were also negative. Both anti-N-methyl-D-aspartate type glutamate receptor (GluR) N2B antibody and anti-GluR δ 2 antibody were positive in CSF, but neither were positive in serum.

Whole body fluorine-18 fludeoxyglucose positron emission tomography ([18 F]FDG-PET) with CT to detect tumor revealed no abnormal uptake. Comparing current brain magnetic resonance imaging (MRI) result with the previous ones indicated limbic system atrophy resulting in ventricular enlargement (Fig. 2-A, B). Diffusion weighted image, fluid-attenuated inversion recovery image (FLAIR) and gadolinium enhancement showed no abnormality. Electroencephalogram showed diffuse dominant theta waves with no spike.

Considering his clinical symptoms like emotional lability and amnesia, limbic system atrophy in MRI and increased number of CSF cells limbic encephalitis was diagnosed. Because other causes such as HIV encephalitis, herpes simplex encephalitis, tumor-associated limbic encephalitis or Hashimoto encephalopathy were ruled out, limbic encephalitis associated with RP was diagnosed, clinically. A course of intravenous 1 g methylprednisolone for 3 days was administered, followed by oral prednisolone 1 mg/kg per day. His cognitive function improved temporarily, but worsened again (Fig. 3). Subsequently infliximab 3 mg/kg was added to the prednisolone. His head MRI had no change but MMSE score was improved gradually, ataxia disappeared through 4 doses of infliximab over a 3-month period, and problematic behavior disappeared. Because of his stable condition as well as the high cost of infliximab, he and his wife refused further infliximab therapy. His condition continued to be stable without infliximab. Prednisolone was tapered down over a 16-month period and finally stopped. The patient was followed up for an additional 9 months after stopping prednisolone without recurrence (Fig. 3). At the end, he could continue active daily living independently, but could not resume his work.

Head MRI (T2WI)

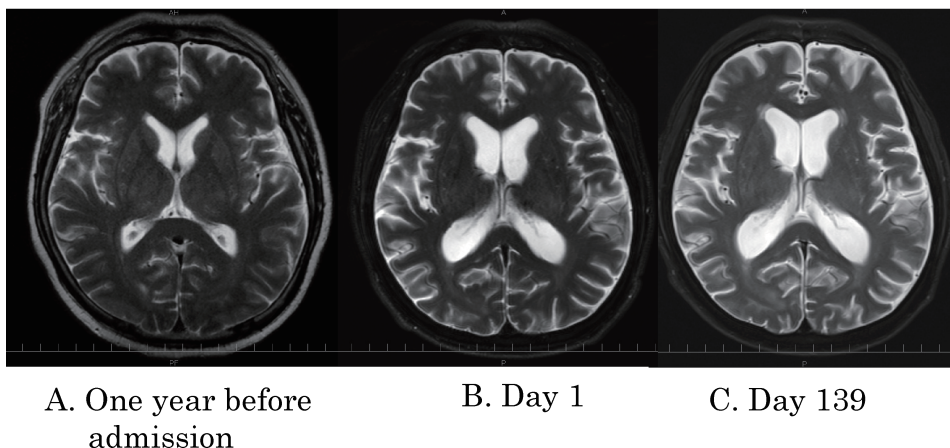


Fig. 2 (A) T2WI one year before admission; (B) T2WI of Day 1 showed ventricular enlargement compared to one year before admission; (C) there was no change after 6 months.

