Hepatitis C virus (HCV) infection is responsible for both hepatic and extra-hepatic disorders (HCV-EHDs); these latter are correlated on one hand clearly with HCV lymphotropism causing immune-system dysregulation as well as with viral oncogenic potential, and on the other hand probably with chronic inflammatory status causing cardio-metabolic complications as well as neurocognitive disturbances. The spectrum of HCV-EHDs ranges from mild or moderate manifestations, such as arthralgia, sicca syndrome, peripheral neuropathy, to severe, life-threatening complications, mainly vasculitis and neoplastic complications. Given the clinical heterogeneity of HCV-EHDs, HCV-infected individuals are inevitably referred to different specialists according to the presenting prevalent symptom(s); therefore, the availability of comprehensive diagnostic guidelines is necessary for a patient’s whole assessment that is decisive for early diagnosis and correct therapeutic approach of various hepatic and HCV-EHDs, regardless of the specific competencies of different physicians or referral centers.

In this respect, a multidisciplinary network of experts, the International Study Group of Extrahepatic Manifestations Related to Hepatitis C Virus Infection (ISG-EHCV), was organized with the intention to formulate diagnostic guidelines for the work-up of possible HCV-EHDs. There was a broad consensus among ISG-EHCV members on the proposed guidelines, which essentially are based on two main levels of patient’s assessment. At the referral stage, it is proposed that all patients with HCV infection should be invariably examined by means of first-line diagnostic procedures including virological and hepatic parameter evaluation, as well as the detection of clinical findings that may suggest one or more HCV-EHDs. This preliminary assessment should reveal specific HCV-EHDs, which will be deeper investigated by means of second-line, targeted investigations.

The proposed multidisciplinary expert statement represents the first attempt to draw comprehensive diagnostic guidelines for HCV-infected individuals encompassing the entire spectrum of HCV-related disorders, namely Hepatitis C virus (HCV) infection is responsible for both hepatic and extra-hepatic disorders (HCV-EHDs); these latter are correlated on one hand clearly with HCV lymphotropism causing immune-system dysregulation as well as with viral oncogenic potential, and on the other hand probably with chronic inflammatory status causing cardio-metabolic complications as well as neurocognitive disturbances. The spectrum of HCV-EHDs ranges from mild or moderate manifestations, such as arthralgia, sicca syndrome, peripheral neuropathy, to severe, life-threatening complications, mainly vasculitis and neoplastic complications. Given the clinical heterogeneity of HCV-EHDs, HCV-infected individuals are inevitably referred to different specialists according to the presenting prevalent symptom(s); therefore, the availability of comprehensive diagnostic guidelines is necessary for a patient’s whole assessment that is decisive for early diagnosis and correct therapeutic approach of various hepatic and HCV-EHDs, regardless of the specific competencies of different physicians or referral centers. In this respect, a multidisciplinary network of experts, the International Study Group of Extrahepatic Manifestations Related to Hepatitis C Virus Infection (ISG-EHCV), was organized with the intention to formulate diagnostic guidelines for the work-up of possible HCV-EHDs. There was a broad consensus among ISG-EHCV members on the proposed guidelines, which essentially are based on two main levels of patient’s assessment. At the referral stage, it is proposed that all patients with HCV infection should be invariably examined by means of first-line diagnostic procedures including virological and hepatic parameter evaluation, as well as the detection of clinical findings that may suggest one or more HCV-EHDs. This preliminary assessment should reveal specific HCV-EHDs, which will be deeper investigated by means of second-line, targeted investigations. The proposed multidisciplinary expert statement represents the first attempt to draw comprehensive diagnostic guidelines for HCV-infected individuals encompassing the entire spectrum of HCV-related disorders, namely
Hepatitis C virus (HCV) infection represents one of the most challenging health problems considering its high prevalence worldwide and its frequent hepatic and extra-hepatic disorders (HCV-EHDs) [1–6]. In terms of morbidity and mortality HCV-infected individuals are at risk of serious hepatic complications, i.e. cirrhosis and liver cancer [7], and less frequently of HCV-EHDs. These latter may be on one hand the result of immune-system dysregulation on due to the lymphotropism of HCV [1–3,6,8] responsible for different autoimmune and/or lymphoproliferative disorders that may severely affect the overall patients’ outcome [1–6,9–11]. On the other hand, the chronic inflammatory status related to HCV infection probably explains the cardio-metabolic complications as well as neurocognitive disturbances. Single HCV-EHDs are characterized by widely variable distribution among patients’ populations from different countries [1–6]; moreover, the percentage of patients with at least one HCV-EHD may increase during the natural course of HCV infection [1–6,10,11]. However, the actual incidence of HCV-EHDs is not systematically investigated worldwide, probably due to their insidious, often subclinical course, and mainly due to the lack of uniform diagnostic approach. As consequence, the overall incidence of HCV-EHDs can be underestimated or in some instances entirely overlooked. The present work is the first attempt to draw comprehensive diagnostic guidelines for patients with HCV-EHDs based on an international, multidisciplinary expert consensus statement.

2. Background

HCV is both hepato- and lymphotropic virus [1–6]; these biological characteristics may explain the variety of HCV-related hepatic and extrahepatic disorders [1–6]. Following the discovery of HCV in 1989 as the main cause of non-A/non-B chronic hepatitis [12], mixed cryoglobulinemia syndrome (MCS) was the first well-recognized condition that may complicate long-lasting HCV infection [1–6,13]. MCS is a systemic, multifaceted condition mimicking various autoimmune-lymphoproliferative diseases. Therefore, initial studies on HCV-related MCS prompted a number of clinico-epidemiological studies regarding other disorders potentially triggered by the same causative agent. During the last decades, an increasing number of clinical studies on large cohorts of chronically HCV infected patients focused on different putative HCV-EHDs [1–6,14]. Fig. 1 shows a provisional classification of the principal HCV-EHDs according to the strength of association with HCV based on multiple clinico-epidemiological, and laboratory parameters [1–6]; in particular, the prominent role of HCV in the large majority of patients with MCS and in a significant percentage of B-cell non-Hodgkin’s lymphomas (B-NHL). Both disorders can be regarded as direct consequence of HCV lymphotropism [1–6,15,16]. The geographical heterogeneous distribution of HCV-EHDS suggests a multifactorial etiopathogenetic mechanism of HCV-EHDs, including environmental and/or predisposing genetic co-factors [1–6,8]. In addition, HCV lymphoproliferative disorders are not systematically investigated worldwide and/or predisposing genetic co-factors [1–6,8]. In addition, HCV lymphoproliferative disorders are not systematically investigated widely, probably due to the insidious, often subclinical course, and mainly due to the lack of uniform diagnostic approach. As consequence, the overall incidence of HCV-EHDs can be underestimated or in some instances entirely overlooked. The present work is the first attempt to draw comprehensive diagnostic guidelines for patients with HCV-EHDs based on an international, multidisciplinary expert consensus statement.
Fig. 1. Various HCV-EHDs can be classified according to the strength of the association evaluated on the basis of epidemiological, clinico-pathological, virological, and laboratory investigations. In particular, the strength of association between HCV infection and systemic autoimmune diseases (SAD) was evaluated by taking into account: a) frequency of HCV infection statistically-significant higher in SAD-HCV populations in comparison with the prevalence of HCV in the general population; b) total number of reported cases of association between SAD and HCV; c) statistically-significant ORs in case-control studies (HCV vs non-HCV cases); and d) pathogenic studies. 1: HCV represents the main etiological agent as concordantly demonstrated by all the above investigations; 2: the association between HCV and disease is demonstrated in a significant proportion of patients compared to the general population (often with heterogeneous geographical distribution), its potential role is supported by in depth clinico-pathogenic studies; 3: a role of HCV infection has been suggested by cohort studies; a possible causative role may be limited to a small number of patients and/or possibly more relevant in specific geographical areas; 4: a number of anecdotal observations suggested a possible role of HCV; further investigations are required. B-cell NHL: B-cell non-Hodgkin's lymphomas; PCT: porphyria cutanea tarda; SS: Sjögren's syndrome; PAN: periarteritis nodosa; IBM: inclusion body myositis; SLE: systemic lupus erythematosus; PM/DM: polymyositis / dermatomyositis; APS: anti-phospholipid syndrome.

