Case Report

Disseminated Primary Varicella Infection During Infliximab Treatment

HARALD VONKEMAN, CHRIS ten NAPEL, HANS RASKER, and MART van de LAAR

ABSTRACT. A young man developed a serious disseminated varicella infection, necessitating antiviral treatment, after being treated with anti-tumor necrosis factor-α therapy for rheumatoid arthritis. (J Rheumatol 2004;31:2517–8)

Key Indexing Terms:
TUMOR NECROSIS FACTOR-α
INFLIXIMAB
TREATMENT
VARICELLA INFECTION

We describe a young man who developed a serious disseminated varicella infection, necessitating antiviral treatment, after being treated with anti-tumor necrosis factor-α (TNF-α) therapy for rheumatoid arthritis (RA).

CASE REPORT

A 32-year-old man with a history of RA presented with a generalized pruritic vesicular rash after being treated with intravenous anti-TNF-α therapy (infliximab). He reported that as a child he had never contracted chickenpox, but 10 days preceding the infliximab infusion, he had been in close contact with children with the disease. The clinically suspected diagnosis primary varicella-zoster virus infection, or chickenpox, was confirmed by immunofluorescence testing in a skin biopsy as well as by culture of vesicular fluid.

During the following days he developed high fever, a dry cough, and progressive respiratory insufficiency. Diffuse bilateral interstitial nodular infiltrates were seen on radiographs of the thorax (Figure 1). A high resolution computer tomography scan of the lungs showed thickening of the interlobular fissures, bilateral nodular infiltrates, and areas with a marked ground-glass aspect. While laboratory tests continued to show normal erythrocyte sedimentation rates and normal C-reactive protein levels, the hepatic enzymes became progressively elevated. He was treated with intravenous acyclovir, after which he improved rapidly. Serologic testing for varicella-zoster virus proved negative at presentation, but showed developing immunity one month later. He recovered completely, save for some mild scarring of the skin. Assuming the varicella-zoster virus infection to have been a primary infection, he was subsequently treated with a second infusion of infliximab, and had no adverse effects.

DISCUSSION

Tumor necrosis factor-α is a proinflammatory cytokine. Infliximab is a chimeric monoclonal antibody of the IgG1 group, its Fc part being human and its Fab of murine origin. The infliximab molecule neutralizes circulating TNF-α by binding the TNF-α molecules. However, infliximab engages with circulating as well as receptor-bound TNF-α. Moreover, circulating infliximab-TNF-α complexes can bind to the TNF receptor. Binding of cytotoxic antibodies, like IgG1 molecules, induces cell death of the receptor cells. Infliximab therefore not only neutralizes circulating TNF-α, but may also inhibit the cellular immunity[1]. Further, several groups have reported that TNF-α has an important inhibitory effect *in vitro* on the replication and spread of varicella infection. This inhibitory effect was shown to be blocked by the addition of mAb against TNF-α[2].

The varicella-zoster virus (human herpesvirus type 3) is a highly contagious, double stranded DNA virus. Varicella infection usually occurs during childhood and is generally benign and self-limiting. More than 90% of adults show serologic immunity. Transmission occurs in a susceptible host via contact with aerosolized droplets or, less commonly, by direct cutaneous contact with vesicle fluid. The average incubation period is 14 to 16 days. Patients develop fever, pharyngitis, and generalized vesicular rash, which resolves in about 6 days[3]. The most common complication is bacterial superinfection of the skin. Hosts with impaired cellular immunity, such as transplant recipients and patients with acquired immune deficiency syndrome, are more susceptible for disseminated varicella. They more frequently experience severe morbidity, such as varicella encephalitis, pneumonia, and hepatitis and have higher mortality rates than normal hosts.

