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

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SUMMARY

The introduction of targeted immunotherapies has greatly improved the therapeutic options of several inflammatory diseases such as psoriatic arthritis. However treatment-related opportunistic infections and viral reactivations may still occur. We describe a case of varicella zoster virus (VZV) encephalitis due to the reactivation of latent VZV infection during a long therapy with the anti-tumor necrosis factor-α (TNF-α) drug Adalimumab. The low incidence of VZV encephalitis in patients treated with biological agents does not justify VZV serological screening in these subjects, but careful monitoring of the patients is recommended to recognize early signs and symptoms of herpes zoster to start prompt antiviral therapy to prevent associated complications.

KEY WORDS: VZV encephalitis, Biological drugs, Opportunistic infections

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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 diabete and this rate is twice that in control patients without psoriasis (Henseler *et al.,* 1995). Likewise, psoriasis it 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, leucocytoclastic 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,

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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/mmc, n.v. <2), elevated proteins (1122 mg/dl, n.v. 150-450), hypoglicorrhachia (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 fa ull 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 restartws.

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 anecephalitis 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 monodermatomen, 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 demage (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

Augustin M., Reich K., Glaeske G., Schaefer I., Radtke M. (2010). Co-morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. *Acta Derm. Venereol.* **90**, 147-151.

Amlie-Lefond C., Jubelt B. (2009). Neurologic manifestations of varicella zoster virus infections. *Curr. Neurol. Neurosci Rep.* **9**, 430-434.

Bongartz T., Sutton A.J., Sweeting M.J., et al. (2006). Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized trials. *JAMA.* **295**, 2275-2285.

Carrasco R., Smith J.A., Lovell D. (2004). Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. *Paediatr. Drugs.* **6**, 137-146.

Chung S.J., Kim J.K, Park M.C. (2009). Reactivation of Hepatitis B Viral Infection in Inactive HBsAG Carriers Following Anti-Tumor Necrosis Factor-{alpha} Therapy. *J. Reumathol.*

di Luzio P.U., Arpinelli F., Visona G. (1999). Herpes zoster and its complications in Italy: an observational survey. *J. Infect.* **38**, 116-120.

Felice C., Aredigo M., Berardesca E. (2009). Biologic therapies for psoriasis. *Rheumatolol.* (Suppl.) Aug; **83**, 62-64.

Gilden D.H., Kleinschmidt-DeMasters B.K., LaGuardia J.J., et al. (2000). Neurologic complications of the reactivation of Varicella-Zoster virus. *N. Engl. J. Med.* **342**, 635-646.

Gilden D. (2004). Varicella Zoster Virus and Central Nervous System Sindromes. *Herpes.* (suppl.) **2**, 89A-93A.

Henseler T., Christophers E. (1995). Disease concomitance in psoriasis. *J. Am. Acad. Dermatol.* **32**, 982-986.

Ito M., Nakano T., Kamiya T., Kitamura K., Ihara T., Kamiya H., Sakurai M. (1991). Effects of tumor necrosis factor alpha on replication of varicella-zoster virus. *Antiviral. Res.* **15**, 183-192.

Keane J., Gershon S., Wise R.P., et al. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N. Engl. J. Med.* **345**, 1098-1104.

Keystone E.C., Kavanaugh A.F., Sharp J.T., et al. (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis. Rheum.* **50**, 1400-1411.

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

fliximab use in young patients treated for inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.* **44**, 265-267.

Oxman M.N., Levin M.J., Johnson G.R., Schmader K.E., Status S.E., et al. (2005). Avaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N. Engl. J. Med.* **352**, 2271-2284

Pastore S., Gubinelli E., Leoni L., et al. (2008). Biological drugs targeting the immune response in the therapy of psoriasis. *Biologics.* **2**, 687-697.

Strangfeld A., Listing J., Herzer P. (2009). Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti-TNF-alfa Agents. *JAMA.* **301**, 737-744.

Vermeire S., Van Assche G., Rutgeerts P. (2009). Serum sickness, encephalitis and other complications of anti-cytokine therapy. Best Practice & Research Clinical Gastroenterology. **23**, 101-112.