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CASE REPORT

Septic Shock after Seasonal Influenza Vaccination in an HIV-Infected Patient during Treatment with Etanercept for Rheumatoid Arthritis: a Case Report

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Anti-tumor necrosis factor alpha (anti-TNF-α) is used in the treatment of rheumatic diseases not responsive to first-line regimens. Data on the safety of anti-TNF-α in HIV-infected patients are scarce and conflicting. We describe a case of septic shock and multiorgan failure that occurred after etanercept initiation and influenza vaccination in an HIV-infected woman with rheumatoid arthritis.

CASE REPORT

A 45-year-old Caucasian woman was diagnosed with HIV infection in 1991 and has been on highly active antiretroviral treatment (HAART) since 1998, with a good immunovirological response. Over a period of 5 years, she has been treated with zidovudine (Retrovir), lamivudine (Epivir), and efavirenz, and she exhibits >700 CD4 cells/ml and a viral load persistently below 50 copies of HIV RNA/ml. In her relevant medical history, acute exacerbations of chronic obstructive pulmonary disease and allergy to sulfonamides were reported.

In December 2008, she experienced an episode of fever and acute symmetrical polyarthritis with pain, swelling, and stiffness of the knees, wrists, and several metacarpophalangeal joints. A wide panel of autoantibodies was negative. Common infectious agents, such as parvovirus B19, *Borrelia*, *Brucella*, and measles virus, among others, were excluded as possible causes. The ultrasound scan of the affected joints showed a marked active proliferative synovitis and a moderate exudative tenosynovitis. Given the persistence of the symmetrical polyarthritis, diagnosis of seronegative rheumatoid arthritis (RA) was made, and in February 2009, a systemic therapy with oral prednisone (25 mg daily), diclofenac (150 mg daily), and hydroxychloroquine (200 mg daily) was started. The patient reported an immediate improvement of joint symptoms. Because of the occurrence of a severe skin allergic reaction, likely related to hydroxychloroquine, the patient started methotrexate (10 mg weekly). In May 2009, this drug was suspended for a hypersensitivity skin reaction. Cyclosporine (150 mg daily 5 days per week) and oral prednisone (5 mg twice daily) were prescribed. The trough drug levels of efavirenz during cyclosporine treatment were 2,174 μg/ml (suggested minimum target concentration, 1,000 to 4,000 μg/ml). Two months later, the patient experienced a flare-up of the rheumatic disease, with fever and worsening of the articular symptoms. Facing clinical deterioration with an increasing number of involved joints, the use of an anti-tumor necrosis factor α (TNF-α) agent was evaluated. Screening for latent tuberculosis, chest radiography, and serology for both type B and C viral hepatitis all provided negative results.

In September 2009, etanercept (2-mg subcutaneous injections twice weekly) was prescribed in addition to oral prednisone (5 mg twice daily). Within 2 weeks, the patient reported a good response to therapy, with a marked improvement of the joint manifestations. The trough level of efavirenz was 2,426 μg/ml. No change in the CD4 cell count and HIV load was detected. In November 2009, the seasonal adjuvanted influenza vaccine was administered. Two weeks later, the patient had an acute febrile arthritis flare-up with severe joint pain, malaise, sore throat, and dysphagia with a palate ulcer. One week later, the patient was hospitalized. Laboratory parameters at admission revealed 549 CD4 cells/ml, with undetectable HIV RNA, a high erythrocyte sediment rate, and C-reactive protein (Table 1).

An abdominal ultrasound examination demonstrated a hepatosplenomegaly with no focal lesions, and a chest radiography revealed mild bilateral interstitial infiltrates predominantly in the middle basal regions. During her hospitalization, the patient remained febrile despite parenteral antibiotic administration with amoxicillin-clavulanate (2.2 g intravenously [i.v.] three times a day) and levofloxacin (500 mg i.v. twice a day). The direct, repeated sputum culture assays for bacteria and acid-fast bacilli and the urine specimen, stool sample, and blood cultures were negative. Furthermore, tests for *Legionella* and pneumococcal urinary antigens, serology tests for *Brucella*, *Chlamydia*, *Coxiella*, and *Mycoplasma*, and a gamma interferon release assay were all negative. The rheumatoid factor and other autoantibodies were absent. A total-body computed tomography scan evidenced the presence of a diffuse lymphadenomegaly and small abscess formations of the right infraspinatus muscle. Antibiotic therapy with i.v. vancomycin at 7.5 mg/kg of body weight every 6 h and i.v. piperacillin-tazobactam at 4.5 g every 6 h was started and resulted in no improvement. We considered an autoimmune disorder following the influenza vaccination the *primum movens* of the patient's clinical deterioration, so at day 21 of admission, a plasma exchange