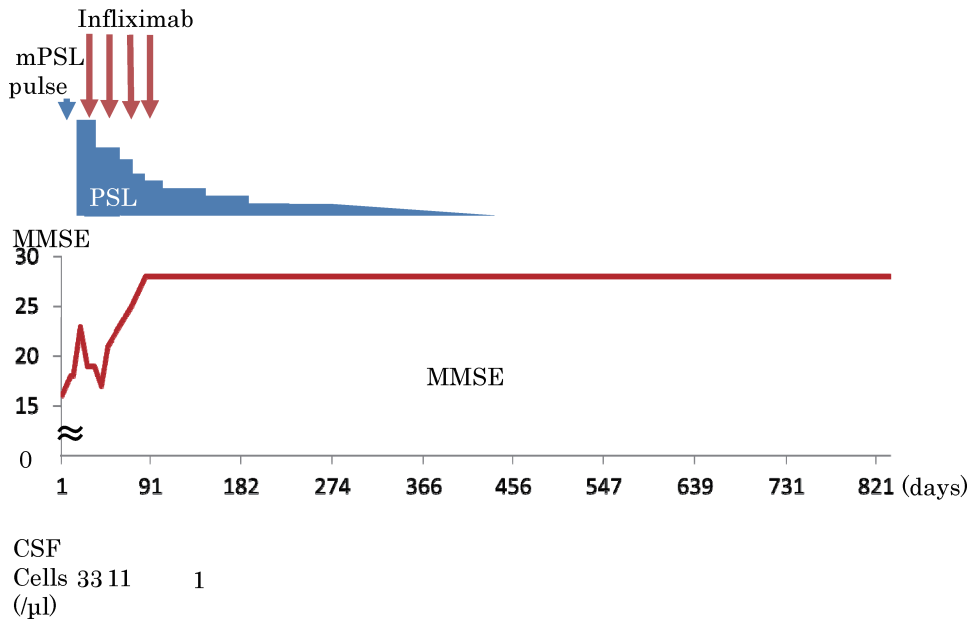


Fig. 3 Clinical course. Cognitive function improved temporarily after methylprednisolone pulse, but worsened again. MMSE score was improved gradually after infliximab.

DISCUSSION

RP, a rare episodic and progressive inflammatory disease presumed to have autoimmune etiology, was first described in 1923.²⁵⁾ RP affects cartilage in multiple organs, such as the ear, nose, larynx, trachea, bronchi, and joints.²⁵⁾ In addition, it can affect proteoglycan-rich tissues such as the eyes, aorta, heart and skin.²⁵⁾ The diagnosis of RP is usually made on the basis of clinical findings.²⁵⁾ McAdam criteria²³⁾ modified by Damiani and Levine,²⁴⁾ which is commonly used as a criterion to confirm the diagnosis of RP, consists of: a) at least 3 of 6 clinical criteria (bilateral auricular chondritis, nonerosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory chondritis and audiovestibular damage); b) 1 or more of the previously-mentioned clinical criteria and biopsy confirmation of cartilage inflammation; or c) chondritis at 2 or more separate anatomic locations with response to steroids and/or dapsone. This case fits criterion b).

RP with CNS manifestations is rare.^{8,22)} We searched MEDLINE in March 2014 using (“Polychondritis, Relapsing” [Mesh] OR “Relapsing polychondritis”) AND (“Encephalitis” [Mesh] OR “Limbic Encephalitis” [Mesh] or encephalitis or encephalopathy or “Limbic Encephalitis” OR “Meningoencephalitis” [Mesh] OR Meningoencephalitis or “nervous system”) as keywords. We retrieved a total of 54 articles, 26 of them including 31 cases that met inclusion criteria (case report or case series written in English or Japanese) (Table 1).^{1-22,26-28)}

As shown in Table 1, 28 out of 31 patients have been treated with a high dose of glucocorticoid.¹⁻²²⁾ Twenty-two out of those 28 patients had symptoms which were well-controlled by initial therapy, but only one could discontinue glucocorticoid therapy.¹⁹⁾ Six patients were refractory to initial glucocorticoid therapy.^{3,4,7,9,11,12)} Additional therapy (cyclophosphamide, intravenous immune globulin, tacrolimus, plasmapheresis, methotrexate and cyclosporin) showed no remarkable effect

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Table 1 Abbreviations: T2WI, T2 weighted image. mPSL, methylprednisolone. PSL, prednisolone. AZP, azathioprine. MONO, monocytes. PMN, polymorphonuclear leukocytes. CYC, cyclophosphamide. MTX, methotrexate. IVIG, intravenous immunoglobulin. nr, not reported.

Cases filled in red were refractory to initial glucocorticoid therapy. Cases filled in blue had good response to initial glucocorticoid therapy. Other patients received no treatment or the results were unknown.^{5,7,21,27,28,30)}

*The clinical course after the second pulse is not shown.

