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Review

REVIEW

Systematic review of mixed cryoglobulinemia associated with hepatitis E virus infection: association or causation?

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Abstract

Background and aim: Mixed cryoglobulinemia (MC) has been associated with several viral infections, and chronic hepatitis C is recognized as a major cause. MC associated with hepatitis E virus (HEV) has been described and little is known about this rare association. The aim of this study is to perform a systematic review of MC associated with HEV, and examine the presence of a causal relationship.
Methods: An experienced librarian conducted a search of databases from each database's inception to 12 December 2016 based on a priori criteria. The risk of bias was assessed, and Hill's criteria were applied to determine causality.
Results: Five publications met inclusion criteria, with a total of 15 cases. Three studies had low, one low to moderate and one moderate risk of bias. Median age was 43 years, and all patients came from Western Europe. Two patients were immunocompetent, while 13 were immunosuppressed, post solid organ transplant and had chronic hepatitis E. Renal involvement was observed in seven patients, mild to moderately severe cryoglobulinemic disease in one patient and severe cryoglobulinemic disease in three patients. One patient improved spontaneously, and another was treated with immunosuppressant reduction leading to viral clearance. Ten patients treated with peg-interferon or ribavirin for 3 months achieved loss of cryoglobulinemia and end-of-treatment response, but sustained virologic response was reported and achieved in two. Immunosuppressant achieved loss of cryoglobulinemia in three patients. One case of chronic renal failure, three cases of end-stage renal disease and one death were observed. Five of the nine Hill's criteria were fulfilled.
Conclusion: MC has been described with HEV infection. A causal relationship between HEV infection and cryoglobulinemia is highly probable.

Key words: hepatitis E virus; hepatitis; virology; mixed cryoglobulinemia; systematic review

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Introduction

Mixed cryoglobulinemia (MC) has been associated with several viral infections and at least nine viruses have been implicated [1]. Hepatitis C virus infection (HCV) is recognized as the major cause of MC reported in 90% of Italian patients in one series [2], although later studies found wide geographical variations [3]. Some cases of MC are related to human immunodeficiency virus (HIV) [4], Hepatitis B virus infection (HBV) [5] and, less frequently, to hepatitis A virus infection (HAV) [6] as well as other viruses. Acute hepatitis E is reported mainly in immunocompetent patients, whereas chronic hepatitis E has been almost always limited to immunosuppression states such as malignancy, HIV infection and solid organ transplantation (SOT) [7,8]. MC associated with hepatitis E virus (HEV) infection in immunocompetent or immunosuppressed patients has been described and little is known about this rare association and whether causal inference could be made. To date, no systematic review addressing this association has been published. The aim of this study is to perform a systematic review of the association between MC and HEV infection, and examine the evidence of a causal relationship.

Methods

Literature search

A comprehensive search of several databases from each database's inception to 12 December 2016, English, French and Spanish languages was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for cryoglobulinemia and hepatitis E. The search strategy is available in supplemental figure. In addition, we searched the first 100 entries of Google Scholar using the terms 'hepatitis E' and 'cryoglobulinemia' to look for articles not indexed in major databases. Reference lists were manually reviewed for additional cases.

Inclusion criteria based on the following definitions

Diagnosis of hepatitis E in immunocompetent patients was based on the detection of anti-HEV IgM with confirmation of acute case detected serologically by HEV RNA in blood or stool [9]. *Diagnosis of hepatitis E in immunocompromised patients* was based on detection of HEV RNA in blood or stool [10]. *Diagnosis of chronic hepatitis E* was defined by persistence of HEV replication for more than 6 months, or more than 3 months in the setting of SOT [11].

Diagnosis of cryoglobulinemia was defined by the presence of cryoglobulins in serum stored at 4 °C for several days in two fractions, and reversibility of the cryoprecipitation in one fraction replaced at 37° when a cryoprecipitate is formed [1,12]. *The classification of cryoglobulinemia* was established by immunofixation or immuno-electrophoresis, which confirms the presence of immunoglobulins, and enables classification into types I to III [12].

