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Literature Review

Giant cell arteritis, polymyalgia rheumatica, and late-onset rheumatoid arthritis: Can they be components of a single disease process in elderly patients?

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Abstract

Objective: To report two patients with giant cell arteritis (GCA) who developed rheumatoid arthritis (RA) and to review the literature in terms of coexistence of RA, GCA, and polymyalgia rheumatica (PMR).

Methods: We conducted a comprehensive review of the English literature from 1980 to 2015 to analyze data on the coexistence of GCA and RA. The PubMed, Web of Science, Proquest, and Ovid databases were searched for articles using the term RA combined with temporal arteritis, GCA, and PMR.

Results: We identified 17 other cases of coexistent GCA and RA reported in the English literature, together with our 2 cases (19 cases). They included 14 females and 5 males, with a mean age of 74.3 years (range: 57–84) at the time of GCA. The mean age at the time of RA diagnosis was 69.6 years (range 24–83). The average time elapsed between the onset of GCA and the development of RA was 6.7 years (range: 3 month–34 years). RA and GCA were reported as the first disease in 10 cases and 4 cases, respectively. The development of these 2 diseases in a narrow period of time appeared in 4 cases (3 months–19 months). PMR was the first disease in 1 case.

Conclusion: RA, GCA, and PMR may appear simultaneously or consecutively; therefore, we suggest that physicians should be alert about such a fact so that a proper diagnosis and treatment could be tailored accordingly

Keywords: Rheumatoid arthritis, giant cell arteritis, temporal arteritis, polymyalgia rheumatica

Introduction

Giant cell arteritis (GCA) is a necrotizing vasculitis affecting medium-sized vessels stemming from the arch of the aorta. Temporal or generalized headache, jaw pain, and visual disturbance as well as systemic manifestation such as fever and weight loss can be observed in the course of GCA. Polymyalgia rheumatica (PMR) is characterized by proximal limb girdle aching and stiffness and is reported in half the cases of biopsy-proven GCA (1). In addition, symmetric polyarthritis can be rarely seen in patients with GCA or PMR, and some of these cases may meet the American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA) (2, 3). On the other hand, inflammation of the small- and medium-sized arteries may be seen in the course of RA. Large vessel involvements such as aortitis or Takayasu's arteritis-like vasculitis and GCA have previously been reported in patients with RA (4-8). This is what leads us to assume that GCA, PMR, and late-onset RA (LORA) could be of an interrelated type of diseases as far as clinical reports are concerned. Because some clinical manifestations of a first disease simulate those of another in the same patient, this overlap may escape the attention of a physician who fails to think of a second disease. This will, in turn, result in delays in diagnosis and in seeking proper treatment. This paper aims to raise the awareness of physicians on the subject of coexisting RA and GCA by presenting two GCA patients who developed RA later on and to conduct a brief review of the literature on RA and GCA.

Material and Methods

We conducted a comprehensive review of the English literature from 1980 to 2015 to analyze data on the coexistence of temporal arteritis and RA. The PubMed, Web of Science, Proquest, and Ovid databases were searched for articles using the term RA combined with temporal arteritis, GCA, PMR, and vasculitis. Articles cited as references in the identified papers were also reviewed. Features of cases reported in an original manuscript are shown in Table 1. Original papers focusing on the coexistence of GCA and RA are briefly discussed in this article. In 9 English articles, we identified 17 patients, together with our 2 cases that developed RA after GCA (Table 1). Informed consent was obtained from the 2 patients discussed here.

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Table 1. Cases of rheumatoid arthritis associated with giant cell arteritis