Fig. 2. The network of HCV-related disorders. The figure is a schematic representation of the network of HCV-related disorders, which encompasses both hepatic and extrahepatic diseases (HCV-EHDs; see also Table 2). Liver involvement represents the most common clinical manifestation of chronic HCV infection, while HCV-EHDs may develop in a subgroup of patients. HCV-EHDs may appear either as organ-specific disorders, i.e. arthritis, neuropathy, glomerulonephritis, etc.) or as systemic auto-immune disorder such as mixed cryoglobulinemia syndrome (MCS). Isolated and totally asymptomatic serum cryoglobulins are generally detectable in over 50% of HCV infected individuals, while classical MCS can be diagnosed in 15% of cryoglobulin-positive patients on the basis of both serological (circulating mixed cryoglobulins) and typical clinic-pathological features (see text). In clinical practice, we can observe a variable combination of hepatic and HCV-EHDs among HCV-infected patients, as well as in the same patient during the long-term follow-up. The most harmful complications of chronic HCV infection may appear abruptly (sensory-motor peripheral neuropathy, glomerulonephritis, widespread vasculitis, etc.) or more often as late manifestations (malignancies), alone or in the setting of MCS. B-NHL: B-cell non-Hodgkin's lymphomas; HCC: hepatocellular carcinoma.
network of experts formed in order to provide a homogeneous diagnostic and therapeutic approach to patients with HCV-EHDS. With regards to the production of diagnostic guidelines the ISG-EHCV convenor and co-convenors invited other ISG-EHCV members on the basis of their well-known expertise in the field of HCV-related manifestations. This task force initially gathered via e-mail and successively via teleconference meetings for the discussion of different issues; in addition, a systematic review of the literature was done in order to identify articles in English or in any language with English abstracts correlated to different topics of the study.

We followed, when available, the disease definitions and the validated classification/diagnostic criteria, as well as standardized methodologies for serological investigations and single organ damage detection [1–6,14,17,18], including current classification criteria for well-defined disorders such as MCS, primary Sjögren’s syndrome (pSS), rheumatoid arthritis (RA), and other autoimmune disorders [17–23].

4. Results

4.1. General patients’ assessment

It is widely demonstrated that different HCV-EHDS (Figs. 1, 2) may potentially develop at any time during the natural course of HCV infection [1–6,10]. Consequently, the ISG-EHCV recommends that all HCV-positive individuals should undergo a comprehensive clinical evaluation at the first visit (Table 1) and at regular time intervals during the follow-up for both liver involvement and HCV-EHDS. For a correct clinical monitoring and early detection of HCV-EHDS each patient should be provided with a booklet for symptom recording.

The patient’s first evaluation is mainly based on a thorough questionnaire and physical examination able to identify different signs and symptoms of HCV-EHDS (Table 1); a core set of laboratory and instrumental investigations is also required in order to reveal the main HCV-related organ- and/or non-organ-specific manifestations (Figs. 2, 3). Patients with clinical and/or laboratory alterations suggestive of one or more HCV-EHDS should be thoroughly evaluated by means of second-line, targeted investigations (Table 1, Fig. 4).

4.2. Diagnosis of single HCV-EHDS

On the basis of careful clinical, laboratory, and instrumental assessment of HCV-infected patients it is possible to identify/classify individuals with liver involvement and/or one or more HCV-EHDS (Fig. 2; Table 2). Clinical characteristics and diagnostic guidelines of different HCV-EHDS are described in detail in the following paragraphs.

4.2.1. Mixed cryoglobulinemia syndrome (MCS)

MCS represents the most common and widely investigated condition among different HCV-EHDS [1–6,24,25]. The disease is generally classified as a systemic small-vessel vasculitis [1–6]; therefore, the terms MCS and cryoglobulinemic vasculitis (CV) are generally referred to the same clinicopathological entity [1–6]. Circulating mixed cryoglobulins represent the biological hallmark of MCS, which is characterized by a typical clinical triad (purpura, weakness, and arthralgias), low C4 level, cutaneous leukocytoclastic vasculitis, and multiple visceral organ involvement (Fig. 1, Fig. 2). With the discovery of the causative role of HCV in the large majority of patients the term ‘essential’ is now referred to a very low percentage of MCS patients [1–6,13]; the association with HCV infection is particularly frequent in some geographical areas, such as Southern Europe, where the presence of other HCV-EHDS are more frequently observed [1–6]. HCV is directly involved in the pathogenesis of the disease through the virus-driven ‘benign’ B-cell lymphoproliferation, which is the pathological substrate of MCS [1–6], and the consequent production of circulating cryo- and non-cryo-precipitable immune complexes responsible for vasculitis manifestations [1–6].

4.2.1.1. Diagnostic guidelines. Serum cryoglobulins are frequently detected in HCV-infected patients (50–70%), often without relevant clinical significance [11–24; Fig. 2]; only a minority of individuals (15%) may develop overt MCS, generally after a long-lasting HCV infection. The levels of serum mixed cryoglobulins may largely vary among patients and a single patient during the natural course of the disease [10]. Therefore, in subjects with suspected MCS the detection of serum mixed cryoglobulins may be temporarily negative; in these cases, repeated search for serum mixed cryoglobulins may be necessary to avoid false-negative determination [1,4,10]. The presence of a low C4 serum level may be helpful. The MCS is characterized by variable symptom combinations; it is not rare to observe in a single patient the entire spectrum of MCS symptoms during the course of the disease: from mild manifestations, like arthralgia, orthostatic purpura, to multiple organ involvement such as glomerulonephritis, sensory-motor neuropathy, and/or B-NHL, generally as late disease complication [1,10]. This multifaceted syndrome may frequently overlap with other disorders making the diagnosis particularly difficult in individual patients [1–6,26]. The

