Granulomatosis with polyangiitis – the incomplete puzzle

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ABSTRACT

Granulomatous with polyangiitis (GPA) is a necrotizing granulomatous vasculitis that mostly affects small-sized vessels. The disease can affect many organs, although renal and respiratory tract involvement are the most frequent and distinguishing features. Musculoskeletal manifestations have been reported in about 50% of patients and can occur as myalgia, oligoarthralgia/arthritis of large joints or polyarthralgia/arthritis of small joints. Infrequently musculoskeletal symptoms can be the first disease manifestation, and in this clinical scenario GPA diagnosis might be delayed or mistaken by other rheumatic diseases. The authors describe three patients with musculoskeletal symptoms as earliest GPA manifestations, illustrating the clinical challenge.

Keywords: Nodules; Arthralgia; Arthritis; Granulomatosis with polyangiitis.

INTRODUCTION

Granulomatous with polyangiitis (GPA) is a necrotizing granulomatous vasculitis that mostly affects small-sized vessels[1,2]. Anti-neutrophil cytoplasmic antibodies (ANCA) are present in about 90% of patients[2], with anti-proteinase 3 (anti-PR3) being the most common[3]. GPA is a multisystemic disease that can affect many organs. Renal and respiratory tract (including upper and lower) are mostly involved, although musculoskeletal manifestations have been described in 40%-65% of patients[2,4]. Arthralgia is the most common symptom[2], mainly located to large joints[5]. However, symmetrical polyarthritis of small joints, mimicking rheumatoid arthritis (RA), has also been reported[6]. Musculoskeletal symptoms can be the first and sole manifestation of disease[7], making GPA diagnosis extremely challenging. Herein, we report three patients with musculoskeletal symptoms as earliest GPA manifestation.

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CASE SERIES

CASE 1

A 55-year-old female presented to Rheumatology clinic with bilateral pain and swelling of wrists, metacarpophalangeal and proximal interphalangeal joints, lasting for six weeks, without evidence of other organ involvement. Examination revealed symmetrical polyarthritis involving the wrists and small hand joints. Initial blood tests demonstrated normocytic normochromic anaemia (haemoglobin 11 g/dL), erythrocyte sedimentation rate (ESR) 104 mm/h, C-reactive protein (CRP) 3.6 mg/dL, positive (56.2 UI/mL) rheumatoid factor (RF) and negative anti-citrullinated peptide antibodies (ACPA). The remaining haematological and biochemical tests, as well as chest and hands X-rays were found to be normal. She was diagnosed with RA and started prednisolone (PDN) 10mg/day (tapering dose to 5mg/day) and methotrexate 10mg/week, with clinical benefit and decrease in inflammatory markers (ESR 65 mm/h and CPR 1.2 mg/dL after six weeks of treatment). Two years later she developed fatigue, dyspnoea, dry cough and weight loss (3 kg in one month). At this time, there was no evidence of active RA. Blood testes demonstrated haemoglobin 11.3 g/dL, white blood cells count 13 x 10^9/L, ESR 98 mm/h and CRP 5.8 mg/dL. Chest X-ray showed a subpleural nodule at the left lower lobe (Figure 1A), which underwent computed tomography (CT)-guided biopsy (Figure 1B). Histology revealed epithelioid granulomas with multinucleated giant cells, without evidence of malignancy, infection or vasculitis. Lung nodule was attributed to RA and methotrexate was switched to

