Abstract

Background  Hidradenitis suppurativa is one of the follicular occlusion diseases favoring the flexural areas of the body. Because of the past failure of medical therapy, surgery is today the definitive therapeutic approach. There is a need for effective medical anti-inflammatory therapy to control the disease and minimize the pathologic and socioeconomic consequences of the disease process. Generally the patients fail to respond to topical or systemic antibiotics and retinoids. Temporary responses are achieved with intralesional steroids and cyclosporin.

Methods  The association of hidradenitis suppurativa with inflammatory bowel disease permitted the opportunity to utilize infliximab and to observe not only its impact on the bowel, but also skin.

Results  Infliximab dramatically and favorably impacted on three cases of hidradenitis, but also in one of the patients who also had pyoderma gangrenosum.

Conclusions  Infliximab appears to be an effective medical approach to the management of hidradenitis suppurativa and also to prepare the patient for "curative" surgery. However, one must be cognizant of the potential of acquired drug resistance or adverse drug reactions, which can be minimized by "no vacations" from this systematic therapy and the use of methotrexate to minimize the above potential problems.

Introduction

The diagnosis of hidradenitis suppurativa is primarily made on the basis of its clinical presentation. Its distribution favors sites that are rich in terminal hairs and apocrine glands, such as the axillae, the anogenital area, and mammary gland sites, as well as the buttocks, nape of the neck, and scalp. It is a chronic inflammatory disorder characterized by recurring abscesses, draining sinuses formation, fibrosis, secondary lymphedema, polyposis of skin, and comedones. A modification of Jemec’s description of the three clinical stages is as follows:

1. primary stage: abscess formation, solitary or multiple without sinus tracts or scarring;
2. second stage: recurrent abscesses, single or multiple, widely separated with some sinus formation and cicatization;
3. third stage: diffuse or broad involvement across regional areas with multiple abscesses, intercurrent sinus tracts, ulcerations with chronic discharge, and scattered areas of hypertrophic scars.

Complications of the disease include genital or breast lymphedema, fistulae to the lower anogenital tract and rectum, amyloidosis, anemia, hypoproteinemia, seronegative spondyloarthropathy, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), uveitis, nephrotic syndrome, and squamous cell cancer with metastatic potential. Patients rarely experience a spontaneous remission. Older patients tend to have a lower recurrence rate. The severity and location of the disease dictate the morbidity and potential for control of the disease, and its physical, mental, and socioeconomic consequences.

In spite of the analogies that have been made with acne vulgaris, the acne pharmacotherapeutic approach has been relatively unsuccessful. Recently, a group of “autoinflammatory” disorders has been identified, characterized by recurrent noninfectious inflammatory episodes in the absence of autoantibodies or antigen-specific T cells and, histologically, by a preponderance of polymorphonuclear cells without a demonstrable infectious agent seen under the microscope or on culture. The listed autoinflammatory diseases include familial Mediterranean fever, mevalonate kinase deficiency, tumor necrosis factor (TNF) receptor-associated periodic syndrome, cryopyrin-associated periodic syndrome, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome, recurrent multifocal osteomyelitis, and Crohn’s and Behçet’s disease. Hidradenitis suppurativa has been included in this group. These disorders have been treated with some success by the use of so-called anti-inflammatory drugs, such as intralesional and systemic corticosteroid therapy, dapsone, cyclosporine, cytotoxic agents, methotrexate, azathioprine, and mycophenolate mofetil, and, currently, the anti-tumor
factor α biologic agents. Interestingly, methotrexate has been reported to be relatively ineffective for hidradenitis suppurativa.

The role of the biologic agents (anti-TNF drugs: etanercept, adalimumab, and infliximab) in inflammatory noninfectious dermatologic conditions is currently being investigated. Amongst the questions still to be answered are their relative and continuous efficacy, and the frequency of potential immediate allergic reactions or late adverse complications, such as infections (especially tuberculosis), demyelinating disorders, autoimmune disease, and malignancy.

Infliximab (Remicade) is a chimeric monoclonal antibody that binds specifically to human TNF-α, decreasing the effect of the cytokine in inflammatory diseases, such as Crohn’s disease, rheumatoid arthritis, psoriasis, pyoderma gangrenosum, SAPHO, subcorneal pustulosis, Behçet’s disease, and hidradenitis suppurativa.