Table 1

<p>| HCV-infected individuals: detection of extra-hepatic manifestations. |</p>
<table>
<thead>
<tr>
<th>Signs and symptoms (anamnestic/present)</th>
<th>First line laboratory investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Weakness</td>
</tr>
<tr>
<td>Fever</td>
<td>Routine blood chemistry</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Virological tests (HBV, HIV)</td>
</tr>
<tr>
<td>Skin inv.</td>
<td>Orthostatic purpura</td>
</tr>
<tr>
<td>Necroting vasculitis</td>
<td>Complement C3/C4</td>
</tr>
<tr>
<td>Skin ulcers</td>
<td>Protein electrophoresis</td>
</tr>
<tr>
<td>Bullae/hyperpigmentation/ erosions at sun-exposed areas</td>
<td>Serum immunofixation</td>
</tr>
<tr>
<td>Pruritus</td>
<td>ANA, anti-ENA</td>
</tr>
<tr>
<td>Arterial/muscular inv.</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Myalgia, fibromyalgia</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Abdominal &amp; thyroid ultrasonography</td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td></td>
</tr>
<tr>
<td>Salivary gland inv.</td>
<td>Siccus syndrome (ocular/oral)</td>
</tr>
<tr>
<td>Edema</td>
<td>TSH</td>
</tr>
<tr>
<td>Renal inv.</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Vascular inv.</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Hyperviscosity syndrome</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Heart/lung inv.</td>
<td>Dyspnea, edema, hemoptysis</td>
</tr>
<tr>
<td>Pleural/pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Lower limb claudication, Heart failure</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Neurological inv.</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td></td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Stroke, TIA</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive disturbances</td>
<td></td>
</tr>
<tr>
<td>Hematological inv.</td>
<td>Anemia</td>
</tr>
<tr>
<td>Adenopathy</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td></td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td></td>
</tr>
<tr>
<td>Monoclonal component</td>
<td></td>
</tr>
<tr>
<td>Endocrine inv.</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

Inv.: involvement; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; RF: rheumatoid factor; ANA: anti-nuclear antibodies; anti-ENA: antibodies anti-extractable nuclear antigens; GFR: glomerular filtration rate; TSH: thyroid-stimulating hormone; EKG: electrocardiogram.
4.2.2. Arthritis

Patients with HCV infection, especially those with HCV-related MCS, suffer often of arthralgia and rarely of overt arthritis [1–6,9,25,26,28]. The latter commonly appears as mono- or oligo-arthritis with non-erosive, scarcely aggressive joint involvement if compared with classical RA [9,21]. Patients with MCS may develop mild oligo-arthritis, while RA-like poly-arthritis may be sporadically observed in HCV-infected patients, either as distinct HCV-EHD or as self-limiting adverse effect of alpha-interferon treatment [9,29]. Considering the relatively high prevalence of both HCV infection and classical RA in the general population, it is possible to observe a simple disease association [9; Table 2].

Thus, differential diagnosis between HCV-related arthritis and classical RA is mandatory in patients with recent onset inflammatory joint involvement.

4.2.2.1. Diagnostic guidelines. Table 3 reports the main clinico-radiological and serological parameters able to differentiate between arthritis complicating HCV infection and classical RA [9,29]. In particular, HCV-related arthritis is non-erosive and seronegative (absence of anti-cyclic citrullinated peptide antibodies) (see also Figs. 3 and 4; Table 4).

The presence of a rheumatoid factor activity may be confusing as it is positive in both classical RA and MCS. Overall, accurate patient’s classification is essential for the therapeutic implications: mild–moderate HCV-related arthritis is commonly responsive to conventional disease-modifying anti-rheumatic drugs (DMARDs), while patients with concomitant HCV infection and RA may be safely and successfully treated with biological DMARDs; in particular, anti-TNF alpha antibodies are generally well tolerated despite the associated HCV infection [30].

4.2.3. Sjögren’s syndrome /sicca syndrome

Sicca syndrome is the clinical hallmark of pSS [19,20] and has been reported in 10–20% of unselected HCV infected patients (Table 2); the histopathological hallmark of SS (focal lymphocytic sialadenitis) has been reported in 25% of HCV infected patients [31]. The possible link between SS and HCV is supported etiopathogenically by several studies that have detected the virus in human salivary glands and that have demonstrated the capability of HCV to infect and replicate in the salivary gland tissue of HCV infected patients with sicca syndrome/SS [32]. Epidemiologically, a recent study has reported a prevalence of HCV infection of 13% in nearly 800 patients with SS [33], and a recent meta-analysis has estimated a 3-fold enhanced risk for the development of SS/sicca in HCV infected patients compared with non-infected individuals.
Fig. 4. Clinical assessment of single HCV-EHDs. The figure shows in detail the diagnostic guidelines with first- and second-line investigations to detect single HCV-related extrahepatic disorders (HCV-EHDs) (see also text, Table 1, and Fig. 3). NADA: LAD; Doppler-US: transcranial color-Doppler ultrasonography; MRI: magnetic resonance imaging; CT: computed tomography angiography; PET: positron emission tomography; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; ANA: anti-nuclear antibodies; EDA: anti-nuclear extractable antigen antibodies; URO-D: uroporphyrinogen decarboxylase; GN: glomerulonephritis (diffuse membranoproliferative glomerulonephritis in about 80% of cases).

Table 2
Classification of possible HCV-related extrahepatic disorders (HCV-EHDs)

<table>
<thead>
<tr>
<th>HCV-related extrahepatic disordersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Systemic:</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>Other vasculitic syndromes (rare)</td>
</tr>
<tr>
<td>PCT, sicca syndrome</td>
</tr>
<tr>
<td>arthritis, myositis</td>
</tr>
<tr>
<td>2. Organ-specific:</td>
</tr>
<tr>
<td>peripheral neuropathy, CNS infl.</td>
</tr>
<tr>
<td>thyroid/gonadal infl., type 2 diabetes</td>
</tr>
<tr>
<td>metabolic dis/cardiovascular infl.</td>
</tr>
<tr>
<td>ILD, lichen planus, others</td>
</tr>
<tr>
<td>3. Constitutional:</td>
</tr>
<tr>
<td>fatigue, chronic pain</td>
</tr>
<tr>
<td>fibromyalgia</td>
</tr>
<tr>
<td>4. Malignancies:</td>
</tr>
<tr>
<td>B-NHL, other B-cell neoplasm</td>
</tr>
<tr>
<td>papillary thyroid cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant/overlapping conditionsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSS, RA, SLE, SSC, PM/DM, others</td>
</tr>
</tbody>
</table>

4.2.3.1. Diagnostic guidelines. A first line assessment of HCV-infected patients should include the routinely detection of sicca syndrome/SSA (Table 1). HCV-associated SS is indistinguishable in most cases from the primary form using the most recent set of classification criteria [35]. The main differential aspect between primary and HCV-related SS is the immunological pattern, with a higher frequency of cryoglobulinemic-related markers (mixed cryoglobulins, RF, hypocomplementemia) and a lower frequency of anti-Ro/SS-A and anti-La/SS-B autoantibodies in HCV-related SS ([35]; Tables 3, 4). Cryoglobulinemia seems to be the key immunological marker of HCV-associated SS, having a close association with RF activity and complement activation. This immunological pattern may contribute to the potential enhanced risk of development of B-cell lymphoma in SS-HCV patients [31–38]. A careful evaluation and follow-up of HCV patients with associated SS to aid early diagnosis and treatment of possible B-cell lymphoma should be recommended, especially in those with concomitant positive mixed cryoglobulinemia.

