Case Report

Familial Vasculitides: Churg-Strauss Syndrome and Wegener's Granulomatosis in 2 First-degree Relatives

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ABSTRACT. Churg-Strauss syndrome (CSS) and Wegener's granulomatosis (WG) are uncommon primary vasculitides, characterized by the involvement of the small to medium size vessels and by the frequent presence of serum antineutrophil cytoplasmic antibodies (ANCA). The pathogenesis of ANCA associated vasculitides is unclear, but roles for both genetic and environmental factors have been suggested. Familial cases of WG, but not CSS, have been reported. We describe the occurrence of CSS in a man and, 5 years later, WG in his son. These patients live together in an urban area of Northern Italy and share the HLA haplotype A*03; B*07; C*w07; DRB1*0404, DQB1*0302. To our knowledge, this is the first report of the familial clustering of CSS and WG in first-degree relatives. (J Rheumatol 2003;30:618–21)

Key Indexing Terms:
FAMILIAL VASCULITIDES
CHURG-STRAUSS SYNDROME
WEGENER'S GRANULOMATOSIS
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

Churg-Strauss syndrome (CSS) and Wegener's granulomatosis (WG) are systemic vasculitides affecting small to medium size vessels[1]. Antineutrophil cytoplasmic antibodies (ANCA) are the serological markers for these diseases, mainly present in diffuse and active WG; whereas in CSS, ANCA are reported with variable frequency[2]. CSS and WG are uncommon diseases, with an annual incidence of 1.3/million and 8/million, respectively[3].

The pathogenesis of systemic vasculitides is unknown; however, there is evidence that genetic factors influence the susceptibility to these diseases, including the reports of familial cases of giant cell arteritis (GCA)[4,5], Takayasu's arteritis[6,7], and polyarteritis nodosa (PAN)[8,9], as well as WG[10-16] and microscopic polyangiitis (MPA)[16,17]. To date, familial clustering of CSS has not been observed.

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We describe the occurrence of CSS and, 5 years later, WG in 2 first-degree relatives living in a city in northern Italy, who share the HLA haplotype A*03; B*07; C*w07; DRB1*0404, DQB1*0302. To our knowledge, this is the first report of the association of CSS and WG in members of the same family.

CASE REPORT

Case 1. A bank worker born in 1935 and living in Milan reported "chronic sinusitis" since the age of 25 and new onset asthma at the age of 54. At this time, prick tests for food or inhalant antigens were negative. There was no family history of atopic or autoimmune diseases. In January 1995, he complained of nasal obstruction, due to a nasal polyp. The histological examination of the surgically removed polyp showed an inflammatory infiltrate comprising lymphocytes, eosinophils, and neutrophils. In September 1995, he came to our rheumatic disease unit with a 2 month history of general malaise, evening fever, anorexia, weight loss of about 16 kg, and some episodes of diplopia in the right eye, as well as numbness and tingling paresthesias of the lower extremities. Examination showed sinus tachycardia, barely elicitable knee and ankle reflexes, distal symmetric epicritical hypoesthesia in the lower limbs in a "stocking" distribution, and pinprick sensation. Laboratory tests revealed elevation of erythrocyte sedimentation rate (ESR) (50 mm/h, Westergren), C-reactive protein (CRP) (5.7 mg/dl; normal < 1.2), and serum IgE levels (246 IU/l; normal < 100), as well as eosinophilic leukocytosis (white blood cell count 16,580/mm^3; eosinophils 37% = 6134/mm^3). Liver and renal function tests were normal. Rheumatoid factor was positive (499 IU/ml; normal < 15), whereas ANCA, antinuclear (ANA), anti-dsDNA, and anti-extractable nuclear antigen (ENA) autoantibodies were negative. Parasitic and fungal infections were ruled out by appropriate tests. The bone marrow examination showed a marked hyperplasia of the eosinophilic compartment, without differentiation abnormalities. Thorax computed tomography (CT) revealed bilateral pulmonary infiltrates with a "ground-glass" appearance and a mild bilateral pleural effusion. A mild obstructive functional defect and a normal diffusion capacity for carbon monoxide were also found. Bronchoalveolar lavage (BAL) showed a high degree of eosinophilic alveolitis (56.3%; normal < 0.5%) and transthoracic echocardiography revealed a mild pericardial effusion. Neuroophthalmological examination revealed a defect of the right lateral rectus muscle. Neurophysiological study

revealed a sensorimotor peripheral neuropathy with axonal damage at the lower limbs, more severe in the right. Brain CT scan showed no significant abnormalities. The patient was considered to fulfill the American College of Rheumatology (ACR) classification criteria for CSS[18], and therapy with prednisone 1 mg/kg and oral cyclophosphamide 2 mg/kg daily was started[19]. One month later, prednisone was tapered to a maintenance dose of 2.5 mg daily. The therapy allowed complete clinical recovery, as well as normalization of the laboratory indicators. In November 1997, both prednisone and cyclophosphamide were stopped. In June 1998, a new neurophysiological study showed a marked improvement in the sensory and motor nerve velocities. In February 2002, he was almost asymptomatic, reporting only slight foot paresthesias after prolonged walking. His laboratory measures were within normal limits and he required no immunosuppressive therapy.