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TABLE 1 Hematological laboratory parameters[a]

Point in clinical progression	ESR (mm/h)	CRP (mg/dl)	LDH (IU/ml)	Hb (g/dl)	No. of RBC/mm^3	No. of WBC/mm^3	% NEU	No. of PLT/mm^3
Hospital admission (Nov. 2009)	106	32.1	631	8.5	3,470,000	11,900	88	556,000
ICU admission (Jan. 2010)	140	23.9	4,268	7.0	2,363,000	4,000	83.8	14,000
Discharge to medical ward (Feb. 2010)	33	8.3	1,446	10.4	2,620,000	12,800	74.0	98,000
Discharge to home (Apr. 2010)	46	2.6	549	10.5	3,500,000	7,800	75.0	138,000
Last control (Apr. 2011)	5	1	420	13.2	4,380,000	6,400	45.2	290,000

[a] ICU, intensive care unit; ESR, erythrocyte sediment rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; Hb, hemoglobin; RBC, red blood cells; WBC, white blood cells; NEU, neutrophils; PLT, platelets.

was performed. The following day, the patient's clinical condition rapidly worsened. She became obtunded and confused, with a Glasgow coma score of 9. Bilateral pulmonary consolidations with pleural effusions and acute oligo-anuria were reported, and a diagnosis of adult respiratory distress syndrome with acute renal failure was made. Blood test values were as follows: a prothrombin time of 49%, a partial thromboplastin time of 40.3 s, a D-dimer concentration of 49,480 IU/ml, a platelet count of 14,000/mm^3, and an antithrombin III level of 55% (Table 1). Consequently, the patient was intubated, mechanically ventilated, and transferred to the intensive care unit, where a first cycle of hemodialysis was performed. A diagnosis of disseminated intravascular coagulopathy and multiorgan failure secondary to septic shock was made. All the hemocultures obtained were negative. Intravenous meropenem (1 g every 8 h), i.v. linezolid (600 mg every 12 h), and i.v. echinocandin (75-mg loading dose and then 50 mg daily) were started.

Because of a progressive improvement of clinical conditions, the patient was extubated on day 5. Antibiotic therapy was discontinued at day 12, and prednisone at 12.5 mg twice a day was started again. After 5 cycles of hemodialysis, kidney function tests returned to normal values; on day 13, the patient was transferred back to the medical ward.

On April 2010, the patient was discharged to home in good clinical condition. Two weeks later, she had a recurrence of the arthritis symptoms not responding to the increasing oral steroid therapy. Furthermore, a marked hypogammaglobulinemia never reported before was found (Table 2). The patient was treated with i.v. immunoglobulin at 3 g/kg daily for 2 days, and further i.v. immunoglobulin cycles were performed every 2 to 4 weeks to maintain the IgG value above 500 mg/dl. Twelve months after the septic shock, during the low-dose chronic steroid therapy (prednisone at 5 mg daily), the patient was in good clinical condition, with no recurrence of arthritis symptoms and a normal inflammatory index.

The prevalence of rheumatic manifestations in patients with HIV infection is around 9% (1). Various rheumatic syndromes can affect HIV-infected patients at any stage of the infection. Before the use of HAART, reactive arthritis, psoriatic arthritis, painful articular syndrome, and diffuse infiltrative lymphocytic syndrome were more common, whereas now, after the introduction of HAART, immune reconstitution inflammatory syndromes and drug-induced conditions, such as myopathies, rhabdomyolysis, lipodystrophy, and osteoporosis, are prevalent (2). Although a majority of patients respond well to nonsteroidal anti-inflammatory drugs and to corticosteroids, a few are refractory to them and require disease-modifying antirheumatic drugs. Most antirheumatic therapies used in HIV-negative individuals appear to be safe and effective also in HIV-infected patients. Arthropathies not responding to conventional disease-modifying antirheumatic drugs may require TNF-α blockade to reduce the inflammation and the damage caused by the immune response driven by TNF-α (1). At low concentrations in tissues, TNF-α is thought to have beneficial effects, such as increasing host defense mechanisms against infections. During disease progression, TNF-α, if released at high concentrations, works as a proinflammatory cytokine and can lead to excessive inflammation and organ injury (3). Clinical trials with etanercept, a soluble TNF-α receptor, have shown an overall high efficacy and good safety profiles in HIV-negative patients treated for arthropathies, but its use in patients with HIV infection has not been studied in detail. Favorable clinical outcomes without either severe adverse events or HIV infection disease progression were reported in many published cases of Reiter's syndrome, psoriatic arthritis, RA, and Crohn's disease treated with infliximab, etanercept, or adalimumab in HIV-infected patients (4–7). The anti-TNF-α agents may also be safely used in the setting of other chronic viral infections, like hepatitis B and C (8–10). However, the risk of opportunistic infections, particularly tuberculosis and sepsis, are among the main limits to the use of these biologic agents. The occurrence of septic shock and the exacerbation of severe infections were already reported in patients with RA treated with etanercept or other TNF-α antagonists (11–14). Obviously, a successful therapy with anti-TNF-α agents has to be stopped due to severe intercurrent infections (15, 16).

