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Resolution of Severe Pyoderma Gangrenosum in a Patient with Streaking Leukocyte Factor Disease after Treatment with Tacrolimus (FK 506)

Kareem Abu-Elmagd, MD; David H. Van Thiel, MD; Brian V. Jegasothy, MD; Jerry C. Jacobs, MD; Patricia Carroll, MD; Horacio Rodriquez-Rilo, MD; Cheryl D. Ackerman, MD; John J. Fung, MD, PhD; and Thomas E. Starzl, MD, PhD

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Severe, lifelong, unresolving pyoderma gangrenosum occurs in association with recurrent episodes of sterile pyoarthrosis and the presence of a serum factor (called "streaking leukocyte factor") (1) responsible for enhancing random migration of purified human neutrophils and mononuclear leukocytes in vitro. Pyoderma gangrenosum is only one feature of this unusual disease. Minor trauma of any sort leads to an excessive accumulation of both mononuclear and polymorphonuclear leukocytes in tissue. This causes subcutaneous induration, sterile abscesses, sterile pyoarthrosis, and extensive areas of skin necrosis similar to those occurring in classical pyoderma gangrenosum, except that the lesions are larger and more confluent. The arthritic lesions are characterized by synovial fluid leukocyte counts greater than 100 000/mm^3 and a severe synovitis (1). We describe a patient with the streaking leukocyte factor syndrome who has been treated successfully with tacrolimus (FK 506, Prograf, Fujisawa Pharmaceutical Co., Osaka, Japan).

Case Report

The patient was a 31-year-old white man who has had a lifelong history of recurrent and chronic sterile abscesses involving the soft tissues, skin, and joints, which began in infancy and was shown to be associated with "streaking leukocyte factor" in his serum (1). Because of the hypertrophic and erosive nature of the arthritic process, the patient had surgical procedures on multiple large joints. His history is summarized in Table 1. The patient was referred to the autoimmune clinic at the University of Pittsburgh Medical Center in April 1991 with a well-established clinical, histopathologic,

From the Pittsburgh Transplant Institute and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and Columbia University College of Physicians and Surgeons, New York, New York. For current author addresses, see end of text.

Table 1. Chronology of the Patient's Medical Problems

Infancy	Sterile abscesses at injection sites
Age 2	Chronic sterile pyoarthrosis of the left ankle
Age 4	Chronic sterile pyoarthrosis of the right ankle
Age 7	Right elbow chronic sterile pyoarthrosis; right hip chronic sterile arthrosis with dislocation
Age 8	Right elbow sterile pyoarthrosis and chronic leg ulceration
Age 9	Sterile abscess of the forehead
Age 11*	Bilateral massive leg ulceration
Age 12 to 31	Recurrent leg and thigh ulcerations as well as new ulcer formation in the perineum, groin, and chest wall
Age 13	Severe acne with facial, neck, and chest wall ulceration and scarring
Age 28	Sterile pyoarthrosis with destruction of the right elbow and hip

* Treated since that age with plasmapheresis and different combinations of prednisone (20 to 60 mg/d), tetracycline (2 g/d), thalidomide (300 mg/d), sulfasalazine (3 g/d), and dapsone (200 mg/d).

and serologic diagnosis of this syndrome. Before his referral, he had been treated at Columbia-Presbyterian Medical Center (New York, New York) and the National Institutes of Health with plasmapheresis, high doses of steroids, a wide range of immunosuppressive cytotoxic agents, and thalidomide, but none of these treatments yielded a response.

Laboratory results included normal counts and types of leukocytes, T cells, and T-cell responses to mitogens; a normal nitroblue tetrazolium test; normal in-vitro phagocytosis of yeast by leukocytes as well as normal levels of serum immunoglobulins, complement factors C_{1q}, C_4, C_2, $C_{1\ INH}$, and total hemolytic complement. The laboratory abnormalities the patient had consistently were an anemia of chronic disease (hemoglobin, 90 to 120 g/L); an increased erythrocyte sedimentation rate (35 to 95 mm/h); an increased platelet count (350 to 726 × 10^9/L); increased levels of α_1, α_2, and β globulins; and an increased complement C_3 level (297 to 340 mg/dL [2.97 to 3.40 g/L]).

