Digestive and Liver Disease 48 (2016) 780–784

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the *Gruppo Italiano di Studio delle Crioglobulinemie – GISC*

Cesare Mazzaro[a,*], Luigino Dal Maso[b,**], Teresa Urraro[c], Endri Mauro[d], Laura Castelnovo[e], Pietro Casarin[d], Giuseppe Monti[e], Valter Gattei[a], Anna Linda Zignego[c], Gabriele Pozzato[f]

[a] *Clinical and Experimental Onco-Hematology Unit, CRO Aviano National Cancer Institute, Aviano, Italy*
[b] *Epidemiology and Biostatistics Unit, CRO-Aviano National Cancer Institute, Aviano, Italy*
[c] *Centro Manifestazioni Sistemiche da Virus Epatitici, University of Florence, Firenze, Italy*
[d] *Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy*
[e] *Department of Internal Medicine, Saronno General Hospital, Saronno (VA), Italy*
[f] *Department of Medical and Surgical Sciences, University of Trieste, Trieste, Italy*

ARTICLE INFO

Article history:
Received 10 November 2015
Accepted 29 March 2016
Available online 2 April 2016

Keywords:
Cryoglobulinemia
Entecavir
Hepatitis B virus
Vasculitis

ABSTRACT

Background: Cryoglobulinemic vasculitis (CV) related to Hepatitis-B Virus (HBV) is rare and its treatment is ill-defined.
Aims: To describe clinical and treatment characteristics of HBV-related CV patients. In addition, the efficacy of treatment with antiviral agent nucleotide (NUC), including Entecavir, Adefovir, and Lamivudine, was explored.
Methods: In four Italian centres, 17 HBV-positive CV patients (median age 56 years, range 45–70) were enrolled.
Results: The extrahepatic manifestations were: purpura (100%), arthralgias (71%), peripheral neuropathy (29%), chronic hepatitis (47%), liver cirrhosis (29%), and glomerulonephritis (18%). Mixed cryoglobulinemias were type II (88%) and type III (12%). The median cryocrit was 3% (range 1–14), rheumatoid factor was 200 U/L (range 20–5850), C4 was 12 mg/dl (range 2–31), ALT 71 U/L (range 36–114). All patients were HBsAg-positive and 80% anti-HbeAg-positive. At enrollment, they were treated with steroids (eight), Entecavir (five), Alpha-IFN (two), Adefovir and Lamivudine (one each). After NUC treatment, no disease progression was observed and, in all patients, HBV-DNA became undetectable. Moreover, a regression of purpura and a reduction of cryocrit were observed. Four patients died during therapy, two of kidney failure and two of liver cirrhosis.
Conclusion: NUC therapy appeared to be safe and effective in CV-related HBV.

1. Introduction

Infection with hepatitis B (HBV) is a serious worldwide public health problem. It is estimated that about 350 million people are chronically infected with HBV. The clinical manifestations of HBV range from acute or fulminant hepatitis to various forms of chronic infection, including an inactive carrier state, chronic hepatitis, cirrhosis, and hepatocellular carcinoma [1,2].

About 20% of HBV patients develop extrahepatic manifestations; among them, polyarthritis nodosa and glomerulonephritis are the most severe. Other manifestations (e.g., dermatitis, polyarthralgias and arthritis, respiratory disease, aplastic anemia) are rare and cryoglobulinemic vasculitis (CV) occurs in approximately 3% of patients [3,4]. No association has been found between these manifestations and viral genotypes [3,4]. Reported cases of HBV-related CV are rare, the most effective treatment is still unknown, as no definitive guidelines have been issued to date. The conventional

* Corresponding author at: Clinical and Experimental Onco-Hematology Unit, CRO Aviano National Cancer Institute IRCCS, Via Franco Gallini 2, Aviano, Pordenone 33081, Italy.
** Corresponding author at: Epidemiology and Biostatistics Unit, CRO Aviano National Cancer Institute IRCCS, Via Franco Gallini 2, Aviano, Pordenone 33081, Italy.
E-mail addresses: cesare.mazzaro@gmail.com (C. Mazzaro), epidemiology@cro.it (L. Dal Maso).

http://dx.doi.org/10.1016/j.dld.2016.03.018
1590-8658/

immunosuppressive therapy used in rheumatologic disorders is not indicated in HBV-related CV, while antiviral therapy with nucleotide analogues seems to be the best treatment in these cases. Evidence on the efficacy of the antiviral treatment of HBV-related CV with nucleoside analogues is limited, since only case reports are presently available in the literature [5–11]. According to Brouet et al. [12], the cryoglobulinemias are classified in three types. In type I, the cryoglobulins are formed by monoclonal immunoglobulins only, commonly IgM. This type of cryoglobulins are associated with lymphoproliferative disorder (multiple myeloma or Waldenström's disease). In types II and III (so called mixed cryoglobulinemias, MC), the cryoglobulins are immune-complexes composed by polyclonal IgGs, the antigen(s), and monoclonal or policlonal IgMs, respectively. The IgM are endowed with rheumatoid factor activity, i.e., against polyclonal IgG [12–14]. Types II and III are associated with chronic viral infections (i.e., HBV and HCV), connective tissue diseases, and lymphoproliferative disorders.