4.2.4. Porphyria cutanea tarda

The porphyrias are a clinically and genetically heterogeneous group of relatively rare metabolic disorders due to altered heme biosynthesis pathway [39]. Porphyria cutanea tarda (PCT) represents the most common clinical variant of porphyrias; it can be categorized in two different subtypes, i.e. familial and sporadic [36]. The disease is characterized by low activity of uroporphyrinogen decarboxylase, the enzyme involved in the heme synthesis. The uroporphyrinogen decarboxylase deficiency is necessary but not sufficient for the clinical development of PCT; therefore, possible pathogenetic co-factors have been proposed, including hepatotropic virus infection [1,25,39,40]. Since 1992, a pathogenetic model of the disease has been proposed [41].
of MALT lymphomas have been reported in association with HCV [48] but a geographical variability is possible in this setting: peculiar sites are liver, salivary glands and ocular adnexa [37,38,53–55]. In some cases, MZL appear disseminated in HCV-positive patients and a specific MZL subtype is not identifiable [56].

As outlined by epidemiological studies, a subset of apparently de novo diffuse large B-cell lymphoma emerged as a separate entity associated with HCV infection. HCV-positive DLBCL commonly present with advanced stage, extranodal localizations like spleen and liver and elevated levels of serum lactate dehydrogenase [57–60]. Recently, a “HCV Prognostic Score” based on performance status, albumin and HCV-RNA load has been proposed as a specific prognostic tool for HCV-associated DLBCL. Further studies also suggest that HCV-associated DLBCL arises more frequently from a preceding low-grade MZL in comparison to de novo DLBCL [49,57,59] and therefore pathologist should be aware of reporting a possible residual part of indolent NHL in the diagnostic sample.

### 4.2.5.1. Diagnostic guidelines

In subjects with HCV infection, diagnosis of lymphoma must be suspected on the basis of clinical symptoms and/or laboratory alterations (Table 1; Figs. 3–4) and confirmed by histological examination of involved tissue (nodal and more frequently extranodal); specific NHL type must be defined according to WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues [61]. Cytology and flow cytometry analyses are generally not sufficient to establish a definitive diagnosis of NHL. However, in the absence of nodal and extra-nodal disease, a diagnosis of monoclonal B-cell lymphocytosis (MBL) can be achieved in HCV-positive subjects with peripheral blood and bone marrow examinations [56,62]. In specific situations as in splenic marginal zone lymphoma (SMZL), a reliable diagnosis can be assessed with bone marrow histology and phenotype evaluated by immunohistochemistry and flow cytometry without need of splenectomy [63]. Overlapping histological features between HCV-positive and HCV-negative cases have been reported [62] but differential diagnosis between MBL and SMZL can be difficult in cases with a splenomegaly explained by liver-related complications of HCV infection [38]. HCV-related lymphoproliferative disorders can present with a serum monoclonal component but also a monoclonal gammapathy of undetermined significance frequently occurs in HCV-positive subjects [64–66].

Staging of HCV-associated NHL is to be performed according to the Lugano classification [67]. MZLs are generally not staged with positron emission tomography (PET) because they are generally not fludarabine-sensitive diseases but must be staged by means of PET is indicated in DLBCL and in indolent NHL in case of suspected transformation [[58]; Fig. 4].

### 4.2.6. Auto-immune cytopenias

The specific tropism of HCV for circulating blood cells has been suggested by several studies, providing a link between HCV and the development of auto-immune severe cytopenias [70]. Therefore, patients with chronic HCV infection, especially those with an hypersplenism, may present with cytopenias (Table 1), often mild and asymptomatic. 40

The most frequent is a thrombocytopenia, which has a chronic and mild clinical course. Wang et al. [71] reported a 10-fold higher frequency of thrombocytopenia in HCV infected patients that was correlated with the severity of liver disease, as compared with HCV-negative controls. Some HCV infected patients may present with severe auto-immune cytopenias, related or not to anti-viral therapy, including thrombocytopenia (\(<30 \times 10^9/L\) ), Coombs-positive autoimmune hemolytic anemia or Evans syndrome. These cytopenias has been reported in treatment-naïve HCV positive patients, some of whom may present concomitant auto-immune diseases, cryoglobulinemia or HCV infection [72,73]. Chiao et al. [74] have estimated that HCV infection is associated with an increased risk of developing thrombocytopenia and autoimmune hemolytic anemia (2-fold and 3-fold higher risk, respectively) in comparison with non-infected patients. Finally, isolated cases of pure red-cell aplasia have also been described in HCV patients [72].

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**Table 3**

Differential diagnosis between some HCV-EHDs and idiopathic rheumatic diseases.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mixed cryog. HCV+</th>
<th>Sicca syndrome</th>
<th>pSjögren’s syndrome</th>
<th>Arthritis HCV+</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Weakness</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>+++</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Oligo arthritis</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>++/–</td>
</tr>
<tr>
<td>Erosive arthritis</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>++/–</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>++/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>++/–</td>
</tr>
<tr>
<td>Renal inv.</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
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<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
</tr>
<tr>
<td>B-NHL</td>
<td>+/–</td>
<td>–</td>
<td>–/–</td>
<td>–/–</td>
<td>+/–</td>
</tr>
</tbody>
</table>

**Laboratory alterations**

| Mixed cryoglobulins                           | +++              | –/–            | ++                  | –/–            | –/–                |
| Low complement C4                             | +++              | –/–            | ++                  | –/–            | –/–                |
| RF                                            | –/–              | –/–            | ++                  | –/–            | –/–                |
| Anti–CCP Ab                                   | –/–              | –/–            | –/–                 | –/–            | –/–                |
| ANA                                           | –/–              | –/–            | –/–                 | –/–            | –/–                |
| Anti–SSA/SSB Ab                               | –/–              | –/–            | –/–                 | –/–            | –/–                |
| Salivary gland biopsy                         | –/–              | –/–            | –/–                 | –/–            | –/–                |
| HCV                                           | +++              | +++            | –/–                 | –/–            | –/–                |

Colored areas highlight the parameters useful for differential diagnosis.


---

**Role of HCV infection**

The role of HCV infection has been demonstrated in patients with sporadic PCT [41–43]. A direct role of HCV can be excluded considering the absence of altered porphyrine metabolism in HCV-positive patients without PCT; molecular mimicry between predisposed host and HCV antigens is a probable pathogenetic mechanism of PCT, while altered genes connected with iron metabolism may enhance the immune-reactivity of PCT patients [39–43].

**4.2.5.1. Diagnostic guidelines.** In HCV-infected patients, diagnosis of PCT can be adequately supported by typical cutaneous lesions, i.e. bullae, hyperpigmentation, and erosions at sun-exposed areas such as hands and face. It should be definitely ascertained by means of simple laboratory investigations (Table 1, Figs. 3–4), namely uroporphyrinogen decarboxylase deficiency and elevated levels of serum and urinary porphyrins [39].