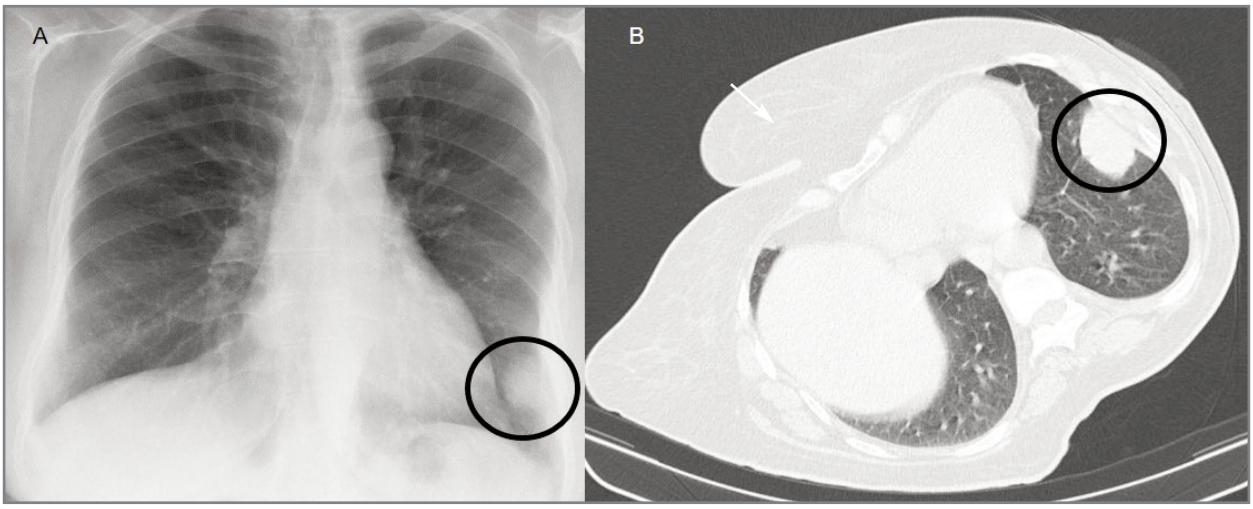

FIGURE 1. Chest X-ray (A) and computed tomography (B) showing a subpleural nodule at the left lower lob

leflunomide. Two months later, she developed sudden aphonia and referred worsening dyspnoea and cough, associated with daily fever. Blood tests had raised white blood cells count (15.5 x 10^9/L) and inflammatory markers (ESR 120 mm/h and CRP 14.6 mg/dL). Chest X-ray demonstrated hypotransparency in the lower third of the left pulmonary field, associated with blunting of the ipsilateral costophrenic angle (Figure 2). Pneumonia was assumed and she was admitted into hospital for intravenous antibiotics. During hospital stay she repeated chest CT, which showed an increase in left lower lobe nodule and a new right paravertebral pulmonary nodule (Figure 3). Bronchofibroscopy demonstrated a nacreous, vascularized mass in the anterior portion of the trachea, immediately bellow the vocal folds, without evidence of alveolar haemorrhage. Laryngeal observation showed swollen, hyperaemic vocal folds, associated with an abnormal mass at the upper trachea and neck CT demonstrated slight, polypoid, soft tissue thickening at infraglottic stage, immediately bellow the cricoid cartilage, with air column diameter reduced at this level (Figure 4). Histological examination showed an intense inflammatory infiltrate, without haemorrhage; no microorganisms using Periodic Acid-Schiff, Grocott and Ziehl-Neelsen stains, as well as neoplastic tissue were found. Microbiology

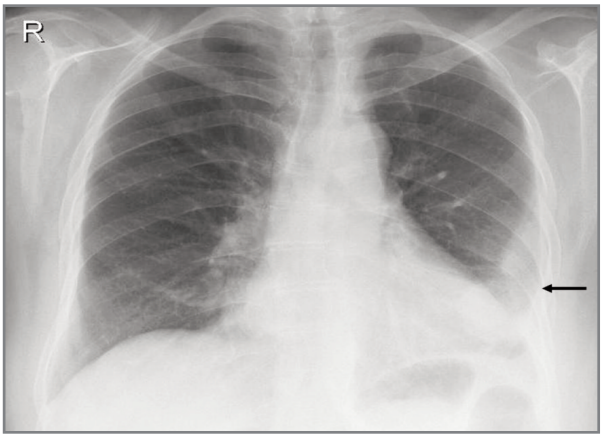

FIGURE 2. Chest X-ray showing hypotransparency in the lower third of the left pulmonary field, associated with blunting of the ipsilateral costophrenic angle

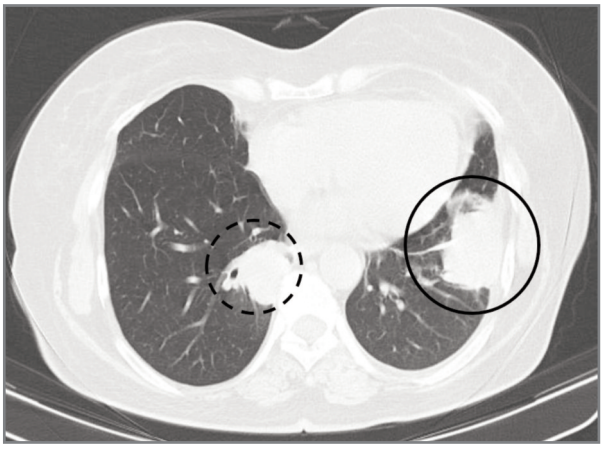

FIGURE 3. Chest computed tomography showing persistent left lower lobe nodule (continuous line) and a new right paravertebral pulmonary nodule (dashed line)

