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Literature Review

Symmetric polyarthritis as an initial symptom in granulomatosis with polyangiitis: A report of six cases and review of the literature

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Abstract

Granulomatosis with polyangiitis (GPA) is a primary systemic vasculitis characterized by granulomatous inflammation. Arthritis in GPA is most commonly associated with large joints, particularly the knees and ankles; however, symmetrical polyarthritis of small joints has been rarely reported in literature. Here, we describe retrospective analysis of six patients with GPA showing initial symptom of symmetrical polyarthritis who were followed-up by three different rheumatology departments. Male sex, anti-cyclic citrulinated peptide negativity, and early arthritis period are important clues for GPA.

Keywords: Granulomatosis with polyangiitis, arthritis

Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a rare systemic disease characterized by necrotizing granulomatous vasculitis, affecting mainly the upper airways, lungs, and kidneys (1). The clinical manifestations of GPA are broad and often involve multiple organ systems. The most common symptoms are related to the upper and lower airways, particularly recurring bloody rhinorrhea, rhinosinusitis, and cavitary and nodular lesions in the lungs (2). Arthritis is most commonly associated with large joints, particularly the knees and ankles, and is seldom deforming (3). In our knowledge, symmetrical polyarthritis of small joints has been rarely reported in literature. We report an analysis of symmetrical polyarthritis as an initial symptom in six patients with GPA and a literature review to evaluate their value in early diagnosis.

Case Presentations

This was a descriptive, multicenter study conducted at three different rheumatology departments in Turkey through a retrospective analysis of the medical records of six patients who had onset of GPA with small joint symmetrical involvement, according to the 1990 criteria of the American College of Rheumatology.

Case 1

A 37-year-old male patient presented with bilateral pain and swelling of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint, knee, and ankle joints over 3 months. Examination revealed symmetrical polyarthritis in small hand joints, knee, and ankles. Initial blood tests demonstrated the following results: serum white blood cells (WBC) count, 16900/μL (4000-10000); erythrocyte sedimentation rate (ESR), 108 mm/h (0-20); C-reactive protein (CRP), 198 mg/L (0-5); rheumatoid factor (RF), 237 IU/mL (negative, <15 IU/mL); cyclic citrulinated peptide (CCP), 3 IU/mL (negative, <5 IU/mL); blood urea nitrogen (BUN) 49 mg/dL (5-24); and creatinine, 3.2 mg/dL (0.7-1.3). The rest of the routine hematological and biochemical tests and chest posteroanterior (PA) radiography were found to be normal. Continuous use of non-steroidal anti-inflammatory drugs for the past 3 months and the normal urine analysis suggested acute renal failure. A diagnosis of seropositive rheumatoid arthritis (RA) was established and a treatment regimen of prednisolone 10 mg/day, hydroxychlorokine 200 mg/day, and sulfosalazine 1000 mg/day was initiated. Methotrexate was not prescribed because of elevated creatinine levels. Ten days after discharge, the patient was hospitalized again with complaints of fatigue, fever, and polyarthralgia. Laboratory results were as follows: ESR, 128 mm/h; CRP, 151 mg/L; BUN, 51 mg/dL; and creatinine, 2.04 mg/dL. In addition, microscopic hematuria and proteinuria (1.1 g/day) was detected. The emerging proteinuria and hematuria suggested that glomerulonephritis occurred because of vasculitis. Serologic testing showed elevated anti-neutrophil cytoplasmic antibodies (c-ANCA:11; negative, <5). A renal biopsy was performed; renal histology showed

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extracapillar glomerulonephritis. The tentative diagnosis of GPA was confirmed by renal biopsy. Pulse methylprednisolone (500 mg/day) was administered for 4 days, and the use of cyclophosphamide (1 g/month) was initiated. His renal functions returned to normal. He was followed-up for 1 year. There was no recurrence of the GPA in the last year.