Diagnosis of cryoglobulinemic disease (CD) was established by the presence of circulating cryoglobulins and typical organ involvement, mainly skin, kidney or peripheral nervous system [1]. *Severity of CD*: in the absence of standardized disease severity of CD, experts classified the disease into mild to moderately severe, severe and life-threatening [1]. Mild to moderately severe CD is identified by the presence of purpura, arthritic manifestations, mild neuropathy or glomerulonephritis without renal failure. Severe CD is identified by the presence of cutaneous ulcers, ischemia, severe neuropathy, glomerulonephritis with renal failure and/or nephrotic syndrome or gastrointestinal involvement. Life-threatening CD is identified by the presence of rapidly progressive glomerulonephritis, central nervous system involvement, intestinal ischemia or alveolar hemorrhage.

Response to antiviral treatment was assessed by sustained virologic response (SVR) defined by absence of HEV RNA 24 weeks after the end of treatment [13].

Assessment of causal relation between MC and HEV infection was performed by applying the nine Hill's criteria for causation on the documented cases [14].

We excluded duplicated studies and cases with the presence of concomitant acute or chronic liver disease.

Data extraction and assessment

Two reviewers (F.B., S.H.) assessed the quality of the studies and extracted the relevant data based on the inclusion/exclusion criteria.

Risk of bias assessment (methodological quality)

Given that there are no available validated tools to assess the risk of bias (i.e. methodological quality) of case reports and case-series, we derived items from the Newcastle-Ottawa Scale (NOS) that were appropriate for this systematic review. We removed from the NOS the items that related to comparability and adjustment (because the studies included were non-comparative). We retained for the purpose of bias assessment the items that focused on selection, representativeness of cases, and ascertainment of outcome and exposure. This resulted in five criteria in the form of questions with a binary response (yes/no), whether the item was suggestive of bias or not. These questions are listed in Table 1. We considered the quality of the report good (low risk of bias) when all five criteria were fulfilled, moderate when four were fulfilled and poor (high risk of bias) when three or fewer were fulfilled. This tool has been previously applied [15]. No disagreements were found between the reviewers.

Results

Study characteristics

The flow diagram of study selection is shown in Figure 1. We identified six publications between 2007 and 2016 that met the inclusion criteria [16–21]. One publication was excluded due to a potential co-presence of HCV and HEV [21]. Of the remaining five studies, four publications were full-text articles [16,17,20,22] and one was in the form of a letter to the editor [23]. There were four case reports [16,20,22,23] and one case-series [17]. Three studies were likely at low risk of bias and one at moderate risk. The case-series publication included 11 cases: 4 cases had low and 7 had moderate risk of bias (Table 1).

Patient characteristics

Demographics and disease features (Table 2)

Among the 15 cases, the median age was 43 years, the male-to-female ratio was 7 and all patients came from Western Europe. Two patients were immunocompetent without evidence of

chronic hepatitis E and 13 patients were immunosuppressed status post SOT, who also had chronic hepatitis E with persistent HEV replication (>6 months in 12 patients; >3 months in 1 patient) [19]. Genotype 3 testing failed in 1 patient, was not performed in 1 patient and was confirmed in 13 patients. All patients had type II or type III MC. Anti-HEV IgG, anti-HEV IgM and HEV RNA were detected in the cryoprecipitate in one patient.

MC occurred during active viral infection in 14 patients and following HEV clearance obtained by reduction of immunosuppression medications in 1 patient [18]. Renal involvement was observed in seven patients: menbranoproliferative glomerulonephritis (MPGN) in three patients, relapsing IgA nephropathy in two patients, nephroangiosclerosis in one patient, whereas renal biopsy was not performed in one patient. Rash, arthralgia and thrombocytopenia were noted in one patient who had renal disease [18]. CD was observed in four patients, was mild to moderately severe in one patient with self-limited severe arthritis and rash, and severe with MPGN in three patients. Data regarding the presence or absence of CD were lacking for the remaining seven patients.

