

Chapter 16: Extrahepatic manifestations

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Introduction

Patients with chronic hepatitis C virus (HCV) infection are at risk of a great number of extrahepatic manifestations (EHMs) (Table 1) – up to 40-76% of patients infected with HCV develop at least one EHM during the course of the disease (Cacoub 2000; Cacoub 1999). EHMs are often the first and only clinical sign of chronic hepatitis C infection. Evidence of HCV infection should always be sought out in cases of non-specific chronic fatigue and/or rheumatic, haematological, endocrine or dermatological disorders. The pathogenesis of EHM is still not fully understood, although most studies suggest that the presence of mixed cryoglobulinaemia, particular lymphotropism of the virus, molecular mimicry and non-cryoglobulinaemic autoimmune phenomena constitute the major pathogenic factors (Ferri 2007). Nevertheless, pathogenesis and epidemiology of many EHMs requires further investigation (Figure 1). Our aim is to give a brief insight into the epidemiology, pathogenesis, clinical relevance and therapeutic management of HCV-associated EHM (Zignego 2007a).

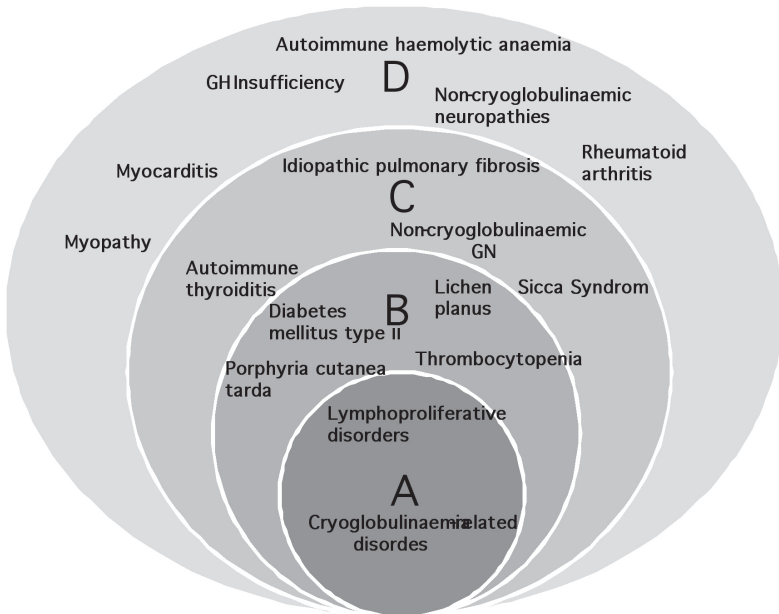


Figure 1. Schematic representation of EHM categories (modified after Zignego 2007a). A) Associations that rest upon strong epidemiological evidence and clear pathogenetic mechanisms; B) Associations that rest upon high prevalence, but still unclear pathogenetic mechanisms; C) Associations for which the high prevalence in HCV collectives could be due to HCV infection and/or confounding factors; D) Anecdotal observations.

Organ/System	Manifestation
Endocrine disorders	
	Autoimmune thyroidopathies (in particular, Hashimoto thyroiditis)
	Insulin resistance/diabetes mellitus*
	GH-insufficiency
Rheumatic disorders	
	Mixed cryoglobulinaemia*
	Cryoglobulinaemic vasculitis*
	Peripheral neuropathy*
	Membrano-proliferative glomerulonephritis (GN)*
	Membranous GN*
	Rheumatoid arthralgias/oligo-polyarthritis
	Rheumatoid factor positivity*
	Sicca syndrome
Haematologic disorders	
	Lymphoproliferative disorders/Non-Hodgkin Lymphomas*
	Immune thrombocytopaenic purpura (ITP)
	Monoclonal gammopathies*
	Autoimmune haemolytic anaemia
Dermatologic disorders	
	Palpable purpura
	Porphyria cutanea tarda (PCT)
	Lichen planus
	Pruritus
Miscellaneous	
	Chronic fatigue*, subclinical cognitive impairment, psychomotoric deceleration, symptoms of depression*
	Myopathy
	Cardiomyopathy/Myocarditis
	Idiopathic pulmonal fibrosis
* Associations that rest upon strong epidemiological prevalence and/or clear pathogenetic mechanisms	

Table 1. HCV-related extrahepatic manifestations.

