Case Report

Wegener's Granulomatosis in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To describe 2 cases of coexisting rheumatoid arthritis (RA) and Wegener's granulomatosis (WG), and to summarize the clinical and serological data for all 6 patients reported in the English literature since 1966.

Methods. Medline review over a 35-year period (1966–2002) revealed 4 reported cases of RA associated with WG. Patients were diagnosed based on symptoms, radiographic changes, bronchoalveolar lavage fluid analysis, hematuria, serology, and biopsy. We describe 2 additional cases of WG developing in Caucasian women with RA. These are the first reported patients to possess positive antineutrophil cytoplasmic antibodies (ANCA) and autoantibodies to proteinase 3 (PR3).

Results. All 6 cases of coexisting RA and WG were female. The diagnosis of RA preceded WG diagnosis in all cases; mean age at RA onset was 43.7 ± 15.0 years, duration of RA prior to WG diagnosis 7.9 ± 9.1 years. Clinical findings included erosive articular disease on radiographs (n = 4; 67%), positive rheumatoid factor (n = 6; 100%), upper respiratory involvement (n = 5; 83%), lower respiratory signs (n = 4; 67%), renal involvement (n = 2; 33%), and positive ANCA (n = 2/3; 67%). Five patients were treated with corticosteroids and cyclophosphamide, with clinical improvement.

Conclusion. Although rare, WG may develop in patients with preexisting RA and may present with end-organ involvement. (J Rheumatol 2003;30:2064–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS WEGENER'S GRANULOMATOSIS RHEUMATOID FACTOR
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES PROTEINASE 3

Rheumatoid arthritis (RA) and Wegener's granulomatosis (WG) share some common clinical manifestations, but the prevailing evidence indicates that these diseases are distinct entities, each with a different immunopathogenesis. Patients with either RA or WG may present with nonspecific findings of fever, malaise, weight loss, arthralgias, and myalgias. Distinguishing features of RA include synovitis leading to erosive bone lesions and possible joint deformity. Patients with RA or WG may exhibit symptoms involving the ocular, vascular, dermatological, pulmonary, renal, and nervous systems. Although patients with RA often demonstrate production of rheumatoid factor (RF), i.e., autoantibodies against the Fc fragment of IgG, it is not specific for RA.

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Patients with WG can be distinguished from RA by the presence of symptoms of refractory sinusitis, rhinitis, and otitis media with purulent or bloody discharge. These symptoms may be accompanied by destructive changes such as saddle-nose deformity. The lower respiratory manifestations of WG are often more dramatic than those seen in RA, including bloody or purulent sputum and intraalveolar hemorrhage. Serological tests for WG may detect the production of antineutrophil cytoplasmic antibodies (ANCA) directed mainly against proteinase 3 (PR3).

There are 4 previously reported cases of RA associated with WG in the English literature. We describe 2 additional cases, with the additional diagnostic information of c-ANCA against PR3, and discuss the clinical and laboratory manifestations as well as treatment options.

A literature review using the Medline key words "rheumatoid arthritis" and "Wegener's" produced 4 other cases of RA associated with WG over a 36-year period (1966 to 2002)[1-3]. All patients exhibited characteristics of both RA and WG, and fulfilled current ACR criteria for both diagnoses[4,5]. The diagnosis of RA and WG was based on symptoms, clinical and radiographic findings, biopsy, and serology. We describe 2 cases at our institution that fulfilled American College of Rheumatology (ACR) criteria for both RA and WG. Clinical and serological data from all cases are summarized in Table 1.

Table 1. Review of all 6 patients with RA and WG reported in the English literature.

