Successful Treatment of Renal Amyloidosis Due to Familial Cold Autoinflammatory Syndrome Using an Interleukin 1 Receptor Antagonist

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Familial cold autoinflammatory syndrome (FCAS) is an autosomal dominant disorder characterized by episodic fever, arthralgias, conjunctivitis, and rash triggered by cold exposure. FCAS is rarely associated with progressive renal insufficiency caused by renal amyloidosis. The genetic defect in patients with this disorder is caused by a mutation in the gene encoding the protein cryopyrin, leading to uninhibited activation of systemic inflammation through specific cellular signaling with increased production of a number of key cytokines, including interleukin 1. We describe the successful treatment of a patient with renal amyloidosis caused by FCAS by using a novel interleukin 1–receptor antagonist. Use of specific anticytokine therapy may be a new paradigm in the treatment of patients with renal amyloidosis caused by systemic inflammatory diseases.

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INDEX WORDS: Amyloidosis; anakinra; familial cold autoinflammatory syndrome; interleukin 1.

Familial cold autoinflammatory syndrome (FCAS) is an autosomal dominant inflammatory disease categorized by recurrent intermittent episodes of rash, fever, arthralgia, and conjunctivitis after generalized exposure to cold. Attacks usually occur 1 to 3 hours after cold exposure and last less than 24 hours. The cause of FCAS is a defect in a protein termed cryopyrin that results from a mutation in the *CIAS1* gene (also known as *NALP3/PYPAF1*) localized on chromosome 1q44.[1] Defective cryopyrin causes enhanced expression of a number of key cytokines, including interleukin 1 (IL-1), leading to systemic inflammation. Muckle-Wells syndrome and chronic infantile neurological cutaneous articular syndrome are 2 inflammatory conditions also resulting from mutations in *CIAS1*. Although occurring in up to a third of patients with Muckle-Wells syndrome, only a small percentage of patients with FCAS develop progressive chronic kidney disease secondary to AA renal amyloidosis. The main therapy for patients with FCAS has been supportive care with nonsteroidal anti-inflammatory drugs or corticosteroids for local symptomatic relief, but previously there was no definitive treatment for the disease. Recently, several patients with *CIAS1* genetic mutations were treated with anakinra (Kineret; Amgen, Thousand Oaks, CA), an IL-1 receptor antagonist resulting in significant clinical attenuation and prevention of inflammatory episodes.[2-4] Characteristic upregulation of inflammatory markers also was prevented in patients treated with anakinra.[3] We present the case of a patient with FCAS complicated by renal amyloidosis and progressive renal insufficiency treated with anakinra who had a marked decrease in proteinuria and attenuation of progressive renal failure.

CASE REPORT

A 61-year-old white woman with FCAS was referred to the Nephrology Service in June 2002 at the University of California Davis Medical Center for evaluation of proteinuria. Pertinent past medical history included an episode of poststreptococcal glomerulonephritis at age 14 years, hypertension with left ventricular hypertrophy, long-term nonsteroidal anti-inflammatory use of oxaprozin (Daypro; Par Pharmaceutical, Woodcliff Lake, NJ), anemia, migraine headaches, and hypothyroidism. Since birth, she had experienced typical FCAS symptoms of fever, rash, malaise, conjunctivitis, and arthralgias after cold exposure. FCAS diagnosis was confirmed by genetic testing

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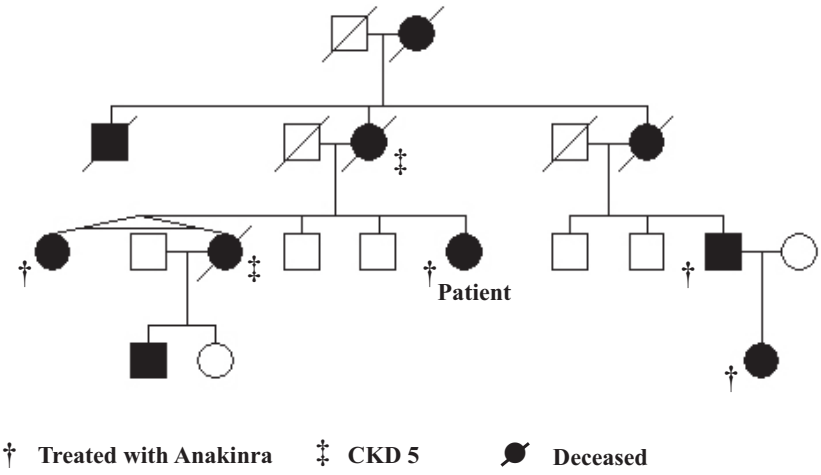

Figure 1. Family pedigree shows FCAS-affected family members and those receiving anakinra therapy. The patient described in this case report is noted.

performed at the University of California, San Diego, showing an L353P mutation. Numerous family members were afflicted with the same condition (Fig 1), some of whom developed stage 5 chronic kidney disease.