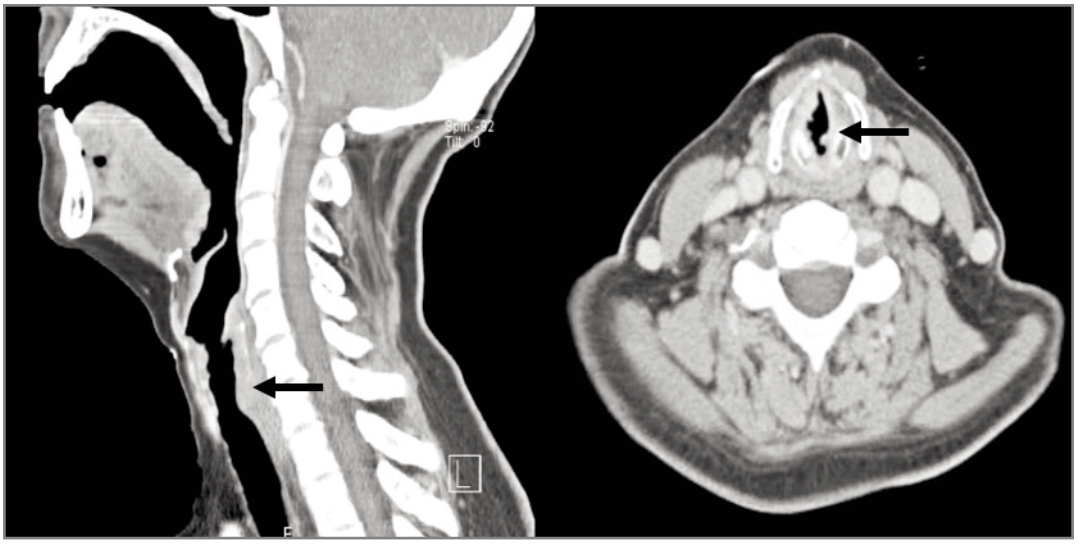

FIGURE 4. Neck computed tomography showing reduced air column diameter due to soft tissue thickening at infraglottic stage

examination was negative, including for mycobacteria. At this point GPA diagnosis was considered and ANCA were requested. Anti-PR3 antibodies turned out to be positive (24 UI/mL), supporting the diagnosis. She had no clinical or laboratory evidence of kidney involvement. The patient started prednisolone (PDN) 1mg/kg/day in association with rituximab (two infusions of 1g, 2 weeks apart), with symptomatic improvement, lung nodules resolution and normalization of inflammatory markers and anti-PR3 titer (1.5 UI/mL 9 months after rituximab).

CASE 2

A 45-year-old healthy woman, who worked as a cleaner, presented to Rheumatology clinic with mechanical joint pain of both first carpal-metacarpal joints and knees lasting for two years. Hands x-ray had signs of bilateral rhizarthrosis. Blood tests showed ESR 59 mm/h and CRP 1.6 mg/dL, without any other abnormalities. She had no swollen joints on physical examination and was prescribed acetaminophen and non-steroidal anti-inflammatory drugs, with little benefit. Three months later she reported worsening complaints, with new onset night pain. Her general practitioner prescribed PDN 5mg/day, with pain relief. In the next two weeks she developed cough, occasionally with pinkish sputum, epistaxis, nasal crusts, sensation of hearing loss, anorexia and subfebrile temperatures. Blood tests revealed microcytic, hypochromic anaemia (haemoglobin 8.7 g/dL), leucocytosis (13.2 x 10^9/L) with neutrophilia, thrombocytosis (949 x 10^9/L), ESR 120 mm/h, CRP 12.43 mg/dL, creatinine 2.8 mg/dL (normal values three months before), haematoproteinuria, positive RF, negative ACPA and positive anti-PR3 antibodies (62 UI/mL). Chest X-ray showed an heterogeneous hypotransparency at left apex and a peripheral right pulmonary nodule (Figure 5A), which were also documented in chest CT (Figure 5B); bronchofibroscopy had no evidence of alveolar haemorrhage, malignancy or infection. Audiogram revealed bilateral sensorineural hearing loss and renal biopsy documented crescentic, pauci-immune glomerulonephritis. The patient was diagnosed with GPA and treated with steroids (intravenous methylprednisolone pulses 1g/day for 3 days, followed by PDN 1mg/Kg/day) in association with intravenous cyclophosphamide (0.5-1g/m^2, monthly, 6 months), with clinical and laboratorial improvement (anti-PR3 titer 0.7 UI/mL after finishing cyclophosphamide).

