Relapsing Polychondritis With Meningoencephalitis

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PRACTICE **POINTS**

- Meningoencephalitis (ME) is a potentially rare complication of relapsing polychondritis (RP).
- Treatment of ME due to RP can include high-dose steroids and biologics.

Relapsing polychondritis (RP) is a rare autoimmune disease of the cartilaginous structures of the body with many systemic manifestations including meningoencephalitis (ME). We present a case of a man with RP-associated ME that was responsive to steroid treatment. An updated literature review of 7 cases of RP-associated ME also is provided. Early diagnosis of this condition may be of benefit to this select population of patients, and further research regarding the prognosis, mechanisms, and treatment of RP may be necessary in the future.

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Relapsing polychondritis (RP) is an autoimmune disease affecting cartilaginous structures such as the ears, respiratory passages, joints, and cardiovascular system.[1,2] In rare cases, the systemic effects of this autoimmune process can cause central nervous system (CNS) involvement such as meningoencephalitis (ME).[3] In 2011, Wang et al[4] described 4 cases of RP with ME and reviewed 24 cases from the literature. We present a case of a man with RP-associated ME that was responsive to steroid treatment. We also provide an updated review of the literature.

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Case Report

A 44-year-old man developed gradually worsening bilateral ear pain, headaches, and seizures. He was briefly hospitalized and discharged with levetiracetam and quetiapine. However, his mental status continued to deteriorate and he was subsequently hospitalized 3 months later with confusion, hallucinations, and seizures.

On physical examination the patient was disoriented and unable to form cohesive sentences. He had bilateral tenderness, erythema, and edema of the auricles, which notably spared the lobules (Figure 1). The conjunctivae were injected bilaterally, and joint involvement included bilateral knee tenderness and swelling. Neurologic examination revealed questionable meningeal signs but no motor or sensory deficits. An

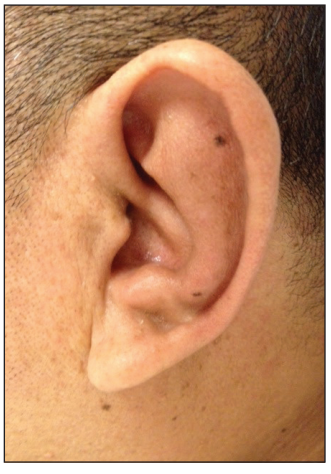

Figure 1. Auricular erythema and edema on the left ear with sparing of the lobule.

extensive laboratory workup for the etiology of his altered mental status was unremarkable, except for a mildly elevated white blood cell count in the cerebrospinal fluid with predominantly lymphocytes. No infectious etiologies were identified on laboratory testing, and rheumatologic markers were negative including antinuclear antibody, rheumatoid factor, and anti–Sjögren syndrome antigen A/Sjögren syndrome antigen B. Magnetic resonance imaging revealed nonspecific findings of bilateral T2 hyperdensities in the subcortical white matter; however, cerebral angiography revealed no evidence of vasculitis. A biopsy of the right antihelix revealed prominent perichondritis and a neutrophilic inflammatory infiltrate with several lymphocytes and histiocytes (Figure 2). There was degeneration of the cartilaginous tissue with evidence of pyknotic nuclei, eosinophilia, and vacuolization of the chondrocytes. He was diagnosed with RP on the basis of clinical and histologic inflammation of the auricular cartilage, polyarthritis, and ocular inflammation.

The patient was treated with high-dose immunosuppression with methylprednisolone (1000 mg intravenous once daily for 5 days) and cyclophosphamide (one dose at 500 mg/m^2), which resulted in remarkable improvement in his mental status, auricular inflammation, and knee pain. After 31 days of hospitalization the patient was discharged with a course of oral prednisone (starting at 60 mg/d, then tapered over the following 2 months) and monthly cyclophosphamide infusions (5 months total; starting at 500 mg/m^2, then uptitrated to goal of 1000 mg/m^2). Maintenance suppression was achieved with azathioprine (starting at 50 mg daily, then uptitrated to 100 mg daily), which was continued without any evidence of relapsed disease through his last outpatient visit 1 year after the diagnosis.

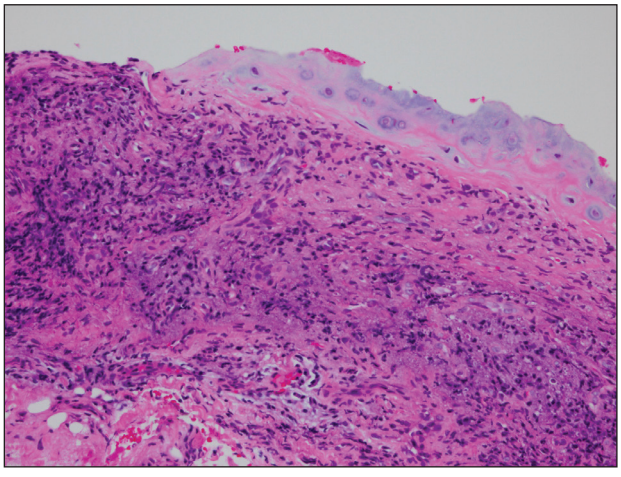

Figure 2. Histopathology revealed prominent neutrophilic inflammatory infiltrate with scattered lymphocytes and histiocytes. Degeneration of the cartilaginous tissue also was evident with pyknotic nuclei, eosinophilia, and vacuolization of the chondrocytes (H&E, original magnification ×40).

