Treatment with rituximab of cryoglobulinemic vasculitis, which persisted despite successful treatment of HCV with antiviral treatment

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Background

Cryoglobulinemia is the most frequent extrahepatic manifestation of chronic hepatitis C (HCV). Cryglobulinemia can lead to vasculitis in target organs such as the skin, joints, peripheral nerves and the kidney. The treatment of HCV related cryoglobulinemic vaculitis targets either the HCV viral trigger or downstream pathogenic events by less specific immunosuppression. Eradication of HCV by anti-viral therapy should always be tried, because this approach can eradicate cryglobulins and improve vasculitis. In case of failure of this approach, limited data concerning the optimal treatment regimen are available. The place for anti-CD20 monoclonal antibody rituximab therapy is still an ultimate choice in case of failure of more classic approaches.

Case report

A 75-year old man was admitted to our hospital with purpura (Fig. 1) and multiples ulcers of both legs (Fig. 2), resistant to medical and surgical treatment (graft) since 12 months. A cutaneous biopsy revealed leucocytoclastic vasculitis (Fig. 3). Work-up of the etiology of this leucocytoclastic vasculitis showed type III cryoglobulinemia in relation with a hepatitis C infection of genotype 1b. Treatment with prednisone was unsuccessful.

Fig. 1: purpura of the right thigh

Fig. 2: multiples ulcers of the left leg calf and foot

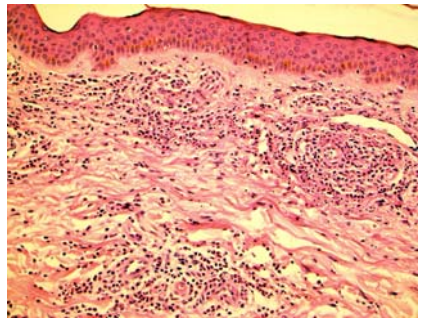

Fig. 3: skin biopsy: leucocyctoclastic vasculitis

We began a treatment with peginterferon alpha-2a and ribavirin which permitted rapid resolution of ulcers but which had to be stopped after 8 months because of extreme fatigue. Despite sustained viral response (the patient is still aviremic 2 years after antiviral treatment), type III cryoglobulinemia persisted, at a concentration of 1.25 g/l one month after stopping the antiviral treatment. The patient developed, one year after stopping antiviral treatment, painful paresthesias and hyposensitivity of both legs with difficulty to walk in relationship with a clinically severe polyneuropathy, which was confirmed by a ENMG. A biopsy of sural nerve showed an acute and chronic neuritis with perivascular, predominantly lymphocytic infiltration (Fig. 5), compatible with cryoglobulinemic vasculitis. We decided to administer a cycle of four weekly perfusions of rituximab (375 mg/m2). Four months later pain and paresthesias of the legs disappeared with decrease of distal hyposensitivity of both legs. ENMG showed mild improvement of nerve conductance parameters. The concentration of cryoglobulinemia dropped from 0.39 g/l before rituximab treatment to 0.17 g/l after treatment. The clinical and biologic evolution, as well as the treatment administered, is summarized in Fig. 4.

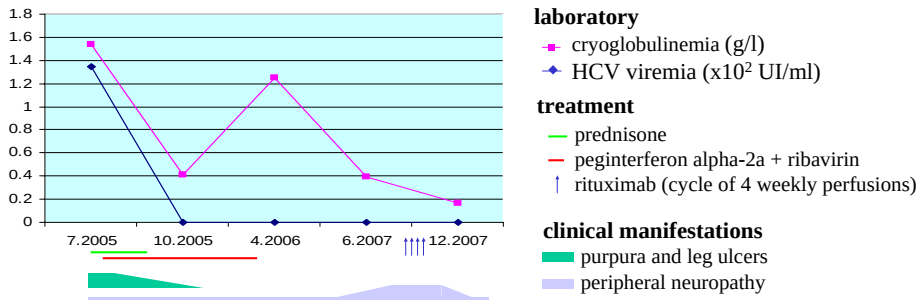

Fig. 4. Diagram of the clinical evolution, the main laboratory investigations and the treatment of the patient

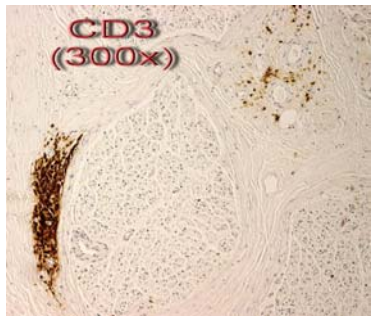

Fig. 5. Nerve biopsy showing perivascular cell infiltrations, predominantly of T-lymphocytes ($CD3^+$)

Conclusions

Despite successful antiviral treatment of hepatitis C infection with peginterferon-α and ribavirin, cryoglobulins may persist and still cause clinically significant cryoglobulinemic vasculitis. This phenomenon is known to exist, but is quite rare, and occurred in 2 out of 25 patients (8%) treated successfully with peginterferon alpha-2b and ribavirine in the greatest case series described today (1). The persistance of cryoglobulins after elimination of HCV reflects a clonal B cell expansion evolving independently of chronic stimulation by HCV.

Rituximab was used until now essentially as rescue treatment in cryoglobulinemic vasculitis refractory to antiviral treatment (2,3). In this case report we show its successful use in peripheral neuropathy asssociated with cryoglobulinemic vasculitis after elimination of HCV by antiviral treatment.

Although rituximab is a treatment option in cryoglobulinemic vasculitis, its place in treating hepatitis C associated cryoglobulinemic vasculitis warrants further investigation in randomized, placebo-controlled studies.

References

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3) Cai FZJ et al. Treatment of cryoglobulinemia associated peripheral neuropathy with rituximab. J Rheumatol 2006; 33: 1197-8