Case 2

A 62-year-old male patient presented with morning stiffness, arthralgia, and bilateral symmetric arthritis of PIP joints, wrists, knees, and ankles, without fever which had persisted for two months. His past medical history was normal. The results of his cardiological, pulmonary, dermatological, abdominal, and neurological examinations were unremarkable. Laboratory results were as follows: ESR, 80 mm/h; CRP, 20 mg/L; RF, 180 IU/mL; and CCP, 1 IU/mL. Active seropositive RA was diagnosed, and treatment was initiated with methotrexate. After 6 months, he presented with fever and bloody sputum. The new laboratory tests were as follows: WBC, 340/µL; CRP, 23 mg/L; ESR, 45 mm/h; and creatinine, 3.2 mg/dL. The thorax computerized tomography (CT) revealed multiple pulmonary nodules and consolidation. The autoantibody c-ANCA was found to be positive. With a diagnosis of GPA, he was transferred to the intensive care unit; however, he died because of Acinetobacter septicemia.

Case 3

A 52-year-old male patient was referred to our clinic because of the insidious onset, in previous three months, of arthralgia and symmetrical polyarthritis involving small joints of the hands. His past medical history was normal. The results of his cardiological, pulmonary, dermatological, abdominal, and neurological examinations were unremarkable. Laboratory findings showed an increase in the level of inflammatory markers, which were positive for c-ANCA. RF was positive (56.8 IU/mL) and CCP was negative (<0.5). A 24-hour urine collection yielded 1.5 g of protein. GPA was diagnosed; pulse steroid (1 g/day, total 3 days) and three courses of cyclophosphamide (1 g/month) were administered. He is still being followed up and no relapse has been reported till date.

Case 4

A 47-year-old male patient presented with bilateral symmetric arthritis of the wrists, 2-3. MCP and PIP joints with fatigue and dyspnea which had persisted for two months. Laboratory investigations demonstrated the following results: ESR, 68 mm/h; CRP, 195 mg/L; RF, 180 IU/mL; CCP, 2.3 IU/mL; and creatinine, 4.8 mg/dL. Microscopic hematuria was detected in urine analysis. The pulmonary CT scan showed extensive ground glass opacities consistent with intra-alveolar bleeding with bilateral pleural effusion. Because of pulmonary hemorrhagic and pleural effusion, laboratory tests for autoantibodies were performed; ANA IFA (+) and C-ANCA were revealed to be positive. GPA was diagnosed, and three methylprednisolone pulses (1 g/day) were administered. An immunosuppressive therapy with cyclophosphamide (1 g) and plasmapheresis was started for life-threatening state with pulmonary hemorrhage Under immunosuppressive therapy, the patient presented with pretibial edema 3 months later, and then rituximab (1000 mg) was administered twice on days 1 and 15. After the second rituximab infusion, pulmonary hemorrhage regressed and creatinine levels decreased (1.8 mg/dL). Till date, no relapse of disease has been reported.

Case 5

A 29-year-old male patient presented with bilateral arthritis of MCP, PIP, and knee and ankle joints which had persisted for 2 months. Initial laboratory test results were as follows: WBC, 13300/µL; CRP, 171 mg/L; ESR, 90 mm/h; RF, 10.1 IU/mL; CCP, 3 IU/mL; and creatinine, 1 mg/dL. The patient was followed for early arthritis in our clinic. After one month, he presented with fever, fatigue, and cough. The thorax CT showed multiple pulmonary nodules and consolidation, and therefore, a biopsy was performed. Surgical biopsy of the lung nodule showed necrotizing vasculitis that affected pulmonary arteries with granulomatous changes. The autoantibody C-ANCA was found to be positive. GPA was diagnosed and pulse methylprednisolone (1 g/day, total 3 g) and cyclophosphamide (1 g/month) was initiated; after 1 year, mycofenolatmofetil (900 mg/m^2 body surface/day) was administered as a maintenance therapy. Under immunosuppressive therapy with mycophenolate mofetil, the patient presented with hematuria and proteinuria, and rituximab (1000 mg) was administered twice on days 1 and 15. To date, he is alive and there has been no new relapse of the disease.

Case 6

A 43-year-old male patient presented with a 10-month history of morning stiffness and bilateral symmetric arthritis of the MCP and PIP joints. The results of the initial laboratory tests were as follows: WBC, 11000/µL; CRP, 15.4 mg/L; ESR, 49 mm/h; RF, 11.1 IU/mL; and CCP, 2.8 IU/mL. The rest of the routine hematological and biochemical tests were found to be normal. He was diagnosed with seronegative RA, and treatment regimen comprising methotrexate, sulfasalazine, and prednol was initiated. After 9 months, he was admitted to our hospital with fever, cough, and bloody sputum. Thorax CT scan revealed cavitations and pulmonary nodules. Biopsies of the largest nodule in the left lung showed necrotic tissues, foci of neutrophils with nuclear dusts, and granulomas. The autoantibody c-ANCA was revealed to be positive. Prednisolone and cyclophosphamide were initiated after the diagnosis of GPA. The patient was given prednisolone and a total of six pulses of cyclophosphamide intravenously. After 1 year, control thorax CT reported a progression and rituximab was included in the therapy. The clinical and radiological findings improved significantly.

