Case Report

Hypocomplementemic Urticarial Vasculitis, Jaccoud's Arthropathy, Valvular Heart Disease, and Reversible Tracheal Stenosis: A Surfeit of Syndromes

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ABSTRACT. We describe a patient who, during 29 years of observation, manifested polyarthralgia and polyarthritis leading to progressive deformity of the joints of hands and feet (without loss of cartilage or erosion of bone); persistent urticaria made worse by cold and accompanied by hypocomplementemia; and progressive cardiac valvular disease with mitral and aortic stenosis and regurgitation. In 1996, she developed subglottic tracheal stenosis that resolved by the end of 1997 without a change in treatment, which has consisted of low dose azathioprine, glucocorticoid, and nonsteroidal antiinflammatory drugs. Tests for cryoprecipitable protein, antineutrophil cytoplasmic antibodies, antinuclear antibody, and rheumatoid factor were negative. Skin biopsy was consistent with "leukocytoclastic vasculitis." The pathogenesis of this remarkable combination of syndromes is unknown. (J Rheumatol 2001;28:383–6)

Key Indexing Terms:
HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS JACCOUD'S ARTHROPATHY
VALVULAR HEART DISEASE

Palazzo, *et al*[1] described 3 patients with Jaccoud's arthropathy, hypocomplementemic urticarial vasculitis syndrome (HUVS), and cardiac valvulopathy. A fourth patient with this unusual combination of rare syndromes has been reported[2]. We describe a 54-year-old white woman, followed since 1971 for clinical manifestations of Jaccoud's arthropathy, HUVS, and cardiac valvulopathy. She also developed reversible subglottic tracheal stenosis.

CASE REPORT

In 1971, at age 27 years, the patient presented with a 2 month history of pain in the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands, and the heel and toes of both feet. The legs were covered with urticarial papules. The rash worsened on exposure to cold; an ice cube test resulted in a urticarial lesion. Skin biopsies of the leg lesions were performed in 1971 and 1972. Both showed extensive fibrinoid necrosis of vessels constituting the cutaneous vascular plexus. Neutrophilic debris surrounded all affected vessels. A diagnosis of leukocytoclastic vasculitis was made.

Treatment with prednisone 20 mg daily was begun. Both the arthralgia and the skin lesions resolved with this regimen. Attempts to reduce the dose of prednisone led to recurrence of rash and joint symptoms. Throughout her course, hives occurred on a daily basis and were most extensive on the lower extremities, buttocks, and trunk. Hives tended to persist 24 to 48 h, but left no residua on clearing. Treatment with prednisone, 10 mg daily or every other day, was required to keep the rash under moderate control. Antihistamines failed to control the hives.

During the subsequent years, arthralgia and arthritis affected primarily the PIP and MCP joints and the interphalangeal and metatarsophalangeal joints of the feet. Radiographs showed fusiform swelling of the MCP joints without loss of joint space or bony erosion. Despite addition of low dose azathioprine, 50 mg per day, and tolmetin 400 mg twice a day, joint symptoms persisted and extensive deformities of the hands and feet developed. By 1977, she had developed marked ulnar deviation, swan neck, and boutonniere deformities, necessitating surgical correction the following year. The inflammatory component of the joint disease was maintained under moderate control with continuation of prednisone, azathioprine, and tolmetin. Figure 1 shows a radiograph of the hands taken in 1997.

In 1971, a grade 2/6 systolic ejection murmur was heard at the left sternal border. By 1978, she was noted to have a grade 3/6 systolic murmur most prominent over the left 4th and 5th intercostal spaces adjacent to the sternum. A diastolic murmur was also heard. An echocardiogram showed mild aortic regurgitation and stenosis. Serial echocardiograms over the subsequent decades showed gradual progression of valvular disease. By 2000, she had mild mitral stenosis and moderate mitral regurgitation, moderate aortic stenosis and regurgitation, moderate tricuspid regurgitation, and trace pulmonic regurgitation. To date, there has been no clinical evidence of congestive heart failure.