CASE 3

A healthy 26-year-old woman, with no history of drug use, presented to Rheumatology clinic with inflammatory, symmetrical and additive arthralgia of the elbows, wrists, metacarpophalangeal joints, knees and metatarsophalangeal joints, associated with morning stiffness lasting for more than an hour. On physical examination she had polyarthritis with involvement of metacarpophalangeal and metatarsophalangeal joints. Blood tests demonstrated normochromic normocytic anaemia (haemoglobin 11 g/dL), raised inflammatory markers (ESR 51 mm/h, CRP 7.1 mg/dL), positive RF (>300

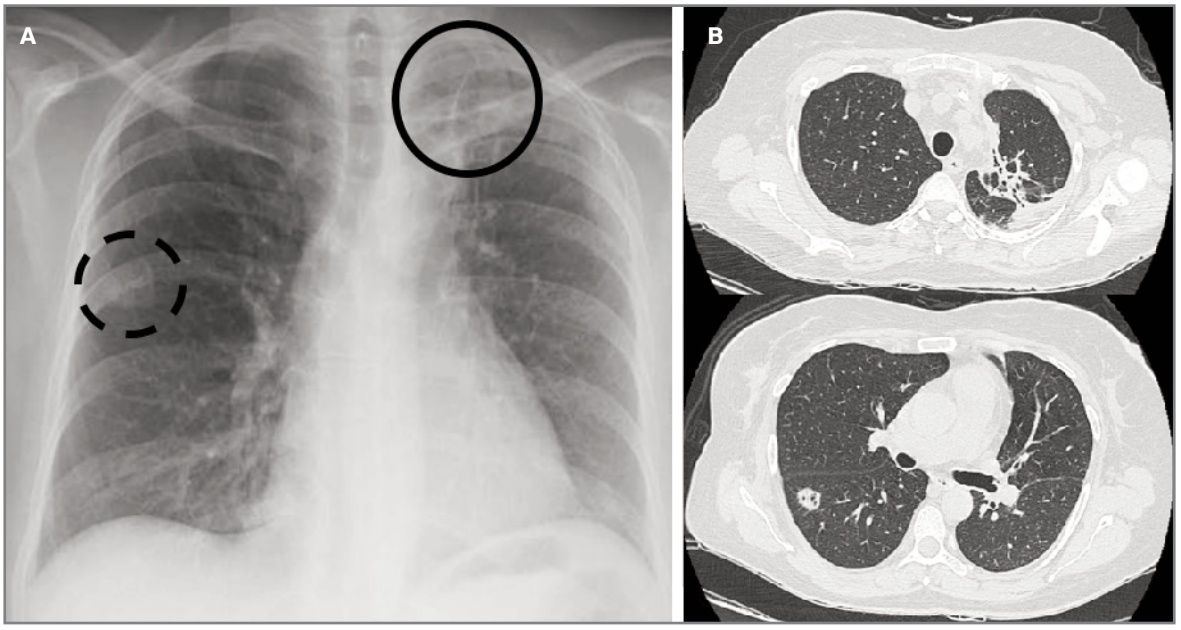

FIGURE 5. Chest X-ray (A) showing an heterogeneous hypotransparency at left apex (continuous line) and a peripheral right pulmonary nodule (dashed line) and corresponding computed tomography (B) with a retractile consolidation on the left upper lobe and lung nodule on the right upper lobe