Patient management (Table 3 and Figure 2)

One patient with self-limited arthritis required no treatment. Fourteen patients required intervention: immunosuppressant dose reduction (1 patient), antiviral monotherapy (10 patients) and immunosuppressant (3 patients). Interestingly, immunosuppressant dose reduction before occurrence of MC was undertaken in two patients: it was associated with viral clearance in one patient followed by occurrence of MC [18] and was

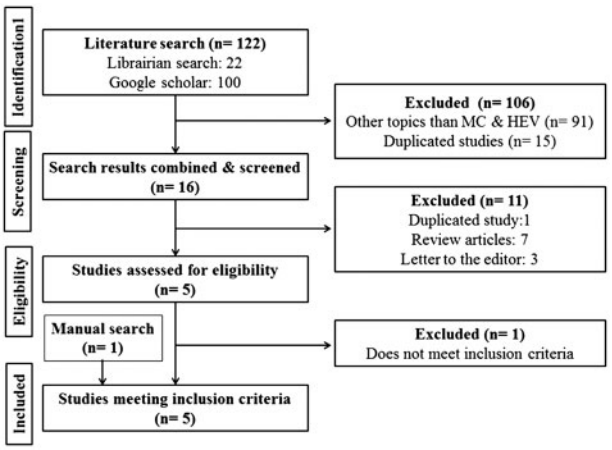

Figure 1. Flow diagram for study selection.

Table 1. Risk of bias assessment of the included studies

First author/year	No. of cases	Question 1	Question 2	Question 3	Question 4	Question 5	Risk of bias
Serratrice 2007 [16]	1	Yes	Yes	Yes	Yes	Yes	low
Kamar 2012 [17]	4	Yes	Yes	Yes	Yes	Yes	low
	7	Yes	Yes	Yes	No	Yes	moderate
Pischke 2014 [18]	1	Yes	Yes	Yes	No	Yes	moderate
Del Bello 2015 [19]	1	Yes	Yes	Yes	Yes	Yes	low
Guinault 2016 [20]	1	Yes	Yes	Yes	Yes	Yes	low

Questions 1–5 comprise the tool for risk of bias assessment of case reports and case-series:
1. Did the patient(s) represent the whole case(s) of the medical center? (The studies did not mention whether the reported patient(s) represented the whole case(s) of the medical center and we assumed that the authors have reported all the cases in their center giving the rarity of this association.)
2. Was the diagnosis correctly made?
3. Were other important diagnoses excluded?
4. Were all important data cited in the report?
5. Was the outcome correctly ascertained?

Table 2. Cases of mixed cryoglobulinemia associated with HEV infection

First author/year	No.	Country	Age/sex	IC/IS	HEV infection		Mixed cryoglobulinemia			
					PCR	Genotype	CD	Manifestations	Renal biopsy	CD severity
Serratrice 2007 [16]	1	France	51/Female	IC	(+)	3	(+)	Arthritis—rash	–	Mild/mod
Kamar 2012 [17]	7	France	NR	IS/SOT	(+)	3	NR	–	–	–
	1		26/Male	IS/KT	(+)	3f	(–)	RF-NS	Relapse IgAN	–
	1		40/Male	IS/KT	(+)	3f	(–)	RF-NS	Relapse IgAN	–
	1		24/Male	IS/KT	(+)	3f	(+)	RF-NS	MPGN	Severe
	1		58/Male	IS/LT	(+)	3c	(–)	RF	NAS	–
Pischke 2014 [18]	1	Germany	35/Male	IS/LT	(+)	Not done	(+)	Rash-arthralgia-RF; Thrombocytopenia	Not done	–
Del Bello 2015 [19]	1	France	46/Male	IS/KT	(+)	3f	(+)	RF	MPGN	Severe
Guinault 2016 [20]	1	France	48/Male	IC	(+)	Not possible[a]	(+)	RF-NS	MPGN	Severe
Total: 5 studies	15	France: 14 Germany: 1	Median: 43 Male: 7 Female: 1	IS 13 IC 2	All (+)	Genotype 3: 13	(+): 4 (–): 4		MPGN: 3 IgAN: 2 NAS: 1	Mild/mod: 1 Severe: 3