In 1995, she noted upper retrosternal chest pain, orthopnea, and "very noisy" respiration. A chest radiograph showed narrowing of the trachea in the subglottic region; a tomogram of the neck is shown in Figure 2. Rigid bronchoscopy of the airway showed a fibrous, circumferential obstruction in the subglottic region. Dilatation was unsuccessful. Surgical intervention was recommended, but was declined by the patient. During the subsequent 2 years, her breathing gradually improved. A lateral radiograph of the neck, in January 1999, showed a normal epiglottis and no evidence of tracheal narrowing.

Laboratory studies. The hemoglobin concentration, total and differential leukocyte count, platelet count, blood urea nitrogen, serum creatinine, and urinalysis have remained normal throughout the illness. Antineutrophil cyto-

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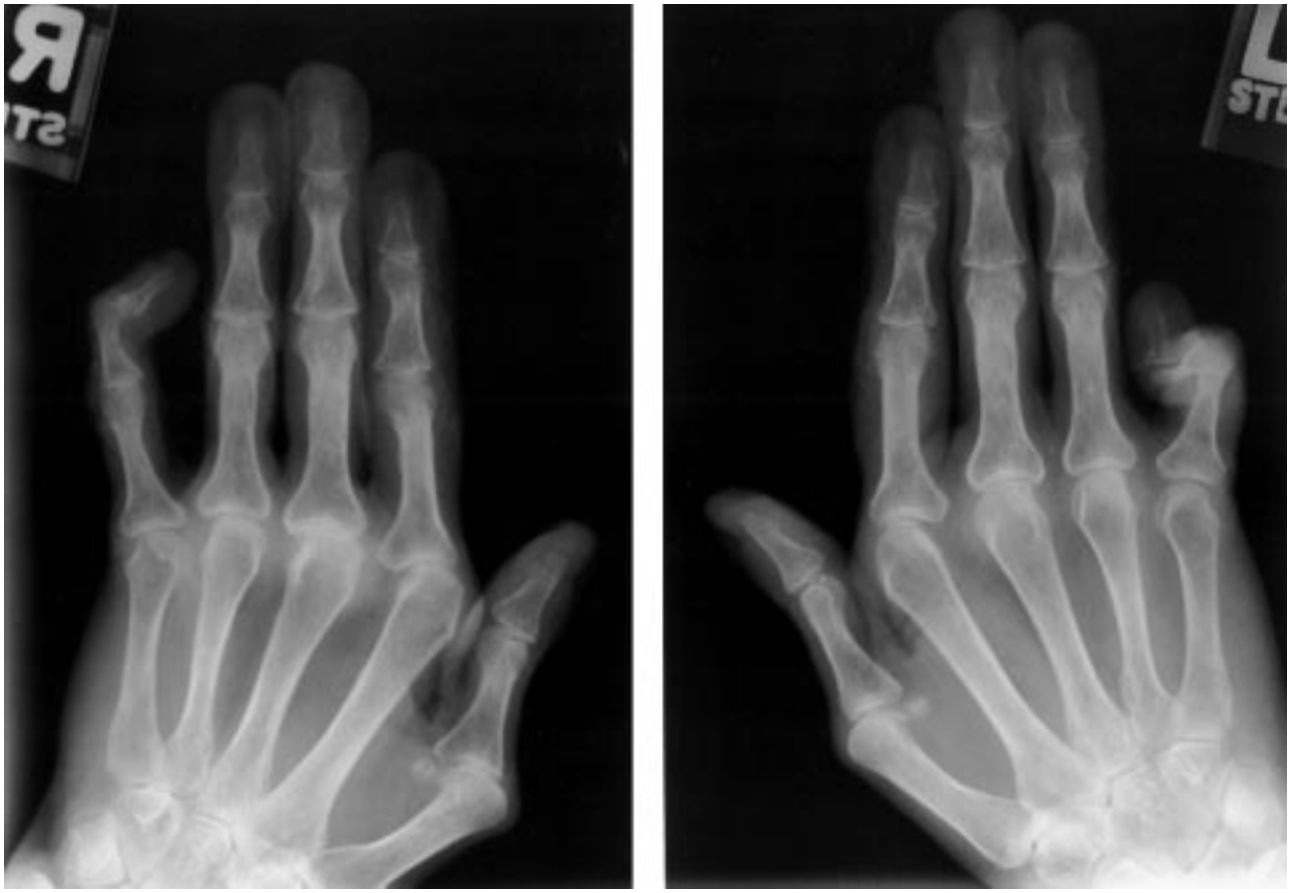