Comment

Auricular inflammation is a hallmark of RP and is present in 83% to 95% of patients.[1,3] The affected ears can appear erythematous to violaceous with tender edema of the auricle that spares the lobules where no cartilage is present. The inflammation can extend into the ear canal and cause hearing loss, tinnitus, and vertigo. Histologically, RP can present with a nonspecific leukocytoclastic vasculitis and inflammatory destruction of the cartilage. Therefore, diagnosis of RP is reliant mainly on clinical characteristics rather than pathologic findings. In 1976, McAdam et al[5] established diagnostic criteria for RP based on the presence of common clinical manifestations (eg, auricular chondritis, seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation). Michet et al[6] later proposed major and minor criteria to classify and diagnose RP based on clinical manifestations. Diagnosis of our patient was confirmed by the presence of auricular chondritis, polyarthritis, and ocular inflammation. Diagnosing RP can be difficult because it has many systemic manifestations that can evoke a broad differential diagnosis. The time to diagnosis in our patient was 3 months, but the mean delay in diagnosis for patients with RP and ME is 2.9 years.[4]

The etiology of RP remains unclear, but current evidence supports an immune-mediated process directed toward proteins found in cartilage. Animal studies have suggested that RP may be driven by antibodies to matrillin 1 and type II collagen. There also may be a familial association with HLA-DR4 and genetic predisposition to autoimmune diseases in individuals affected by RP.[1,3] The pathogenesis of CNS involvement in RP is thought to be due to a localized small vessel vasculitis.[7,8] In our patient, however, cerebral angiography was negative for vasculitis, and thus our case may represent another mechanism for CNS involvement. There have been cases of encephalitis in RP caused by pathways other than CNS vasculitis. Kashihara et al[9] reported a case of RP with encephalitis associated with antiglutamate receptor antibodies found in the cerebrospinal fluid and blood.

Treatment of RP has been based on pathophysiological considerations rather than empiric data due to its rarity. Relapsing polychondritis has been responsive to steroid treatment in reported cases as well as in our patient; however, in cases in which RP did not respond to steroids, infliximab may be effective for RP with

Relapsing Polychondritis and Meningoencephalitis Cases (2010-2016)

Reference (Year)	Age, y/ Sex	External Involvement	Neurologic Findings	Response to Steroids
Sampaio et al[7] (2010)	70/M	Ears, nose, eyes	Hallucinations	Yes
Storey et al[11] (2010)	73/M	Right ear	Fever, headache, seizures, aphasia, hallucinations	No (death)
Choi and Lee[12] (2011)	68/F	Ears	Confusion, dysarthria, agraphia	Yes
Garcia-Egido et al[10] (2011)	57/M	Ears, eyes	Fever, headache, seizures, hearing loss	No (responded to infliximab)
Fujiwara et al[13] (2012)	60/M	Ears	Headache, dysarthria, hemiparesis	Yes
Prinz et al[8] (2012)	63/M	Ears	Headache, confusion	Yes
Mattiassich et al[14] (2013)	49/M	Ears	Altered mental status	Yes
Kondo et al[15] (2014)	58/M	Ears, eyes	Altered mental status	No (responded to infliximab)
Niwa et al[16] (2014)	59/M	Ears	Hand tremor, bradykinesia, gait disturbance	Yes
Coban et al[17] (2015)	44/F	Ears, hand arthritis	Stroke with hemiparesis	Yes
Ducci et al[18] (2016)	69/M	Ears, ankle arthritis	Altered mental status, ataxia, vertigo	Yes
Baba et al[19] (2016)	72/M	Ears	Altered mental status, dysarthria, neck stiffness	Yes
Jeon[20] (2016)	48/F	Ears, eyes	Headache, neck stiffness	No (death)
	56/M	Ears, eyes	Headache, hallucinations, agitation	Yes
	48/M	Ears	Disorientation, dysphasia	No (lost to follow-up)
Liu et al[21] (2016)	72/M	Ears, eyes	Fever, cognitive disorder, mania	No (responded to tocilizumab)
Current case	44/M	Ears, eyes	Altered mental status, hallucinations	Yes

Abbreviations: M, male; F, female.

ME.[10] Further research regarding the treatment outcomes of RP with ME may be warranted.

Although rare, additional cases of RP with ME have been reported (Table). Wang et al[4] described a series of 28 patients with RP and ME from 1960 to 2010. A PubMed search of articles indexed for MEDLINE that were published in the English-language literature from 2010 to 2016 was performed using the search terms *relapsing polychondritis* and *nervous system*. Including our patient, RP with ME was reported in 17 additional cases since Wang et al[4] published their findings. These cases involved adults ranging in age from 44 to 73 years who were mainly men (14/17 [82%]). All of the patients presented with bilateral auricular chondritis, except for a case of unilateral ear involvement reported by Storey et al.[11] Common neurologic manifestations included fever, headache, and altered mental status. Motor symptoms ranged from dysarthria and agraphia[12] to hemiparesis.[13] The mechanism of CNS involvement in RP was not identified in most cases; however, Mattiassich et al[14] documented cerebral vasculitis in their patient, and Niwa et al[16] found diffuse cerebral vasculitis on autopsy. Eleven of 17 (65%) cases responded to steroid treatment. Of the 6 cases in which RP did not respond to steroids, 2 patients died despite high-dose steroid treatment,[11,20] 2 responded to infliximab,[10,15] 1 responded to tocilizumab,[21] and 1 was lost to follow-up after initial treatment failure.[20]

Conclusion

Although rare, RP should not be overlooked in the inpatient setting due to its potential for life-threatening systemic effects. Early diagnosis of this condition may be of benefit to this select population of patients, and further research regarding the prognosis, mechanisms, and treatment of RP may be necessary in the future.

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