Lymphoproliferative disorders

Mixed cryoglobulinaemia (MC)

Cryoglobulinaemia refers to the presence of abnormal immunoglobulins in the serum, which have the unusual property of precipitating at temperatures below 37°C and redissolving at higher temperatures. The phenomenon of cryoprecipitation was first described in 1933 (Wintrobe 1933). Cryoglobulins (CGs) are nowadays classified, on the basis of

their clonality, into three types [Table 2]. Type II CG and type III CG, consisting of monoclonal and/or polyclonal immunoglobulins, are prevalent in patients with a chronic HCV infection, while type I CGs, consisting exclusively of monoclonal components, are mostly found in patients with lymphoproliferative disorders (multiple myeloma, B cell lymphoma, Waldenström macroglobulinaemia). Type II or type III mixed cryoglobulinaemia is found in 19%-50% of patients with chronic HCV, but leads to clinical manifestations, through vascular precipitation of immunocomplexes, in only 30% of them (Lunel 1994; Wong 1996). Asymptomatic mixed cryoglobulinaemia, during the course of chronic HCV infection, may evolve into symptomatic disease. Patients with symptomatic mixed cryoglobulinaemia exhibit higher cryoglobulin concentrations (cyocrit >3%) (Weiner 1998) and lower concentrations of complement factors C3 and C4. Thus CG-triggered complement activation may constitute a key incidence in cryoglobulinaemia-derived pathogenesis.

Factors that seem to favour the development of MC are female sex, age, alcohol intake (>50g/d), advanced liver fibrosis and steatosis (Lunel 1994; Wong 1996; Saadoun 2006).

Clonality	
Type I	Monoclonal immunoglobulins (IgG or IgM)
Type II	Polyclonal immunoglobulins (mainly IgG) and monoclonal IgM with rheumatoid factor activity (RF)
Type III	Polyclonal IgG and IgM

Table 2. Classification of cryoglobulinaemia types.

Diagnosis. Detection of CG is carried out by keeping patient serum at 4° for up to 7 days. After cryoprecipitate is visible, CG can be purified and characterized using immunofixation electrophoresis. In case of evidence of mixed cryoglobulinaemia in HCV-positive patients, the presence of cryoglobulinaemic-syndrome must be sought out. Vigilant monitoring is required, as asymptomatic mixed cryoglobulinaemia patients may develop MC-related disorders in the course of the disease. The diagnosis of the MC syndrome is based on serologic, pathologic and clinical criteria (Table 3).

Serologic	Histopathologic	Clinical
C4 reduction	Leukocytoclastic vasculitis	Purpura
Positive rheumatoid factor (RF)	Infiltrates of monoclonal B-cells	Fatigue
CGs type II or III		Arthralgien
HCV antibodies		Membranoproliferative GN Peripheral neuropathy

Table 3. Diagnostic criteria of cryoglobulinaemic syndrome.

In the presence of mixed CG, low C4 counts, leucocytoclastic vasculitis and purpura, a definite symptomatic MC can be diagnosed. Rheumatoid factor (RF) determination constitutes a reliable surrogate parameter for detection of CG. Finally, presence of CG may impair HCV RNA determination as viral RNA can accumulate in precipitated cryocrit (Colantoni 1997).

Clinical features of mixed cryoglobulinaemia. HCV-related MC proceeds mostly asymptotically and has no significant influence on the course of chronic liver inflammation. On the other hand, symptomatic mixed cryoglobulinaemia is associated with higher mortality (Ferri 2004). Clinical manifestations of symptomatic mixed cryoglobulinaemia are listed below:

Systemic vasculitis: HCV-related vasculitis relies on a deposition of immunocomplexes, containing CGs, complement and large amounts of HCV antigens in the small- and medium-sized blood vessels. HCV accumulates in the CG-immunoglobulins. Pathohistological findings reveal a leucocytoclastic vasculitis (Agnello 1997). The most common symptoms of mixed cryoglobulinaemic vasculitis are weakness, arthralgia and purpura (the Meltzer and Franklin triad). Mixed cryoglobulinaemic vasculitis may also lead to Raynaud's Syndrome and Sicca Syndrome, glomerulonephritis and peripheral neuropathy.

Renal impairment: The predominant renal impairment associated with mixed cryoglobulinaemia is the membranous proliferative glomerulonephritis (MPGN), characterized in most cases by proteinuria, mild haematuria and mild renal insufficiency. The presence of kidney impairment is considered to be a negative prognostic factor in the course of the disease (Ferri 2004). In 15% of patients, MC-related nephropathy may progress towards terminal chronic renal failure requiring dialysis (Tarantino 1995).