Patient	Year	Sex	Age at RA Diagnosis*, yrs	Age at WG Diagnosis**, yrs	Interval Between Diagnoses, yrs	RA Manifestations	WG Manifestations	Positive Autoantibodies and Tests	Radiographs	Biopsy	Therapy	Followup
1[3]	1974	F	40	59	19	Polyarthritis	Dysphagia, DOE, stridor, laryngeal edema	RF, ANA LE cells, BUN 50 mg/dl, CrC1 35 ml/min	Rheumatoid erosive changes	Laryngeal ulcer: granulomatous reaction with many giant cells	Phenyl-butazone gold, old tuberculin injections	D
2[2]	1976	F	45	45	8 mo	Symmetric polyarthritis wrists, MCP, PIP joints	Sinusitis, deafness, facial pain, SOB	RF, immune complexes, ESR, eosinophilia	Pulmonary infiltrates	Left tympanic membrane and vocal cords: granulomatous changes	HCQ, CYC	I
3[2]	1976	F	73	75	2	Symmetric polyarthritis, subcutaneous nodules, vasculitic nailfold lesions, sensory neuropathy	Otitis, hemo-ptysis, pleurisy and effusion, episcleritis, sinusitis, nasal obstruction	RF, immune complexes, ESR	Periarticular osteoporosis	Nasal: necrotizing granulomas	Prednisone, azathioprine, CYC	I
4[1]	1992	F	33	38	5	Morning stiffness, contracture elbows, right index and middle finger swelling, L knee joint	Epistaxis, saddle nose, perforated nasal septum	CRP, RF, RAHA and Waller-Rose, immune complexes	Hands joint space nar-rowing, ulnar deviation, ankylosis of wrists and elbows	Nasal: arteritis with cellular infiltration, giant cells, epidermoid cells	NSAID, gold, prednisolone, CYC	I
5	2002	F	36	37	11 mo	Symmetric polyarthritis wrists, MCP, PIP joints	Epistaxis, sinusitis otitis, saddle nose, pulmonary hemorrhage, hematuria	ESR, RF, cANCA, PR3	Erosive changes, subluxation, cavitary lesions†	None	NSAID, CYC prednisone	I
6	2002	F	35	55	20	Symmetric polyarthritis MCP, PIP joints, knees and shoulders	Cough, SOB, Hemoptysis	ESR, RF, cANCA, PR3	Erosive changes, cystic cavitary lesions†	Lung: granulomas with capillaritis	Prednisone, CYC	I

* Age at first RA symptom, ** age at first WG symptom, † on chest radiograph. MCP: metacarpal phalangeal, PIP: proximal interphalangeal, DOE: dyspnea on exertion, SOB: shortness of breath, RF: rheumatoid factor, ANA: antinuclear antibody, LE: lupus erythematosus, BUN: blood urea nitrogen, CrCI: creatinine clearance, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RAHA: rheumatoid arthritis hemagglutination, cANCA: cytoplasmic staining for antineutrophil cytoplasmic antibodies, PR3: anti-proteinase 3, HCQ: hydroxychloroquine, CYC: cyclophosphamide, D: died, I: improved.

CASE REPORTS

Case 1. A 37-year-old Caucasian woman was referred to our outpatient rheumatology clinic with an 18-month history of worsening bilateral hand, wrist, and foot pain and swelling with associated prolonged morning stiffness. She had been seen by a rheumatologist in January 2001, and was diagnosed with RA based on her symptoms, synovitis, and positive RF. She was prescribed prednisone 15 mg QD and methotrexate (MTX), but stopped her medications after less than one week due to symptoms of abdominal discomfort. She refused other disease modifying agents for rheumatic disease (DMARD) therapy due to fear of their side effects, and was taking only over-the-counter nonsteroidal antiinflammatory drugs (NSAID) and vitamins, with little improvement. Her history included recent refractory S*taphylococcus aureus* otitis media and rhinosinusitis associated with eustachian tube dysfunction requiring bilateral myringotomy and tube placement. Over the next months she developed occasional epistaxis and a saddle-nose deformity (Figure 1).

Examination revealed no evidence of septal perforation or polychondritis. She displayed symmetric polyarthritis with synovitis involving bilateral wrists and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. She had flexion contractures of both elbows and subluxation of her right wrist. Subcutaneous nodules were not present. Her lungs were clear to auscultation and she had a normal cardiovascular and neurological examination. Serologic tests showed a positive RF (1:235 titer), erythrocyte sedimentation rate (ESR) > 100 mm/h, and negative human immunodeficiency virus (HIV), antinuclear antibody (ANA), hepatitis C and hepatitis B. She had a mild microcytic anemia with hemoglobin of 9.0 g/dl and hematocrit 29.2%, and thrombocytosis (platelet count of 509,000/µl). Chemistry and liver profiles were normal. Tuberculin skin testing was negative. Hand radiographs showed periarticular osteopenia, carpal subluxation, and marginal erosions (Figure 2). She was prescribed glucocorticoids and DMARD therapy, but did not fill her prescriptions due to fear of side effects.