HLA molecular typing showed the genotype A*02,*03; B*07,*51; C*w05,*w07; DRB1*0404, *1101; DQB1*0301, *0302.

Case 2. In November 2000, a 33-year-old male teacher was admitted to another hospital with a 4 week history of migratory arthralgias, chest pain, and low grade fever. He was the cohabiting son of Case 1. His history was unremarkable. His living mother and 2 brothers were in good health, without history of autoimmune disease. An extensive clinical investigation was unrevealing, except for a low titer of anti-Proteus OX2 antibodies. Two weeks later, he was discharged with the diagnosis of "polyarthritis of uncertain etiology," and oral therapy with 6-methylprednisolone (6-MP) 8 mg, hydroxychloroquine 400 mg, and doxycycline 200 mg daily was prescribed, without significant clinical improvement. In January 2001, he was admitted to our unit because of the abrupt onset of intense myalgias of the calves, hampering walking. Examination revealed bilateral conjunctival hyperemia, as well as mild swelling of the left wrist and metacarpophalangeal joints; there was no evidence of oral or nasal lesion. Two days later, he was febrile (39.2°C) and necrotic-hemorrhagic lesions of the gums and several painful oral ulcers were seen. Anterior rhinoscopy revealed a red nasal mucosa with crusting and small granulomatous lesions. Laboratory investigations showed an elevation of ESR (51 mm/h) and CRP (12.4 mg/dl), as well as a low grade normochromic normocytic anemia (hemoglobin 13.1 g/dl; mean corpuscular volume 89 fl). An extensive search for bacterial and viral infections was negative. ANCA with cytoplasmic pattern (cANCA; titer 1/640) and anti-proteinase 3 (PR3) antibodies (250 EU/dl; normal < 5) were found. ANCA with perinuclear pattern (pANCA), rheumatoid factor, ANA, anti-dsDNA, and anti-ENA antibodies were negative. C3c and C4 serum levels were within normal ranges. Renal function tests showed a progressive increase in serum creatinine and in blood urea nitrogen levels from normal values on admission to 2.5 mg/dl and 95 mg/dl, respectively, after 2 weeks. At the same time, macroscopic hematuria, proteinuria (1500 mg/24 h), and pyuria were also found. Suddenly, hemoglobin levels fell from 13.1 to 8.7 g/dl, in the absence of gastrointestinal blood loss. Chest radiography revealed diffuse confluent opacities through both lung fields, despite the lack of hemoptysis and dyspnea. High resolution CT of the thorax confirmed the presence of diffuse pulmonary infiltrates, predominantly in the middle and upper lobes, with a "ground-glass" appearance. Fiberoptic bronchoscopy showed erythematous bronchial mucosa, with several hemorrhagic spots. BAL cytology was consistent with alveolar hemorrhage due to alveolar capillaritis, as shown by the presence of a high number of erythrocytes, siderophages, and neutrophils (24.7%) (normal < 3%). Cultures of BAL fluid were negative for pathogens, including Mycobacteria species. The patient fulfilled 3 of 4 ACR classification criteria for WG[20]. Because of the severity of the clinical picture, we decided to treat him with IV pulse of 6-MP (1 g daily for 3 days) and cyclophosphamide (500 mg weekly for 2 weeks). Then he was given oral prednisone 1 mg/kg daily for one month, later tapered, and oral cyclophosphamide 2 mg/kg daily. The chest radiograph became completely normal after 2 weeks of immunosuppressive treatment. One month later, serum creatinine and blood urea nitrogen levels were reduced to 1.5 mg/dl and 50 mg/dl, respectively. In March 2001, according to our protocol of systemic vasculitides treatment, he was randomized to receive oral methotrexate (MTX) 15 mg once weekly, and cyclophosphamide was discontinued. In November 2001, treatment with low dose prednisone (5 mg every other day) was stopped, continuing the oral MTX therapy. In February 2002, he was symptom-free, his laboratory findings were normal, and cANCA and anti-PR3 antibodies were negative.

HLA molecular typing showed the genotype A*01,*03; B*07, *1517; C*w07; DRB1*0404,*1501; DQB1*0302, *0602. HLA molecular typing of his mother showed the genotype A*01,11; B*1517,50; C*w07; DRB1*1501,*0301; DQB1*0201,*0602.