The hallmark of the disease has been detection of a chemokinetic factor in the patient's serum that caused wild random migration of purified normal human neutrophils and mononuclear leukocytes by up to 200%, which did not influence chemotaxis (1). This factor has continued to be present during a period of 6 years despite various therapeutic attempts (*see* Table 1). The methods used to measure the leukocyte random migration and isolation of the serum factor have been previously described (1).

On 9 May 1991, after Food and Drug Administration and Local Investigational Review Board approvals (the patient gave informed consent), he was started on tacrolimus (FK 506), a new powerful immunosuppressive macrolide antibiotic (2). He received an oral dose of 0.15 mg/kg twice daily. Twelve-hour tacrolimus trough plasma levels were measured with an enzyme-linked immunoassay (3). Dose adjustments were guided by the drug plasma levels, the patient's clinical response (skin and joint lesions), and the biochemical evidence of renal insufficiency (an increase of serum creatinine greater than 2 mg/dL) (4). Because of the presence of a severe, disabling osteoporosis as well as recurrent vertebral compression and stress fractures, preexisting steroid therapy (20 to 60 mg/d) was rapidly tapered after starting tacrolimus treatment to a steroid dose of 5 mg orally every other day. All other therapeutic agents were discontinued before the initiation of tacrolimus therapy.

Full dermatologic and medical examinations were done at each clinic visit. The assessments made included those quantifying pain, subcutaneous induration, erythema, cutaneous ulceration, arthritis, and drainage from the pyoderma gangrenosum lesions. Renal function, serum cholesterol, blood glucose, and electrolyte levels were also monitored.

After 4 weeks, a marked reduction in his pain, lesion erythema, ulcer size, and drainage from lesions was evident. Complete clinical remission and healing of all disfiguring, large open sores was achieved after 12 weeks of tacrolimus (FK 506) therapy (Figure 1). Tacrolimus trough plasma levels were maintained at high levels for the initial 4 weeks (1.5 to 3.8 ng/mL) and subsequently at an average of 1.1 ng/mL. A recent effort to decrease his tacrolimus dosage resulted in low drug plasma levels (< 0.7 ng/mL) and a reappearance of focal subcutaneous areas of induration. These new lesions disappeared completely after an increase in the tacrolimus dose and maintenance of the drug plasma trough level at 1 ng/mL.

The patient had transient trembling, paresthesias, and insomnia with high tacrolimus (FK 506) trough plasma levels. These were accompanied by increases in the serum creatinine and blood urea nitrogen levels to a maximum of 2.4 mg/dL and 51 mg/dL, respectively. A concomitant increase in blood pressure was treated with a calcium-channel blocker and a beta-adrenergic blocking agent. Intermittent hyperkalemia required treatment with fludrocortisone acetate (Florinef, Bristol-Myers Squibb, Somerville, New Jersey). Levels of serum creatinine, blood urea nitrogen, and serum potassium have stabilized at 1.9 mg/dL (168 μmol/L), 28 mg/dL (10.0 mmol/L), and 4.9 mEq/L (4.9 mmol/L), respectively. No clinically significant change has occurred in the levels of blood glucose, cholesterol, or serum triglycerides.

For the first time since birth, the patient does not have the skin lesions and the active joint disease. Moreover, he is now able to resume a full activity schedule. Six months after the start of tacrolimus (FK 506) treatment, a repeated assay of his serum for the streaking leukocyte factor showed an activity level equal to the control serum as well as the buffer solution, which contains 1% albumin and 10% fetal calf serum. The assay method used was identical to that used before tacrolimus therapy (1). Because of the instability of the factor and other logistic problems, it has not been possible to do sequential studies in this patient to determine whether variations in the serum activity of the enhancing factor occur at different tacrolimus doses or drug plasma levels.