[a]Genotyping not possible due to failure to amplify sufficient HEV RNA.
NR: not report; IC: immunocompetent; IS: immunosuppressed; SOT: solid organ transplantation; KT: kidney transplantation; LT: liver transplantation; CD: cryoglobulinemic disease; RF: renal failure; NS: nephrotic syndrome; IgAN: IgA nephropathy; MPGN: membrano-proliferative glomerulonephritis; NAS: nephroangiosclerosis; Mild/mod: mild to moderately severe.

Table 3. Modality and site-effects of treatment of mixed cryoglobulinemia associated with HEV infection

First author/year	No.	Treatment	Doses	Duration	Side effects	Management
Kamar 2012 [17]	7	Ribavirin (majority)	Not report	3 months	Not report	–
	1	Ribavirin	600 mg	3 months	No	–
	1	Reduce immunosuppressant (tacrolimus)	–	–	No	–
	1	Immunosuppressant (rituximab)	375 mg/m^2/week	4 weeks	No	–
	1	Pegylated interferon	135 μg/week	3 months	No	–
Pischke 2014 [18]	1[a]	Immunosuppressant (steroids)	–	2 courses	Mucositis/death	Supportive
Del Bello 2015 [19]	1[b]	Ribavirin	1200 mg/d	1 month	Anemia	reduce ribavirin—erythropoietin transfusion–
		Ribavirin	600 mg/d	2 months	No	
Guinault 2016 [20]	1	Plasmapheresis	–	7 sessions	No	–
		Immunosuppressant (steroid pulses)	1 mg/kg/d	18 days	No	–
Total: 4 studies	14	Reduce immunosuppressant: 1 Antivirals: 10 Immunosuppressant: 3			Side effects: 2 No side effects: 5 Not report: 7	

[a]Mixed cryoglobulinemia appeared after viral clearance.
[b]Immunosuppressant reduction before appearance of mixed cryoglobulinemia.

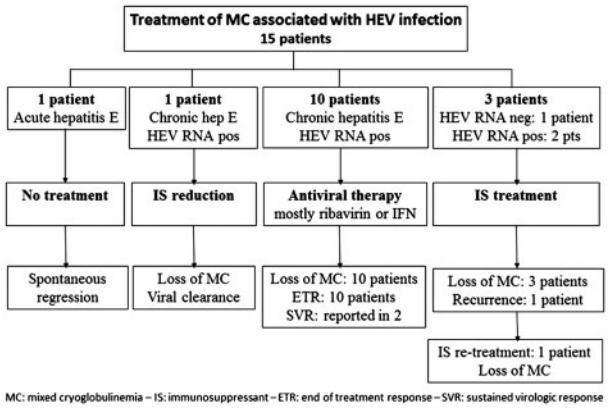

Figure 2. Treatment of mixed cryoglobulinemia associated with HEV infection.

unsuccessful in a second patient who also developed later MC [19]. IS dose reduction with the intention to treat MC associated with chronic hepatitis E was undertaken in one patient, leading to viral clearance. Ten patients were treated with antiviral monotherapy for 3 months (most of them receiving ribavirin). Loss of cryoglobulinemia and end-of-treatment response, defined by the absence of HEV RNA at the end of the treatment, were obtained in all of them but SVR was reported and obtained in two cases and not reported for the remaining cases. Three patients were treated with immunosuppressants (rituximab in one patient and steroids in two patients) with loss of cryoglobulinemia in two patients and two episodes of cryoglobulinemia responding to retreatment in the third patient.