It is estimated that several hundred thousand patients have been treated with infliximab worldwide. Although generally presumed to be safe, serious infectious complications have been reported at a rate of roughly 5 per 100 patient-years. While there is global concern for possible reactivation of dormant bacterial infections like tuberculosis, to date few viral complications have been reported[4,5]. Varicella infection may be a more frequent complication among children treated with anti-TNF-α therapy[6]. However,

From the Department of Rheumatology and the Department of Internal Medicine, Medisch Spectrum Twente, Enschede, The Netherlands.

Supported by an unrestricted research grant from Schering-Plough Netherlands.

H.E. Vonkeman, MD; J.J. Rasker, MD, PhD, Professor; M.A.F.J. van de Laar, MD, PhD, Professor, Department of Rheumatology; C.H.H. ten Napel, MD, PhD, Department of Internal Medicine.

Address reprint requests to Dr. H.E. Vonkeman, Department of Rheumatology, Medisch Spectrum Twente, PO Box 50000, 7500 KA, Enschede, The Netherlands. E-mail: H.Vonkeman@ziekenhuis-mst.nl

Submitted March 10, 2004; revision accepted July 5, 2004.

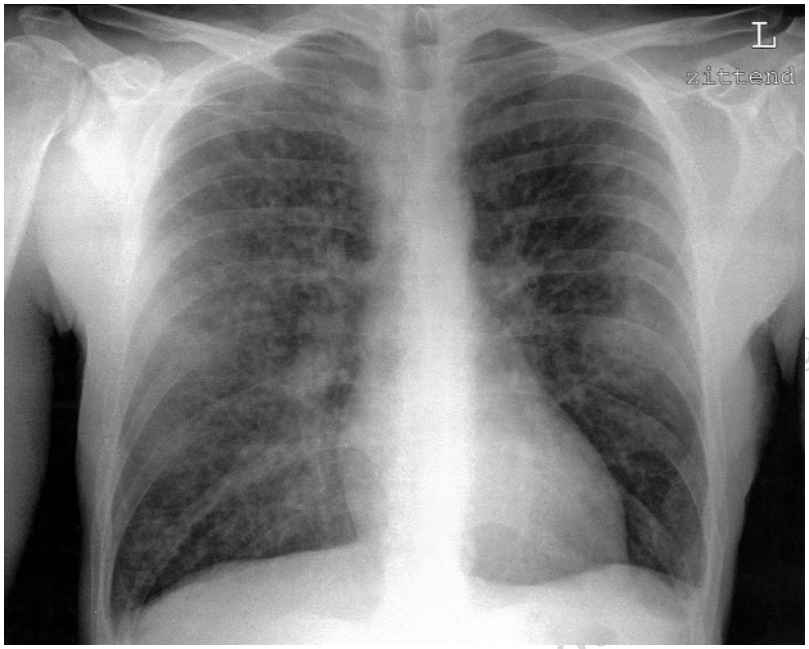

Figure 1. Radiograph of the thorax shows diffuse bilateral interstitial nodular infiltrates.

disseminated varicella has also been described in otherwise healthy adults not receiving anti-TNF-α therapy.

Treatment with infliximab can lead to significant, albeit transient, impaired cellular immunity, which might be sustained during continuous intermittent treatment. If administered during the incubation period of a primary infection with varicella-zoster virus, it can lead to a serious disseminated form of the disease, necessitating antiviral treatment.

REFERENCES

1. Ziolkowska M, Maslinski W. Laboratory changes on anti-tumor necrosis factor treatment in rheumatoid arthritis. Curr Opin Rheumatol 2003;15:267-73.
2. Ito M, Nakano T, Kamiya T, et al. Effects of tumor necrosis factor alpha on replication of varicella zoster virus. Antiviral Res 1991;15:183-92.
3. Straus SE, Ostrove JM, Inchauspe G, et al. NIH conference. Varicella-zoster virus infections. Biology, natural history, treatment, and prevention. Ann Intern Med 1988;108:221-37.
4. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor-α neutralizing agent. N Engl J Med 2001;345:1098-104.
5. Ricart E, Pannaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. Am J Gastroenterol 2001;96:722-9.
6. Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: Interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum 2003;48:218-26.