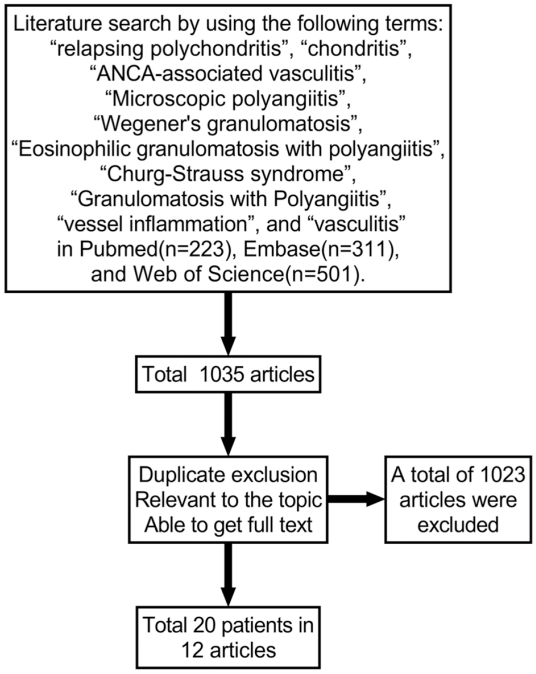
Relapsing polychondritis with ANCA-associated vasculitis: is it a coincidence or an overlapping condition?

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", "eosinophilic 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, otitis, 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

Table I. Results of GRADE assessment.

Author(s)	Certainty assessment						
	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
File (1)	Case series	Serious	Serious	Serious	Not serious	Serious	Very low
Mattiassich (2)	Case report	Serious	Serious	Serious	Serious	Serious	Very low
Cañas (3)	Case series	Serious	Serious	Serious	Serious	Serious	Very low
Ullrich (4)	Case report	Serious	Serious	Serious	Not serious	Serious	Very low
Breviglieri (5)	Case report	Serious	Serious	Serious	Not serious	Serious	Very low
Masterson (6)	Case report	Serious	Serious	Serious	Serious	Serious	Very low
Subhadarshani (7)	Case report	Serious	Serious	Serious	Not serious	Serious	Very low
Weber (8)	Case report	Serious	Serious	Serious	Not serious	Serious	Very low
Small (9)	Case report	Serious	Serious	Serious	Serious	Serious	Very low
Tominaga (10)	Case report	Serious	Serious	Serious	Serious	Serious	Very low
Westbrook (11)	Case report	Serious	Serious	Serious	Serious	Serious	Very low
Handrock (12)	Case series	Serious	Serious	Serious	Serious	Serious	Very low

Table II. The clinical characteristics of 20 patients with relapsing polychondritis combined with ANCA-associated vasculitis.

Study	Sex/Age (years)	Organ involvement	Auricular chondritis	Auricular biopsy	Fulfill the diagnosis		Vasculitis diagnosis	Vasculitis	ANCA	Treatment		Outcome
					RP	AAV				GC	Others	
File (1)	M/58	E, K, J, S	Yes	No	Yes	Yes	Antecedent	MPA	p-ANCA	GC	CTX/AZA	Died
	F/63	E, K, J, Ey	Yes	No	Yes	Yes	Concomitant	MPA	p-ANCA	GC	CTX	Recovered
	F/56	E, K, J	–	–	Yes	Yes	Subsequent	MPA	p-ANCA	GC	CTX	Recovered
Mattiassich (2)	M/49	E, K, N, J	Yes	Yes	Yes	Yes	Antecedent	–	c-ANCA	GC	CTX/MMF	Recovered
Cañas (3)	F/50	E, K, N, J, Ey	Yes	Yes	Yes	Yes	Concomitant	–	c-ANCA	GC	–	–
	F/48	E, K, N, J, Ey	Yes	–	Yes	Yes	Concomitant	–	c-ANCA	GC	CTX	Recovered
	F/50	E, N, J, Ey	Yes	–	Yes	Yes	Concomitant	GPA	c-ANCA	GC	CTX Rituximab	Recovered
Ullrich (4)	M/67	E, K, J	Yes	No	Yes	Yes	Antecedent	GPA	c-ANCA	GC	MTX	Recovered
Breviglieri (5)	F/66	E, K, J, S	Yes	No	Yes	Yes	Subsequent	MPA	p-ANCA c-ANCA	GC	CTX	Recovered
Masterson (6)	F/68	E, K, Ey, J	Yes	–	Yes	Yes	Subsequent	–	p-ANCA	GC	AZA	Recovered
Subhadarshani (7)	F/22	E, Ey, S, H, L	Yes	No	Yes	Yes	Antecedent	GPA	c-ANCA	GC	CTX/AZA	Recovered
Weber (8)	F/40	E, K, S, L, J	Yes	Yes	Yes	Yes	Subsequent	MPA	p-ANCA	GC	SAS/CTX	Recovered
Small (9)	M/59	E, K, L	–	–	Yes	Yes	Subsequent	GPA	–	GC	CTX	Recovered
Tominaga (10)	F/63	E, K	–	–	Yes	Yes	Subsequent	MPA	p-ANCA	GC	–	–
Westbrook (11)	F/13	E, Ey	–	–	Yes	Yes	–	GPA	–	GC	CTX	–
Handrock (12)	–	E, Ey, K, N, H, S	–	–	Yes	Yes	–	GPA	c-ANCA	–	–	–
	–	E, K	–	–	Yes	Yes	–	GPA	c-ANCA	–	–	–
	–	Ey, K, N, H, S	–	–	Yes	Yes	–	MPA	–	–	–	–
	–	E, K	–	–	Yes	Yes	–	MPA	p-ANCA	–	–	–
	–	Ey, N	–	–	Yes	Yes	–	MPA	–	–	–	–