Treatment side effects were reported in seven cases: ribavirin-induced anemia in one case necessitating dose reduction, recombinant erythropoietin administration and blood transfusion [19]; severe fatal intestinal mucositis following corticosteroids reduction in one case [18]; and absence of side effects in five cases. These data were not reported for the seven other treated cases.

Final outcome

The final outcome revealed spontaneous regression in one patient who had severe arthritis, improved kidney function in nine patients, chronic renal failure in one patient, end-stage renal disease 2–3 years after diagnosis in three patients and one death due to severe intestinal mucositis (Table 4).

Generalizability of the results

Given the good- and moderate-quality assessment of all included studies and the reports from three different centers, we believe that our results could be applied to all patients with cryoglobulinemia associated with HEV infection. However, we could not exclude a selection bias favoring the report of more severe cases.

Application of Hill's criteria

We applied 'Hill's criteria for causation' to the 15 documented cases (Table 5). Five of the nine criteria were fulfilled, which we consider as highly probable for a causal relationship.

Discussion

HEV is a rising threat in non-endemic regions, and there has been a renewed interest in its epidemiology, clinical manifestations and prevention [7,11,24,25]. HEV manifestations may range from acute, which may result in acute liver failure [26], to chronic in immunosuppressed individuals, and it may also masquerade through a myriad of extra-hepatic manifestations [24]. MC has been recognized as an extra-hepatic manifestation of HCV for a long time. The prevalence of HCV infection in MC ranges from 40 to 90%, whereas HCV-negative MC accounts for about 5–10% [27].

We identified 15 cases of MC associated with HEV. Of note, all patients originated from Western Europe, where HEV genotype 3 is prevalent, and all cases were reported by three major groups in France and Germany, which had extensive experience with HEV. In two studies of kidney- and liver-transplant patients with cryoglobulinemia, no cause of cryoglobulinemia was found in a significant number of patients [28,29]. HEV infection was not tested in these patients and it is unknown whether they had past or ongoing HEV infection. It is possible that MC associated with HEV infection is underreported.

Table 4. Results of treatment of mixed cryoglobulinemia associated with HEV infection

First author/year	No.	Treatment	Before treatment		Results of treatment				Outcome
			RNA	eGFR	Cryo	ETR	SVR	eGFR	
Kamar 2012 [17]	7	Ribavirin (majority)	(+)	NR	(–)	Yes	NR	Improved[a]	Improved
	1	Ribavirin	(+)	eGFR 35	(–)	Yes	Yes	eGFR 35	Chronic renal failure
	1	IS reduction	(+)	eGFR 39	(–)	–	–	eGFR 35	ESRD 2 years after diagnosis
	1	IS (rituximab)	(+)	eGFR 37	(–)	–	–	Dialysis dependent	ESRD 3 years after diagnosis
	1	Pegylated interferon	(+)	eGFR 35	(–)	Yes	NR	eGFR 27	ESRD 2 years after diagnosis
Pischke 2014 [18]	1	IS (steroids)[b]	(–)	eGFR 28	Recurrent	Negative before treatement		eGFR 87	Death (mucositis)
Del Bello 2015 [19]	1	Ribavirin[c]	(+)	eGFR 41	(–)	Yes	Yes	eGFR 60	Improved
Guinault 2016 [20]	1	plasmapheresis – IS(steroids)	(+)	eGFR 19	(–)	–	–	eGFR 38	Improved
Total: 4 studies	14	IS reduction: 1 Antivirals: 10 IS: 3	(+):13 (–): 1		(–): 13 Recurrent: 1	Yes: 10	Yes: 2 NR: 8		Improved: 9 Chronic renal failure : 1 ESRD: 3 Death: 1

[a]Outcome not reported in details but significant amelioration of serum creatinine at the end of antiviral treatment was observed.
[b]Cryoglobulinemia appeared after viral clearance following reduction of immunosuppressive drugs.
[c]Immunosuppressant reduction before occurrence of mixed cryoglobulinemia.
NR: not reported; IS: immunosuppressant; eGFR: estimated glomerular filtration rate given in mL/min/m^2; Cryo: cryoglobulinemia; ETR: end-of-treatment response; SVR: sustained virologic response; ESRD: end-stage renal disease.