	Sex	Age at onset of GCA	Age at onset of RA	Lag time between 2 diseases	RF	ACPA	Erosion	PMR	Extraarticular Symptoms	References
1	M	67	78	11 years	+	+	+	-	Pleurisy	Our case
2	M	65	74	9 years	-	-	+	-	Mononeuropathy+SCN	Our case
3	F	76	76	4 months	-	NA	+	-	-	1
4	F	83	79	4 years	-	NA	-	-	-	1
5	F	75	78	3 years	-	NA	+	-	-	1
6	F	84	84	6 months	-	NA	-	-	-	1
7	F	79	77	2 years	-	NA	-	-	-	1
8	F	84	83	6 months	-	NA	-	-	-	1
9	F	61	61	3 months	+	NA	+	-	-	4
10	F	79	81	19 months	NA	NA	+	+	-	5
11	F	80	70	10 years	+	NA	+	-	Felty's syndrome	14
12	M	66	49	17 years	+	NA	+	-	-	14
13	M	75	29		+	NA	+	-	-	14
14	F	57	12 JRA 24 RA	34 years	+	NA	+	-	-	7
15	M	75	75	-	+	NA	+	-	Interstitial lung disease	11
16	F	79	77	2 years	+	NA	-	-	Pulmonary nodulosis	9
17	F	82	75	7 years	-	+	+	-	-	8
18	F	77	74	3 years	-	NA	+	-	-	6
19	F	69	79	10 years	NA	NA	+	+69 yrs	-	6

ACPA: anticitrullinated peptide antibody; JRA: juvenile rheumatoid arthritis; SCN: subcutaneous nodule; NA: information not available

Case Presentation

Case 1. An 82-year-old man had been diagnosed with GCA on the basis of fever, weight loss, and temporal headache in 2000. Temporal artery biopsy confirmed the diagnosis of GCA. No arthritis or arthralgia was observed on the first evaluation. Laboratory tests revealed the following: Hemoglobin (Hb) 13 g/dL, white blood cell (WBC): 13900/mm^3, platelet 536 000/mm^3, erythrocyte sedimentation rate (ESR): 98 mm/h, rheumatoid factor (RF) (–), antinuclear Antibody (ANA) (–), alkaline phosphatase: 344 U/L (N=40–130), GGT: 116 U/L (N=8–61), AST: 28 U/L (N=0–40), and ALT: 43 U/L (N=0–41). Prednisolone therapy was started at a dose of 1 mg/kg (60 mg) in addition to azathioprine at a dose of 100 mg/day. A month later, all clinical manifestations and laboratory abnormalities resolved. Steroid dosage was gradually decreased and stopped together with azathioprine after 1 year. The patient was admitted to our hospital with polyarthritis, including metacarpophalangeal, proximal interphalangeal, and wrist joints symmetrically as well as the left shoulder joint, in 2011. His ESR and CRP levels were 39 mm/h and 3.99 mg/dl, respectively. RF and anticitrullinated protein antibody (ACPA) antibodies were positive (RF: 93.1 U/L and ACPA: strongly positive). Erosions were detected in MCP joints and in the left styloid of the ulna. Methotrexate (MTX) and a low dose of prednisolone (LDP) were started at a dose of 10 mg/week and 10 mg/day, respectively. His articular manifestations resolved within 2 months. Over the past 4 years, polyarticular arthritis episodes have developed but have been treated with MTX and LDP. In 2013, a pleurisy attack occurred, which resolved spontaneously. This patient has been on MTX and LDP.

Case 2. A 75-year-old man was admitted to our hospital with headache and jaw claudication 10 years previously (in 2005). On physical examination, temporal arteries were bilaterally tender, palpable, and hyperemic. No arthritis could be observed. Laboratory evaluation showed the following: Hb 12.9 g/dL, WBC 16300/mm^3, platelet count 527000/mm^3, ESR 123 mm/h, RF (–), ANA (–), ALT 289 U/L (N=0–41), and AST 91 U/L (0–40). Temporal artery biopsy showed GCA. Prednisolone and MTX were started at doses of 60 mg/day and 15 mg/week, respectively. The patient presented with right foot drop after 1 month of therapy. ENMG showed mononeuropathy localized to the peroneal nerve associated with sensory motor polyneuropathy. Sural nerve biopsy was normal. However, mononeuropathy was considered to be secondary to GCA, and cyclophosphamide (1 g, IV) was added to the treatment instead of MTX. After 6 infusions of cyclophosphamide, mononeuropathy resolved completely and MTX was started as maintenance therapy. MTX and low doses of prednisolone were discontinued in 2011 because of long-term remission of GCA. Six months later, the patient presented with arthritis in the right knee joint. Synovial fluid analysis showed inflammatory features (WBC: 5700/mm^3). Until 2014, the patient had a history of bilateral knee joint arthritis. In March 2014, the patient was admitted to our hospital