Discussion

The streaking leukocyte factor is a proteinaceous factor with a molecular weight of 160 kd that is found in the serum of some patients with recurrent sterile abscesses (1, 5). It is thought to be responsible for pro-

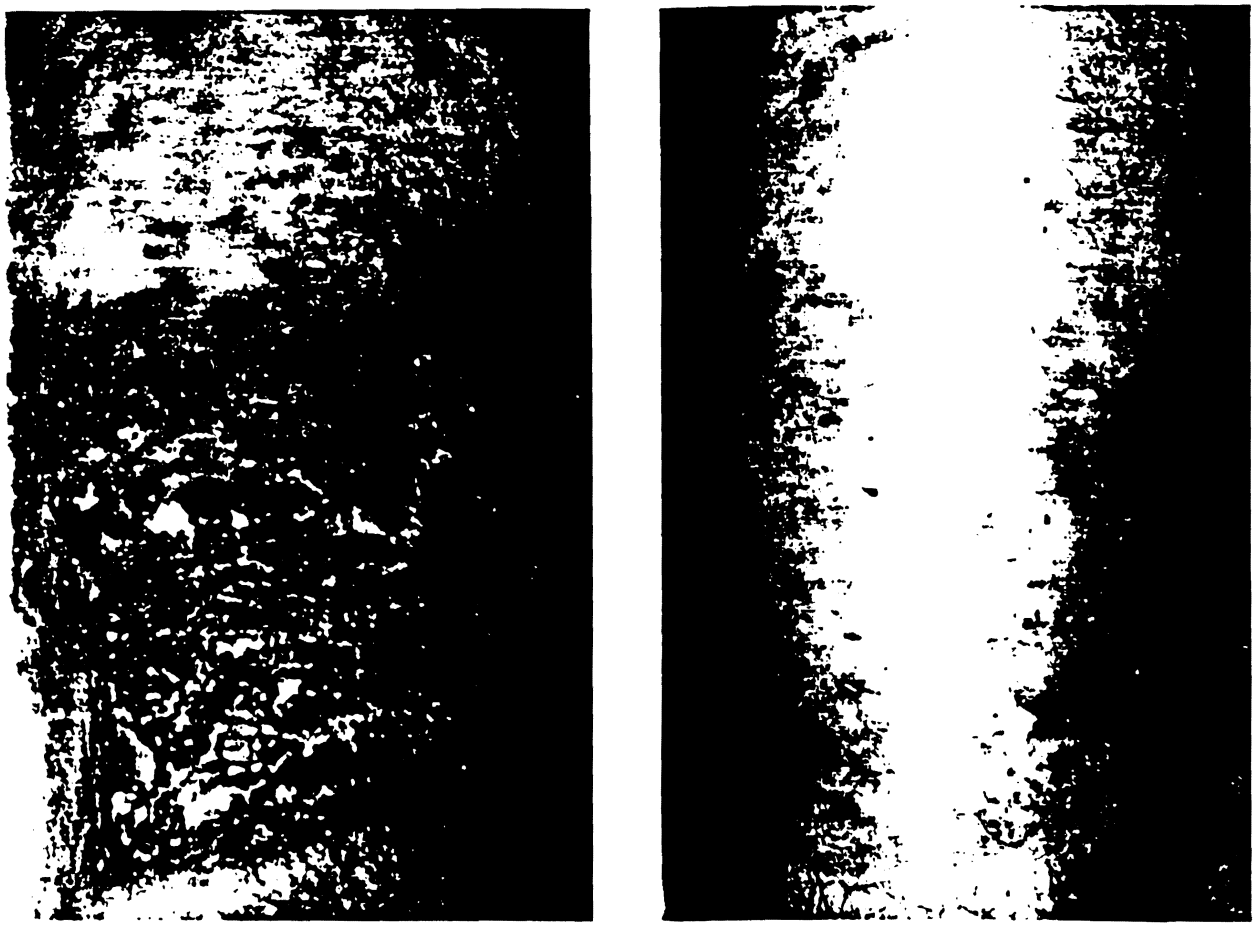

Figure 1. Ulcer in patient with streaking leukocyte factor disease. Left. A large necrotic ulcer on the front of the lower right thigh region. **Right.** Marked improvement and healing of the ulcer was noted during 12 weeks of tacrolimus (FK 506) treatment.