Table 5. Application of Hill's criteria on 15 cases of mixed cryoglobulinemia (MC) associated with HEV infection

Hill's criteria	Hill's definition	Application	Result
1. Strength (effect size)	'A small association does not mean there is not a causal effect, though the larger the association, the more likely that it is causal'	Low number of reported cases	Not fulfilled
2. Consistency (reproducibility)	'Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect'	Reports from three groups interested in HEV infection in 2 countries; Possible unawareness bias for other groups	Not fulfilled
3. Specificity	'Causation is likely if there is very specific population at specific site and disease with no other likely explanation'	Specific population with no other explanation; 13 immunosuppressed patients with chronic hepatitis E genotype 3; 2 immunocompetent patients with acute hepatitis E genotype 3	Fulfilled
4. Temporality	'The effect has to occur after the cause'	Simultaneous presence of HEV & MC (14 patients); Occurrence after viral clearance (1 patient) but HEV may trigger autoimmunity	Fulfilled
5. Biological gradient (dose-response)	'Greater exposure should generally lead to greater incidence of the effect'	No study correlates viral load & MC occurrence; Low viral load in one patient at assessment's time	Not fulfilled
6. Plausibility	'Plausible mechanism between cause and effect is helpful'	Immunopathological mechanism; Presence of anti-HEV IgG, anti-HEV IgM and HEV RNA in the only tested patient	Fulfilled
7. Coherence	'Coherence between epidemiological & laboratory findings increases likelihood of effect'	Low number of reported cases	Not fulfilled
8. Experiment	'Occasionally it is possible to appeal to experimental evidence'	Loss of MC after HEV eradication by antiviral treatment in 10 patients	Fulfilled
9. Analogy	'Effect of similar factors may be considered'	Several other viruses cause MC (especially HCV)	Fulfilled

To the best of our knowledge, Guinault *et al*. were the first to isolate anti-HEV IgG, IgM and HEV RNA from the precipitate in a patient with severe CD [20]. This finding favors a causal relationship between HEV infection and MC. HEV RNA was not assessed in the cryoprecipitate in any of the previous reports. Moreover, a recent retrospective cross-sectional study examined 68 German patients with cryoglobulinemia [30] and revealed a statistically significant difference in the presence of anti-HEV IgG antibodies in patients with essential cryoglobulinemia when compared with cryoglobulinemia of other defined causes ($p = 0.043$). This study suggests that previous HEV infection might play a role in some cases of cryoglobulinemia that are currently classified as essential.

HEV could trigger an autoimmunity response that may account for the development of extra-hepatic manifestations after viral clearance, as MC was observed in a patient following viral clearance [24,31]. Reports of chronic hepatitis E have been almost limited to immunosuppressed patients infected with genotype 3. All 13 patients with chronic hepatitis E in this review had immunosuppressed status post SOT and genotype 3 was confirmed in 12 patients and was not done in 1 patient.

Renal involvement was reported in nearly half of patients in this review. Although it is difficult to implicate HEV infection in the two cases of relapsing IgA nephropathy, it is possible that HEV may have triggered this relapse given that, in one patient, proteinuria returned to its baseline, and cryoglobulinemia had become undetectable when viral clearance was achieved following ribavirin monotherapy.

Similarly to MC associated with chronic hepatitis C, the treatment of MC associated with chronic hepatitis E could also depend on the severity of CD [1]. In the absence of life-threatening CD, the treatment could be directed toward eradication of viral replication with or without immunosuppressant.

The first-line therapy for HEV in chronic hepatitis E is to reduce the immunosuppressant dose when possible, especially that of agents targeting T-cells. This treatment may achieve viral clearance in one-third of patients [32] and this was the method of treatment in one patient in our review, leading to viral clearance [17].