UI/mL) and negative ACPA and antinuclear antibodies. RA was assumed and the patient started prednisolone 5mg/day in association with methotrexate 10mg/week, with clinical improvement. Two months later she developed toe numbness and cyanosis of the first, second and fifth right toes, with progression to necrosis in two weeks, which prompted hospital admission. She performed arterial and venous doppler ultrasound of lower limbs, as well as transthoracic echocardiogram, which exclude thrombus/emboli. Electromyography documented mononeuritis multiplex. Blood tests showed normal creatinine, normal urine sediment, negative antiphospholipid antibodies, negative cryoglobulins, negative syphilis, hepatitis B/C virus and human immunodeficiency virus serologies and positive anti-PR3 antibodies (74 UI/mL). The patient was diagnosed with GPA and treated with steroids (intravenous methylprednisolone pulses 1g/day, 3 days, followed by PDN 1mg/Kg/day in tapering doses) in association with intravenous cyclophosphamide (0.5-1g/m^2 monthly, for 6 months). She went into clinical remission (anti-PR3 titer 29 UI/mL after finishing cyclophosphamide) and was kept under maintenance treatment with mycophenolate mofetil. Three years later inflammatory poliarthralgias recurred (without arthritis on physical examination), associated with episcleritis of the left eye and purpuric lesions of both lower limbs. Blood tests documented raised anti-PR3 titer (82 UI/mL), raised inflammatory markers, normal creatinine but with new onset haematoproteinuria. At this point the patient restarted steroids (PDN 0.5 mg/kg/day) and was treated with rituximab (two infusions of 1g, 2 weeks apart), with symptomatic improvement and normalization of inflammatory markers and anti-PR3 titer (2.3 UI/mL 6 months after rituximab). Since then the patient has been kept under maintenance with rituximab 500mg on demand, with the recurrence of inflammatory articular and ocular symptoms, associated with an increase in inflammatory markers and anti-PR3 titers, dictating the need for retreatment.

DISCUSSION

GPA is a heterogeneous disease and presentations can be variable and sometimes unspecific.

Musculoskeletal symptoms have been reported in 40%-65% of GPA patients[2,4] and according to Rodrigues *et al.* can be the first disease manifestation in a quarter of patients[7]. Arthralgia is more common than

arthritis[2] and monoarticular, oligoarticular, and polyarticular involvement can all be seen. GPA arthritis most frequently affects large joints, particularly the knees and the ankles[6], although symmetrical polyarthritis of small joints, mimicking RA, has also been reported[6]. One distinctive articular manifestation that frequently occurs in GPA but is uncommon in other diseases includes migratory arthralgias/arthritis of large joints, in which patients experience severe pain in one joint for a few days before complete resolution, to be shortly followed by similar symptoms in one to two other joints. GPA patients can also report myalgia[4], without any abnormality on clinical examination or blood tests.

Taking into account the diversity of possible musculoskeletal manifestations, GPA diagnosis can be extremely challenging, particularly when these are the first symptoms and occur isolated. It is easily understood that under these circumstances GPA can be misdiagnosed as RA, peripheral spondyloarthropathies, crystal-associated arthropathies, osteoarthritis or even fibromyalgia[4]. The challenge is even greater in patients with symmetrical polyarthritis and positive RF, which has been reported in nearly 60% of patients[4]. In these patients, negative ACPA is an important clue[8], as well as disproportionately high inflammatory markers, and should increase clinician's degree of suspicion.

Regarding treatment, the drug chosen is based on clinical manifestations. According to EULAR recommendations for the management of ANCA-associated vasculitis[9], methotrexate and mycophenolate mofetil should be considered for remission-induction of non-organ-threatening disease, like arthritis and myositis (skeletal muscle only). However, methotrexate should not be used for treating severe disease such as skin involvement with ulceration, non-cavitating pulmonary nodules/infiltrate with haemoptysis or renal involvement[9]. When patients develop organ-threatening or life-threatening manifestations, such as pulmonary haemorrhage, acute-onset mononeuritis multiplex or cardiac/mesenteric involvement, cyclophosphamide or rituximab are the alternatives for remission-induction treatment[9].

Over the last two decades, survival of GPA patients has considerably improved[10], not only due to improvement in treatment strategies, but also due to an earlier recognition of the disease. Therefore, for patients in whom musculoskeletal symptoms are the presenting manifestation of disease, GPA diagnosis can be extremely challenging and clinicians should pay particular attention to disproportionately high inflammatory markers, development of systemic symptoms or evidence of other organ involvement. This is particularly true for patients with positive RF and negative ACPA. Only a high degree of suspicion allows a prompt GPA diagnosis and treatment, with great impact in patients overall survival.

There are very few data in the literature exclusively dedicated to musculoskeletal involvement in GPA[6], which gives greater interest to this case review.

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