Peripheral neuropathy: Peripheral neuropathy, on the basis of endoneural microangiopathy, constitutes a further typical complication of mixed cryoglobulinaemia. MC-related neuropathy, presenting clinically as mononeuropathy or polyneuropathy, is mostly sensory and is characterized by numbness, burning skin crawling and pruritus, predominantly in the hands and feet (Tembl 1999; Lidove 2001). Epidemiological data from Italy suggest that peripheral neuropathy is the second most common symptom after the Meltzer and Franklin triad in patients with symptomatic HCV-associated mixed cryoglobulinaemia (Ferri 2004).

Cirrhosis: The causal association between CG and progression of liver fibrosis, suggested by numerous authors has not been confirmed in a recently published 10-year prospective study. The 10-year rates of progression to cirrhosis were similar in cryoglobulinaemic and non-cryoglobulinaemic HCV-infected patients (Vigano 2007). With respect to this recent data, it is unlikely that mixed cryoglobulinaemia constitutes an independent risk factor for the progression of liver fibrosis.

Malignant lymphoproliferative disorders/NHL

The association between infectious agents and potentially reversible "antigen driven" lymphoproliferative disorders, such as *Helicobacter pylori*-related gastric marginal zone B cell lymphoma has been known for many decades. Recent data suggest a causative association between HCV and Non-Hodgkin Lymphoma (NHL) (Mele 2003; Duberg 2005; Giordano 2007). HCV infection leads per se to a twofold higher risk

of developing NHL (Mele 2003; Duberg 2005). The most prevalent HCV-associated lymphoproliferative disorders according to the REAL/WHO classification are: follicular lymphoma, B cell chronic lymphocytic leukaemia/small lymphocyte lymphoma, diffuse large B cell lymphoma and marginal zone lymphoma, including the mucosa-associated lymphoid tissue lymphoma. Overall, marginal zone lymphoma appears to be the most frequently encountered low grade B cell lymphoma in HCV patients.

HCV-associated lymphoproliferative disorders (LPDs) are observed over the course of MC. 8%-10% of mixed cryoglobulinaemia type II evolve into B cell NHL after long-lasting infection. However, a remarkably high prevalence of B cell NHL was also found in HCV patients without mixed cryoglobulinaemia (Silvestri 1997). Genetic predisposition and factors seem to have a major impact on the development of LPDs in HCV-positive patients (Matsuo 2004).

Aetiology and pathogenesis of LPDs in patients with HCV infection. In the development of LPDs direct and indirect pathogenic HCV-associated factors (Figure 2) are seen. Sustained B cell activation and proliferation, noticed during chronic HCV infection, is an indirect pathogenic mechanism.

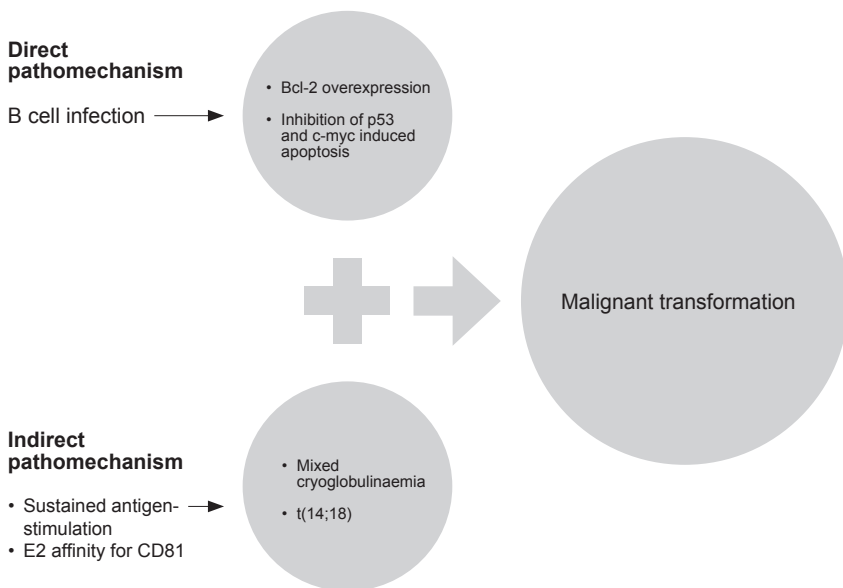


Fig 2. Pathomechanisms involved in the development of malignant lymphoproliferative disorders in patients with chronic HCV infection. Indirect pathomechanism: Sustained antigen stimulation, as binding of viral envelope protein to CD81 receptor, leads to excessive B cell proliferation, which in turn favors development of mixed cryoglobulinaemia and/or genetic aberrations, such as t(14;18) translocation. Direct pathomechanism: Viral infection of B cells, as viral replication in them may result in activation of proto-oncogenes (i.e., Bcl-2) and/or inhibition of apoptotic factors (i.e., p53, c-myc). One of the factors favoring this polyclonal B cell activation and proliferation is probably the HCV E2 protein, which binds specifically to CD81, a potent B cell activator (Cormier 2004).