Year	Age Sex	Associated neurologic disorders (most patients had fever, headache or meningeal irritation signs)	CSF Leucocytes (/mm ³)	MRI	Treatment	neurological response to initial therapy	neurological response at end of follow up	Outcome	treatment successfully discontinued
this case	58 M	amnesia, cognitive impairment, emotional lability, urinary incontinence, euphoria	33 (32 PMN and 1 MONO)	ventricular enlargement	mPSL 1 g/day 3 days→ PSL 1 mg/kg/day→ + infliximab →PSL →stopped	transitory	good	alive	yes
2011 ⁹⁾	57 M	generalized seizure, confusion	700 (MONO 686)	T2WI high, gadolinium-enhanced	high dose i.v. mPSL→ high dose i.v. mPSL+CYC →PSL+CYC→ PSL+MTX→ infliximab	transitory	good	alive	no
2011 ⁷⁾	52 M	amnesia, gait disorders and urinary incontinence, acalculia	231 (PMN 161, MONO 69)	ventricular enlargement	mPSL 500 mg+IVIG 30 g/day 5 days→ PSL 20 mg/day→ Steroid Pulse	transitory	good or transitory*	alive	no
2009 ³⁾	62 M	delirium, hallucinations, agitation, disinhibition, cognitive impairment, seizure, disturbed consciousness, recurrent clonic convulsion	39 (MONO 23)	FLAIR high	iv mPSL 3 days a week 3 weeks→iv mPSL 3 days a week 4 weeks→ PSL 20 mg/day+tacrolimus 3 mg/day	transitory	worsend	alive	no
2008 ¹²⁾	51 M	coordination disorder, distractibility, emotional lability, insomnia, nocturnal myoclonic jerks, perseveration, attention and concentration deficits, confusion, speech latency, word-finding difficulty, myoclonus	39 (MONO 59)	high signal abnormalities	PSL 80 mg/day→ Cyclophosphamide 150 mg/day	worsened	worsend	died (after 10 months of neurological onset)	no
2011 ⁴⁾	73 M	transitory loss of consciousness, confusion, disorientation, confabulation, aphasia, hallucinations, cognitive impairment	89 (MONO 89)	FLAIR high, T2 high	mPSL1500 mg 3 days→ 3500 mg→ mPSL po 24 mg/day→ mPSL 1500 mg+ plasmapheresis→+IVIG	transitory	worsend	died (after 5 month of disease onset)	no
2009 ¹¹⁾	67 F	bradykinesia, disturbed consciousness, reduced willingness, walking disorder	73 (MONO 73)	FLAIR high	mPSL 1000 mg/day 3 days→PSL 40 mg/day→ PSL 60-50 mg/day +MTX 6-8 mg/w+CyA 100-200 mg/day	transitory	worsend	died (after 6 months of neurological onset)	no
1992 ¹⁹⁾	73 F	decreased consciousness, slow in mention, right eyelid paresis, slight unilateral facial weakness	nr	nr	PSL 100 mg/day→ +Cyc 100 mg/day→ PSL 5 mg/day→both stopped	good	good	alive	yes
2011 ⁷⁾	44 M	amnesia, irritated, anxious	190 (PMN17 MONO 171)	T2WI high	mPSL 200 mg 5 days→ 120 mg/day one week→ PSL 60 mg/day +AZP 100 mg/day→PSL 25 mg/day+AZP 100 mg/day	good	good	alive	no
2011 ⁷⁾	44 F	anxiety, insomnia	70 (PMN 28 MONO 42)	normal	mPSL 500 mg iv→mPSL 120 mg/day→+AZP	good	good	alive	no
2011 ⁸⁾	68 F	dysarthria, disorientation, impaired language function, agraphia	100 (PMN 33, MONO 67)	high intensity	mPSL 1 g 3 days→ PSL 1 mg/kg/day→10 mg/day	good	good	alive	no
2010 ¹⁰⁾	70 M	confusion, hallucinations	38	T2WI high, gadolinium enhancement	mPSL 1 g 3 days→ PSL 1 mg/kg/day→15 mg/day	good	good	alive	no
2008 ¹³⁾	66 F	bradykinesia, somnolence, urinary incontinence, mutism, disorientation	90	T1WI low, T2WI high, FLAIR high	mPSL 1000 mg/day 3 days	good	good	alive	no

