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Case report

A pauci-symptomatic case of documented Hantavirus (Puumala) infection in a patient under anti-TNF treatment

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ABSTRACT

We describe the case of an 18-yr-old male under anti-TNF treatment for Crohn's disease for more than 8 months. He developed fever and biological inflammatory syndrome without absolutely no accompanying sign or symptom or paraclinical abnormality despite extensive work-up performed in the context of his immunocompromised state. Symptoms disappeared after 10 days and a diagnosis of Puumala infection was made retrospectively on a serological basis. The case illustrates that anti-TNF treatment does not worsen the course of Puumala infection and could even be associated with a milder clinical picture.

1. Why this case is important

The number of cases of Hantavirus infection is sharply increasing. In Western Europe, the Puumala serotype (PUUV) is responsible for more than 10,000 cases of hemorragic fever with renal syndrome (HFRS) every year.[1] Documented cases of acute PUUV infection are usually very symptomatic: renal symptoms (oliguria and anuria) occur in more than 50% of the cases and creatinin is increased in more than 90%. Hemorrrhagic manifestations are uncommon but thrombocytopenia occurs in 55–70% of the cases. Cardiac, ocular and neurological abnormalities have also been reported in more than 50% of cases.[2,3] The severity of the symptoms can vary greatly between individuals but the genetic factors involved remain controversial. HLA-B27 is associated with a benign course of the disease, with minimal renal involvement.[4] Conversely, the ancestral HLA-B8 DR3 haplotype has been shown to be associated with more severe forms of the infection in adults.[5] This haplotype is also more frequently found in children with Puumala infection than in the general population but it is not associated with a different clinical course.[6] Interestingly, the HLA-B8 DR3 haplotype is in linkage desiquilibrium with an allele of the TNF-α gene associated with a higher secretion of TNF-α (the so-called TNF-2 allele). Accordingly, Kanerva et al. found the TNF-2 allele more frequently in patients hospitalized for acute PUUV infection (42%) than in healthy controls (15%).[7] Similar findings were reported by Makela et al.[8] In a subsequent study, Makela et al. compared the severity of disease in HLA-B8DR3 negative patients with or without the TNF-2 allele and could not find any difference, suggesting that a higher TNF-α secretion does not by itself plays a major role in severe Puumala infection.[9] Finally, Maes et al. showed that patients with the GA-238 allele of the TNF-α gene and considered to be low TNF producers had a more severe clinical form of Puumala Hantavirus infection than high TNF producers.[10] In view of these controversies around TNF-α genetics in susceptibility to Puumala severe infection, we found interesting to describe the case of adult patient on anti-TNF therapy for more than eight months and developing a PUUV hantavirus infection with fever as the sole symptom

2. Case description

The patient is an 18 yrs. Old Caucasian male. He declared bilateral sacroiliitis in 2008. HLA-B27 was absent. At that time, he was simply treated with non-steroidal anti-inflammatory drugs. In September 2009, he developed acute terminal ileitis that led to a diagnosis of Crohn's disease after surgery. After surgery, he received a maintenance treatment with bimonthly injections of infliximab with complete resolution of articular and gastro-intestinal symptoms. Due to cutaneous reactions, infliximab was replaced by adalimumab in February 2010. The treatment was well tolerated and the patient totally asymptomatic. In May 2010, the patient presented vesperal peaks of fever between 38 and 39 °C. He had strictly no other symptoms and could normally attend his classes at high

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school. Since he was treated with anti-TNF medications, he was considered as risk for severe occult infection and a complete work-up was performed. Physical examination was strictly normal. Blood analysis showed only an increased CRP at 98 mg/L ($N < 6$ mg/L). Leucocytes and formula were normal. Platelets were normal at 190,000/μl. Urea was at 0.26 g/L and serum creatinine at 10.5 mg/L. Liver function was normal. Except for CRP, all these values were identical to those measured three months earlier on a routine analysis. Serologies for EBV and CMV were negative for IgM as well for IgG. Blood cultures were performed several times and remained negative including for mycobacteria. Chest X Ray was strictly normal as well as transesophageal echocardiogram. A PET/CT scanning was even performed and was strictly normal exceptfor a moderately increased glucose uptake in the distal ileon and ascending colon. Fever spontaneously subsided after 10 days. The diagnosis finally came out a few days later. In the context of an ongoing epidemy in our region, serum had been sent to an external reference laboratory (Institute of Tropical Medicine, Antwerp) for Hantavirus serology. IgM were positive for Puumala and Hantaan and IgG were negative for both serotypes. Four weeks later, serology was checked again and showed the appearance of IgG specifically directed against the Puumala serotype. Retrospectively, the patient recollected that three weeks before the onset of fever he had cleaned an old wood cabin in a wooded area. In view of the total absence of urinary or renal symptoms, there was unfortunately no urine analysis performed at the acute phase. When the diagnosis of hantavirus infection came out, urinary protein, α1-microglobulin and β2-microglobulin excretions were measured. They were strictly normal.

Other similar and contrasting cases in the literature

To our knowledge, the clinical course of a hantavirus infection in a patient under anti-TNF or other immunosuppressive therapy has never been described before.

3. Discussion

Several articles have shown increased levels of pro-inflammatory cytokines during hantavirus infection and correlated them with the severity of the symptoms.[11–14] On the other hand, it has been shown that TNF-α decreases the accumulation of viral nucleoproteins in Vero E6 cells infected with Sin Nombre virus.[15] Accordingly, hantavirus nucleocapsid proteins antagonize the signaling pathway of TNF-α, suggesting that this cytokine may play a role in the immune response against hantavirus.[16] Our patient was only briefly exposed to contaminated aerosols and became infected while other members of his family had similar activities without clinical evidence for infection. It it therefore possible that TNF-α treatment has been a risk factor for infection. Nevertheless, the mild clinical course and the total absence of renal or hematologic involvement suggest that TNF-α is not required for the clearance of infection and might furthermore play a deleterious role in its manifestations (although we cannot formally rule out a protective genetic background despite the fact that the patient is not HLA-B27). Corticosteroids have been used to treat severe complications of hantavirus infection.[17] In view of the crucial role of T cells secreting IFN-γ in the resolution of the disease,[18] amore targeted approachagainst TNF-α might be an option for severe hemorragic fever with renal syndrome.

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Conflict of interest

The authors declare that there is no conflict of interest in the description of this case.

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