Figure 1. Hand radiographs taken November 1997. Despite previous surgical correction of boutonniere and swan neck deformities (1979), there is swan neck deformity of the left 5th digit and a flexion deformity of the right 5th digit. There is no evident cartilage erosion of the joints. The findings are consistent with the diagnosis of Jaccoud's arthropathy.

plasmic antibody, antinuclear antibody, anti-dsDNA antibody, rheumatoid factor, and cryoprecipitable protein were not detected during 29 years of monitoring. In July 1997, the concentration of immunoglobulin was: IgG 1050 mg/dl (normal 614 to 1295), IgA 219 mg/dl (69 to 309), and IgM 112 mg/dl (53 to 334). Erythrocyte sedimentation rate (ESR) varied between 7 and 26 mm/h (normal 1 to 25).

The total complement activity was normal (CH50 150–250 U/ml) from 1971 to 1973 and became undetectable or markedly reduced from 1974 to the present. The third component of complement, C3, was 175 mg/dl (86–184) in 1972 and became markedly reduced thereafter.

C4 was first measured in 1973 when it was undetectable. C4 remained undetectable or markedly reduced in concentration from 1973 to the present. In November 1998, the 3 components of C1 were measured. The level of all 3 was reduced: C1q 41.4 mg/dl (normal 82–106), C1r 50.6% of standard (normal 61–162), and C1s 53.9% of standard (normal 59–297). The serum was also found to be negative for the presence of anti-C1q antibody (the latter measurements were performed using purified C1q- and collagen-like segment of C1q coated ELISA plates in the Complement Laboratory of the National Jewish Medical and Research Center, Denver, CO, USA). Assays for detection of immune complexes were performed in February 1999. The C1q binding assay showed a value of 4 µg equivalents per ml (normal < 4) and the Raji cell assay showed 24 µg equivalents per ml (normal < 24); thus both values were at the upper end of the normal range (C1q binding assay and Raji cell assay performed at MetPath, Teterboro, NJ, USA).

DISCUSSION

Hypocomplementemic urticarial vasculitis syndrome (HUVS) was first described in 1973 by McDuffie, *et al*[3], who observed 4 patients with recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions associated with synovitis and sometimes abdominal distress. The symptoms were accompanied by hypocomplementemia; low levels of both early (C1, C2, C4) and late reacting (C3 and C5–C9) components of complement were found during acute episodes. Since the initial report, over 75 patients with repeated episodes of persistent urticaria and associated leukocytoclastic vasculitis and hypocomplementemia have been described[4]. Angioedema, ocular inflammation, glomerulonephritis, and obstructive pulmonary disease have been added to the list of prominent clinical characteristics of HUVS[5]. A low molecular weight C1q precipitin, identified as an IgG antibody directed against the collagen-like portion of C1q[6], was found to be closely associated with HUVS, being detected in up to 80% of cases in one large series[4].

Our patient (Table 1; case 5) qualifies for the diagnosis of HUVS based upon the clinical findings of persistent urticarial vasculitis and arthritis, as well as the laboratory findings of decreased total complement and complement components, including C1q, as well as skin biopsies showing leukocytoclastic vasculitis. Like the other 4 cases shown in Table 1, she