One month before referral to the nephrology service, the nonsteroidal anti-inflammatory drug was discontinued. She previously was maintained on 25 mg of the angiotensin receptor blocker losartan (Cozaar; Merck & Co, Whitehouse Station, NJ) for hypertension. Initial physical examination was significant for hypertension, with blood pressure of 162/82 mm Hg, 1^+ bilateral lower-extremity pitting edema, and an indurated papular rash on both arms. Urinalysis was notable for dipstick proteinuria with protein of 300 mg/dL with bland urinary sediment on microscopic examination. Subsequent serological testing included hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, antineutrophil cytoplasmic autoantibody, human immunodeficiency virus, complement level, cryoglobulins, and both serum and urine protein electrophoresis. All test results were unremarkable, except for urine electrophoresis, which showed an abnormal band in the beta region quantified at 7 mg/dL. Follow-up immunofixation testing was negative for a monoclonal protein.

The patient initially was treated with colchicine based on its anti-inflammatory effects in patients with familial Mediterranean fever. Losartan dose was titrated to 100 mg/d, and the patient was started on paroxetine (Paxil; GlaxoSmithKline Inc, Philadelphia, PA) because another family member noted a decrease in symptomatic inflammatory episodes while administered this medication. Initially, the patient did not consent to a renal biopsy. Treatment with colchicine did not alter her proteinuria and was tolerated poorly because of worsening of her migraine headaches. Paroxetine did not decrease the frequency of her symptoms. Three months after the initial consultation, the patient underwent renal biopsy because of worsening proteinuria and an increase in creatinine level from 0.9 mg/dL (80 μmol/L) to 1.2 mg/dL (106 μmol/L). Renal biopsy was definitive for a diagnosis of

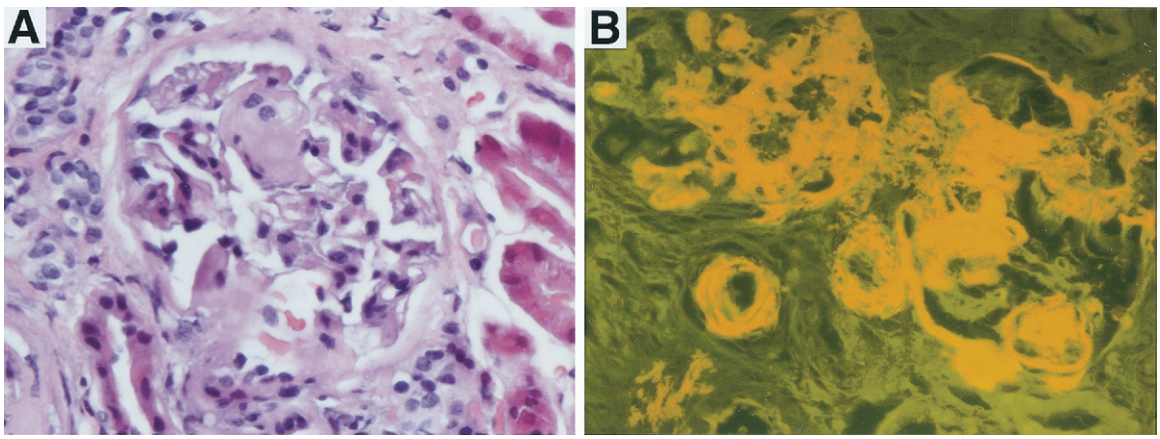

Figure 2. Photomicrographs of the patient's renal biopsy stained with hematoxylin and eosin (A) and viewed under immunofluorescence microscopy stained with Congo Red (B). Amorphous deposits are noted in the glomerulus in Fig 2A and positive immunofluorescence is noted in 2 glomeruli and arterioles consistent with the presence of amyloid deposits in Fig 2B. (Original magnification $\times$400.)