Direct pathogenic mechanisms are based on lymphotropic properties of HCV, hence on the very invasion of HCV into the B cells. HCV RNA sequences were first detected in mononuclear peripheral blood cells (Zignego 1992). Especially CD19⁺ cells seem to be permissive for certain HCV quasispecies (Roque Afonso 1999). Active replication of the HCV genome in B cells is associated with activation of anti-apoptotic gene bcl-2 and inhibition of p53 or c-Myc-induced apoptosis (Sakamuro 1995; Ray 1996). In this light, direct involvement of HCV in the immortalisation of B cells can be envisioned (Zignego 2000; Machida 2004).

Treatment of lymphoproliferative disorders

Mixed cryoglobulinaemia: While asymptomatic MC per se does not constitute an indication for treatment, symptomatic mixed cryoglobulinaemia should be always treated. Because asymptomatic cryoglobulinaemia may evolve into symptomatic in the course of disease, vigilant monitoring is required and introduction of antiviral therapy in terms of prophylaxis should be considered.

A casual correlation between HCV infection and mixed cryoglobulinaemia has been established, the therapeutic approach of symptomatic mixed cryoglobulinaemia should primarily concentrate on the eradication of the virus. Indeed, clinical improvement of MC is reported in 50 to 70% of patients receiving antiviral therapy with interferon α (IFN α) and ribavirin and mostly correlates with a drastic reduction of HCV RNA concentrations (Calleja 1999). However, cryoglobulinaemic vasculitis following successful antiviral treatment persists in a small collective (Levine 2005). On the other hand, IFN α is a promising therapeutic tool irrespective of virologic response. Due to its antiproliferative properties on IgM-RF producing B cells and stimulation of macrophage-mediated clearance of immunocomplexes, IFN α may lead to clinical amelioration even in virological nonresponders. Therefore, therapeutic success should be primarily evaluated on the basis of clinical response irrespective of virologic response. In case of treatment failure of antiviral therapy and/or fulminant manifestations, contraindications or severe side effects, alternative therapeutic strategies, such as cytostatic immunosuppressive therapy and/or plasmapheresis should be taken into consideration (Craxi 2008) (Figure 3; Table 4).

In cases of severe systemic vasculitis, initial therapy with rituximab, a monoclonal chimeric antibody against CD20 B cell specific antigen, is suggested. Its efficacy and safety have also been demonstrated in patients with symptomatic MC resistant to IFN α therapy, although HCV RNA increased approximately twice the baseline levels in responders (Sansonno 2003). In this light, combined application of rituximab with PEG-IFN α plus ribavirin in cases of severe mixed cryoglobulinaemia-related vasculitis resistant to antiviral therapy seems to be the optimal therapeutic strategy, achieving amelioration of MC-related symptoms and a complete eradication of HCV in responders (Saadoun 2008). In severe rituximab-refractory mixed cryoglobulinaemia-related vasculitis or acute manifestations, cycles of plasma exchange plus corticosteroids and eventually cyclophosphamide are indicated.

Effectiveness of antiviral therapy on cryoglobulinaemia-induced peripheral neuropathy is still being discussed. While HCV-related peripheral neuropathy responsive to antiviral

therapy with IFN α and ribavirin in 4 patients with chronic HCV was reported (Koskinas 2007), several authors report on aggravation of cryoglobulinaemic neuropathy or even *de novo* occurrence of demyelinating polyneuropathy during IFN α and PEG-IFN α treatment (Boonyapist 2002; Khiani 2008). Therefore, application of IFN α in presence of HCV-related neuropathy requires a cautious risk-benefit assessment.