Table 1. Clinical, laboratory, and histopathological examination results of six patients with GPA

Patient	Sex	Age	Initial Symptom duration (month)	ESR (mm/h)	CRP (mg/dl)	Proteinuria (mg/24h)	Anti-CCP	RF (IU/ml)	C-ANCA	Biopsy
1	Male	37	3	108	198	ND	3	237	+	Extracapillary glomerulonephritis
2	Male	62	2	80	20	ND	1	180	+	ND
3	Male	52	3	72	55	1500	<0.5	56.8	+	Necrotizing glomerulonephritis
4	Male	47	2	68	195	1000	<0.5	180	+	Necrotizing glomerulonephritis
5	Male	29	2	90	171	ND	3	10.1	+	Necrotizing granulomatosis vasculitis
6	Male	43	10	49	15.4	ND	2.8	11.1	+	Necrotic tissues and granulomas

ESR: erythrocyte sedimentation rate, CRP: C reactive protein, anti-CCP: anti-cyclic citrulinated peptide; RF: rheumatoid factor; ANCA: anti-neutrophilic cytoplasmic antibody; ND: not done

Discussion

Heterogeneous initial symptoms which cause diagnostic problems are not rare in GPA. We have presented an analysis of six patients with initial symptom of symmetrical polyarthritis to study their value in early diagnosis. Early arthritis, male sex, and anti-CCP negativity are important clues for GPA diagnosis.

Muscle and skeletal manifestations occur in 30%-50% of the patients with GPA. The most common musculoskeletal problems include myalgia, arthralgia, and arthritis (4). Arthritis in GPA is most commonly associated with large joints, particularly the knees and the ankles. Hoffman et al. (5) reported 44% joint involvement, including arthralgia or arthritis in GPA. Rodrigues et al. (2) reported 25% musculoskeletal symptoms in the initial presentation of GPA. In our patients, symmetrical small joint polyarthritis was observed as an unexpected arthritis form. Although rare, GPA may develop in patients with preexisting symmetrical polyarthritis. GPA and RA are clinically and immunologically independent diseases; however, some reports on patients with RA developing GPA have been published (6). The arthritis in RA began insidicous, but our patients presented with acute symmetrical polyarthritis. RF was positive in four of the six patients; however, CCP was negative in all six patients. So, CCP may be important for the distinction of these two diseases, and CCP negativity is important for the suspicion in diagnosis. In addition, renal involvement is not expected in RA, and hand X-rays showed no erosions in our patients. Therefore, our patients were not diagnosed as having RA or overlap syndrome. Kamali et al. (7) evaluated anti-CCP positivity in patients with GPA. No positive result for anti-CCP was detected in patients with GPA.

Various case reports have highlighted the challenge of diagnosing GPA early because of atypical presenting symptoms and the involvement of different organ systems. For example, patients initially may present with symmetrical polyarthritis like RA, and although it often takes a long time to set the diagnosis, yet early diagnosis and treatment are important as the progression of the disease can lead to permanent organ damage and can be life-threatening. In our cases, it took 2-9 months for a true diagnosis after initial evaluation. Although there is still no evidence that arthritis as an initial symptom in GPA is more common in males than in females, all six cases of polyarthritis and GPA were males in our report. Symmetrical polyarthritis preceded GPA diagnosis in all cases. Rodrigues et al. (2) shown that the prevalence of the initial clinical manifestations in adults with systemic disease was 64% in upper airways, 36% in lungs, 18% in kidneys, 25% in eyes, 11% in skin, 25% in musculoskeletal system, and 7% in neurological system. But they did not describe the type of musculoskeletal involvement.

In patients with non-characteristic onset, the diagnosis of GPA may be delayed; and in some cases, a few months after the first symptoms appear. In this report, we wanted to emphasize that GPA, although rare, should be considered in the above clinical scenario and treatment should be initiated as soon as possible.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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