Performance of the preliminary classification criteria for cryoglobulinaemic vasculitis and clinical manifestations in hepatitis C virus-unrelated cryoglobulinaemic vasculitis

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ABSTRACT

Background. *Cryoglobulinaemic vasculitis (CV) is often related to hepatitis C virus (HCV) infection, but it can develop in other diseases (e.g. other infections, connective tissue diseases, malignancies) in the absence of HCV infection. A comparison of the performance of the recently published classification criteria for the CV was made between HCV-positive and HCV negative patients with serum cryoglobulins.*

Patient and methods. *500 patients with serum cryoglobulins were studied. Their mean age was 60.77±13.75 years, they were 356 females (71.2%) and 144 males (28.8%). CV was diagnosed in 272 patients (54.4%), while other diseases associated with serum cryoglobulins without CV (CwV) were diagnosed in 228 patients (45.6%).*

Results. *117 HCV negative patients were collected (23.4%) and they were 42/272 (15.4%) among the CV group, while they were 75/228 (32.9%) among the CwV.*

In HCV negative patients the sensitivity and specificity of the classification criteria of CV were 89.5% CI 95% [79.5–99.5] and 90.3% CI 95% [82.8–97.8], respectively, while in HCV positive patients they were 88.3% CI 95% [83.6%–93.1%] and 96.1% CI 95% [91.8–100], respectively. The most frequent disease recognised among the HCV negative patients was Sjögren's syndrome (SS) (55/117, 47.0%), and the sensitivity and the specificity of the CV classification criteria were 88.9% CI 95% [76.5–100] and 91.3% CI 95% [79.2–100], respectively.

Conclusions. *The classification criteria for CV showed a good performance even in HCV-unrelated patients. A slightly lower specificity was observed for the classification of HCV-unrelated CV, since some clinical manifestations included in the clinical item for the classification criteria occurred more frequently in HCV-negative rather than HCV-positive controls with CWV.*

Introduction

Cryoglobulinaemic syndrome or cryoglobulinaemic vasculitis (CV) is a systemic vasculitis associated with serum positive cryoglobulins, *i.e.* immune complexes composed by rheumatoid factor-(RF) monoclonal or polyclonal against polyclonal IgG (type II or type III cryoglobulins, respectively) or immunoglobulins without RF activity (type I), which reversibly precipitate at a temperature below 37°C (1, 2).

The recent formally developed classification criteria for the cryoglobulinaemic vasculitis (CV) showed a sensitivity of 88.5% CI 95% [84.3–92.8] and a specificity of 93.6% CI 95% [89.5–97.7] (3). CV or isolated serum mixed cryoglobulinaemia without vasculitis (CwV) are more often related to hepatitis C virus infection (HCV) (4-6), but they can develop in other diseases, such as connective tissue diseases (in particular Sjögren's syndrome (SS)) (7), other infections (8) and haematological malignancies (9). In particular, the presence of serum mixed cryoglobulinaemia, *i.e.* serum positivity of cryoglobulins, with or without concomitant clinical manifestations of CV, occurs in about 10–15% patients with SS (3), while CV is less frequent but it greatly affects the SS-related morbidity (10).

The biologic, and, to some extent, also

the clinical characteristics of HCV-unrelated CV may be different from HCV-related CV (11). Of note, also the efficacy and safety of novel treatments, *i.e*. B-cell depleting therapy (12), showed some differences between the two groups (13-16). Therefore, a correct classification of both HCV-related and –unrelated CV may be required for epidemiologic and clinical clues. In the study for the development of the classification criteria for CV, both HCV-positive and HCV-negative patients were joined together, based on the consecutive, unselected recruitment of either HCV-positive or -negative subjects, and the criteria were then developed independently from the HCV status. In the present study, the sensitivity and specificity of these developed classification criteria of CV were analysed separately in the two subset of patients, either HCV-positive or negative cases and controls, recruited in the original study. Also, a subanalysis of the sensitivity and the specificity of the CV classification criteria was performed in SS patients, since these represented the largest subgroup within the HCV-negative cases. A clinical and laboratory comparison between HCV positive and HCV negative patients with CV included in the original study is finally reported.

Patient and methods

Five hundred patients with positive serum cryoglobulins were studied (3). Mean age was 60.77±13.75 years, they were 356 females (71.2%) and 144 males (28.8%). A diagnosis of CV was made in 272 patients (54.4%) by the experts (cases). The other 228 patients (45.6%) had other diseases associated with only positivity for serum cryoglobulins without a diagnosis of a CV (controls) (CwV). One hundred and seventeen HCV negative patients were collected (117/500, 23.4%) and they were 42/272 (15.4%) among the CV group, while they were 75/228 (32.9%) among the CwV group. HCV positive patients were 383/500 (76.6%), and they were 230/272 (84.6%) among the CV group, and 153/228 (67.1%) among the CwV group.