**4.2.5.2. B-cell non-Hodgkin lymphoma**

After the first reports of a high prevalence of HCV infection in patients with B-cell non-Hodgkin’s lymphomas (B-NHL) [15,44], during the last 20 years the association between HCV infection and B-cell NHL has been clearly established. In a meta-analysis of case–control studies, the pooled relative risk of all NHL among HCV-positive subjects was 2.5 [45]: the fraction of NHL attributable to HCV is highly heterogeneous by geographical region and may reach 10% in highly endemic areas [1,2,16,46–48]. Marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma and diffuse large B-cell lymphoma (DLBCL) are the histotypes more frequently associated with HCV infection [47].

Mechanisms of HCV-related lymphomagenesis include the continuous stimulation of lymphocyte B-cell receptors by HCV antigens, oncogenic effect mediated by intracellular viral proteins during replication of HCV in B-cells, and B-cell damage through mutation of tumor suppressor genes, caused by a transient intracellular virus (“hit and run” theory) [16]. A subset of HCV-positive DLBCL seems to share molecular features with MZL mutations affecting the NOTCH pathway [49].

Among MZLs, splenic MZL (SMLZ) is frequently reported in association with HCV infection but there is a great geographic variability [46,50,51]. French authors have reported a form of SMLZ associated with HCV infection and type II mixed cryoglobulinemia that affects mostly female subjects [52]. Also extranodal marginal zone lymphomas

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4.2.7 Kidney involvement

A nephropathy may develop in HCV infected persons, with a significantly higher frequency in patients with overt MCS [1–6,10,75]. The predisposing factors include older age, longer duration of HCV infection, and genetic background [75]. The prevalence of kidney involvement tends to increase during long-term follow-up, and glomerulonephritis may severely affect the overall prognosis of HCV-infected individuals.

4.2.7.1 Cryoglobulinemic glomerulonephritis. The pathogenesis of HCV-related cryoglobulinemic nephritis is the ultimate result of polyclonal expansion of B cells triggered by HCV through a sequence of immunological alterations as well as abnormal kinetics and tissue deposition of immune-complexes containing HCV, and ineffective cryoglobulin clearance by monocyte/macrophages, which are implicated in perpetuating glomerular damage [76–82].

<table>
<thead>
<tr>
<th>References</th>
<th>Unselected HCV</th>
<th>CV–HCV</th>
<th>SS–HCV</th>
<th>SLE–HCV</th>
<th>PAN–HCV</th>
<th>RA–HCV</th>
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<td>242</td>
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</tr>
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</thead>
<tbody>
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<td>Arthralgias</td>
<td>552 (19)</td>
<td>301/465 (65)</td>
<td>60/137 (44)</td>
<td>39/45 (87)</td>
<td>19 (61)</td>
<td>31 (100)</td>
</tr>
<tr>
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<td>49/284 (17)</td>
<td>ND</td>
<td>34/38 (89)</td>
<td>ND</td>
<td>31 (100)</td>
</tr>
<tr>
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<td>12/130 (9)</td>
<td>ND</td>
<td>ND</td>
<td>10 (32)</td>
<td>ND</td>
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<tr>
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<td>ND</td>
<td>ND</td>
<td>35 (55)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Purpura</td>
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<td>360 (67)</td>
<td>27/137 (20)</td>
<td>3/15 (20)</td>
<td>21 (68)</td>
<td>ND</td>
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<tr>
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<td>298 (10)</td>
<td>125/340 (37)</td>
<td>237 (98)</td>
<td>4/15 (27)</td>
<td>4 (13)</td>
<td>ND</td>
</tr>
<tr>
<td>Oral ulcers</td>
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<td>ND</td>
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<td>5/38 (13)</td>
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<td>ND</td>
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<tr>
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</table>

<table>
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<tr>
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<th>SS–HCV</th>
<th>SLE–HCV</th>
<th>PAN–HCV</th>
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<td>59 (92)</td>
<td>ND</td>
<td>10 (32)</td>
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<tr>
<td>dsDNA</td>
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<td>ND</td>
<td>40 (62)</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>ENA</td>
<td>14/473 (3)</td>
<td>ND</td>
<td>46/240 (19)</td>
<td>11/38 (29)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>RF</td>
<td>166/400 (42)</td>
<td>373/421 (89)</td>
<td>126/239 (53)</td>
<td>4/15 (27)</td>
<td>17/24 (71)</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Low C3/C4</td>
<td>29/81 (35)</td>
<td>187/246 (76)</td>
<td>117/236 (50)</td>
<td>27/38 (71)</td>
<td>17 (55)</td>
<td>ND</td>
</tr>
<tr>
<td>Cryoglobulins</td>
<td>682/1641 (42)</td>
<td>539 (100)</td>
<td>132/241 (55)</td>
<td>16/29 (55)</td>
<td>21/26 (81)</td>
<td>ND</td>
</tr>
</tbody>
</table>

The data are obtained from a meta-analysis of the reported frequencies in the individual studies (references [1–22]). Colored frequencies highlight the parameters useful for differential diagnosis. In red, frequencies lower than that reported in the corresponding idiopathic disease; in blue, frequencies higher with respect to the idiopathic disease.

ND: no data available; RF: rheumatoid factor; ENA: extractable nuclear antigen antibodies (Ro,La,Sm,RNP); ANA: anti-nuclear antibodies; dsDNA: antibodies against double stranded DNA.
glomerulonephritides may appear with one or more renal symptoms i.e.
isolated proteinuria (~<2 g/24 h), usually with microscopic hematuria
(30%), a nephrotic syndrome (20%), or an acute nephritic syndrome
(15%) (some patients show mixed nephrotic and nephritic syndrome,
a macroscopic hematuria (10%), a chronic renal insufficiency (10%), an
current renal failure (10%), and/or an oligo-anuria (5%) [75].

4.2.7.1.1. Diagnostic guidelines. A membranoproliferative glomeru-
lonephritis may be the presenting symptoms of HCV-associated
MCS, while the overt cryoglobulinemic syndrome can appear as late
manifestation [10]. Therefore, HCV-positive patients with apparently
isolated glomerulonephritis should undergo a careful renal clinico-
sorological assessment at baseline and during the follow-up. Ultra-
son sound kidney examination of patients with glomerulonephritis often
reveals bilateral cortical hyper echogenicity, while urinary sediment
shows polymorphic erythrocytes. Guidelines are mainly based on
renal biopsy that is mandatory in any patient with urinary abnormal-
ities and/or unexplained renal impairment. Histologic features, which
affect the therapeutic approach, are unpredictable and require careful
examination of renal specimens. Three main glomerular patterns can
be recognized as a result of cryoglobulin glomerular deposition [75]:
a) diffuse membranoproliferative glomerulonephritis (80%), b) focal
membranoproliferative glomerulonephritis (10%), and c) mesangial pro-
liferative glomerulonephritis (10%). Interstitial and vascular lesions may
include leukocyte infiltration and fibrosis, usually focal and almost invari-
ably associated with the membranoproliferative forms. Moreover, athero-
sclerotic lesions are present in one third of cases, while frank arteritis is
rare. At immunofluorescence examination diffuse, pseudolinear peripher-
al capillary wall and mesangial staining for IgM, IgG, and C3 are usually
found with a relatively strong staining for IgM. Prominent IgM and IgG
staining is detected in thrombi, while fibrinogen is found in vessel
walls when vasculitis is present. Moreover, electron-dense deposits
(electromicroscopy) are detected in subendothelial and mesangial areas
together with interposition of glomerular basement membrane by mono-
cyes. Cryoglobulin deposits often display short, curved, thick-walled
tubular structures with a diameter of about 30 nm.