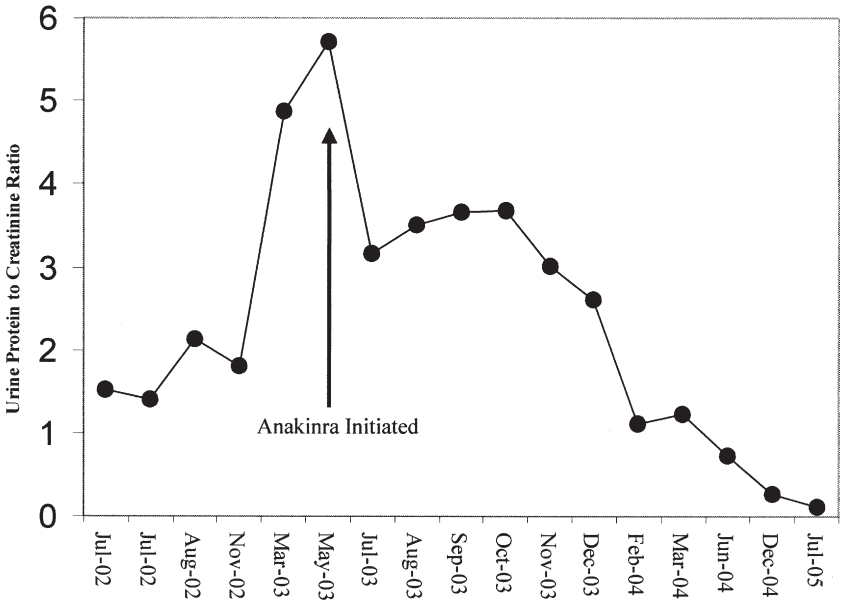

Figure 3. Spot urine protein-creatinine ratios before and after treatment with anakinra. Note the marked decrease in proteinuria associated with anakinra therapy.

amyloidosis (Fig 2). Steroid therapy was offered to the patient, but she declined because of the side-effect profile. During the next 9 months, the patient's proteinuria worsened to protein of almost 6 g/d, and serum creatinine level increased to 1.3 mg/dL (115 μmol/L).

In March 2003, after submitting a request to the University of California Davis Medical Center Institutional Review Board, approval was granted for compassionate use of the recombinant human IL-1 receptor antagonist anakinra for the patient based on preliminary data for its use in patients with Muckle-Wells syndrome.[2] In June 2003, treatment with anakinra was started at a dose of 100 mg/d subcutaneously, but was decreased to 100 mg every other day because of the development of leukopenia (white blood cell count, $3.1 \times 10^3/\mu$L [3.1×10^9/L]). During the next 12 months, proteinuria decreased to protein less than 1 g/d, serum creatinine level remained stable at 1.2 mg/dL (106 μmol/L; Fig 3), and white blood cell count has remained within the normal range. Her lifelong symptoms of FCAS improved significantly within days of starting therapy and resolved completely with continued therapy.

DISCUSSION

FCAS originally was described in 1940,[5] and, until recently, a molecular understanding of the mechanism of disease was lacking. This disorder is exceptional enough that it was not until 2001 that a sizeable population was studied systematically to define disease phenotype and generate proposed diagnostic criteria (Table 1).[6] A study of 6 families consisting of 45 subjects showed key phenotypic characteristics, including age of onset within the first 6 months of life and recurrent fevers, chills, arthralgias, conjunctivitis, and rash. Although more commonly seen in patients with Muckle-Wells syndrome, amyloidosis was described in a few families with FCAS.

Typical laboratory features associated with FCAS include leukocytosis[7] and elevated erythrocyte sedimentation rate. As with other inflammatory conditions, levels of acute-phase reactants, including C-reactive protein and haptoglobin, may be increased.[8] Patients with FCAS also show a large increase in serum IL-6 levels after cold challenge.[3] Skin biopsy shows a dense polymorphonuclear leukocytic infiltrate without evidence of histamine release.[9] Historically, there have been few effective treatments for patients with FCAS, although anabolic steroids, corticosteroids, and colchicine have been used with limited success.[7,10,11]

Hoffman et al[1] identified the *CIAS1* gene on chromosome 1q44 as the gene responsible for both FCAS and Muckle-Wells syndrome. More than 40 *CIAS1* mutations were reported in patients with FCAS, Muckle-Wells syndrome, and chronic infan-

Table 1. Proposed Diagnostic Criteria for FCAS

1. Recurrent intermittent episodes of fever and rash that primarily follow natural, experimental, or both types of generalized cold exposures
2. Autosomal dominant pattern of disease inheritance
3. Age of onset <6 mo
4. Duration of most attacks <24 h
5. Presence of conjunctivitis associated with attacks
6. Absence of deafness, periorbital edema, lymphadenopathy, and serositis