Since SS was the most frequent disease recognised among the HCV negative patients (55/117, 47.0%), the analysis of sensitivity and specificity of the CV classification criteria was also performed in this subpopulation of patients. They were 29/272 (10.7%) among the first group of CV (SS-CV), 25 females (86.0%) and 4 males (14.0%), with mean age of 60.5±10.5 years, and 26/228 (11.4%) among the CwV group (SS-CwV), 25 females (96.0%) and 1 males (4.0%), with a mean age of 57.7±13.6 years.

Demographic characteristics, clinical and laboratory items were collected in the protocol chart as previously described (3).

Statistics

Sensitivity and specificity were estimated with 95% confidence interval.

Student's *t*-test was used to compare the age between HCV-related and HCV-unrelated CV, and between SS-CV and SS-CwV, after verifying the normality of the variable distributions (Kolmogorov test). The χ^2 test or Fisher's test was used to compare qualitative variables, after confirming the necessary assumptions. A p-value <0.05 was considered significant.

Results

Sensitivity and specificity of the classification criteria for cryoglobulinaemic vasculitis in HCV-positive and -negative patients

The sensitivity and the specificity of the classification criteria for the CV in the HCV positive patients were 88.3% CI 95% [83.6%–93.1%] and 96.1% CI 95% [91.8–100], respectively, while the sensitivity and the specificity in HCV negative patients were 89.5% CI 95% [79.5–99.5] and 90.3% CI 95% [82.8–97.8], respectively.

No differences were observed between the two groups of patients (HCV positive and HCV negative) as regards the sensitivity of the single item, *i.e*. the questionnaire, the clinical item, and the laboratory item (Table I). Nor were any differences noted as regards the specificity of questionnaire and the laboratory item (p=0.82 and p=0.29, respectively) (Table I), while a statistically significant difference was observed in the specificity of the clinical item of the criteria (p<0.0001).

When then analysing the specificity of the clinical item in detail (3), controls with CwV were studied. The HCV negative controls showed a higher prevalence of some clinical items if compared with HCV positive controls with CwV. A significant increase was noticed as regards the constitutional symptoms in HCV negative controls, *i.e*. fatigue, low grade fever (37–37.9°C, ≥10 days, no cause), fever (≥38°C, no cause), or fibromyalgia (HCV- *vs*. HCV+ controls: 42/75 *vs*. 56/153, p=0.007; mean difference: 19.2, CI 95% [5.6–32.8], the articular involvement (*i.e*. arthrtalgias or arthritis; HCV- *vs*. HCV+ controls: 54/75 *vs*. 44/153, p<0.0001; mean difference: 43.2, CI 95% [30.8–55.7], the vascular involvement (*i.e* Raynaud's phenomenon, purpura, necrotising vasculitis, skin ulcers, hyperviscosity syndrome; HCV- *vs*. HCV+ controls: 36/75 *vs*. 13/153, p<0.0001; mean difference: 39.5, CI 95% [27.4–51.6], and finally, the neurologic involvement (*i.e*. peripheral neuropathy, mononeuritis, multineuritis, cranial nerve involvement, CNS vasculitis; HCV- *vs*. HCV+ controls: 17/75 *vs*. 11/153, p=0.0008; mean difference: 16.3, CI 95% [5.2–27.3].

Sensitivity and specificity of the classification criteria for cryoglobulinaemic vasculitis in Sjögren's syndrome with mixed cryoglobulinaemia

Sensitivity and specificity of the classification criteria for the CV in SS patients were 88.9% CI 95% [76.5–100] and 91.3% CI 95% [79.2–100], respectively. As regard the single items of the classification criteria for CV (*i.e*. questionnaire, clinical and laboratory), SS patients showed the following results for sensitivity and specificity, respectively: 82.8% CI 95% [68.4–97.1] and 92.3% CI 95% [81.6-100] for the questionnaire item, 79.3% CI 95% [64.1-94.7] and 73.1% CI 95% [55.3–90.9] for the clinical item, 85.2% CI 95% [71.2–99.2] and 82.6% CI 95% [66.4–98.8] for the laboratory item (Table II).

No differences between SS-CV and SS-CwV patients were observed as regards clinical features of lymphoproliferation, including lymphadenopathy, splenomegaly, salivary gland swelling, lachrymal

Table I. Sensitivity and specificity of the classification criteria for CV in HCV-positive and HCV-negative patients.