Within the last 5 years, there have been at least 16 reports in the English literature of patients with hidradenitis suppurativa being effectively treated with infliximab; 11 of these had associated Crohn’s disease. In general, infliximab infusion quickly arrested activity and rendered the disease in remission, but, on discontinuation of therapy, relapses generally occurred. The response to infliximab has stimulated interest in other anti-TNF-α biologics that are given subcutaneously, such as etanercept (Enbrel), a chimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75-kDa (p75) TNF receptor linked to a portion of human immunoglobulin G1 (IgG1), and adalimumab (Humira), a recombinant human IgG1 monoclonal antibody against TNF-α; these drugs are in clinical trials for the treatment of hidradenitis suppurativa, and early reports suggest that they show promise; however, on discontinuation, there is a tendency to relapse. A female patient with severe hidradenitis suppurativa, who was initially responsive to infliximab, became resistant; infliximab was replaced by adalimumab, which not only significantly improved the patient’s skin, but also her anemia, and reduced her transfusion requirements.

Currently, wide excision is the definitive treatment and has the potential to cure the disease. The main objective of surgery is to cure the disease, to preserve or establish function, and for cosmetic purposes. The optimal surgical approach is dictated by the distribution and extent of the lesions and the presence of infection. Failure to excise sufficient tissue invites recurrence, fistulae formation, and scarring. Wide excision with healing by secondary intention is the most frequently elected approach.

**Case Reports**

**Case 1**

Case 1 is a 36-year-old married woman with a history of acne as a teenager. At the age of 24 years, she developed “boils” in both axillae, which were diagnosed as hidradenitis suppurativa, and failed to respond to topical and systemic antibiotics or isotretinoin. Both axillae were excised and grafted (Fig. 1) and, since surgery, she has had no recurrence. She had pilonidal surgery at the age of 28 years. At the age of 30 years, she developed bloody diarrhea and, on gastrointestinal X-ray studies, was noted to have changes in the small bowel consistent with Crohn’s disease. At the age of 32 years, she developed pyoderma gangrenosum of the left pretibial area and “boils” in the right groin, consistent with hidradenitis suppurativa (Fig. 2). Periodic courses of prednisone and azathioprine controlled her bowel complaints, but failed to promote healing of her pyoderma gangrenosum and hidradenitis suppurativa. In view of the presence of hidradenitis suppurativa and pyoderma gangrenosum, and their failure to respond to dapsone, isotretinoin, azathioprine, and oral prednisone, a trial of
Case 2

Case 2 is a 46-year-old man in good health, with no systemic disease complaints or signs, and presently on no medications. He was referred for therapeutic suggestions for the treatment of a complicating lymphedema of the genitals secondary to a severe underlying hidradenitis suppurativa. He has a history of hidradenitis of 20 years’ duration with involvement of the axillae, anogenital area, and buttocks, which has been effectively treated in the past with wide excision and grafts with no recurrence. He has no history of acne, dissecting cellulitis of the scalp, or a pilonidal sinus. Over the last 2 years he has developed progressive lymphedema of the penis and scrotum (Fig. 3). He was treated with 40–60 mg of prednisone, minocycline 100 mg twice daily, and acitretin 25 mg daily for 6 months with no impact. He has no history of tuberculosis, deep mycotic infection, autoimmune syndromes resembling lupus erythematosus, demyelinating disease, or cancer, and his PPD skin test and X-ray of the chest were negative. A course of infliximab infusions (5 mg/kg) was given at weeks 0, 2, and 6, followed by every 6 weeks for three cycles; minocycline, 100 mg twice daily, was also given. He was referred to the Lymphedema Clinic and was treated with decompression techniques. A 6-month follow-up revealed that the patient had improved significantly. Arrangements were made for a plastic surgeon and urologist to perform reconstructive plastic repair of his lymphedematous penis. Unfortunately, 3 weeks later, he experienced a flare. He required three infliximab infusions (5 mg/kg) at weeks 2, 4, and 6 before the activity of his genital hidradenitis had sufficiently cleared to allow the surgeons to perform plastic repair, which was successful. He is currently on minocycline, 100 mg twice daily.

