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CASE BASED REVIEW

Aseptic meningitis in relapsing polychondritis: a case report and literature review

Kai Shen[1] · **Geng Yin**[2] · **Chenlu Yang**[1] · **Qibing Xie**[3]

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Abstract Aseptic meningitis is an extremely rare neurologic complication of relapsing polychondritis (RP). We reported a case of a 58-year-old Chinese female with intractable headache, puffy ears, pleocytosis, and cranial magnetic resonance imaging (MRI) showing thickened and enhanced meninges. She was finally diagnosed of aseptic meningitis due to RP after full exclusion of infectious causes. She gradually developed neurosensory hearing loss, vertigo, and saddle nose while glucocorticosteroid therapy and combined cyclophosphamide could not control her headache. Ultimately, cyclosporin A was tried showing a good response. Only 18 previous cases were found in the literature and the clinical manifestation, cerebrospinal fluid (CSF) characteristics, imaging features, and therapy considerations of RP-related aseptic meningitis were summarized by reviewing the literature. Aseptic meningitis due to RP is a rare condition of undetermined pathoetiology. Its diagnosis is primarily based on clinical manifestations combined with CSF and MRI examinations plus adequate exclusion of possible infections. Corticosteroid is the basic therapy but choice of protocol should be individualized.

Keywords Aseptic meningitis · Cerebrospinal fluid · Magnetic resonance imaging · Recurrent polychondritis

Kai Shen and Geng Yin contributed equally to this work.

✉ Qibing Xie
xieqibing1971@163.com

[1] Department of Hematology, West China Hospital, Sichuan University, Chengdu 610041, China

[2] Department of General Practice, West China Hospital, Sichuan University, Chengdu 610041, China

[3] Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu 610041, China

Introduction

Relapsing polychondritis (RP) is a rare and potentially lethal autoimmune disorder, characterized by recurrent bouts of inflammation and destruction of cartilaginous and other proteoglycan-rich tissues with ears, nose, larynx, and tracheobronchial tree most commonly involved [1]. Both younger and senile patients can be affected by RP with an incidence of 3.5/100,000 in the USA each year [2]. RP as a systemic disease can also be present with polyarthritis, ocular inflammation, skin lesions, cadiac valvular incompetence, renal diseases, and vasculitis. Only approximately 3% of RP patients have neurologic involvement. Heterogeneous manifestations including palsies of cranial nerves, polyneuritis, meningoencephalitis, hemiplegia, and cerebral aneurysms have been described in RP's neurological lesion. General or local seizure, dementia, and stroke have also been reported [2]. Aseptic meningitis is an extremely rare central nervous system (CNS) complication of RP which can be easily mis-recognized as infection or other inflammatory disorders. Herein, we reported a case of a 58-year-old Chinese female with recurrent onsets of RP-related aseptic meningitis manifested by headache, pleocytosis, and thickening meninges on magnetic resonance imaging (MRI). The clinical manifestation CSF characteristics, imaging features, and therapy considerations of RP-related aseptic meningitis were summarized by reviewing the literature.

Case report

A 58-year-old Chinese woman was evaluated in our center in April 2011 for her 10 years history of swelling ears and intermittent headaches. She could not tolerate the headache despite analgesic treatment before admission. She also had sore eyes and arthralgias on both hands. On physical examination, she

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was afebrile and her entire pinnas appeared red and swollen with tenderness. Bilateral scleritis was found by ophthalmologic consultation. Neurologic checkups revealed neck stiffness with no pathologic signs. Laboratory workups showed elevated C-reactive protein at 144 mg/L (normal range, <5 mg/L) and erythrocyte sedimentation rate at 75 mm/h (normal range, <38 mm/h). Antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibodies, and serology for syphilis and HIV were all negative. Cerebrospinal fluid (CSF) analysis showed 150 cells/mm^3 (normal range,<8 cells/mm^3) with 58% polymorphonuclear (PMN) leukocytes, glucose 46.3 mg/dl (normal range, 25–44 mg/dl), chloride 114.2 mmol/L (normal range, 120–130 mmol/L), protein 27.8 mg/dl (normal range, 1.5–4.5 mg/dl), and normal opening pressure. Acid-fast bacilli smear, Gram stain, and Indian ink stain for *Cryptococcus neoformans* were all negative. CSF culture found no growth of bacteria or fungus, and TB-DNA assay of her CSF was also negative. Flow cytometry analysis of CSF found no cells of malignant phenotype. The cranial MR demonstrated obviously thickened and enhanced meninges on T1-weighted sequence (Fig. 1). The diagnosis of RP was established due to her puffy ears, eye lesion, and arthritis, and she was initially treated with oral prednisolone (60 mg/day) plus methotrexate (15 mg/week). She was also given empirical anti-tuberculosis (TB) treatment (isoniazid, rifapentine, and ethambutol) considering her radiologic meningitis without culturing evidence of bacterial or fungal infection in the CSF.