	HCV+ (n=383)	HCV- (n=117)	Difference [$_{95\%}$CI]	*p*-value
Sensitivity [$_{95\%}$CI]	88.3% [83.6%-93.1%]	89.5% [79.5-99.5]	1.2 [-9.7-11.9]	0.84
Questionnaire	83.4 [78.7-88.3]	85.7 [75.1-96.3]	2.3 [-9.4-13.9]	0.71
Clinical item	67.9 [61.7-74.0]	82.9 [71.4-94.4]	15.0 [1.9-28.1]	0.053
Laboratory item	85.1 [80.1-90.2]	79.5 [66.8-92.2]	5.7 [-19.3-7.9]	0.37
Specificity [$_{95\%}$CI]	96.1% [91.8-100]	90.3% [82.8-97.8]	5.8 [-2.7-14.3]	0.16
Questionnaire	94.1 [90.4-97.8]	93.3 [87.7-98.9]	0.8 [-7.5-5.9]	0.82
Clinical item	91.9 [87.3-96.5]	70.0 [59.3-80.7]	21.9 [10.2-33.6]	<0.0001
Laboratory item	76.8 [68.4-85.3]	83.6 [74.7-92.4]	-6.7 [-19.0-5.5]	0.29

Table II. Comparison between sensitivity and specificity for the classification criteria for CV in the whole study population (see ref. 3) and in the SS subgroup.

	CV *vs*. CwV (500 pts)		CV *vs*. CwV in SS (55 pts)	
	Sensitivity [$_{95\%}$CI]	Specificity [$_{95\%}$CI]	Sensitivity [$_{95\%}$CI]	Specificity [$_{95\%}$CI]
Classification criteria	88.5% [84.3-92.8]	93.6% [89.5-97.7]	88.9% [76.5-100]	91.3% [79.2-100]
Items				
Questionnaire	83.8% [79.4-88.2]	93.8% [90.7-97.0]	82.8% [68.4-97.1]	92.3% [81.6-100]
Clinical item	70.2% [64.7-75.8]	84.5% [79.5-89.4]	79.3% [64.1-94.7]	73.1% [55.3-90.9]
Laboratory item	84.2% [79.4-89.0]	79.6% [73.4-85.9]	85.2% [71.2-99.2]	82.6% [66.4-98.8]

CV: cryoglobulinaemic vasculitis; CwV: serum cryoglobulins without vasculitis; SS: Sjögren's syndrome.

gland swelling, B-symptoms (17/29 *vs*. 6/26, p=0.075), while the prevalence of non malignant lymphoproliferative disorders or malignant lymphoma was slightly different (13/29 *vs*. 4/26, p=0.02), as well as the prevalence of lymphoma (10/29 *vs*. 3/26, p=0.046).

The comparison between the sensitivity and the specificity for the classification criteria in CV and in SS-related CV was reported in Table II.

SS-CV was more frequently characterised by the presence of type II cryoglobulinaemia if compared to SS-CwV. Of note, among the clinical manifestations included in the clinical item of the classification criteria for CV (3), only the articular involvement did not significantly differentiate SS-CV from SS-CwV patients (Table III).

Clinical differences between HCV-positive and -negative cryoglobulinaemic vasculitis

By analysing the available data collected for the classification criteria of CV and focusing on the different manifestations of CV, some differences were noticed between HCV-related and HCV-unrelated CV patients (3).

The mean age was different between the two groups (HCV-related CV *vs*. HCV-unrelated CV: 63.5±11.7 *vs*. 58.7±11.6 years), while the sex distribution did not result different (data not shown).

As regards other clinical features, the liver involvement was more frequent in HCV-related cases (188/230 *vs*. 5/42 p<0.0001), while sicca syndrome and malignant lymphoproliferation were more frequent in HCV-unrelated cases (HCV-related *vs*. HCV-unrelated: 56/230 *vs*. 30/42; p<0.0001), and 42/230 *vs*. 15/42; p=0.02, respectively). No differences were observed between the two groups as regards other clinical items, *i.e*. articular, neurological, vascular, and renal involvements, myopathy, and constitutional symptoms (data not shown).