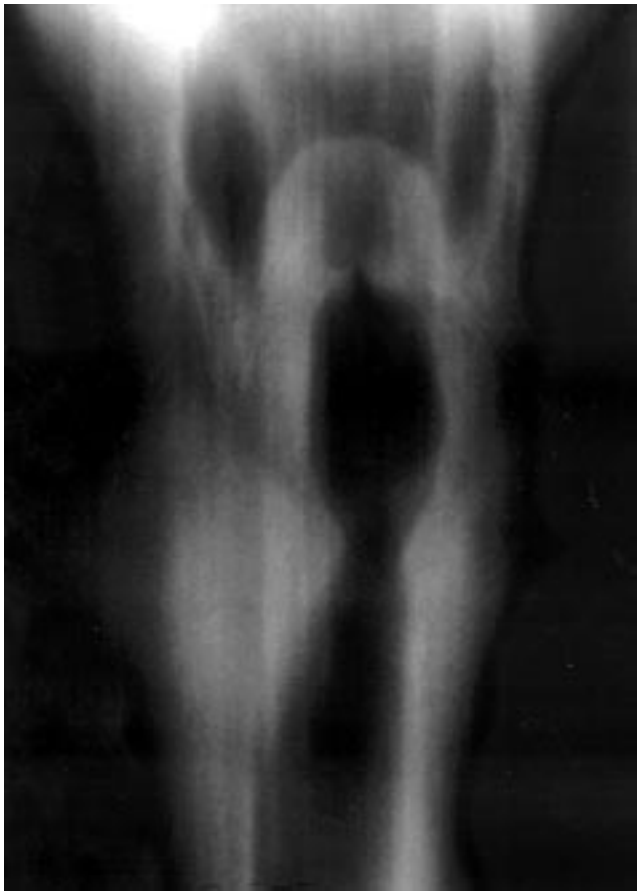

Figure 2. Tomogram of the neck, performed in 1995, shows a smoothly tapering tracheal stenosis about 3.5 cm distal to the true vocal cords. The minimal diameter of the trachea measures 8 mm. The stenotic segment is about 3 cm in length.

Table 1. Clinical and laboratory findings of 5 cases.

	Patient				
	1	2	3	4	5
Urticaria	+	+	+	+	+
Arthralgia	+	+	+	+	+
Vasculitis	+	+	+	+	+
Ocular inflammation	–	+	+	–	–
Abdominal pain	+	+	+	+	–*
Neurologic signs	–	–	–	–	–
Nephrologic signs	–	–	–	–	–
Aortic regurgitation	+	+	+	+	+
Aortic stenosis	–	–	–	–	+
Mitral regurgitation	+	+	+	+	+
Mitral stenosis	+	–	–	–	+
Tricuspid regurgitation	–	–	–	+	+
Jaccoud's arthropathy	+	+	+	+	+
Tracheal stenosis	–	–**	–	–	+
CH50 (60–140 U/ml)	22	< 10	14	2	7***
C3 (75–170 mg/dl)	Low	23	26	28	25
C4 (15–40 mg/dl)	12	4	7	< 10	10
ANA	–	–	–	–	–
Anti-DNA	–	–	–	–	–
C1 esterase inhibitor	NL	NL	NL	High	ND
Hepatitis B Ag	–	–	–	ND	ND
C1q precipitin	–	–	–	–	–
Cryoglobulinemia	–	–	–	–	–

*Patient had 1 episode of abdominal pain leading to surgery for appendicitis; appendix was normal on histologic examination.
**Patient reported to have laryngeal edema: details not given.
***Complement activation enzyme immunoassay units; normal 63–145 units/ml; values from August 1999 are shown for our patient (Patient 5).
NL: normal level; ND: not tested.

did not have detectable antibody to C1q. The laboratory and radiological data do not provide evidence for an alternative diagnosis, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

During the early years of this patient's illness, normal complement levels were found despite active disease. In later years, complement levels were consistently reduced even during periods of improvement in skin and joint disease. Wisnieski, *et al* found that in most patients with HUVS, serum complement levels rose and anti-C1q antibody decreased during sustained, complete pharmacological suppression of skin disease[4]. One of their patients, however, remained markedly hypocomplementemic despite suppression of skin lesions. Perhaps hypocomplementemia occurs only during acute attacks of urticarial vasculitis early in the disease, but becomes persistently decreased later due to constant activation/depletion of complement and/or hyposynthesis. It has been suggested that HUVS may be the final manifestation in a spectrum of disease that begins with idiopathic urticarial vasculitis and normal serum complement levels[4].