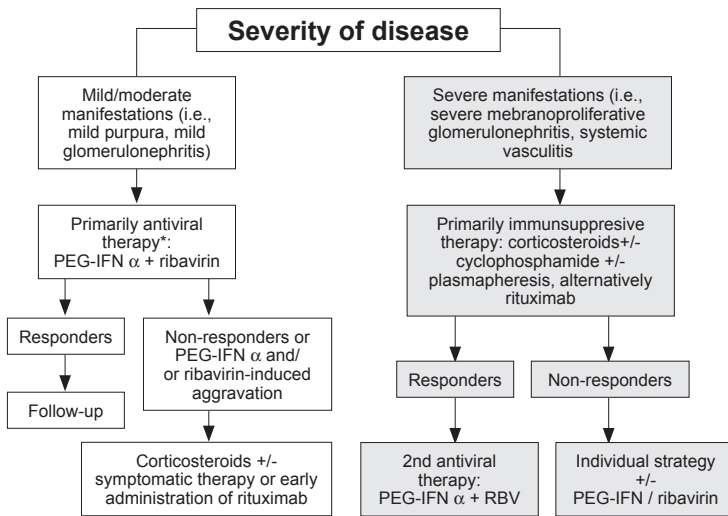


Fig. 3. Therapy algorithm for symptomatic HCV-related mixed cryoglobulinaemia (modified after Craxi 2008). Antiviral therapy, on the basis of PEG-IFN α and ribavirin, is regarded as first line therapy in cases of mild/moderate manifestations. In case of contraindications, patients should be treated primarily with corticosteroids. Non-response to antiviral therapy or drug-induced aggravation make application of corticosteroids essential. Long-term therapy with corticosteroids may result in elevation of viral load and progression of hepatic disease. In this light, rituximab represents an attractive alternative, for in this case, drug-induced viral load elevation is of minor extent. In patients with severe manifestations, treatment should focus on immunosuppression (\pm plasmapheresis). Due to its excellent immunosuppressive properties and relatively mild side effect profile, use of rituximab should be favored in this constellation. In case of good clinical response, consecutive antiviral treatment in terms of PEG-IFN α and ribavirin may serve as a maintenance therapy. Therapy refractory cases require individual treatment according to the particular center experience. Supplementation of therapeutic strategy by antiviral therapy should be taken into consideration.

As eradication of *Helicobacter pylori* may lead to complete remission of MALT lymphoma, so antiviral therapy can lead to regression of low-grade NHL in patients with HCV-related malignant lymphoproliferative disorders. PEG-IFN α plus ribavirin should be regarded in such cases as first line therapy (Giannelli 2003; Vallisa 2005). Thus, remission of the haematologic disorders is closely associated with virologic response or rather achievement of sustained virologic response. Effectiveness of IFN α in this context should be ascribed primarily to its antiviral and less to its anti-proliferative drug properties.

Author	Patients	Therapy	Notes
Zuckerman	N=9 Virological non-responders with symptomatic cryoglobulinaemia after IFN α monotherapy	Standard IFN α plus ribavirin 15mg/kg/d	CGs undetectable within 6 weeks in 7/9 patients; Clinical improvement in 9/9 within 10 week
Sansonno	N=20 Clinical non-responders with vasculitis and peripheral neuropathy after IFN α monotherapy	Rituximab 375 mg/m ² /week for 4 weeks	16 patients with complete clinical response; 12 with sustained response throughout follow-up. Viraemia increase in responders
Saadoun	N=16 Cryoglobulinaemic-vasculitis in relapsers or non-responders to IFN α /PEG-IFN α + ribavirin	Rituximab 375 mg/m ² /wk for 4 weeks combined with PEG-IFN α 1.5 ug/kg/wk plus RBV (600 mg - 1200 mg/d) for 12 months	10/16 complete clinical response; CGs and RNA HCV undetectable in responders
Bruchfeld	N=7 HCV-related renal manifestations (2/7 cryoglobulinaemia-related)	IFN α plus low-dose RBV (200-600mg) or PEG-IFN α plus low-dose ribavirin	Improvement of GRF and proteinuria in 4/7 patients and sustained viral response in 5/7.
Roccatello	N=6 Cryoglobulinaemic-systematic manifestations; predominantly renal (5/6)	Rituximab 375 mg/m ² /wk for 4weeks plus rituximab 375mg/m ² 1 month and 2 months later	Decrease of cryocrit and proteinuria at month 2, 6, 12.
Koskinas	N=4 Cryoglobulinaemic-patients with severe sensory-motor polyneuropathy	INF α -2b 1,5ug/kg/week + ribavirin 10.6 mg/kg/d for 48 weeks	Significant improvement of neurological parameters in 4/4; Undetectable HCV RNA and lower CG-levels in 3/4 at the end of therapy.