Case 3

Case 3 is a 35-year-old obese woman who is an insulin-dependent diabetic. She developed recurrent abscesses of both axillae over 6 years and was treated unsuccessfully by her primary care physician with various systemic antibiotics (doxycycline, trimethoprim and sulfamethoxazole, cephalixin, and ciprofloxacin) and topical retinoids. She was referred to a dermatologist, who sent her to a plastic surgeon who excised and grafted both axillae with an excellent result. Five years ago, she developed bloody diarrhea and, after an X-ray of the bowel, was diagnosed with Crohn’s disease of both the small bowel and colon; this has been effectively controlled with diet, sulfasalazine, prednisone, and azathioprine. Four years ago, she developed a pustular draining edematous eruption involving her buttocks and perineum with some fistulae formation and scarring (Fig. 4). Her dermatologist made a diagnosis of hidradenitis suppurativa. Because of her failure to respond and progression of her disease in spite of a combination of topical acne therapy and systemic antibiotics (minocycline and trimethoprim and sulfamethoxazole), she was referred for therapeutic recommendations. It was suggested that the patient have a PPD skin test, a chest X-ray, and a thorough history and physical examination to rule out the presence of tuberculosis, deep mycotic infection, demyelinating
disease, autoimmune disease resembling lupus erythematosus, and cancer. A trial of infliximab infusions (5 mg/kg) at weeks 0, 2, 6 and then monthly until her eruption cleared was initiated. After four more infusions given every 8 weeks, the referring physician reported almost complete clearing of the eruptions in her groin, buttocks, vulva, and perineum. Three months later, however, she experienced a flare of her perineal eruption and was given four infusions of infliximab (5 mg/kg) at monthly intervals, with almost complete remission, for 4 months; this permitted her to experience the most comfortable summer she has had during the 4 years of her disease.

Discussion

Three cases of hidradenitis suppurativa, two with associated Crohn’s disease, have been reported.

Patient 1 received seven infusions of infliximab (5 mg/kg) over a period of 30 weeks. Currently, her hidradenitis suppurativa has been in remission for the last 4 months. She did not receive immunosuppressive therapy during the period of infliximab treatment or in her current remission. She experienced no immediate or delayed adverse reactions with her infusions. Interestingly, her bowel has been quiet and she has been free of pyoderma gangrenosum.

Patient 2 received five infusions of infliximab (5 mg/kg) over a 26-week period with clearing of the inflammatory component of his disease that permitted effective lymphedema decompression therapy for a 6-month period. Unfortunately, at this time, he experienced a flare-up, but three infusions of 5 mg/kg over a 12-week period reduced the activity of the disease process to allow the surgical team to perform a successful plastic repair. He, too, received no immunosuppressive treatment and experienced no immediate or delayed adverse reactions during infusion therapy.

Patient 3 required seven infliximab infusions of 5 mg/kg over a 24-week period to experience a remission of 3 months’ duration. Three months later, she experienced a flare, which required four monthly infusions of infliximab (5 mg/kg) to again achieve remission lasting for 4 months.

The efficacy and role of infliximab in the management of hidradenitis suppurativa need to be determined by controlled studies with adjunctive therapies. Adjunctive therapies that could help to maintain biologic-induced remission need to be found. The requirement for concomitant immunosuppressive therapy to reduce the potential for immediate and delayed adverse reactions needs to be assessed, and the tachyphylaxis to infliximab for dermatologic diseases should be examined.

Some gastroenterologists use infliximab with Imuran in patients with Crohn’s disease to treat the condition, but also to reduce the potential for tachyphylaxis and adverse reactions, and to later maintain the patients in remission with methotrexate alone.

The use of antibiotics in the management of hidradenitis suppurativa in the initial phase of the disease is controversial; however, in the later stages of the disease, secondary infections occur, and rifampicin with clindamycin has reportedly been helpful.

It appears that infliximab is an excellent “quick fix” for special occasions; however, regular infusions without discontinuation are related to lasting infliximab success in patients with stage II and III disease. Infliximab can also be useful to prepare patients for definitive curative surgical procedures.

References