Patients with autoimmune disorders starting anti-TNF-α antagonists, immunomodulators, or corticosteroid drugs are at risk of a serological nonresponse, of the development of a major adverse event, or of an exacerbation of their autoimmune disease (17, 18). Guidelines recommend that patients at risk for complication of influenza, including those treated with anti-TNF-α drugs, should be vaccinated annually against influenza (19). Usually, patients are required to be on a stable drug treatment before the vaccination is provided, but data on

TABLE 2 Gamma globulin determinations during clinical progression

Point in clinical progression	IgA (mg/dl)	IgM (mg/dl)	IgG (mg/dl)
ICU admission (Jan. 2010)	17	132	1,368
i.v.-Ig treatment initiation (Apr. 2010)	1	8	299
Last control during i.v.-Ig treatment (Apr. 2011)	9	22	634

the effect of anti-TNF-α antagonists on immunogenicity and the response to influenza vaccination are scarce (17, 18). A few recent studies reported that patients treated with anti-TNF-α drugs reach an adequate immunoprotective response against influenza after vaccination, although antibody titers and cellular response rates are lower than those of similar patients not treated with anti-TNF-α and healthy controls (20–22). No grade 3 or 4 clinical or laboratory adverse events following the vaccination were reported, only mild upper respiratory tract infections, fever, myalgia, or headache (20–22). Recently, Shoenfeld and Agmon-Levin suggested that adjuvants, considered to be inert and commonly used to increase a protective response induced by vaccine, can activate the innate and adaptive immune response and inflict an immune-mediated disease by themselves. A new syndrome called the autoimmune/autoinflammatory syndrome induced by adjuvants has been proposed to be involved in the pathogenesis of postvaccination phenomena inducing or aggravating a previously established autoimmune diseases (23).

Our patient was vaccinated against seasonal influenza 2 months after etanercept initiation. The recommendation was based on a multidisciplinary assessment of pro's and con's. Factors supporting the choice of a vaccination were the coexistence of a clinical history of seasonal exacerbations of chronic obstructive pulmonary disease and HIV infection. Furthermore, the patient was stable on therapy with etanercept and steroids, and she had already been vaccinated in the past against influenza, with no adverse events. The only argument against the vaccination was the limited follow-up period after the anti-TNF-α initiation.

This case report suggests that influenza vaccination played a major role in driving the multiorgan failure observed in the patient. In fact, the temporal relationship between the administration of a seasonal adjuvanted influenza vaccine and the occurrence of symptoms indicates a possible reaction to adjuvant exposure, as recently proposed by Shoenfeld et al. (23). Furthermore, before starting etanercept, the patient had already been vaccinated for seasonal influenza without any adverse events. Even if the use of TNF-α is shown to be safe in HIV-infected patients (4–7), the effects of adjuvant exposure on patients with an impaired immune system receiving biological drugs is not yet fully elucidated (24). Clinical trials are warranted in order to investigate the safety of seasonal influenza vaccination in patients receiving TNF-α antagonists.

Written informed consent was obtained from the patient for publication of this case report.

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We declare that we have no competing interests.

P.D.N. and E.N. conceived the study, participated in its design and coordination, and drafted the manuscript. P.D.N. and M.G. wrote the manuscript. E.N. and R.B. were the physicians responsible for the patient. M.G. and G.D.S. provided rheumatological consultation. F.T. and S.R. were the physicians responsible for the treatment of the patient during hospitalization.

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