Unfortunately, 3 months later, she gradually developed neurosensory hearing loss, vertigo, and saddle nose. Moreover, anti-TB therapy failed to control her headache. So she was hospitalized again in October 2011. Recheck of her CSF only demonstrated slightly elevated protein at 5.0 mg/dl and again no evidence of infection. We suspected that her meningitis was non-infectious but RP-related. Thus, anti-TB therapy was discontinued and her regimen was changed to oral dexamethasone 15 mg/day and intravenous cyclophosphamide 1.0 g/month, which could reduce her headache to a tolerable level. However, when dexamethasone was tapered to 12.75 mg/day 4 mongths later, her headache relapsed with obvious vertigo onset. Thus, a third CSF fluid analysis was performed and the result was similar to the second one. Cranial MRI reevaluation revealed persistence of meningeal thickening. Finally, cyclosporin A at 150 mg twice a day was tried for her aseptic meningitis. Surprisingly, her headache and vertigo were dramatically alleviated, and during the next six-month follow-up, her condition remained stable without new onset of headache.

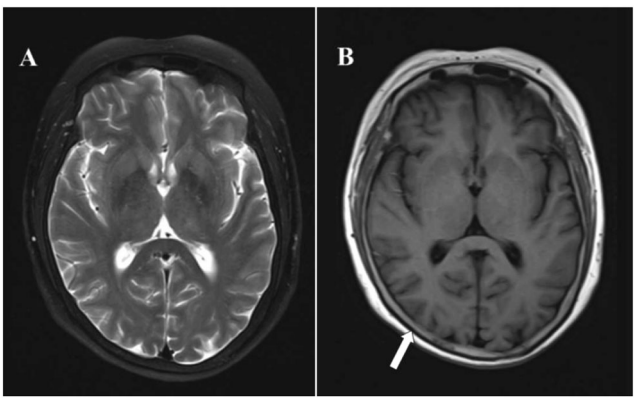

Fig. 1 Axial MRI of the patient. **a** T2-weighted MRI (T2WI) showing no abnormal signal. **b** T1-weighted MRI (T1WI) showing thickened meninges

Discussion

We reviewed the related literature in PubMed and only 19 cases of RP-related aseptic meningitis or meningoencephalitis including ours have been reported (summarized in Table 1). Limited number of clinical literatures showed that aseptic meningitis is an extremely uncommon form of RP's CNS lesion.

In the literature, aseptic meningitis was only reported in middle-aged patients mainly in their forth to seventh decades of life with an average age of 56 years. Only 1 patient in those 19 cases was below 40 years old [11]. Aseptic meningitis showed a slight male predominance (13 males and only 6 females). Our patient was a 58-year-old Chinese woman present with recurrent chondritis of both ears, polyarthritis, scleritis, and chondritis of nasal cartilage (saddle nose deformity) and audiovestibular damage (neurosensory hearing loss and vertigo), which fulfilled the diagnostic criteria of RP proposed by McAdam [16]. Her stubborn headache was regarded to be RP-related by exclusion of all possible infectious causes and her response to steroid and immunosuppressive agents further confirmed the diagnosis. At onset, most such patients might have atypical manifestations of RP including dizziness, arthralgia, fever, weight loss, and fatigue. Subsequently, RP-related meningitis would be manifested by fever, headache, and signs of meningeal irritation [14]. However, fever was not always present and could be low degree in a chronic course. Other neurologic manifestations were also reported along with meningitis presentation including cognitive impairment, visual disturbance, memory loss, acoustic decline, emotional alteration, hallucination, seizure, and so on. Those symptoms indicated the involvement of cerebral parenchyma or even cranial nerves [13]. Thus, the term meningoencephalitis could be also seen in the literature. Our case had an extremely prolonged course of headache and no fever was present. Neck stiffness was also present indicating meningitis.