Discussion

CV is a small- to medium-vessel immune complex vasculitis related to HCV infection in the majority of cases (1-6). HCV-unrelated cases account for 10–20% in different surveys (11, 17). In the recent study for the development of the CV classification criteria (3), a multicentre study involving specialists of different branches of medicine, the frequency of HCV negative CV was relevant, accounting for about 15% of the CV. Of note, novel treatment strategies have been tested in HCV-unrelated CV, with contrasting results and a different safety profile if compared to HCV-related CV (13-16). Therefore, a correct classification of CV in the less frequent subset of HCV negative patients is relevant to better plan both epidemiologic and clinical studies. In the present analysis of the database collected for the development of the preliminary classification criteria for the CV (3), the above mentioned classification criteria for CV maintained a high sensitivity and specificity also in HCV negative patients. The slightly lower specificity observed in HCV negative patients was imputable to a significantly lower specificity of the clinical item included in the criteria. In particular, 30% of the HCV negative controls with cryoglobulinaemia without vasculitis suffered from connective tissue diseases and related symptoms (*e.g*. arthralgias, arthritis, constitutional symptoms, Raynaud phenomenon), thus decreasing (18, 19) the overall criteria specificity in the HCV negative subset.

Sensitivity and the specificity were nearly 90% also in the most important subset of patients within the HCV negative CV, that is the patients with SS-CV (3). Thus, the criteria may be preliminary applied also in SS-related cryoglobulinaemia. Overall, present data imply a greater contribution of the questionnaire and the laboratory items, if compared to the clinical item, for the correct classification of HCV-unrelated CV, *i.e*. the anamnestic presence of purpura, the presence of RF, low C4 and/or a serum monoclonal component. On the other hand, the contribution of the clinical items remains relevant for classification of HCV-unrelated CV. In fact, the exclusion of the clinical item did not lead to a better classification of HCV-unrelated CV (sensitivity 66.7%, specificity 100%, when both the questionnaire and the laboratory items were satisfied). Of note, if the tree-based model of the classification criteria for CV is used (3), the usefulness of the proposed sequence of the classifica-

Table III. Comparison between SS-CV and SS-CwV patients as regards clinical parameters and the single items included in the classification criteria for CV.

	SS-CV (n=29)	SS-CwV (n=26)	*p*-value
Age (mean±SD)	60.5 ± 10.5	57.7 ± 13.6	0.38
Sex (F/M)	25/4	25/1	0.35
Type of cryoglobulins (II/III)	22/7	7/19	<0.0001
Positive questionnaire item			
- Question 1[a]	24/29	2/26	<0.0001
- Question 2[b]	24/29	2/26	<0.0001
- Question 3[c]	2/29	2/26	1.0
Positive clinical item			
- Constitutional symptoms[d]	24/29	14/26	0.02
- Articular involvement[f]	22/29	20/26	0.93
- Neurological involvement[g]	27/29	12/26	<0.0001
- Vascular involvement[h]	20/29	6/26	0.001
Positive laboratory item			
- Rheumatoid factor	25/29	13/26	0.004
- Low C4	18/29	5/26	0.002
- Serum monoclonal component	24/29	7/26	<0.0001

SS: Sjögren's syndrome; CV: cryoglobulinaemic vasculitis; CwV: serum cryoglobulins without vasculitis; SD: standard deviation; F: female; M: male.
[a]Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?
[b]Have you ever had red spots on your lower extremities which leave a brownish colour after their disappearance?
[c]Has a doctor ever told you that you have viral hepatitis?
[d]Fatigue, low grade fever (37-37.9°C, >10 days, no cause), fever (>38°C, no cause), fibromyalgia.
[f]Arthralgias, arthritis.
[g]Purpura, skin ulcers, necrotising vasculitis, hyperviscosity syndrome, Raynaud's phenomenon.
[h]Peripheral neuropathy, cranial nerve involvement, vaculitic central nervous system involvement.

tion items (questionnaire item, then laboratory item, then clinical item) is reinforced.

Finally, the clinical differences between HCV-related CV and HCV-unrelated CV detected in the present study confirm previous published observations (3), since typical SS-related clinical characteristics (*e.g.* sicca syndrome and non malignant or malignant lymphoproliferation) were more frequently recognised in HCV-unrelated CV (3). Clinical and biologic differences have been elucidated between HCV-related CV, linked to bone marrow and liver B-cell clonal expansion, and SS-related CV, linked to chronic inflammation of MALT (20). Of note, also in the present study, a statistically higher association with lymphoma of HCV-unrelated, rather than HCV-related cryoglobulinaemia, was observed. Then, the occurrence of cryoglobulinaemia should warn for lymphoma (already existing, or as a possible complication) much more in SS than in HCV-related CV.

In conclusion, also the minor subset of patients with HCV-unrelated cryoglobulinaemia can be correctly classified as having or not a CV by using the recently developed classification criteria for CV. Sensitivity and specificity remain high, though a slightly lower specificity is observed. This was linked to a higher prevalence of some clinical manifestations of CV in HCV-negative controls with cryoglobulinaemia but without vasculitis. The tree-based model proposed for the classification criteria for CV, implying the sequence of the questionnaire item, then of the laboratory item, and finally of the clinical item, is well supported.

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