with symmetric polyarthritis, including knee, wrist, MCP, and shoulder joints as well as a 35° loss of extension in both elbows. No pain or tenderness was observed in the temporal artery. Laboratory evaluation was significant for acute-phase response (ESR: 63 mm/h, CRP 7.32 mg/dL). RF and ACPA were negative. X-ray for hand joints showed erosions in MCP levels, and joint space narrowing was observed across knee joints. Treatment of MTX and LDP was started. Ever since, the patient has experienced a few arthritis attacks in his right knee joint.

Some clinical and laboratory features of cases

We identified 19 cases of coexistent GCA and RA reported in the English literature (1, 4-11) (Table 1). They included 14 females and 5 males, with a mean age of 74.3 years (range: 57–84) at the time of GCA. The mean age at the time of RA diagnosis was 69.6 years (range 24–83). The average time elapsed between the onset of GCA and the development of RA was 6.7 years (range: 3 month–34 years). RA and GCA were reported as the first disease in 10 cases and 4 cases, respectively. The development of these two diseases in a narrow period of time appeared in 4 cases (3 months–19 months). PMR was the first disease in 1 case. Extraarticular events were as follows: subcutaneous nodules in 3 cases, pleurisy in 1 case, interstitial fibrosis in 1 case, pulmonary nodules in 1 case, and Felty's syndrome in 1 case. Erosion was reported in 14 cases (73 %). RF was positive in 8 cases (47%), negative in 9 cases (52 %), and not reported in 2 cases.

Discussion

While vascular involvement ranging from small to large vessels may be seen in the course of RA (4), polyarthritis satisfying the ACR classification criteria for RA may be rarely seen in patients with GCA (2, 11). However, no close relationship between these diseases has been ascertained so far. Ginsburg et al. (11) investigated the frequency of polyarthritis in patients with GCA. They found that 22 of 520 (4.2%) patients with biopsy-proven GCA had persistent symmetric polyarthritis. The rheumatoid factor was positive in 3 of 22 patients (19 of the 22 were seronegative). Ten of the 19 patients demonstrated radiographic evidence of joint space narrowing and/or erosions. Nine patients had onset of polyarthritis was prior to the diagnosis GCA, 3 had coincidental onset, and 7 developed polyarthritis within 3 years after the onset of GCA.

Gran et al. (3) found that 11 of 231 (4.8%) patients with PMR developed RA. However, 10 of the patients were ruled out from the study because they had been diagnosed as having RA earlier. Taking these 10 patients into account, the frequency of coexistence of PMR and RA increases up to 9% (2). This figure seems to be high compared with the that for the general population in terms of the prevalence of RA. Of the 11 abovementioned cases, 10 had pure PMR and 1 suffered from both PMR and GCA. RF was positive in 6 cases. Gran et al. did not observe the development of RA in 29 patients with isolated GCA.

Salvarani et al. (2) investigated the development of RA in the course of GCA in a large population. They found that 30 of 128 patients with GCA had peripheral musculoskeletal manifestations and 6 of 128 (5 %) patients with GCA met the classification criteria for RA. These 6 patients were seronegative for RA. They compared the prevalence of RA in patients with GCA with that reported in a population-based study (Minesota Rochester) (13). However, the authors used only 2 of their patients for comparison despite the fact that they reported 6 RA patients, and they found no differences (15.6/1000 vs. 13.4/1000). In our opinion, if they had considered all the patients with RA for evaluation, their results would have been more objective, in which case, the values would most probably have corresponded to 46.8/1000 vs. 13.4/1000.

Narváez et al. (14) found that 20% of their patients with PMR developed clinically detectable peripheral arthritis either at diagnosis or during the course of the disease, while 11% of the patients with GCA (8/73) developed peripheral arthritis. Peripheral arthritis in these patients was associated only with the presence of PMR.