2008 ¹²⁾	68 M	comprehension problems, emotional lability, confusion, language problems, amnesia, executive dysfunction, visuospatial impairment, mild anomia	4 (MONO 2)	T2WI high	PSL 80 mg/day	good	good	alive	no
2007 ¹⁴⁾	40 M	confusion, somnolence	1500 (PMN 1245)	T2WI high, FLAIR high	intravenous steroid therapy	good	good	alive	no
2007 ²⁶⁾	64 M	amnesia, disorientation, acalculia, reduced willingness	14 (MONO 14)	T2WI high, FLAIR high	PSL 30 mg po→ PSL 20 mg/day po	good	good	alive	no
2006 ¹⁵⁾	71 F	confuse, aphasia, weakness of right extremities	110 (MONO 100)	enhanced	hydrocortisone 200 mg/day→ PSL 60 mg/day→ PSL 20 mg/day	good	good	alive	no
2004 ¹⁷⁾	38 M	right-side weakness, diplopia, right side hemiplegia, with hyperreflexia and clonus at the ankle, confuse	nr	T2WI high	corticosteroid therapy→ PSL 1 mg/kg/day+AZP	good	good	alive	no
2004 ²⁾	45 M	confusion, euphoria, hyperactive behavior, disorientation, amnesia, fever, inappropriately jocular affect, disjointed speech, confabulation, attention deficits	8000 (MONO 7520)	T2WI high	high dose mPSL→ PSL 40 mg/day	good	good	alive	no
2004 ¹⁶⁾	49 M	disorientation, somnolent, ataxic, disorientation, gait disorder	145 (PMN 55 MONO 81)	T2WI high	1 g mPSL 3 days→ PSL 40 mg/day a week→ 20 mg→10 mg/day+ 200 mg hydroxychloroquine per day	good	good	alive	no
2004 ¹⁾	57 M	amnesia, anxiety, depressive state	119 (MONO 105)	T2WI high, FLAIR high, gadolinium enhanced	mPSL 1 g/day 3 days 2 course →60 mg/day	good	good	alive	no
2004 ²⁾	62 M	acalculia, confusion, euphoria, amnesia	24000 (MONO 21360)	T2WI high, FLAIR high	methylprednisone pulse→ PSL 40 mg/day po	good	good	alive	no
1995 ¹⁸⁾	36 M	horizontal diplopia	5 (5 MONO)	T2WI high, gadolinium enhancement	PSL 20 mg taper over 2 weeks→ 30 mg/day→3 months→ 10 mg/day	good	good	alive	no
1991 ²⁰⁾	64 M	change in mental status, hallucination	100 (2PMN, 96 MONO)	nr	PSL 100 mg iv→ 60 mg/day→ +Cyclophosphamide 125 mg/day	good	good	alive	no
1983 ²²⁾	58 F	unsteady in walking, confused, hallucination, disorientation, nystagmus, facial weakness	nr	nr	PSL 80 mg/day→ dapsone 200 mg/day	good	good	alive	no
2012 ⁶⁾	60 M	acalculia, dyslexia, right left agnosia, mild right hemiparesis	138 (MONO 128 PMN 10)	FLAIR high, enhanced	PSL iv→PSL po 20 mg	good	good	improved	no
1984 ²¹⁾	51 M	left facial weakness, ataxia, dementia, confuse	normal	nr	steroid	no	no	alive	no
2011 ⁷⁾	54 M	bipolar disorder, memory loss, hallucinations, amnesia, disorientation, insomnia, irritability	800 (MONO 800)	T2WI high	mPSL 1000 mg iv 3 days→ PSL 80 mg/day+AZP	nr	good	alive	no
2009 ⁵⁾	29 M	nr	32 (PMN 32)	T2WI high, FLAIR high	oral steroid→ azathioprine+adalimumab	nr	nr	alive	no
2000 ²⁸⁾	75 F	tremor	nr	T2WI high	nr	nr	nr	alive	no
2008 ³⁰⁾	61 M	convulsions, decreased interest, slurred speech, hallucinations, somnolent, rigidity	312 (MONO 299)	T2WI high, FLAIR high, gadolinium enhancement	no treatment (supportive therapy alone)	good	good	alive	no
2006 ²⁷⁾	53 M	cognitive impairment, difficulties with problem solving, amnesia, uncharacteristically aggressive and abusive behavior, disorientation, psychomotor dysfunction	nr	DWI high	palliative care	no (no treatment)	no (no treatment)	died (after 18 months from onset)	no

and 3 patients died.^{3,4,7,11,12} Only one who was treated with infliximab⁹ had a good outcome, so we chose infliximab as a second-line agent.

This is the first case report of RP with CNS manifestations treated with an anti-TNF- α agent who did not show deterioration of signs and symptoms after stopping therapy.

Infliximab may be a good choice for RP with CNS manifestation refractory to initial glucocorticoid therapy.⁹ Infliximab has a large molecular weight, so it is impossible for it to permeate the blood-brain barrier. Then why does it work? One potential explanation is that breakdown of the blood-brain barrier by inflammation may permit infliximab to access cerebral parenchyma, resulting in the suppression of TNF- α mediated inflammatory processes.²⁹ Although theoretically it may be reasonable to stop infliximab when neurologic symptoms are stable, if breakdown of the blood-brain barrier by inflammation is important for the effect of infliximab, it would be wise to closely observe the clinical course when discontinuing infliximab.

CONCLUSION

Anti-TNF- α agents may be a treatment of choice for RP with CNS manifestations refractory to initial glucocorticoid therapy. In addition, anti-TNF- α agents may be discontinued, but it would be prudent to closely observe the clinical course when stopping infliximab.

The authors declare no conflict of interest associated with this article.

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