Table 4. Treatment of cryoglobulinaemia-related disorders in patients with chronic HCV infection.

Treatment of HCV infected patients with high-grade NHL should be based on cytostatic chemotherapy. HCV infection does not constitute a contraindication for cytostatic chemotherapy. Unlike HBV infection, antiviral prophylaxis before chemotherapy introduction is not obligatory. Chemotherapy may lead to a substantial increase in viraemia. Consecutive exacerbation of the infection, making discontinuation of chemotherapy mandatory, is unlikely to occur. However, treatment-related liver toxicity is more frequent in HCV-positive NHL and is often associated with severe hepatic manifestations (Besson 2006; Arcaini 2009). Current data suggest that antiviral treatment may serve as maintenance therapy for achieving sustained remission of NHL after chemotherapy completion (Gianelli 2003).

Further haematological manifestations

HCV-associated thrombocytopenia

Thrombocytopenic conditions (platelet counts below $150 \times 103/\mu\text{L}$) are often observed in patients with chronic hepatitis C and result mainly from advanced liver fibrosis and manifest cirrhosis (Wang 2004). Lack of hepatic-derived thrombopoietin can *inter alia* be recognized as an important causal factor (Afdhal 2008). As HCV RNA can be abundant in platelets (Takehara 1994) and megakaryocytes of thrombocytopenic patients, direct cytopathic involvement of HCV can be hypothesized (Bordin 1995; De Almeida 2004). Furthermore, it has been suggested that exposure to HCV may be a causative factor for the production of platelet-associated immunoglobulins, inducing thrombocytopenia through a similar immunological mechanism to that operating in immune thrombocytopenic purpura (ITP) (Aref 2009). There is a high HCV prevalence in patients with ITP (García-Suaréz 2000), and these patients exhibit diverse characteristics to HCV-negative patients with ITP, which supports the hypothesis of direct viral involvement in the development of thrombocytopenia (Rajan 2005).

There is no consensus regarding the optimum treatment of HCV-related ITP. Along with classical therapeutic approaches such as corticosteroids, intravenous immunoglobulins and splenectomy, antiviral therapy constitutes another option. Substantial increase of platelets after application of antiviral therapy is registered in a significant percentage of patients with HCV-related ITP (Iga 2005), although evidence from further studies is required to confirm this hypothesis. However, caution is recommended in thrombocytopenic patients treated with PEG-IFN α plus ribavirin as significant aggravation of HCV-related ITP may occur under this regimen (Fattovich 1996). On the other hand, long-term use of steroids and immunosuppressive drugs respectively is limited by an increased risk of fibrosis progression and a substantial elevation of virus. A new orally active thrombopoietin-receptor agonist, eltrombopag, may be used in thrombocytopenic HCV patients in the future. Its efficacy was recently documented in patients with HCV-related ITP (Bussel 2007) as well as in HCV-positive patients suffering from thrombocytopenia due to cirrhosis (McHutchison 2007). In case of refractory disease or aggravation during the course of antiviral therapy, rituximab should be considered (Weitz 2005).

HCV-related autoimmune haemolytic anaemia

Interpretation of autoimmune haemolytic anaemia (AHA) as a possible EHM is based mainly on a few well-documented case reports (Chao 2001; Fernández 2006; Srinivasan 2001). AHA has been frequently observed in HCV patients treated with IFN α with and without ribavirin and consequently recognized as a possible side effect of antiviral treatment (De la Serna-Higuera 1999; Nomura 2004). Recently, a large-scale epidemiological study confirmed a high incidence of AHA in HCV patients undergoing antiviral treatment. However, the incidence rate of AHA in treatment-naïve HCV patients was statistically insignificant (Chiao 2009). In this light, there is, for the time being, little evidence for regarding AHA as a possible EHM of chronic HCV infection.

HCV-related glomerulonephritis

Glomerulonephritis (GN) constitutes a rare extrahepatic complication of chronic HCV. Predominant manifestations are cryoglobulinaemic or non-cryoglobulinaemic membranous proliferative GN and mesangioproliferative GN. Far less common is membranous nephropathy (Arase 1998). Other forms of GN do not correlate significantly with HCV infection (Daghestani 1999). Microhaematuria and proteinuria are among the most frequent medical findings in patients with membranous proliferative GN. Approximately 50% of patients exhibit a mild renal insufficiency. 20-25% may present an acute nephritic syndrome (haematuria, hypertension and proteinuria) as in 25% of patients nephrotic syndrome represents the initial manifestation. In contrast, >80% of patients with HCV-related membranous nephropathy suffer primarily a nephrotic syndrome (Doutrelepont 1993; Rollino 1991). The mesangioproliferative form proceeds mostly asymptotically, where typical findings such as haematuria and proteinuria are often missing (McGuire 2006).