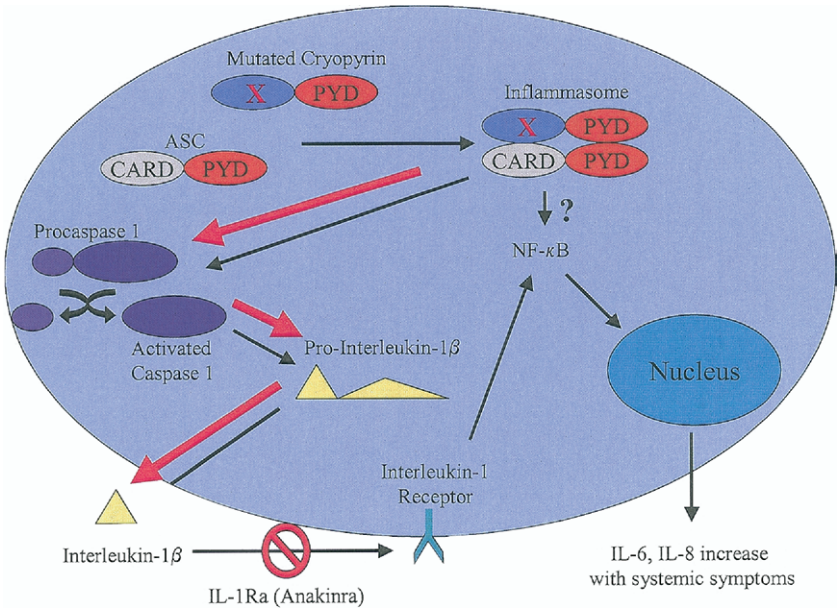

Figure 4. Mutated cryopyrin (denoted by X) interacts with ASC through PYRIN-PYRIN domain interactions free of regulatory control as a result of the mutation. This results in amplified activation of downstream mediators through the normal signaling cascade through procaspase 1 and pro–IL-1β. Anakinra effectively competes with IL-1β for the IL-1 receptor, thereby blocking release of the inflammatory cytokines that lead to typical FCAS symptoms. Abbreviations: PYD, PYRIN domain; ASC, apoptosis-associated specklike protein with a caspase recruitment domain; NF-κB, nuclear factor-κB; IL-1Ra, IL-1 receptor antagonist. (Adapted from The Lancet, volume number 364, Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist, Hoffman HM, Rosengren S, Boyle DL, et al, pp 1779-1785, copyright 2004, with permission from The Lancet.)

tile neurological cutaneous articular syndrome. Central to each of these disorders is uninhibited activation of the inflammatory cascade through specific cellular signaling (Fig 4). *CIAS1* encodes a protein termed cryopyrin. Cryopyrin interacts with another protein termed "apoptosis-associated specklike protein" with a caspase recruitment domain through PYRIN-PYRIN interactions in a complex known as the inflammasome. The PYRIN domain is a protein motif identified in proteins involved in apoptotic and inflammatory pathways.[11,12] Activation of the inflammasome by a number of infectious and noninfectious triggers leads to the cleavage of procaspase to activated caspase 1 and the eventual cleavage of pro–IL-IB, allowing for the release of active IL-1B.[13] IL-1B then is available to bind to the IL-1 receptor and further mediate inflammatory cytokine production.[14] In vitro evidence suggests that the inflammasome activates nuclear factor-κB directly, leading to the production of a number of proinflammatory cytokines, including IL-6 and IL-8. Additional in vitro evidence suggests that mutations in cryopyrin cause a constitutively active or hyperresponsive inflammasome, resulting in increased cytokine release and systemic inflammatory symptoms.

The *CIAS1* mutation L353P was identified in approximately 90% of reported North American patients with FCAS and is caused by a common ancestor. The family described in this report has the same mutation, but is not related to the other families. Whereas several members of the family described in this report developed renal disease, presumably caused by amyloidosis, this complication was not described in other L353P families. In addition, only 1 sister of a set of identical twins in this family developed amyloidosis, reaffirming the complex cause of amyloidosis.

Anakinra is a recombinant IL-1 receptor antagonist protein currently approved for use in patients with rheumatoid arthritis for whom treatment has failed with 1 or more other disease-modifying antirheumatic drugs. Preliminary results for anakinra use in patients with rheumatoid arthritis are encouraging; however, its efficacy in patients with diseases caused by mutations in *CIAS1* is astonishing. In almost every case reported, there is near resolution of disease symptoms within 24 to

48 hours of the initial injection.[2,3] Although rare, the hereditary periodic fever syndromes provide a unique opportunity to study inflammatory pathways. This case report exemplifies the significant role for chronic inflammation in the development of AA amyloidosis and shows a unique disease-specific therapy previously not available. This patient has now received anakinra for 3 years, and to our knowledge, this is the longest treatment duration known. More importantly, this patient has gained a quality of life she never thought possible. Performing a repeated renal biopsy had been considered to assess histological change after anakinra therapy, but given the risks of renal biopsy and her clinical improvement, it was considered not to be clinically indicated. Follow-up echocardiogram confirmed persistent left ventricular hypertrophy without evidence of cardiac amyloidosis. The successful treatment of renal amyloidosis through blockade of IL-1 shows that specific anticytokine treatment may provide directed therapies for other conditions associated with chronic systemic inflammation.

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