Patients with diffuse membranoproliferative glomerulonephritis
show a more pronounced C4 hypocomplementemia, higher levels of
proteinuria and a stronger association with serositis, hepatosplenomegaly,
leukopenia, peripheral neuropathy, and cardiac involvement compared
to patients with other patterns of glomerulonephritis. Significant
prognostic variables include older age, male gender, increased serum
creatinine and proteinuria at the time of renal biopsy, number of clinical
relapses, and poor blood pressure control.

4.2.7.2. HCV-associated non-cryoglobulinemic glomerulonephritis. Due
to the diverse histologic patterns and the specific therapeutic impli-
cations, biopsy should be done, if not specifically contraindicated, in
every HCV infected patient who presents with urinary abnormalities
or unexplained renal insufficiency. A number of alternative renal
patterns, beside cryoglobulinemic nephritis, can be found, including
membranous nephropathy, focal segmental sclerosis, IgA nephropathy
and other proliferative glomerulonephritis (non-cryoglobulinemic
membranoproliferative glomerulonephritis, fibrillary and immunotactoid
glomerulopathies, and anti-cardiolipin-associated thrombotic microan-
giopathy) [82]. These all are conditions in which the electron microsco-
py evaluation is mandatory.

4.2.8. Endocrine and metabolic disorders

The most frequent endocrine and metabolic diseases in the setting of
HCV-EHVs are auto-immune thyroid disorders (AITD) [83–88] and type
2 diabetes mellitus (T2DM) [89–96]; an increased prevalence of gonadal
dysfunction is also reported in HCV-infected male individuals [97–100].

4.2.8.1. Thyroid disorders. A higher prevalence of thyroid disorders was
observed in patients with HCV-associated MCS, not only with respect
to controls, but also to HCV patients without cryoglobulinemia.

Consequently, a careful monitoring of thyroid function is advisable
[83–85]. IFN-α therapy was a well-known risk factor for the develop-
ment of AITD and dysfunctions [84]. The presence of higher risk of
AITD and hypothyroidism, and increased circulating thyroperoxidase
antibodies, in female gender, characterized thyroid disorders of HCV
infected patients with/without MCS [86]. Interestingly, higher prevalence
of papillary thyroid cancer has been found in chronically HCV-infected
patients than in controls, as in HCV-related MCS patients, particularly
in those with AITD [84,87,88].

4.2.8.1.1. Diagnostic guidelines. These findings suggest a careful
monitoring of thyroid function and nodules in patients with risk factors
(female gender, borderline baseline TSH levels, thyroperoxidase anti-
bodies positivity, hypoeoic and small thyroid) for the development of
thyroid autoimmunity in HCV-positive patients, with/without MCS
(Table 1; Figs. 3–4). These patients should undergo the determination
of free thyroxine (FT4), TSH, anti-thyroglobulin and thyroperoxidase
auto-antibodies and thyroid ultrasonography approximately every
year. In patients with thyroid nodules, if larger than 1 cm or in the
presence of suspected malignancy, a fine-needle aspiration should be
performed (Table 1; Figs. 3–4).

4.2.8.2. Diabetes and insulin resistance. The liver plays an important
role in the carbohydrate metabolism, thus chronic liver diseases are known
to have a higher prevalence of disturbed glucose homeostasis, impaired
glucose tolerance or insulin resistance [89,90], leading eventually to
 overt T2DM [91]. Several epidemiological studies have evidenced
higher percentages of HCV infection markers in T2DM patients than in
controls. Analyses in HCV-infected patients without cirrhosis, or with
MCS, showed higher prevalence of T2DM compared to HCV-negative
controls or HCV-infected patients [92–94].

How HCV leads to diabetes is still a matter for debate. The type of di-
babetes manifested by HCV-infected patients is not the classical T2DM.
Patients with HCV-associated T2DM were leaner than T2DM controls,
and showed significantly lower low density lipoprotein (LDL)-choler-
sterol, and systolic and diastolic blood pressures [93,94]. Furthermore,
patients with HCV-related MCS and T2DM had non-organ-specific
autoantibodies more frequently (34% vs 18%) than non-diabetic HCV-
related MCS patients [93]. An immune-mediated mechanism has been
postulated for diabetes in HCV-infected patients with/without MCS
[93]. Moreover, clinical trials on HCV patients report improvement of
glucose metabolism after effective antiviral treatment [95] suggesting
a direct role of HCV in beta-cell dysfunction. In addition, in HCV-
infected patients the T2DM itself seems to have an unfavorable impact
on hepatocellular carcinoma development [96], as well as an increased
risk to develop renal complications [101].

4.2.8.2.1. Diagnostic guidelines. A periodic evaluation of glycaemia,
HbA1c, and lipids in HCV infected patients is recommended (Table 1;
Fig. 3).

4.2.8.3. Gonadal dysfunction. Abnormal serum levels of sex hormones can
be observed in HCV-related MCS [97]. An erectile dysfunction has been
reported in some HCV-infected males during interferon-alpha treat-
ment [98,99]. In a large series of untreated HCV-infected males a signif-
icantly higher prevalence of erectile dysfunction with abnormally low
plasma levels of testosterone compared to controls has been described
[100]. In these HCV-infected males, the correction of hormonal deficien-
cy may improve the patient’s quality of life and may positively affect
the autoreactive immune-system alterations.

4.2.8.3.1. Diagnostic guidelines. For a comprehensive diagnostic ap-
proach, HCV-infected male patients should be evaluated for hormonal
status and possible erectile dysfunction (Table 1).

4.2.9. Neurological and psychiatric disorders

The involvement of peripheral and/or central nervous system (CNS)
represents one of the most frequent HCV-EHVs [102–108]. Possible path-
genic mechanisms include direct HCV neuro-invasion, autoantibody-
mediated injury of nervous tissue, ischemic alterations secondary to
immune-complex-mediated vasculitis or accelerated atherosclerotic vas-
culopathy [102–111]. Up to 50% of HCV-infected patients may develop a
variable combination of different subclinical/clinical manifestations:
a) peripheral sensory, motor or sensorimotor mono-/polyneuropathies,
small fiber sensory polyneuropathy (less frequently large fiber sensory
neuropathy), and autonomic neuropathy; b) CNS manifestations
(encephalopathy syndromes, myelitis, encephalomyelitis), and/or cere-
brovascular events as consequence of vasculitis/ ischemic damages;
c) neuropathological/psychiatric manifestations; d) iatrogenic neuro-
logic manifestations, mainly triggered by alpha-interferon treatment,
e) neurocognitive disturbances [112–114]. Contributing factors to
these neurological manifestations include long-lasting HCV infection,
positive serum cryoglobulins (mainly clinically overt MCS), concomitant
cardiovascular/metabolic disorders, male gender, smoking, and/or other
infectious diseases [104,106]. The clinical onset of peripheral neuropathy
is often subacute with distal, symmetric, sensory or sensorimotor
polyneuropathy, and less frequently asymmetrical sensory/motor
impairment. The most common symptoms are sensory loss, paresthesia,
numbness, cramps, burning feet, and tingling [102–108] (Table 1;
Figs. 3–4). In few cases, severe sensory-motor manifestations, often as
asymmetric mononeuritis may appear abruptly. HCV-associated restless
legs syndrome has been reported as expression of small fiber sensory
polyneuropathy [105,115,116].