Figure 1. Case 1: saddle-nose deformity. She had no evidence of septal perforation by examination or radiographic findings.

Figure 2. Case 1: frontal radiographs of hands reveal marginal erosions involving the second PIP joint of the left hand (arrow), periarticular osteopenia involving the metacarpals, and swelling about the second and third PIP joints.

Three months after her original visit she presented to the emergency department with a 24 h history of worsening dyspnea. She was found to be anemic, with hemoglobin 6.8 g/dl and hematocrit 22%. She had a prothrombin time of 17.6 s (normal 12.3–14.2 s), international normalized ratio 1.73, and adjusted partial thromboplastin time 33.3 s (normal 23.3–35.6 s). Urinalysis showed 17 red blood cells/high power field without proteinuria. At the time of hospitalization, antiglomerular basement membrane antibodies, lupus anticoagulant, and antiphospholipid antibodies were negative. Serum ANCA returned a positive result by ELISA, with a cytoplasmic pattern on immunofluorescent staining (cANCA). Her PR3 autoantibody titer was 47.5 U/ml (normal < 3.5 U/ml).

Initial chest radiograph showed widespread alveolar opacities. She developed massive hemoptysis shortly after admission, followed by hypoxic respiratory failure requiring intubation, 100% oxygen, and high positive end-expiratory pressures. Bronchoalveolar lavage (BAL) fluid analysis revealed bloody fluid containing 10,157 red blood cells/mm^3, 133 nucleated cells/mm^3 (segmented neutrophils 27%, lymphocytes 2%, eosinophils 2%, macrophages 68%). Pathological examination of BAL fluid confirmed hemosiderin-laden macrophages. An open lung biopsy was deemed too great a risk due to her active alveolar hemorrhage, coagulopathy, and hypoxic respiratory failure. Sputum, blood, and BAL cultures did not grow bacteria, viruses (including respiratory syncytial virus), mycobacteria, or fungi. Chest computerized tomography (CT) revealed extensive alveolar opacities consistent with pulmonary hemorrhage. Over the ensuing weeks, chest radiographs showed progression and development of multiple pulmonary cavitary lesions.

She was treated with pulse intravenous methylprednisolone, 1 g/day for 3 days, and 2 doses of monthly intravenous cyclophosphamide (750 mg/m^2 body surface area), and then switched to oral cyclophosphamide after she improved. Although she had persistent microscopic hematuria, her serum creatinine remained normal and there was no evidence of proteinuria. A renal biopsy was not performed because the microhematuria resolved with immunosuppressive therapy. She improved clinically, as did her chest radiographs, and there was normalization of her PR3 autoantibody levels. She was discharged from hospital taking oral cyclophosphamide 50 mg daily and oral prednisone 15 mg daily.

Case 2. A 55-year-old Caucasian woman had a 20-year history of RA. Her RA diagnosis was based on her symptoms of polyarthralgias involving her hands, knees, and shoulders. She had synovitis of her MCP and PIP joints, and her hand radiographs showed erosive changes of PIP joints bilaterally. Laboratory examination at the time of RA diagnosis revealed microscopic hematuria of 100 red blood cells/mm^3. She was followed by a rheumatologist and treated with various NSAID and then MTX 7.5 mg weekly, 7 years prior to her presentation. In 1997, she developed morning cough productive of sputum mixed with blood. Chest radiographs showed bilateral cystic lesions that were initially presumed to be secondary to rheumatoid lung disease. Prednisone 10 mg daily was added, with mild improvement in symptoms. In March 2002, a chest CT revealed findings consistent with a fungus ball and sputum cultures grew *Aspergillus fumigatus*. She was given itraconazole, and MTX was discontinued. She was referred to us for further evaluation and management.