The second line of treatment to eradicate HEV in chronic hepatitis E is the use of antivirals monotherapy. Peg-interferon could induce rejection in SOT patients and should be avoided in that setting, while ribavirin is considered the antiviral treatment of choice, especially in the SOT recipient, according to a recent systematic review of the literature [33]. A 3-month course of ribavirin 600 mg/day is appropriate in SOT recipients with chronic hepatitis E genotype 3 according to a large multicenter retrospective study published recently [13]. In MC associated with HCV infection, SVR was achieved in more than half of the patients treated with pegylated interferon plus ribavirin in a previous meta-analysis [34] and in most patients treated with sofosbuvir-based direct-acting antiviral regimens in a recent case-series study (83%) [35]. In our review, loss of cryoglobulinemia and end-of-treatment response were achieved in 10 patients treated with antiviral monotherapy (pegylated interferon or ribavirin). Further studies are needed to confirm these initial results and to document the rate of SVR in this setting.

Immunosuppressant may be indicated for the treatment of CD in the absence of viral replication or in severe CD. In our review, immunosuppressant was given despite viral replication in two patients: in one patient, no antiviral therapy at that time had been given to HEV-positive kidney transplant patients [17,19]; and, in a second patient, a low viral load 1 week after admission was present [20].

Association does not entail causation, and the most important, and perhaps most difficult, question to answer is whether MC is simply associated with HEV infection or caused by this infection. The British medical statistician and father of modern randomized controlled trials, Sir Austin Bradford Hill, published in 1965 nine 'viewpoints' to establish a causal relationship between a putative cause and an effect (Table 5) [14]. Since then, these 'viewpoints', known in the literature as 'Hill' criteria', have become a frequently cited framework for causal inference in epidemiological studies. We cautiously apply Hill's criteria to examine the relation between MC and HEV, and we do not attempt to give definitive conclusions. In our review, four of the Hill's criteria were not fulfilled by the documented cases. The non-fulfillment of the strength and coherence effects is due to the low number of reported cases and this is subject to change if more cases are recognized. Second, the lack of consistency criteria could be due to a possible unawareness bias. Lastly, the non-fulfillment of biological effect criteria is due to the lack of evidence. Lack of known evidence does not signify absence of true evidence, as it is impossible to determine its validity without intentional experimentation. Moreover, we are aware that the way each criterion should be applied, interpreted and weighted must be carefully measured against the novel types of data available in each unique situation [36]. Given the absence of a scoring system when Hill's criteria are applied, we consider the fulfillment of five criteria as highly probable for a causal link.

We acknowledge that our review entails several shortcomings. First, the methods of diagnosis and classification of cryoglobulinemia were not mentioned in published reports. We presumed that when the diagnosis of MC and its type was made, the validated laboratory methods were implemented. Second, for seven patients, it was not possible to establish whether CD was present or absent, what were the doses of antiviral monotherapy and what were the ensuing side effects of treatment. Third, SVR, which is the most important index for the efficacy of antiviral treatment, was not reported in 8 of 10 patients treated with antiviral monotherapy, although loss of cryoglobulinemia and end-of-treatment response were obtained in all of them. Fourth, our proposed tool for risk of bias assessment of case reports and case-series has not been validated, although it was derived from a commonly used instrument. We derived simple and reproducible questions that included important parameters to fit the question at hand. Lastly, the number of published cases is too small to allow precise characterization of this possible extra-hepatic manifestation of HEV and could limit the evaluation of a causal relationship. Further studies are needed to delineate the frequency of MC associated with HEV, its pathophysiology, its relationship with the viral load and to establish the rate of SVR of antiviral monotherapy.

In conclusion, MC has been described with HEV infection. A causal relationship between HEV infection and cryoglobulinemia is highly probable.

Conflict of interest statement: none declared.

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