4.2.9.1. Diagnostic guidelines. All patients with suspected peripheral
nerve involvement should be investigated by means of electromyogra-
phy with neurophysiological tests. When appropriate, mainly for
intra-epidural nerve fiber density analysis, a peripheral nerve exami-
nation (mainly sural biopsy), should be done [116] (Table 1; Figs. 3–4).
CNS involvement is less frequently reported [103–106,108]; well-
documented observations of HCV-associated vasculitis involvement of
CNS are rare and include mostly cryoglobulin-positive patients [105].
CNS involvement may present with different symptoms, such as fatigue,
depression, cognitive impairment, stroke episodes, transient ischemic
attacks, progressive reversible ischemic neurological deficits, lacunar in-
farctions, or encephalopathic syndrome, which are generally attribut-
able to ischemic events (vasculitis/vasculopathy) and exceptionally to
hemorrhage [103–106,108]. Patients with possible CNS involvement
should be carefully evaluated by means of detailed neurological exami-
nation, disease duration, previous/ongoing treatment (especially inter-
erfons), laboratory (serum cryoglobulins, monoclonal component),
and instrumental investigations (Table 1; Figs. 3–4). The detection of
CNS vasculitis/vasculopathy alterations should include: transcranial
color-Doppler ultrasonography and magnetic resonance imaging; this
latter plays an important role in the workup of patients with suspected
vasculitis, even though the abnormalities found on magnetic resonance
imaging are not diagnostic. Functional brain magnetic resonance imag-
ing studies and 18F-fluoro-deoxyglucose positron emission tomogra-
phy scan could be useful for specific CNS manifestations. Computed
tomography presents limited spatial resolution; however, it can show
parenchymal brain calcifications found within old ischemic lesions
[103–106,108,106,118]. Anglo-magnetic resonance imaging is pre-
ferred to computed tomography angiography to evaluate both vessel
walls and lumen [117]. Neuropsychiatric disorders and neurocogni-
tive dysfunction are reported in nearly 50% of patients with chronic HCV
infection, which are independent of the presence/severity of hepatic in-
volve,ment, HCV genotype and/or viral load [106]. Fatigue, sleep distur-
bance, depression, and reduced quality of life are commonly associated
with neurocognitive alterations in non-cirrhotic HCV-infected patients
[106]. These subjects should be evaluated for possible neurocognitive
decline over time, including motor activity with sleep–wake-rhythm,
questionnaires for depression and health-related quality of life [119].
Finally, patients with chronic HCV infection often have experience of un-
favorable psychological conditions because of low socioeconomic status,
concomitance of other infections, such as HBV or HIV, discrimination,
and limited access to adequate health care [120]. An accurate environ-
mental and individual psychological assessment of these patients is
mandatory for comprehensive counseling approach and management of
the overall HCV syndrome [120].

4.2.10. Cardiovascular

HCV infection has been reported as an independent risk factor for the
development of some harmful cardiovascular manifestations such as
carotid atherosclerosis, heart failure and ischemic stroke, associated
to an excess of cardiovascular mortality [121–125]. It is well-known
that atherosclerosis is a chronic inflammatory disease secondary to
multifactorial pathogenesis; its incidence is significantly higher in pa-

dients with autoimmune and/or infectious diseases [126,127]. Thus,
chronic HCV infection can be reasonably identified as a potential
pro-atherogenic condition considering the complex of HCV-driven auto-
immune/inflammatory alterations, characterized by increased levels of
pro-atherogenic chemokines and cytokines [85,128] (Figs. 1–2). More-
over, HCV may be considered a ‘metabolic’ virus, since it can pro-
mote insulin resistance and type 2 diabetes, two other and frequently
associated pro-atherogenic conditions [91,94]. Finally, HCV may di-
rectly promote atherosclerotic lesions as suggested by HCV detection
and replication within carotid plaques [129].

4.2.10.1. Diagnostic guidelines. Considering the increased prevalence
and prognostic relevance of cardiovascular events, it is clearly
opportunity to include these harmful manifestations among HCV-EHDs.
Therefore, a noninvasive screening (Table 1; Figs. 3–4) for cardiovas-
cular alterations (Doppler ultrasound studies, EKG) is recommendable at
the first patient’s assessment followed by careful monitoring during the
follow-up.

4.2.11. Other systemic autoimmune diseases (SAD) and overlap syndromes

In addition to the previously mentioned associations with SS and RA,
chronic HCV infection has been reported in patients with other SAD
([110–140]; Table 4).

Systemic lupus erythematosus (SLE) patients have an increased fre-
quence of HCV infection [130–133]. Although the pathogenic role of
HCV infection in these patients is unclear, it is possible that HCV may
act as a triggering factor in some patients with a definite genetic back-
ground. Several SLE criteria, specific to “idiopathic” SLE, are rarely pres-
ent in chronic HCV infection (malar rash, discoid/subacute cutaneous
lesions, neurological manifestations, high titer of ANA or anti-dsDNA
and presence of anti-Sm antibodies) ([131,134]; Table 4); in these pa-
defs, a true overlap between SLE and HCV infection may be considered
(135). In contrast, some patients with HCV-EHDs may present a
‘mild’ SLE, mainly characterized by articular involvement, hematologic
features, hypocomplementemia and lower titers of ANA and anti-
dsDNA; in this subset of patients, chronic HCV infection (often in the
presence of cryoglobulinemia) may produce a ‘lupus-like syndrome’
[135].

Excluding cryoglobulinemia vasculitis, polyarteritis nodosa (PAN) is
the most-frequent systemic vasculitis associated with chronic HCV
infection. Saadoun et al. [136; Table 4] identified 31 (19%) patients
with PAN from a cohort of 161 patients with HCV-related vasculitis
(mainly cryoglobulinemia vasculitis). These HCV-PAN compared to
HCV cryoglobulinemia vasculitis patients exhibited a higher frequency
of fever and weight loss, severe hypertension, gastrointestinal involve-
ment, severe acute sensorimotor multifocal mononeuropathy, edema
and kidney and liver microaneurysms and increased C-reactive protein
levels.

