Listeria monocytogenes Sepsis in Patients Treated with Anti-Tumor Necrosis Factor-alpha

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Tumor necrosis factor-alpha, a pro-inflammatory cytokine produced primarily by activated monocytes and macrophages, has a broad-spectrum biological activity. It exerts its action through activation of endothelial cells, lymphocytes and platelets, expression of adhesion molecules, cytokines, and major histocompatibility complex class II molecule, thus playing a pivotal role in host defense against various infectious agents [1]. Elevated levels of TNFα in certain inflammatory conditions make it a potential therapeutic target. Anti-TNFα is emerging as a promising therapy in refractory rheumatoid arthritis, spondyloarthropathies and inflammatory bowel diseases, but beneficial effects have also been reported in other inflammatory diseases such as ocular, muscular and skin diseases and vasculitides [2].

Three TNFα-blocking agents are currently available: infliximab, a chymeric anti-TNFα antibody given intravenously; adalimumab, a fully human anti-TNFα antibody; and etanercept, a soluble p75 TNFα receptor given subcutaneously.

Over 300,000 patients worldwide, during some 600,000 patient/years, have thus far been treated with TNFα neutralizing agents. Although uncommon, the clinically significant side effects are tuberculosis reactivation and autoimmune phenomena (demyelinating disorders and anti-DNA antibodies). This, together with the growing number of reports on new-onset lymphoma arising among patients treated with anti-TNFα, has raised major concern in the medical community. To date, 158 new cases of lymphoma have been reported in association with anti-TNFα therapy. Causality, however, cannot easily be established since rheumatoid arthritis and non-Hodgkin's lymphoma are also associated, and follow-up post-marketing cohort studies are short relative to carcinogenesis.

During the last year, several *Listeria* infections were reported in patients treated with anti-TNFα, increasing the degree of alertness to such opportunistic infections in these patients. We report two cases of *Listeria* sepsis following infliximab treatment.

Patient Descriptions

Patient 1

A 55 year old woman was admitted after 5 days of fever, chills, malaise and mild dysuria. Ten years previously she had been diagnosed with rheumatoid arthritis, which remained active in spite of multiple therapeutic attempts with hydroxychloroquine, sulphasalazine, azathioprine, cyclosporine, methotrexate and leflunomide (alone and in combination). Two years prior to the present admission she began therapy with infliximab infusions at a dose of 3 mg/kg with methotrexate 12.5 mg/week and prednisone 10 mg/day, and the response was favorable. She received her recent course 2 weeks prior to her current illness.

Upon admission the patient was febrile (38.5°C) but her physical examination was remarkable only for joint deformities typical of rheumatoid arthritis. White blood cell count numbered 5,500 with 85% neutrophils, and urine analysis showed abundant white and red blood cells. Blood and urine cultures were obtained and the patient was given ofloxacin for presumed urinary tract infection. Twenty-four hours later urine cultures grew *Escherichia coli* and blood culture grew *Listeria monocytogenes*; the patient was readmitted for ampicillin and gentamycin therapy, which resulted in a complete clinical and laboratory resolution of her illness.

Patient 2

A 48 year old man had been diagnosed with Crohn's disease in 1968. Between 1968 and 1977 he underwent six operations, including subtotal colectomy and resection of the terminal ileum. In April 2002 he developed a perianal fistula and abscess that was successfully treated with augmentin. In November 2002 he was seen because of severe anal and rectal discomfort with diarrhea. A colonoscopy revealed large Crohn's-type hemorrhoids and ulceration of the stenosed ileocolic anastomosis and two ulcers in the neoterminal ileum. Since the patient had suffered side effects from mesalazine and steroid therapy in the past, he was offered treatment with infliximab. He received 350 mg (5 mg/kg) of intravenous infusion. Nine days later he developed rigors, fever of 39°C and headaches.

On admission he was febrile but physical examination was unremarkable. White blood count revealed a total of 12,000 k/L with 74% neutrophils. Chest X-ray was normal, as were urine analysis and biochemical tests. A computerized tomography scan and ultrasound of the abdomen

TNFα = tumor necrosis factor-alpha

revealed lesions compatible with multiple small splenic abscesses. Both transthoracic and transesophageal echocardiography were normal. Blood cultures grew *Listeria monocytogenes* for which the patient was treated with ampicillin, gentamycin and mertonidazole resulting in complete clinical and laboratory resolution of his illness.

Comment

Listeria monocytogenes is a Gram-positive rod infecting predominantly pregnant and immune compromised patients. It is widespread in the environment and can be isolated from soil, vegetation and animals. It is a food-borne infection colonizing milk, dairy products, meat and vegetables with 2–6 weeks incubation. Its overall estimated annual incidence in the United States is 8 cases per million in the general population with a 25% mortality. Most cases are sporadic and only rare outbreaks have been reported. Following ingestion, this intracellular organism causes mainly systemic and organ-invasive syndromes including sepsis, visceral abscesses, central nervous system infections, peritonitis, osteomyelitis, endocarditis, pleuropulmonary infections, gastroenteritis and chorioamnionitis. A rare asymptomatic carrier state also exists.

Cellular invasion occurs through the binding of the bacterial protein internalin to its cell membrane receptor, followed by phagocytosis. The phospholipase listerolysin enables phagosome rupture, and bacterial intracellular trafficking is facilitated by binding of the ACT-A protein to host actin fibers. Bacterial spread occurs in a cell-to-cell fashion.

TNFα is critical in host defense against *Listeria*, as demonstrated by numerous animal models. TNFα is produced within minutes of infection and its serum levels increase in parallel to the bacterial load, peaking before host death. Animal studies have demonstrated that treatment with anti-TNFα, both before or during listerial infection (particularly in the first 3 days of infection), resulted in premature host death with large numbers of bacterial copies per cell. Pro-inflammatory effects of TNFα on *Listeria*-infected different cell lines (monocytes, macrophages, T lymphocytes, neutrophils), were abolished by anti-TNFα therapy, thus providing more information on its essential role in host defense mechanisms.

Until recently, only rare *Listeria* infections were reported in anti-TNFα-treated patients. Kamath et al. [3] as well as Morelli and Wilson [4] reported listerial infection in a Crohn's patient treated with infliximab. In another report, two rheumatoid arthritis patients with severe listeriosis developed acute cholecyctitis, meningoencephalitis and brain abscess following anti-TNFα treatment; both patients died. Recently, Slifman et al. [5] reported 15 cases of *Listeria monocytogenes* infection associated with anti-TNFα therapy (64% with rheumatoid arthritis and 39% with Crohn's disease), resulting in 6 deaths.

Although most of the patients reported were immune compromised – due both to their chronic inflammatory illness and to receiving concurrent immune suppressive therapy – anti-TNFα therapy is probably a major risk for the development of listeriosis. Thus, alertness among all medical disciplines is crucial when signs of infection occur. Patients should be warned to avoid soft cheeses, non-pasteurized dairy products and undercooked meats during therapy, and physicians should be aware of the possibility of *Listeria* infection in such individuals.

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Capsule

Classic conditioning, timing, and the cerebellum

Timing of movements is crucial for the survival of animals, and the nervous system is continuously trying to optimize this timing. A well-studied example is classical conditioning of the eyelid blink response, whose timing is ultimately determined by the interval between the onset of the conditioned stimulus and that of the unconditioned stimulus. Using a novel eyelid movement-recording technique and cell-specific mutant mice, Koekkoek et al. show that cerebellar long-term depression is not only necessary for adapting the amplitude of trained movements but also for learning the appropriate timing via an input-specific mechanism.

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