Relapsing polychondritis with ANCA-associated vasculitis: is it a coincidence or an overlapping condition?

Sirs,

Occasionally, we encounter patients who develop overlapping features of relapsing polychondritis (RP) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Although this is rare, there is a strong association between RP and AAV, with approximately 30% of patients with RP having other diseases, particularly systemic vasculitis (1, 2). In the modern era of biologics, RP combined AAV is becoming increasingly well known.

We conducted a systematic literature review of publications in PubMed, Embase, and Web of Science up to and including December 31, 2021. The following terms were used including "relapsing polychondritis", "chondritis", "ANCA-associated vasculitis", "microscopic polyangiitis", "Wegener's granulomatosis", "cosinophilic granulomatosis with polyangiitis", "Churg-Strauss syndrome", "granulomatosis with polyangiitis", "vessel inflammation", and "vasculitis". We included only patients with a diagnosis of RP and AAV mentioned in the literature; articles containing terms of suspected diagnosis and possible diagnosis were excluded (Fig. 1). The literature search yielded 12 eligible articles after excluding duplicate publications, unrelated to the topic, and unavailable full-text articles (1-12). The results of the GRADE evaluation of all included articles are presented in Table I. A total of 20 patients were identified, with a female/male ratio of 11/4, a mean age of 51.5 years (range 13-68), and a median age of 56 years based on the available data (Table II). All patients had auricular chondritis (n=11). In five patients, the diagnosis of AAV and RP was simultaneous. In 4 patients, the diagnosis of vasculitis was antecedent to RP, and the diagnosis of vasculitis was subsequent to RP in the other six patients. Among the three types of AAV, MPA (n=9) was the most frequent, followed by GPA (n=7), and no EGPA was reported. Renal involvement manifested as haematuria, proteinuria and abnormal renal function in 16 patients, and central nervous system damage in 7 cases. All patients were treated with glucocorticoids, including methylprednisolone, prednisone, and steroid pulses. The use of immunosuppressive agents included cyclophosphamide, mycophenolate mofetil, azathioprine, sulfasalazine and rituximab. Eleven of the patients mentioned in the article had a good prognosis, and one patient eventually died of pancytopenia.

Fig. 1. Flow diagram of the study selection process.

Although the relationship between RP and AAV is controversial, RP is usually considered to be a secondary phenomenon of AAV (12, 13). Handrock et al. (12) described six cases of RP (two with GPA, three with MPA and one with polyarteritis nodosa) that occurred in the setting of systemic vasculitis. File et al. (1) reported three cases of RP in combination with AAV. Two cases developed RP 1.5 years after the onset of AAV, while the other case developed RP simultaneously with AAV. It is noteworthy that chondritis may be an epiphenomenon of some well-defined inflammatory process. This applies not only to systemic vasculitis but also to systemic lupus erythematosus and other rheumatic diseases (12).

Specks et al. (14) reported that 8 of 22 RP patients were all positive for p-ANCA. However, a study that enrolled 33 patients with RP showed that 8 patients were positive for ANCA (3 for c-ANCA and 5 for p-ANCA) (15). It is suggested that there may not be a clear point-to-point association between RP and ANCA. The p-ANCA may be more likely when the lungs and kidneys are involved, while nasal and auricular involvement may be more likely to be c-ANCA (12). In one study, ANCA was found to be elevated in 24% of patients during the active phase of RP and paralleled the disease activity, while it was not elevated in patients in remission (15, 16). Some studies found that ANCA is an important feature that distinguishes RP from GPA and other diseases (17). It is definite that ANCA is predictive of underlying vasculitis.