HCV has been associated with inflammatory myopathies, mainly
with polymyositis [137]. A recent case–control Japanese study [138]
has reported a higher frequency of HCV infection in patients with inclu-
sion body myositis (IBM) compared to those with polymyositis and
general population (28% vs 4.5% vs 3.4%, respectively), suggesting a pos-
sible etiopathogenic link between HCV and IBM. Other SAD associated

with HCV have been reported in less than 20 cases, including systemic sclerosis, Behçet disease, giant cell arteritis, Takayasu’s arteritis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Henoch–Schönlein purpura, adult-onset Still disease, relapsing polychondritis, IgG4-related disease or mixed connective tissue disease [135,137].

4.2.11.2. Diagnostic guidelines. The degree of overlap between SAD criteria and HCV-EHDs varies depending on the autoimmune disease, and should be evaluated taking into account those clinic-immunological features that are typical of each SAD but that are infrequently reported into the spectrum of the HCV-EHDs (Tables 1–4). For SLE, the presence of cutaneous or neurological lupus together with high titers of anti-dsDNA or anti-Sm antibodies highly suggests a true coexistence of SLE and HCV infection. With respect to PAN, several of the 1990 criteria for the classification of PAN, such as weight loss, myalgias or weakness, peripheral neuropathy, elevated creatinine, and positive HBV markers, are often observed in HCV patients. Although cryoglobulinemia vasculitis could histologically mimic cutaneous or renal involvement observed in microscopic polyarteritis, classic PAN shows necrotizing inflammation of small or medium-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Thus, the key difference between the two types of systemic vasculitis most frequently associated with HCV (PAN and cryoglobulinemia vasculitis) is the different size of the vasa involved. The high specificity of this histologic criterium may be useful in the differential diagnosis of PAN or HCV-related cryoglobulinemia vasculitis. The criteria of Bohan and Peter show a small degree of overlap in the large majority of cases, may be able to evidence overt HCV-EHDs or to suggest the subclinical presence of such complications. Frequent clinical monitoring of patients with chronic HCV infection may be decisive for early diagnosis of different HCV-EHDs and opportune therapeutic decisions. This approach may improve the patients’ quality of life and prognosis, mainly in individuals with more severe visceral organ damages and/or malignancies (Table 2).

5. Discussion

The large diffusion of HCV infection in the general population and its frequent hepatic and extrahepatic manifestations are a serious medical problem that involves transversely different medical subspecialties [1,2,6,11,120]. The HCV syndrome is an important model of chronic multisystem disease needing very often a long-term multidisciplinary management [1–6]. The necessarily holistic approach to these patients represents a great challenge for the clinicians because of the variety and unpredictability of HCV-EHDs. HCV-infected individuals are often referred to different tertiary centers according to the presenting/prevalent symptom(s) with the potential risk to underestimate the remaining clinical manifestations.

As regards the diagnostic aspects, previously published studies generally analyzed a single manifestation at once in the variegated field of HCV-EHDs [1,2]. The present work represents the first attempt to draw comprehensive diagnostic guidelines for HCV-infected individuals by encompassing the entire spectrum of HCV-EHDs, based on specific expertise of different co-authors. Considering the heterogeneity of HCV syndrome and in particular of HCV-EHDs, the preparation of diagnostic guidelines is a particularly difficult task; they should be sufficiently inclusive and thorough with respect to various symptoms that may complicate the natural course of HCV infection, but at the same time easily manageable in the clinical practice by different specialists dealing with HCV-infected patients. The patient’s assessment at the first referral and during the follow-up should be based on the routinely adoption of standardized core set of diagnostic procedures, possibly integrated by deeper clinical investigations focusing on specific clinical manifestations. There was a broad consensus among ISG–EHCV members on item selection of baseline clinical evaluation; while for single HCV-EHDs, i.e., rheumatic, renal, hematological, and endocrine manifestations, targeted second line diagnostic procedures were proposed by the expert panel. Moreover, when available classification/diagnostic criteria for single disorders were properly taken into account [17–23].

The HCV lymphotropism along with its striking association with MCS was firstly demonstrated in the early nineties soon after the HCV discovery [12,13,150,151]. These important findings prompted an increasing number of studies on different autoimmune-lupusproliferative HCV-EHDs [1–6]. Apart from hepatic manifestations, a significant percentage of HCV-infected individuals may remain totally asymptomatic for years or the entire life, even though immunological alterations such as high serum levels of rheumatoid factor and/or cryoglobulinemia may be frequently found [1–7]. In particular, circulating cryoglobulins may be detected in almost half of HCV-infected patients but without any clinical significance, while overt MCS may develop in about 15% of cryoglobulinemic patients [1–6] see ref. of the group of Zignego at the last EASL. Possible overlapping conditions may regard HCV-infected patients with auto-immune features mimicking classical rheumatic diseases, mainly RA and pSS [1–6,9,38]. In these instances,
it is necessary to correctly differentiate patients with true ‘primary’
auto-immune diseases and concomitant HCV infection from
HCV-infected patients with HCV-EHDs [1,2,6,28,38]. The MCS may be
correctly classified following the criteria elaborated by international
study group proposed by the Italian Study Group on Cryoglobulinemia
[17,18] in the majority of cases, there are some patients with difficul-
ties to distinguish between true HCV-related MCS and other well-
known conditions, particularly pSS [1,2,6,28]. For the latter, the term
of ‘overlapping syndrome’ may be rather appropriate, taking into ac-
count the negative impact of both HCV infections per se and
cryoglobulinemia vasculitis, when it is present, on the whole patients’
outcome [1,9].

The spectrum of HCV-EHDs is extremely heterogeneous; it includes
immune-mediated, organ- and non-organ specific disorders as well as
neoplastic manifestations [1–6,47]. The possible multistep contribu-
tion of different pathogenic cofactors, genetic and environmental, may
be decisive for the appearance of specific clinical phenotypes. HCV-EHDs
can be observed at any time during the natural history of HCV infection
and vary combined in individual patients and among patients’ pop-
ulations from different geographical areas [1–6,9,152–162]. Some
harmful, life-threatening complications may appear abruptly; thus,
careful clinical monitoring of HCV-infected patients is crucial for early
diagnosis and treatment of these unpredictable manifestations. It is
also possible that recently available direct-acting antiviral treatments
leading to HCV eradication in a very high percentage of patients
[163–166] may affect in the near future the natural history of HCV infec-
tion including its EHDs. Considering HCV-EHDs, some preliminary studies
regarding small patients’ series demonstrated a marked improvement or
disappearance of some symptoms, particularly MCS or lymphoma com-
plications [1–6]. However, it is also possible that profound HCV-driven
immune-system alterations may result totally or at least in part irrevers-
able in some patients, mainly in those with long-lasting viral infection.
Thus, current antiviral treatments might lead to novel, unforeseeable sce-
narios. Future clinical trials focusing on patients with sustained virological
response might elucidate the above questions; these studies may be deci-
sive in order to quantify the actual percentage of remission of different
HCV-EHDs, as well as to identify possible predictive factors of different
disease outcomes.

In conclusion, a multidisciplinary approach to HCV-infected patients
is greatly advisable since the first patient’s evaluation; comprehensive
clinical assessment following standardized diagnostic guidelines is
critical for the whole patients’ management and therapeutic strategies,
as well as for pathogenic studies focusing on homogeneous clinical
subsets.

Appendix A

International Study Group of Extrahepatic Manifestations
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Q3 Uncited references

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