The pathomechanism of renal impairment is yet not fully understood. It can be hypothesized that glomerular injury is primarily caused by a deposition of circulating immunocomplexes containing anti-HCV antibodies, HCV antigens and complement factors. Formation and deposition of such immunocomplexes occurs also in the absence of CGs. HCV-proteins in glomerular and tubulointerstitial structures are immunohistologically detectable in approximately 70% of the patients with chronic HCV (Sansonno 1997). Further possible pathomechanisms of glomerular injury encompass formation of glomerular autoantibodies, glomerular impairment due to chronic hepatic injury, or IgM overproduction with consecutive glomerular IgM deposition as result of HCV-triggered cryoglobulinaemia type II. GN prevalence in HCV patients is estimated at 1.4% and is comparably high to its prevalence among blood donors (Paydas 1996).

HCV induced GN has mostly a benign prognosis (Daghestani 1999). 10-15% of patients with nephritic syndrome experience spontaneous complete or partial remission. Frequently persisting mild proteinuria exhibits no tendency to progression. It is estimated that only approximately 15% of the patients with HCV-related GN develop terminal renal failure requiring dialysis (Tarantino 1995). Nevertheless, presence of kidney impairment is considered to be a negative prognostic factor for long-term survival (Ferri 2004).

Patients with HCV-related GN should be primarily treated with antivirals. Sustained viral response leads normally in cases of mild renal impairment to amelioration of proteinuria or even full remission of GN. In case of high baseline viraemia and advanced renal insufficiency application of antiviral therapy is subject to certain limitations (Sabry 2002). Despite amelioration of proteinuria achieved after antiviral therapy, significant improvement of renal function is often lacking (Alric 2004). PEG-IFN and ribavirin dosage must be cautiously adjusted to glomerular filtration rate (GFR), in order to prevent mainly ribavirin accumulation with consecutive haemolytic anaemia (Fabrizi 2008). Even in advanced renal failure, use of ribavirin is recommended, due to superior efficacy of the combination therapy vs. IFN monotherapy (Bruchfeld 2003; Baid-Agrawal 2008). In patients with GFR <30 ml/min ribavirin dosage should not exceed 600mg/week. Careful dosage augmentation may be undertaken

in the absence of side effects. Ribavirin dosages up to 100-400mg/day was done under vigilant blood level monitoring in dialysis patients. Ribavirin-induced haemolytic anaemia was efficiently treated by administration of erythropoetin and erythrocyte concentrates (van Leusen 2008). As determination of ribavirin blood levels is not an established laboratory procedure, implementation of such a therapeutic approach in clinical routine remains arduous.

Fulminant manifestations with impending acute renal failure make administration of corticosteroids, immunosuppressive drugs such as cyclophosphamid and eventually plasmapheresis necessary (Garini 2007; Margin 1994). In cases of simultaneous bone marrow B cell infiltration and/or resistance to conventional therapy, application of rituximab is indicated (Roccatello 2004). Rituximab may be used as an alternative first line therapy in severe renal manifestations (Roccatello 2008). Antiviral and immunosuppressive therapy should always be supplemented with symptomatic therapy with ACE inhibitors or AT1 receptor antagonists (Kamar 2006).

Endocrine manifestations

Thyroid disease is found more commonly in patients with chronic HCV infection than in general population. About 13% of HCV-infected patients have hypothyroidism and up to 25% have thyroid antibodies (Antonelli 2004). On the other hand, there is evidence that IFN α may induce thyroid disease or unmask preexisting silent thyroidopathies (Graves disease, Hashimoto thyroiditis) (Prummel 2003). In addition, some studies suggest that thyroid autoimmune disorders were significantly present in patients with chronic hepatitis C during but not before IFN α therapy (Marazuela 1996; Vezali 2009). In this light, the role of chronic hepatitis C infection per se in the development of thyroid disorders remains to be determined. The presence of autoantibodies against thyroid with/without clinical manifestations increases the risk of developing an overt thyroiditis significantly during antiviral therapy. Therefore, monitoring of the thyroid function should be performed during treatment.