DISCUSSION

We describe the occurrence of different systemic vasculitides, CSS and WG, in 2 first-degree relatives living together in the same city of Northern Italy and sharing the HLA haplotype A*3; B*07; C*w07; DRB1*0404, DQB1*0302. The father had CSS 5 years before the onset of WG in his son. To our knowledge, the aggregation of CSS and WG in members of the same family has not been reported previously.

Familial clustering of systemic vasculitides has been described, usually with the simultaneous or later occurrence in the same family of a single type of vasculitis, such as GCA[4,5], Takayasu's arteritis[6,7], PAN[8,9], WG[10-16], MPA[16,17], and pANCA glomerulonephritis[21,22]. The association of 2 different vasculitides, such as PAN and WG, has also been reported[15]. The most common type of familial recurrence of WG is among siblings[10-13,15,22]. However, other modalities of familial aggregation of WG have been observed, such as mother–daughter[14], father–daughter[15], and second and fourth-degree related family members[16]. Interestingly, we observed an unusual familial clustering of 2 different systemic vasculitides between a father and son.

The familial association of systemic vasculitides suggests that genetic factors may confer susceptibility to these diseases[23]. HLA-B8[24] and DR2[25] were shown to be associated with WG, but the HLA typing studies did not give conclusive results[23]. It is noteworthy that our patients, sharing the HLA haplotype A*03, B*07, C*w07, DRB1*0404, DQB1*0302, developed different systemic vasculitides 5 years apart. Besides the genetic predisposition, other factors are needed to trigger the disease process[15]. The observation of identical twins discordant for WG[26] or its occurrence among unrelated members of the same family[27], and the development of WG and other ANCA associated vasculitides in subjects exposed to silica[22,28,29], suggest that environmental factors may be involved. Infectious agents may also have a role in the WG etiology, and mainly in triggering its relapses[30]. In CSS, many patients have a history of atopy, and different putative triggering factors have been identified[31]. Because our patients had upper or lower airway disease and both lived in a city, we can also hypothesize a role for environmental factors, such as air pollution.

The hypothesis that environmental agents may trigger the disease in genetically predisposed subjects implies variations in genes encoding for the proteins crucial for the immune response regulation[32]. Beyond the major histocompatibility complex, other immune response gene regions, such as those encoding for Fcγ receptors, pro- and antiinflammatory cytokines, costimulator molecules, T cell receptor, immuno-

globulins, CD40-CD40L, and Fas-FasL, may be involved in the pathogenesis of the systemic vasculitides[32]. In this respect, it has been shown that GCA and a strictly related condition, such as polymyalgia rheumatica, are associated with the tumor necrosis factor (TNF) alleles, TNFA2 and TNFB3, respectively, independently of any HLA-DRB1 association[33]. In addition, another genetic factor implicated in PMR/GCA susceptibility may be the interleukin-1RN*2 polymorphism of the interleukin-1Ra gene[34], whereas the G/R 241 polymorphism of the adhesion molecule ICAM-1 gene may be a genetic risk factor in some[35] but not in other[36] populations.

WG is associated with polymorphism of the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) gene, but not of TNF-α and interleukin 1ß[37] or IL-4[38] genes. CTLA-4, a counterreceptor for the B7 family of costimulatory molecules, plays a critical role in downregulating T cell activation and in maintaining immunologic homeostasis[39]. The polymorphism of the CTLA-4 gene observed in WG and the lack of its negative immune modulation may account for an excessive T cell antigenic activation, contributing to WG vascular inflammation and tissue destruction[37]. Moreover, a significant shift to genotype AA of the IL-10 polymorphism[40] and a CA repeat polymorphism of the IL-10 gene, *IL-10.G*[38], as well as a trend to genotype CG for transforming growth factor-ß1[40] have recently been reported in WG. Similar immunogenetic studies are lacking in CSS.

In this complex scenario, we describe the occurrence, in a 5 year period, of CSS and WG in 2 first-degree relatives sharing the HLA haplotype A*03; B*07; C*w07; DRB1*0404, DQB1*0302. Although they were exposed to the same environmental factors and shared a similar genetic background, they suffered from close but clinically different systemic vasculitides. This could be explained assuming that both diseases have a partial common polygenic background and that the son has inherited a common HLA haplotype (HLA-A*03; B*07; C*w07; DRB1*0404; DQB1*0302) and other susceptibility genes from the father. The HLA haplotype (HLA-A*01; B*1517; DRB1*1501, DQB1*0602) and other genes inherited from the mother could have had a modifying effect, producing a different clinical phenotype in the same environmental context.

Considering the interaction of both genetic predisposition and environmental influences, such familial clustering between father and son of 2 different systemic vasculitides, 5 years apart, seems to underline a predominant pathogenic role of the genetic factors. Further studies are needed to understand the etiology and pathogenesis of the systemic vasculitides.

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