Review of systems was notable for a 17-pound weight loss in the previous 2 months, no fever, and no history of sinusitis or otitis, but continued cough with small volume hemoptysis. There was no family history of connective tissue disease. Examination revealed no evidence of saddle nose deformity, otitis media, or sinusitis. She displayed symmetric

polyarthritis with swelling of MCP and PIP joints. There was no evidence of rheumatoid nodules; however, bilateral lower extremity nonpalpable purpura with bilateral ankle edema was present. Her lungs were clear to auscultation, with normal cardiovascular and neurological examinations.

Serology showed a positive RF (titer 75.5 IU/ml), ESR > 100 mm/h, and negative HIV, ANA, hepatitis C, and hepatitis B serological studies. Her complement levels and SSA and SSB antibodies were normal. She had mild microcytic anemia with hemoglobin 10.0 g/dl and hematocrit 32.2%, and thrombocytosis with a platelet count of 603,000/µl. Urinalysis showed no hematuria. Chemistry and liver profiles were normal. Serum ANCA returned a positive result by ELISA with cytoplasmic staining by immunofluorescent antibody (cANCA). PR3 autoantibody titer was > 100 U/ml. Aspergillus antibody IgG was positive. Hand radiographs showed periarticular osteopenia and marginal erosions of the PIP and MCP joints.

A chest radiograph showed large cystic lesions bilaterally with air-fluid levels and debris (Figure 3A). Chest CT scan confirmed that the cystic lesions did not communicate with the airways. She underwent thoracotomy with open lung biopsy that revealed granulomatous inflammation with capillaritis consistent with WG (Figure 4). Stains for mycobacteria and fungi were negative. She was treated with daily oral cyclophosphamide, prednisone, and itraconazole, with clinical improvement. Followup chest radiographs revealed marked decrease in size of cystic lesions (Figure 3B).

Summary. These cases represent 2 of 6 cases of RA and WG overlap reported in the English literature (Table 1)[1-3]. In all reported cases, RA manifestations preceded the diagnosis of WG. All 6 cases occurred in women, with ages ranging from 33 to 73 years (mean 43.7 ± 15.0 yrs). The time interval between the diagnosis of RA and of WG varied between 8 months to 19 years (mean 7.9 ± 9.1 yrs).

In all cases a diagnosis of RA was based on symptoms of symmetric polyarthritis, morning stiffness, and positive RF. Four out of 6 had radiographic evidence of erosions with subluxation or ankylosis. Most patients had symptoms of upper respiratory involvement including sinusitis (n = 4), otitis media (n = 3), saddle-nose deformity (n = 2), septal perforation (n = 1), and stridor from laryngeal edema (n = 1).

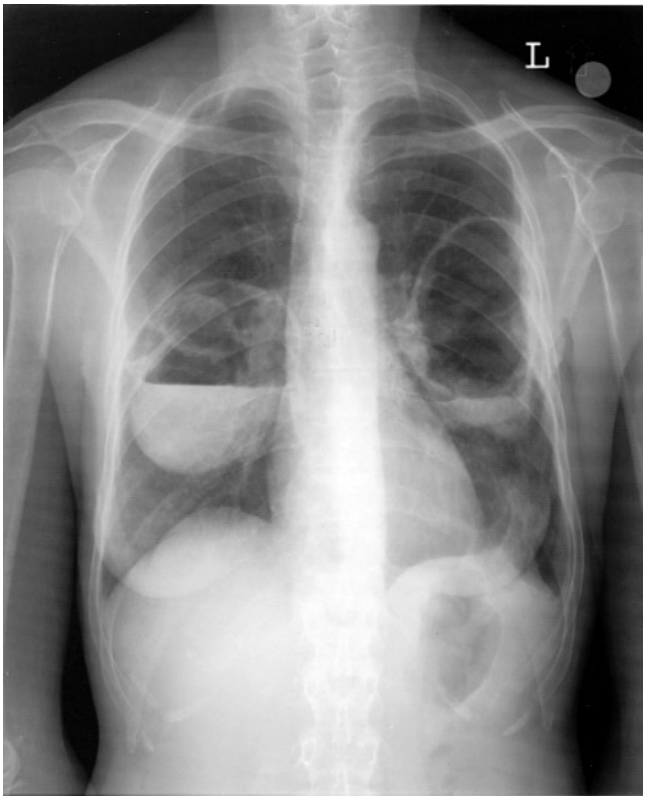
Four of 6 cases had evidence of pulmonary involvement including dyspnea (n = 4), hemoptysis (n = 3), and infiltrates or cavitary lesions on chest radiograph (n = 3). Two of the 6 cases had renal involvement, consisting of proteinuria (n = 1), increased blood urea nitrogen and decreased creatinine clearance (n = 1), and persistent microhematuria (n = 1).