The clinical features of HUVS and presence of anti-C1q antibodies in SLE suggest that HUVS is a syndrome related to SLE[4]. Siegert, *et al* showed that in SLE there was a positive correlation between the titer of antibody to C1q and evidence of nephritis, dermatitis, hypocomplementemia, antibody to native DNA, and circulating immune complexes[7]. These investigators were not able to confirm a direct influence of anti-C1q antibody on complement activation *in vitro* or *in vivo*[8]. It is assumed that in both SLE and HUVS[3] complement activation is mediated by immune complexes; the identity of these complexes in HUVS is not known. The failure to detect anti-C1q antibodies in the 5 hypocomplementemic patients listed in Table 1 provides further evidence against a primary role of anti-C1q antibody–C1q antigen complexes in activation of the complement system.

Jaccoud's arthropathy, also known as "chronic post-rheumatic fever arthropathy," is a rare, slowly progressive process that deforms the fingers and occasionally the toes[9]. The arthropathy is attributed to repeated inflammation of the fibrous articular capsule of the small joints of the hands and feet. There is no cartilage loss or erosion of juxtaarticular bone. Jaccoud's arthropathy may develop in patients with SLE, and rarely in scleroderma, Sjögren's syndrome, and mixed connective tissue disease[1]. Our patient had no history of rheumatic fever, and although the distinction between

hypocomplementemic urticarial vasculitis and SLE is often difficult, the absence of serologic findings of SLE and of glomerular disease during a 29 year course make it very unlikely that the patient has SLE.

Valvulopathy has been noted in several systemic rheumatic diseases[10]. Echocardiographic studies in patients with SLE, ankylosing spondylitis, and RA have revealed that valvular disease is frequently present and associated with substantial morbidity and mortality[10]. All 5 patients shown in Table 1 had aortic and mitral regurgitation accompanied by aortic stenosis in one and mitral stenosis in 2 cases. Surgery to replace damaged valves was performed in Patients 2 and 4; histologic examination showed inflammation and fibrosis of aortic and mitral valves in Case 2 and vasculitis with fibrinoid necrosis and a mixed cellular infiltrate in Case 4. Prior to the reports of Palazzo, *et al*[1] and Hong, *et al*[2], valvular heart disease appears not to have been noted in patients with HUVS.

The etiology of the transient tracheal stenosis that developed in our patient is uncertain. There was no history of preceding external or internal trauma, specifically she had not been intubated or subjected to surgery on the neck. Upper airway obstruction may be found in several connective tissue diseases, including relapsing polychondritis, RA, SLE, scleroderma, and Sjögren's syndrome[11]. Additionally, Grillo, *et al* have described idiopathic laryngotracheal stenosis[12]. Of the 49 patients in their series, 46 had involvement of the subglottic larynx and all required either surgical or medical intervention[12]. There have been no reports of the reversible subglottic stenosis accompanying our patient's constellation of syndromes; in some cases of relapsing polychondritis, tracheal obstruction responds to treatment with antiinflammatory agents[13].

An immune response to common elements in cardiac valves, capsular tissue of certain joints, trachea, and C1q might constitute the basis for the combination of syndromes seen in the 5 cases listed in Table 1. None of the 5 cases, however, had detectable antibody to intact C1q or, in our case, the collagen-like region of C1q. The possibility that antibody to the collagen-like structure of C1q is involved cannot be completely excluded because the determinants might not be detected in intact C1q or the collagen-like region of C1q, but may instead be an occult determinant or neoantigen that is only revealed after activation of C1q or its degradation by enzymes involved in inflammation[14]. Further, it is possible that a collagen or a collagen-like molecule is the target involved, but the damage may be mediated by cells of the immune system rather than by antibody. The latter possibility might account for the tissue injury observed, but would not explain the persistent complement activation/depletion observed in the 5 patients with this unusual constellation of syndromes.

We describe a fifth case of hypocomplementemic urticarial vasculitis, Jaccoud's arthropathy, and valvular heart disease. The case was complicated by reversible tracheal stenosis. Like 4 other cases, this patient had no detectable antibody to the C1q component of complement.

Added in proof

After submission of this report, progression to critical aortic stenosis necessitated replacement of the aortic valve with a St. Jude prosthetic valve. The native valve surface showed linear subendothelial infiltrate of acute and chronic inflammatory cells, with fibrin matrix deposition. At a deeper level, healing subacute valvulitis was seen. These changes were superimposed on chronic fibrocalcific valvular degeneration.

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