The clinical manifestations of MC are due to the deposition of immune-complexes in several organs and tissues. MC may determine not only purpura, arthralgias and asthenia, but also more serious lesions of the skin (large ulcers), and neurologic and renal involvement [15–19]. The therapy of MC is based on immunosuppressive agents (steroids, cyclophosphamide, azathioprine, cyclosporine) for patients with mild-to-moderate disease, whereas more aggressive treatments, such as corticosteroids or plasmapheresis or high-dose cyclophosphamide, are needed in patients with severe disease [20,21]. More recently, data on the efficacy and safety of anti-CD20 monoclonal antibodies in MC vasculitis have emerged [22,23].

The purpose of this retrospective study was to assess the treatment in a group of patients with HBV-related CV.

2. Patients and methods

Seventeen consecutive patients (10 females and 7 males) affected by HBV-related CV were included in this study. All cases were enrolled between 2006 and December 2014 at the Department of Internal Medicine of Pordenone General Hospital, at the 'Centro Manifestazioni Sistemiche da Virus Epatitici', University of Florence, and at the Department of Internal Medicine of the Saronno General Hospital.

The inclusion criteria of this retrospective study was the presence of chronic HBV associated with clinical symptoms of CV. All patients were positive for HBV surface antigen (HBsAg) and measurable levels of serum HBV-DNA were detectable. The patients showing anti-Hepatitis C and/or anti-human immunodeficiency virus (HIV) antibodies or with concomitant malignant diseases were excluded.

Clinical and biological data were recorded for each patient at onset, during follow-up, and at the end of follow-up. The visits were scheduled every 3 months and information collected until June 2015. Liver function as well as kidney function testing and haematological parameters, laboratory assessment, including determination of complement components, rheumatoid factor and cryoglobulin serum levels were carried out using standard methods. MC was classified as type II in presence of monoclonal IgM complexed with polyclonal IgG, and type III in presence of polyclonal immunoglobulins. Patients showing elevated creatinine levels and 24 h proteinuria underwent biopsy for kidney involvement. Liver biopsies were performed in patients showing only signs of chronic liver disease. The grading for liver fibrosis was performed by means of transient elastography [24].

Table 1
Baseline, clinical, biochemical and histological features of 17 patients with HBV positive cryoglobulinemic vasculitis.[a]

	Median (range)	*N* (%)
Males		7 (41%)
Type II cryoglobulinemia		15 (88%)
Age	56 (45–70)	
ALT (6–78 U/L)[b]	71 (36–114)	
Creatinine (0.50–1 mg/dl)[b]	1.0 (0.7–2.4)	
Cryocrit (%)	3.0 (1.0–14.0)	
Rheumatoid factor (0–25 IU/ml)[b]	200 (20–5850)	
C4 (10–40 mg/dl)[b]	12 (2–31)	
Clinical manifestations		
Purpura		17 (100%)
Arthralgias		12 (71%)
Leg ulcer		1 (6%)
Peripheral neuropathy		5 (29%)
Raynaud phenomenon		3 (18%)
Glomerulonephritis		3 (18%)
Chronic hepatitis		8 (47%)
Liver cirrhosis		5 (29%)

ALT, alanine aminotransferase.
[a] Followed for a median time of observation of 5.2 years (range 0.5–19 years).
[b] Normal values.

2.1. Treatment

Due to the retrospective nature of our study, the included patients had received different treatments. High-dose corticosteroids (1–10 m/kg) were administered to treat systemic vasculitis and critical manifestations of MC (renal, neurological and hyperviscosity syndromes) [21]. Low-medium corticosteroid doses (0.1–0.5 mg/kg/day) were used in mild or moderate cryoglobulinemic vasculitis (purpura, arthralgias, peripheral neuropathy) [21]. Antiviral therapy was also not homogeneous; indeed, some patients were treated with interferon-alpha-2b (5 MU/die for 6 months), others with Entecavir 0.5 mg/day, or with Adefovir 10 mg/die and even with Lamivudine 100 mg/die. Biochemical and clinical parameters were measured every two months during treatment, while HBsAg, HBV-DNA, cryoglobulins, RF and complement fraction C4 every 6 months.

2.2. Outcome measures

As previously reported [25], four types of response to treatment were initially defined (virological, biochemical, immunological, and clinical) and herein presented at 48 months of continuous treatment (after enrollment).

2.3. Statistical analysis

Descriptive statistics of relevant variables were performed using median and range. Mean and standard deviation (SD) were not informative and not presented because of the limited number of patients.

3. Results

3.1. Patients' characteristics

The study enrolled 17 patients (seven males, 41%), median age 56 (range 45–70 years) with HBV-related CV. Table 1 shows patients' biochemical, clinical, and histological characteristics. All of them presented purpura on the leg and asthenia, and 12 of them (71%) also arthralgias. Peripheral neuropathy was found in five cases (29%), and one of them showed a large ulcer on the left leg (6%). Fifteen cases (88%) had type II MC and two cases