As mentioned above, erosive and destructive polyarthritis can be seen in patients with coexistent RA and GCA. In line with this, we found that 73% of the 19 patients reported so far to suffer from coexistent RA and GCA had erosions. Unlike reports that RF occurs only rarely in patients with RA and GCA, we determined that nearly half of our patients had RF positivity. Similarly, Gran et al. (3) showed that 6 of 10 (60 %) patients with coexistent PMR and RA had RF positivity. Thus, considering the similarity between some clinical and laboratory findings, we can speak of a relationship between these 3 diseases. However, there arises a need for explaining the reasons why not many cases suffering from these 3 diseases at the same time have been reported in the literature. One reason seems to be clinical overlaps and the lack of awareness on the part of physicians. If the first disease of a patient is RA, it becomes harder for the second disease, namely GCA, to be noticed by the physician and vice versa. For instance, physicians tend to attribute temporal headache and jaw pain on eating to the involvement of the temporomandibular joint with the destructive arthritic process (15). Another example is that occipital headaches may be attributed to cervical spine disease. In the same vein, the diagnosis of PMR may also prove extremely difficult in the presence of seropositive RA because the symptoms of PMR in an RA patient tend to be mistaken for the exacerbation of RA itself (15). However, we assume that if the same drugs are prescribed for curing these 3 diseases, chances are that the development of a second disease is precluded. For example, in our first case, we used prednisolone and cyclophosphamide and then added MTX for GCA and mononeuropathy. Interestingly enough, polyarthritis developed only 6 months after the medication had been discontinued. While it can be considered a sheer coincidence, it can also lead us to think of a causal relationship: the discontinuation of the drugs probably eased the way for a second disease. In contrast, GCA developed in 2 cases with RA while they were still under treatment with TNF-alpha blockers, including adalimumab and etanercept (9, 10). TNF-alpha blockers have been considered for treating vasculitis such as GCA. On the other hand, cases of vasculitis induced by anti-TNF blockers have also been reported (9, 10). Exactly how mechanism underlying vasculitis induced by anti-TNF-alpha blockers works remains unknown. Guillevin et al. (16) proposed that TNF-alpha antagonists may be associated with a humoral immune response, leading to the deposition of antibodies and/or immune complexes within the vessel wall due to the activation of the T-cell immune response. The presence of TNF/anti-TNF complexes within the capillary wall in patients with small vessel vasculitis during the treatment with anti-TNF-alpha blockers has been reported (16).

In our second case, RA developed 11 years after the diagnosis of GCA. Although ACPA antibody and RF were positive, his articular symptoms were not persistent. We observed polyarticular and episodic patterns in this patient. MTX and low-dose prednisolone were very effective. This articular feature and its well response to steroid have also been reported by Salvarani et al. (2). In RA, it is well known that the presence of ACPA antibody and RF leads to a severe and persistent disease. Hence, while the discrepancy in our case may be a sheer coincidence, it may question the role of these antibodies in elderly onset RA. In the first case, we observed that persistent polyarthritis needed MTX and low doses of prednisolone. During the follow-up period, the low disease activity

continued. It is tempting to speculate that seropositivity is not a strong enough predictor in elderly onset RA in terms of the severity of the disease.

Genetic, environmental, and hormonal factors shared for these 3 diseases may provide a background for the development of these disorders. A prospective study on clinical features of PMR and LORA with PMR-like onset showed that 20% of PMR patients progressed to overt RA during the follow-up period (16). It has been shown that serum cortisol and dehydroepiandrosterone sulfate (DHEAS) levels decreased in patients with PMR and LORA, which leads to an increase in the levels of IL-6 (18). Moreover, it has been reported that the HLA-DRB1 SE allele is associated with both PMR- and RF-negative LORA (19). Thus, although the exact nature of the relationship between RA and GCA is still unknown, we can speculate the development of these two diseases is a complication of the chronic inflammatory disease and a nonspecific arterial response to a generalized inflammatory process in the presence of common genetic background and hormonal changes predisposing to both GCA and RA.

In conclusion, we would like to draw attention to the possibility that RA, GCA, and PMR appear simultaneously or consecutively; therefore, we suggest that physicians should be alert to such a fact so that proper diagnosis and treatment could be tailored accordingly.

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