Pleocytosis is a hallmark of meningitis and was demonstrated almost in all patients except one [5]. Both PMN and mononuclear cell predominance in CSF were seen in the literature with mononuclear cell predominance as the most common, which accounted for 12 of the 19 cases. All cases

Table 1 Summary of patients with relapsing polychondritis and meningitis in the literature

Year	Age/sex	Accompanied symptoms	CSF			Protocol	Outcome	Relapse
			Leukocyte (per mm^3)/PMN%	Protein (mg/dl)	Glucose (mg/dl)			
1988 [3]	30/F	Hearing loss unsteadiness	37/4	18	52	ND	ND	No
	75/M	Hearing loss and personality changes	90/60	98–140	ND	GS	Improved	No
	62/M	Hearing loss	6/0	12	70	ND	ND	ND
1988 [4]	52/M	Generalized tonic-clonic seizure, impaired cognitive function, impaired visual acuity, and hearing loss	360/38.9	176	normal	GS	Improved	Yes
1994 [5]	70/F	Confusion, memory loss, unstable gait	2037/86.9	ND	ND	GS	Improved	No
1996 [6]	70/M	Hearing loss	2600/90	40	37.2	GS	Improved	Yes
1996 [7]	60/M	Ataxia, hearing loss, hydrocephalus	149/20.8	140	22	GS + AZP	Improved	Yes
1998 [8]	66/M	Focal seizure	26/53.8	59	68	GS	Improved	No
2005 [9]	57/F	Deafness, general convulsion, delirium, personality change	196/36.7	89	50	GS	Improved	Yes
2006 [10]	71/F	Confusion, cerebral infarction	110/0	116	67.6	GS	Improved	Yes
2007 [11]	40/M	Confusion	1500/83	85	43	GS	Improved	ND
2008 [12]	51/M	Coordination problems, distraction, word finding difficulty, emotional lability, jerking, confusion	39/35	89	52	GS + CTX	Died	ND
2009 [13]	56/F	Abducens nerve palsy	640/94	114	62	GS	Improved	No
2011 [14]	54/M	Emotional disturbance, acoustic and visual, hallucination, memory loss	800/0	53	normal	GS + AZP	Improved	Yes
	44/M	Memory loss, irritability, anxiety	190/8.9	57	normal	GS + AZP	Improved	Yes
	52/M	Anxiety, insomnia, memory loss, deafness, gait change, urinary incontinence, expressive and receptive aphasia, dullness, acalculia, and papilledema	230/7.0	51	24	GS	Improved	Yes
	44/F	Anxiety, insomnia	70/40	71	31	GS + AZP	Improved	No
2014 [15]	56/M	Mental change	204/18	162	normal	GS + CTX	Improved	Mo
Our case	58/M	None others	150/58	27.8	56.3	GS + CTX CSA	Improved	Yes

ND not described, *GS* glucocorticosteroid, *CTX* cyclophosphamide, *AZP* azithiopurine, *CSA* cyclosporin A

including ours showed dramatically high level of CSF protein (ranged from 10 to 176 mg/dl). However, CSF glucose was not universally elevated. Several authors reported normal glucose in CSF [4, 14, 15]. Increased open pressure of CSF was also reported [10, 13, 15] but not in our case. Thus, the pleocytosis and high protein level in the CSF were characteristic of aseptic meningitis of RP, which has reflected the inflammatory nature of this condition. However, this CSF feature is not specific. For example, mononuclear predominance in CSF might resemble tuberculous meningitis while extreme PMN infiltration in CSF could mimic the purulent bacterial infection. Thus, repeated CSF culture and serologic assays should be performed for the exclusion of possible infectious causes including bacterial, fungal, and viral meningitis.