An elevated ESR and positive RF (or differential agglutination titer) were observed in all cases at some time during the disease course. Patient 1 had a positive ANA with LE cells on peripheral smear. Three of the 6 cases were reported in the 1970s, and predated the advent of newer serological tests such as ANCA and autoantibodies to PR3. Patient 4 had negative ANCA serology, whereas our patients (Patients 5 and 6) displayed both a positive cANCA and high titers of antibody to PR3. In our patients, PR3 titers decreased with immunosuppressive therapy and correlated with the patients' clinical improvement.

All but one patient had biopsies revealing granulomatous vasculitis consistent with WG. In all 5 of 6 patients that were treated with steroids and cyclophosphamide, clinical improvement was noted. In Patient 1, cyclophosphamide was not used, and the patient died.

DISCUSSION

The association of RA and WG appears to be rare, with only 4 cases reported in the literature since 1966, plus our 2 reported cases.



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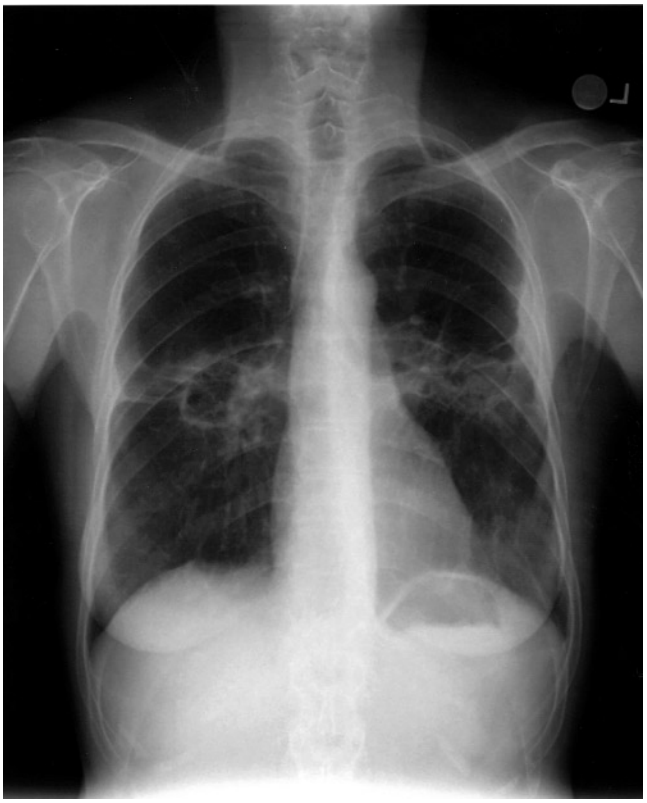

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Figure 3. A. Case 2: Posterior anterior projection chest radiograph shows large cystic lesions of bilateral lungs with multiple air-fluid levels consistent with WG and fungus ball. B. The same patient 4 months after initiation of oral cyclophosphamide, showing resolution of air-fluid levels and decreased size of bilateral cystic lesions.