The differential diagnosis of RP and GPA is particularly important due to their many similar clinical manifestations, including saddle nose and tracheal involvement, arthritis, and cutaneous vasculitis (12). Bosch et al. (18) described a case of a patient initially misdiagnosed with RP, who subsequently developed pulmonary and renal involvement and positive for c-ANCA, eventually leading to a definitive diagnosis of GPA. Unfortunately, antibody to collagen II is not very helpful. In one study, only 33% of RP patients were able to detect antibodies to collagen II, and they faced difficulties with low specificity and sensitivity as well as the high price of the assays (19, 20). At the same time, c-ANCA is not a specific marker for GPA and may also be present in RP. However, necrotising glomerulonephritis, oitis, sinusitis, nasal septal perforation, and ptosis, may be more indicative of GPA (12). More importantly, auricular chondritis is considered to be a hallmark of RP, which occurs in up to 94% of all RP cases (21). Histological methods are also helpful. Finally, in the absence of other identification methods, the overlap between RP and GPA is the only conclusion, which may be limited to less than 5% of cases (12). Despite the absence of type II collagen in the glomerulus, 29 of the 129 patients with RP reported in the Mayo clinical study still had renal involvement (22). Clinical manifestations consist of hematuria, proliferative glomerulonephritis, crescentic nephritis, segmental glomerular necrosis, IgA nephropathy, and membranous nephropathy. Hypertension can be caused by renal artery involvement (23, 24). It is noteworthy that renal lesions are not only associated with RP but also with vasculitis and other...
causes. For example, membranous nephrupathy may be caused by nonsteroidal anti-inflammatory drugs used to treat arthralgia in RP (1). The prognosis for RP combined with renal vasculitis is poor, with a 10-year survival rate of only 10%, with the cause of death being a renal failure (25). Because of the poor response of AAV to steroids, treatment should include additional cyclophosphamide or other immunosuppressive agents, and therapy needs to be initiated and administered rapidly (1). In conclusion, renal vasculitis requires more aggressive immunosuppressive therapy, as well as regular and long-term follow-up of renal function and ANCA.

Of the 20 patients with RP combined with AAV reported in this study, 7 patients (35%) had CNS involvement. Trentham et al. investigated 36 patients with RP and found that 3% of these patients exhibited neurological manifestations (26). Zeuner et al. described the clinical presentation of 62 patients with RP and found that 9.7% of them showed CNS involvement (27). A French study included 142 patients with RP and showed that CNS involvement occurred in 8% of these patients (28). A recent Chinese study showed that up to 13.81% of Chinese RP patients exhibited CNS involvement (29). Therefore, the incidence of CNS in patients with RP combined with AAV is quite high compared to the above data. When RP is combined with AAV, the clinical manifestations of the neurological system are severe and heterogeneous and can manifest as hypertrophic pachymeningitis, multiple intracranial vascular lesions, aseptic meningitis, motor disturbances, sensory impairment, stubborn headache, memory loss, and stroke (30). These symptoms indicate possible involvement of brain parenchyma and even cranial nerves (31). A definitive diagnosis of the nervous system resulting from RP combined with AAV is challenging because of the infrequency of brain tissue biopsies, the heterogeneity of neurological symptoms, and the fact that neurological symptoms may occur before, simultaneously with, or after typical RP manifestations such as auricular perichondritis (29). If neurologic symptoms occur during an episode of systemic RP, the diagnosis may be hindered when the patient is taking immunosuppressive drugs for systemic disease, and opportunistic infections need to be excluded at the same time (32).
Relapsing polychondritis as a secondary phenomenon of AAV. Vasculitis should not be considered solely based on ANCA, instead, a comprehensive assessment should be made with the clinical manifestations of other organ involvement. RP and GPA present with many common manifestations, with auricular chondritis serving as one of the markers for differential diagnosis. Regardless of the sequence of presentation of both RP and AAV, the development of renal and neurologic symptoms significantly increases the possibility of underlying AAV, with a worse prognosis and requiring more aggressive treatment. Cyclophosphamide, IL-6 and TNF-α inhibitors are effective in patients with RP combined with AAV (36, 37). The treatment with biological agents can be used if traditional drugs are not effective or not tolerated (38). The mechanism of RP combined with AAV is still unclear and warrants further study.

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References