M; male; F: female; GC: glucocorticoids; CTX: cyclophosphamide; MTX: methotrexate; MMF: mycophenolate mofetil; AZA: azathioprine; SAS: sulfasalazine; E: ENT (ears, nose, and throat); Ey: eye; H: heart; K: kidney; S: skin; N:nervous system; L: lung; J: joint.

causes. For example, membranous nephropathy 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).

CNS involvement is mostly thought to be caused by vasculitis, and possible mechanisms involved include local haemodynamic abnormalities, thrombosis secondary to local circulatory stagnation, and vasodilatory deformation, but remain to be confirmed (3, 33). In conclusion, when RP is combined with AAV, the possible presence of neurological damage cannot be ignored. Cerebrospinal fluid examination, especially increased intracranial pressure and high protein level, is useful in detecting this disease, however, this is not specific (30, 33). MRI is an important tool to detect CNS lesions in patients with RP (34).

ANCA is an autoantibody that targets neutrophil and monocyte cytoplasmic components and is classified according to immunofluorescence staining models as c-ANCA, whose target antigen is protease-3 (PR-3), and p-ANCA, whose target antigen is myeloperoxidase (6). One study demonstrated that ANCA (specific for both myeloperoxidase and protease 3) is detected in up to 25% of RP patients, but only 10% have clinical manifestations of vasculitis (6), so many ANCA-positive RP patients have no or limited symptoms of vasculitis (5). In the present study it can be seen that some patients presented with ANCA-negative RP, but RP and ANCA vasculitis overlap (12), and some patients presented with ANCA-positive RP with an unknown classification of AAV (2, 3, 6). On the one hand, this may be related to RP disease activity, and on the other hand, it is related to the degree of awareness and level of detection of renal and lung biopsies and detection of anti-neutrophil cytoplasmic antibodies in the era 30 years ago. A retrospective analysis that included 33 patients with RP showed that only 24% of patients with low titers of ANCA positivity (cANCA: 1:10-1:50, pANCA: 1:10-1:100) could be seen during active disease, and ANCA paralleled RP disease activity. ANCA may also not be elevated in patients with limited and remission disease (15). Data from a collection of 98 ANCA-positive patients also showed that ANCA titers measured by ELISA did not correlate with the severity of vasculitis, but that the disappearance of ANCA was always associated with the absence of disease activity (35). The classic study by Handrock *et al*. suggested that the presence of ANCA in RP may indicate that polychondritis occurs in the course of primary systemic vasculitis, such as Wegener's granulomatosis (12). In conclusion, ANCA positivity alone should not be directly considered as vasculitis, and certainly, the occurrence of ANCA in RP should encourage a thorough investigation of the presence of vasculitis, which determines the treatment and prognosis of the disease (12).

In conclusion, RP is a primary disease in most cases, but it can also exist 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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