Varicella zoster virus encephalitis during treatment with anti-tumor necrosis factor-α agent in a psoriatic arthritis patient

Giovanni Buccoliero, Gaetano Lonero, Chiara Romanelli, Pietro Loperfido, Francesco Resta

S.C. Malattie Infettive, Presidio Ospedaliero Centrale, Stabilimento "San G. Moscati", AUSL TA

INTRODUCTION

According to the current knowledge of the molecular and cellular basis, psoriasis is defined as in immune-mediated chronic inflammatory and hyperproliferative skin disease. Psoriasis is one of the most common chronic and recurrent dermatoses affecting approximately 2% of the general population in Western countries. The disease can affect people of all ages, although its onset can occur in early adulthood. Approximately 10%-30% of patients with psoriasis develop psoriatic arthritis (PsA). Patients with psoriasis more often have systemic disorders such as obesity, heart disease and type 2 diabetes and this rate is twice that in control patients without psoriasis (Henseler et al., 1995). Likewise, psoriasis is recorded in patients with Crohn’s disease and ulcerative colitis (Augustin et al., 2010).

The clinical results of conventional therapies of psoriasis are not satisfactory. A new generation of biological drugs targeting molecules and cells involved in perturbed pro-inflammatory immune response in the psoriatic skin and joints has been recently designed and applied clinically. These agents include the anti-TNF-α agents (Etanercept, Infliximab and Adalimumab) with clinical efficacy in both moderate-severe psoriasis and psoriatic arthritis (Pastore et al., 2008; Felice et al., 2009). Antibody formation versus these biological drugs is associated with allergic reactions and loss of response. Side-effects include the occurrence of skin manifestations (viral, bacterial and fungal infections, dermatitis herpetiformis, leukocytoclastic vasculitis, alopecia), opportunistic infections (Vermeire et al., 2009) and rare but often lethal hepatosplenic T-cell lymphoma (Mackey et al., 2007).

Among the latter, particularly fearful is the risk of reactivation of latent tuberculosis infection (Keane et al., 2001), while little is known about the risk of reactivation of latent viral infections,
such as the reactivation of hepatitis B virus (HBV) infection in inactive HBsAg carriers (Chung et al., 2009).

The most common viral reactivation associated with anti-TNF-α monoclonal antibody treatments, in particular adalimumab and infliximab, is varicella zoster virus (VZV) infection that causes the herpes zoster with an incidence rate per 1000 patient-years of 11.1 (Strangfeld et al., 2009). Herpes zoster is a self-limiting, dermatomally localized vesicular rash, often accompanied in 19.6% of cases by postherpetic neuralgia (di Luzio P.U. et al., 1999) and other rare but severe neurological complications (1.4 cases/1000 person per year, Oxman M.N. et al. 2005), including optic neuritis, aseptic meningitis, meningo-encephalitis.

CASE REPORT

In April 2008 a 38-year-old woman with psoriatic arthritis (PsA), started a treatment with subcutaneous administration of Adalimumab at a dose of 40 mg every two weeks. In September 2009 she came to our observation as the first consultation for severe headache, fever and meningism. No co-morbidity or previous or concomitant therapy were recorded. Four days after the onset of the symptoms, vesicular rash monodermatomen appeared on the trunk, without neuropathic pain. On admission our hospital normal ESR (11 mm/h) and mild leucocytosis (WBC 9200 cell/ml) were recorded. Chest X-ray was normal. The electroencephalogram (EEG) activity was abnormal showing diffuse slow theta waves. Brain computed tomography (CT) scan was negative, while magnetic resonance imaging (MRI) of the brain was not performed because the patient was claustrophobic. The blood specimens taken under febrile peaks were negative for bacterial infection. Lumbar puncture was performed on the first day; limpid, high pressure cerebrospinal fluid (CSF) showed lymphocytic pleocytosis (1400 cells/mm, n.v. <2), elevated proteins (1122 mg/dl, n.v. 150-450), hypoglicorrachia (32, vn 40-80) and was negative for bacterial infection. Real-time polymerase chain reaction (PCR) analysis of CSF sample showed a clear positivity for VZV by Herpes test, searching for an extensive panel of viruses such as CMV, EBV, VZV, HHV-6, HSV 1,2. VZV immunoglobulins M and G were both positive. An HIV screen was negative, lymphocytic profile was within normal limits (T-helper 1738/ml 48%, T-suppressor 831/ml 23%). No other causes of immunological impairment were found. Based on these findings a diagnosis of VZV acute encephalitis was made and Adalimumab was stopped. Promptly, high dose intravenous (i.v.) acyclovir 10 mg/kg/day divided q8h and i.v. steroid (dexamethasone 0.1 mg/kg every 6 hours) were supplied to ameliorate her clinical status. Antiviral therapy was instituted and was continued for 3 weeks. After 2 weeks full remission of symptoms without neurologic sequelae and normal EEG were recorded. Antiviral therapy was prolonged up to 3 weeks. After two months of follow-up, neurologic and EEG examinationss were normal but Adalimumab was not restartwes.