MRI is a useful tool in detecting the CNS lesion for RP patients. Kothare SV et al. [8] reported a case of severe RP-related meningitis, and MRI study of this patient's brain revealed a high-intensity area on the T2-weighed image. Ota M et al. [9] demonstrated a slight thickening of the dura mater in a RP-related aseptic meningitis patient accompanied by delibrium. High-intensity areas along the frontal, parietal, and temporal sulci were also noted with gadolinium enhancement in his study. In a case report by Kao KT et al. [11], MRI with gadolinium enhancement showed T2 and FLAIR hyper-intensity in bilateral anterior temporal lobe, left insular cortex, right basal ganglia, anterior limb of the internal capsule, and left posterior frontal corona radiate. Besides abnormal enhanced signals involving leptomeninges, periventricular and deep white matter, basoganlions, and cranial nerves have also been described in the literature and these findings are consistent with the diagnosis of meningitis or meningoencephalitis [12, 14, 15]. Similarly, in our case, enhancement of dura mater on contrast-enhanced T1-weighted MRI was obvious. Thus, we believe thickened meninges is the most common radiologic finding for aseptic meningitis in RP patients. Nevertheless, Yaguchi H et al. [13] and Hsu KC et al. [10] reported normal MRI results in clinically diagnosed RP-related aseptic meningitis which indicated that a normal MRI cannot fully exclude the possibility of meningitis.

Currently, the etiology RP is yet to be elucidated. The pathogenesis of RP involves an autoimmune response to as yet unidentified cartilage antigens such as type II collagen and matrilin-1, followed by cartilage matrix destruction by proteolytic enzymes [2]. Several researches have supported a pathogenic role for the humoral and cellular immune systems. The earliest neuropathologic study of meningits due to RP dated back to 1998 by Stewart et al. [4] who demonstrated diffuse vasculitis involving both medium-small-sized and small-sized veins along with nearby white matter necrosis of the autopsied brain. In the same year, Brod S et al. [3] described lymphocytic infiltration in the meninges and speculated that remnants of the notochord could serve as antigens in the CNS. These studies showed a strong relationship between vasculitis and neurological disorders in some patients with RP. Our patients refused brain biopsy and we speculate that vasculitis or non-specific inflammation involving the meninges is responsible for its MRI imaging feature and clinical picture.

As brain biopsy is seldom performed and diagnosis of aseptic meningitis due to RP is primarily based on clinical aspects. The symptoms of meningitis could occur previous to, concomitantly with or after, the presentation of typical RP manifestations like auricular chondritis. Aseptic meningitis could precede the diagnosis of RP, and the interval between the onset of meningoencephalitis and the onset of the typical RP signs was from 1 day to 15 months [14]. This delay has proposed to a challenge for the early diagnosis. If neurological symptoms occurred during the flare-up of systemic RP, the diagnosis could still be thwarted when patients are on immunosuppressants for systemic disease and opportunistic infections are in the differential [12]. Finally the diagnosis of aseptic meningitis due to RP is made when the diagnosis of RP is adequate and neurologic infection, cranial malignancies, and other autoimmune disorders involving the brain are fully eliminated.

Till now, no consensus on the therapy for aseptic meningitis due to RP has been established because of its rarity, the diversity of presentations, and varied disease course [2]. All the current therapy is empirical or even anecdotal since large sample cohort study and clinical trial are unavailable. Corticosteroids as the first-line treatment of RP has been proved to be beneficial to most RP patients with meningitis and are used as the basic protocol for all the reported cases. Commonly after one to three boluses, the patient is switched to oral glucocorticoid therapy, 1 mg/kg/day, for 3 to 4 weeks. The response rate to corticosteroid in high as has been described in 15 of the total 18 cases including our patient. Nevertheless, as a relapsing and refractory disorder in nature, recurrence of meningitis is common as was described in seven cases during the dose tapering. Thus, dependency on high steroid dose is common. Immunosuppressive agents are indicated for patients with severe respiratory or vascular involvement and for those with steroid dependency or resistance. In the literature azathioprine or cyclophosphamide were combined with corticosteroid in five cases for the treatment of aseptic meningitis. Recently, biological agents, including anti-TNF agent infliximab, were reported to be effective for refractory RP [17]. In our case, the patient's headache appeared refractory to prednisone and cyclophosphamide therapy. However, cyclosporin A which was not previously reported for RP-related meningitis seemed to be instantly effective in controlling the pain. Hereby, we believe that individualized therapy should be tried for the RP-related meningitis and cyclosporin A might be an alternative.

Conclusions

This case-based review highlighted the importance of the awareness of aseptic meningitis due to RP as a rare and easily misdiagnosed condition of undetermined pathoetiology. Its diagnosis is primarily based on clinical manifestations combined with CSF and MRI examinations plus adequate exclusion of possible infections or other etiologies. Corticosteroid and immunosuppressive agents are serving as the base of therapy but choice of protocol should be individualized.

Compliance with ethical standards

Disclosures None.

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