Association between chronic HCV infection and development of insulin resistance and diabetes mellitus has been discussed in the past (Knobler 2000; Mason 1999; Hui 2003; Mehta 2003). In the meantime, a causal association is backed up by studies demonstrating that antiviral therapy with consecutive sustained viral response correlates with improved diabetic metabolic status and resolution of insulin resistance (Kawaguchi 2007). A recently published meta-analysis of retrospective and prospective studies confirms a high risk for the development of diabetes mellitus type II in patients with chronic HCV infection (OR=1.68, 95%, CI 1.15-2.20) (White 2008). Viral induction of insulin resistance seems to be HCV-specific, as prevalence of diabetes mellitus in HBV-infected patients is significantly lower (White 2008; Imazeki 2008). The pathomechanism of HCV-induced insulin resistance is yet not fully understood. It has been suggested that the appearance of insulin resistance could correlate with certain genotypes of HCV. Furthermore, HCV-dependent upregulation of cytokine suppressor SOC-3 may be responsible for the induction of cell desensitization towards insulin. Insulin resistance in turn, represents an independent risk factor for progression of liver fibrosis in patients with chronic HCV infection (Moucarri 2008; Kawaguchi 2004).

Finally, the link between HCV, growth hormone (GH) insufficiency and low insulin-like growth factor (IGF-1) has been hypothesized. Reduced GH secretion could be the result of a direct inhibitory effect of HCV infection at the level of the pituitary or hypothalamus (Plöckinger 2007).

Dermatologic and miscellaneous manifestations

A multitude of cutaneous disorders has been sporadically associated with chronic HCV infection (Hadziyannis 1998). Epidemiologic studies have confirmed the existence of a strong correlation between the sporadic form of porphyria cutanea tarda (PTC) and HCV, though the presence of HCV in PTC patients seems to be subject to strong regional factors. Indeed, HCV prevalence in PTC patients is higher than 50% in Italy, while only 8% in Germany (Fargion 1992; Stölzel 1995).

Strong evidence of a close association between HCV and lichen planus was provided by studies performed in Japan and southern Europe (Nagao 1995; Carrozzo 1996), yet these observations do not apply to all geographic regions (Ingafou 1998). HLA-DR6 has been recognized as a major predisposing factor for development of lichen planus in HCV-positive patients. One hypothesis suggests that geographical fluctuation of HLA-DR6 is responsible for the diverse prevalence among HCV patients (Gandolfo 2002).

Idiopathic pulmonary fibrosis (IPF) represents potentially an EHM, as prevalence of anti-HCV in patients with this disease is notably high (Ueda 1992). Interestingly, alveolar lavage in therapy-naïve HCV patients yielded frequently findings consistent with a chronic alveolitis. Alveolar lavage in the same patients after completion of antiviral therapy showed a remission of inflammatory activity (Yamaguchi 1997). Involvement of CGs in the genesis of IPF is also probable (Ferri 1997).

Numerous central nervous manifestations have been described in association with HCV infection. Cryoglobulinaemic or non-cryoglobulinaemic vasculitis of cerebral blood vessels may be responsible for the relatively high prevalence of both ischaemic and haemorrhagic strokes in young HCV-positive patients (Cacoub 1998). Transverse myelopathies leading to symmetrical paraparesis and sensory deficiency have been recently observed (Aktipi 2007).

Furthermore, chronic HCV infection is associated with significant impairment of quality of life. 35-68% of HCV patients suffer from chronic fatigue, subclinical cognitive impairment and psychomotor deceleration. Symptoms of depression are evident in 2-30% of HCV patients examined (Perry 2008; Forton 2003; Carta 2007). Psychometric as functional magnetic resonance spectroscopy studies suggest altered neurotransmission in HCV-positive groups (Weissenborn 2006; Forton 2001). In addition, significant tryptophan deficiency is detectable in patients with chronic HCV infection. Resulting deficiency of the tryptophan-derived serotonin is likely to favor an occurrence of depressive disorders. There is evidence to suggest that antiviral therapy can lead to elevation of tryptophan blood levels and thus contribute to amelioration of depressive symptoms in HCV patients (Zignego 2007c).

Occasionally, chronic HCV infection has been seen in association with cardiac pathologies such as chronic myocarditis and dilatative/hypertrophic cardiomyopathy. Pathogenesis seems to rely on genetic predisposition and is assumed to be immunologically triggered (Matsumori 2000).

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