gressive destruction and scarring of the skin and joints because it enhances random migration of polymorphonuclear and mononuclear leukocytes to areas of minor trauma. A fatal instance of this syndrome has been described recently (5).

Although the physical characteristics of this protein are not well known, it is too small to be an immunoglobulin and too large to be a classical cytokine. It is probably mutant secretory protein that has an abnormal effect on circulating leukocytes. The similarities and differences between this abnormal leukocyte-enhancing "streaking" factor and other chemokinetic factors present in normal serum, such as albumin and leukokinesis-enhancing factor, are described elsewhere (6). The action of this abnormal leukocyte migration factor can be inhibited partially by corticosteroids and large doses of tetracycline (7–9). The former agents may either block its action at a receptor site or, more likely, directly modify leukocyte responses so that they no longer react to the factor. Tetracycline probably acts as a nonspecific inhibitor of protein synthesis, limiting the production and secretion of the factor. Neither of these agents was successful in controlling the patient's disease.

Tacrolimus (FK 506) is a novel macrolide antibiotic isolated from the soil fungus *Streptomyces tsukubaensis* (2). The drug has a wide range of immunosuppressive activities, because it inhibits the activation and proliferation of $CD4^+$ T-helper lymphocytes (10). The clinical experience during the previous 3.5 years has shown that a high therapeutic index exists for tacrolimus in patients who have transplanted organs (11) and for patients with either recalcitrant psoriasis or pyoderma gangrenosum (12, 13). Previously there were encouraging results (13) after treating pyoderma gangrenosum; therefore, we decided to use tacrolimus for our patient. Interestingly, after using standard doses of tacrolimus in our patient (who had normal hepatic function), tacrolimus completely eliminated the streaking factor from our patient's serum. This was associated with complete healing, although there is still scarring of the chronic skin ulcers, which had never resolved during the preceding three decades.

The specific mode of action by which tacrolimus (FK 506) might alleviate this syndrome is unclear. However, the failure to detect the serum factor after treatment suggests that its synthesis or release or both was inhibited. This probably re-established the normal physiologic balance between the antagonistic activity of both the leukokinesis-enhancing factor and the cell-directed inhibitor (6). Although it is not known whether tacrolimus has a direct inhibitory effect on leukocyte random mobility and chemotaxis, the drug appears to have no effect on lymphocyte chemoattractant-stimulated movement (14).

The adverse effects caused by tacrolimus (FK 506)

include impairment of renal function, alteration in glucose homeostasis, and neurotoxicity (4). In our patient, the only potentially serious side effects were increases in serum creatinine and blood urea nitrogen levels, which responded quickly to a dose reduction and stabilized at a slightly increased level.

Any child with pyoderma gangrenosum, especially at sites of recent immunizations (15), may have the "streaking leukocyte factor" syndrome. Recognition of this potentially fatal syndrome is essential (5), and when the condition is unresponsive, treatment with tacrolimus (FK 506) should be considered.

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Requests for Reprints: Kareem Abu-Elmagd, MD, Pittsburgh Transplant Institute, 3601 Fifth Avenue, Falk Clinic 5C, Pittsburgh, PA 15213.

Current Author Addresses: Drs. Abu-Elmagd, Van Thiel, Carroll, Rodriquez-Rilo, Fung, and Starzl: Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Drs. Jegasothy and Ackerman: Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.
Dr. Jacobs: Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York 10032.

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