DISCUSSION

VZV is known to be responsible for a broad spectrum of neurological diseases, ranging from the most common complication of zoster, as postherpetic neuralgia, myelitis, meningitis and encephalitis (Amlie-Lefond et al., 2009). VZV encephalitis is a rare and severe clinical manifestation due to a primitive viral infection or a reactivation of latent VZV (Gilden et al., 2008). Viral reactivation may occur under immunosuppressive conditions. Psoriasis and presence of comorbidity per se and related treatment such as cyclosporine, methotrexate as well as the new biological drugs commonly predispose to an immunosuppressive condition that could explain a VZV reactivation and its complications. The pathogenesis underlying the reactivation of latent VZV in the brain may be multifactorial and remains undefined. In vitro studies have shown that replication of VZV and VZV antigen expression are inhibited by TNF-α and that this antiviral activity can be completely blocked by monoclonal antibodies against TNF-α (Ito et al., 1991). To date, VZV infections in patients on anti-TNF-
α agents were mainly a paediatric issue, with some cases of severe primary varicella complicated by aseptic meningitis in etanercept-treated children with juvenile rheumatoid arthritis (Carrasco et al., 2004).

In 2004, Keystone et al. reported a case of Herpes zoster that developed anecaphalitis with mild neurologic sequelae, in a patient with rheumatoid arthritis receiving long-term Adalimumab plus Methotrexate. To date, however, cases of VZV encephalitis associated with only Adalimumab treatment in PsA patients have never been reported, in our knowledge.

In our patient, a history of chickenpox as a child at the age of 10 years, the skin manifestation of vesicular rash monodermatom, the positive serology for VZV immunoglobulins M and G, the presence VZV-DNA in CFS suggested a VZV reactivation rather than a new infection occurred in an immunologically frail predisposed patient due to psoriasis per se and also to Adalimumab treatment.

The report of this case is a further contribution to the literature. No post-herpetic neuralgia and no neurological sequelae might be explained by the prompt antiviral and steroid therapy. In fact the use of acyclovir within 72 hours, with its inhibition of VZV replication, and steroid with its anti-inflammatory effect reduce the neurological damage (Gilden et al., 2004).

In conclusion, the introduction of targeted immunotherapies has greatly advanced the therapeutic options for several inflammatory diseases, but opportunistic infections and viral reactivations may still occur.

Defining the infectious complications associated with different targeted immunotherapies may provide a better understanding of the host defences required to control certain pathogens and develop more effective prophylactic and monitoring strategies.

Although VZV latent infection is widespread in the normal population, the incidence of VZV encephalitis is too low in normal individuals and in patients treated with biological agents to justify VZV serological screening in these subjects. However, but it is very important to identify early signs and symptoms of herpes zoster in these patients to start prompt efficient antiviral therapy to prevent the development of complications.

REFERENCES


Mackey A.C., Green L., Liang L.C., et al. (2007). Hepatosplenic T-cell lymphoma associated with in-