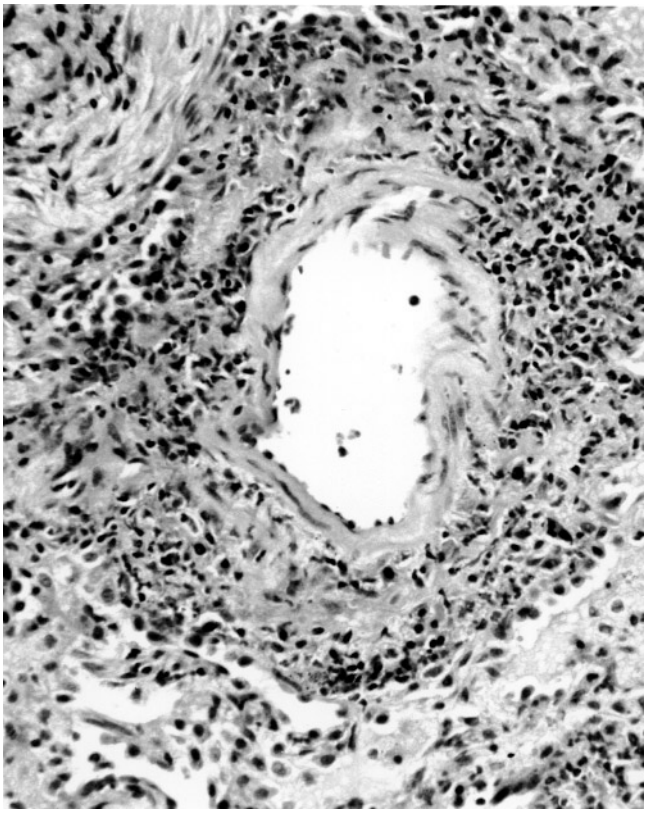

Figure 4. Case 2: Lung biopsy revealed focal necrotizing vasculitis involving a medium size muscular pulmonary artery (H&E stain, original magnification ×40).

All patients fulfilled ACR criteria for RA based on symptoms of morning stiffness, symmetric hand, wrist and foot arthritis, and positive RF. Moreover, all patients had elevated acute phase reactants. WG was diagnosed later based on upper and lower respiratory tract symptoms, renal involvement, serology, and, in most cases, a positive biopsy for granulomatous vasculitis.

Because the majority of patients with WG have symptoms of arthralgia and arthritis[6], erosive radiographic changes are important findings in recognizing comorbid RA. All patients reviewed here had varying degrees of radiographic changes of arthritis, with most displaying erosive or destructive changes. The incidence of erosive disease in WG patients is unknown; however, a review of patients with WG suggests that it is very uncommon[7]. Only one case of WG presenting with erosive arthritis has been described[8]. That patient was seronegative for RF and had mild MCP erosions that resolved with cyclophosphamide therapy[8]. Although such cases may represent an uncommon presentation of WG, the destructive arthropathy seen in our cases strongly supports a diagnosis of comorbid RA.

The majority of patients reviewed here had respiratory involvement. Otitis media and sinusitis were the most common signs, followed by saddle-nose deformity. The presence of chronic otitis and sinusitis, especially with cultures positive for *S. aureus*, and saddle-nose deformity in patients with RA should raise suspicion for coexisting WG. Although RA vasculitis may present with alveolar hemorrhage, bleeding is generally subclinical[9]. The large pulmonary cystic lesions seen in our Case 2 are more characteristic of WG than RA. We suspect that the positive sputum cultures for *Aspergillus* were secondary to the already-present cystic lesions rather than primary infections. Moreover, the CT findings of a fungus ball supported a secondary infection.

To date no serological test is specifically diagnostic of RA or WG. RF may be positive in 50% of patients with WG, but the RF titer does not correlate with disease activity[7]. Therefore, the presence of RF does not help distinguish the 2 diseases among cases of RA associated with WG. The correlation between cANCA and WG has been well established[10-13]. Antibodies to PR3 have been determined as more specific to WG, with PR3 titers more closely correlating with disease activity than ANCA titers[14,15]. Among RA patients with vasculitis, 20–49% exhibit a positive ANCA, but most if not all reveal a perinuclear staining pattern (p-ANCA) and are myeloperoxidase positive instead of c-ANCA and anti-PR3 positive[16-19].

The presence of cANCA and PR3 autoantibodies in RA patients who have symptoms of WG may help establish a diagnosis of comorbid WG. We describe the first 2 cases of patients with WG and RA who displayed high titer cANCA and anti-PR3 antibodies. However, false positive cANCA with antibodies directed against PR3 has been described in a patient with pulmonary aspergillosis and oxalosis[20]. Postmortem findings in this case did not reveal evidence of vasculitis or granulomatous disease. This case emphasizes the need for tissue confirmation when the diagnosis remains in question prior to initiating immunosuppressive therapy.

RA and WG have traditionally been thought to exist as 2 separate autoimmune disease entities. However, our cases in addition to other case reports reviewed emphasize the possibility of overlapping syndromes of RA and WG.

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