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Review

Incidence of thyroid disorders in mixed cryoglobulinemia: Results from a longitudinal follow-up

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ABSTRACT

No study has evaluated the incidence of new cases of thyroid autoimmunity (AT) and dysfunction (TD) in hepatitis C-associated mixed cryoglobulinemia (MC) patients.
We aimed to evaluate the incidence of new cases of AT and TD in a wide group of MC patients vs. age- and gender-matched controls from the same geographic area.
After exclusion of MC patients with TD at the initial evaluation, the appearance of new cases of TD was evaluated in 112 MC patients and 112 matched controls, with similar iodine intake (median follow-up 67 months in MC vs. 78 in controls).
A high incidence ($P < 0.05$) of new cases of hypothyroidism, TD, anti-thyroperoxidase antibody (AbTPO) positivity, appearance of a hypoechoic thyroid pattern, and thyroid autoimmunity in MC patients vs. controls was shown. A logistic regression analysis showed that in MC, the appearance of hypothyroidism was related to female gender, a borderline high initial thyroid-stimulating hormone (TSH), AbTPO positivity, a hypoechoic, and small thyroid.
In conclusion, we show a high incidence of new cases of AT and TD in MC patients. MC patients at high risk (female gender, a borderline high initial TSH, AbTPO positivity, a hypoechoic, and small thyroid) should have periodically thyroid function follow-up.

Contents

1. Introduction

The most important systemic hepatitis C virus (HCV)-related extra-hepatic disease (HCV-EHD) is HCV-related mixed cryoglobulinemia (MC + HCV), and the most frequent and clinically important endocrine HCV-EHDs are thyroid disorders.

Many studies have been addressed to evaluate the prevalence of thyroid autoimmunity (AT) in HCV-infected patients, reporting conflicting results.

A large study investigated the prevalence of thyroid disorders in 630 consecutive patients with HCV chronic hepatitis (CHC) with respect to a control group from an iodine-deficient area (389 subjects), another control group living in an area of iodine sufficiency (268 persons), and

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86 patients with chronic hepatitis B virus (HBV) infection. Patients with CHC had more frequently hypothyroidism (13%), anti–thyroperoxidase antibodies (AbTPO) (21%), or anti–thyroglobulin antibodies (AbTg) (17%) than the control groups [1,2]. Also, a meta-analysis of the literature reported a significant association between CHC and AT [3–5]. Furthermore, more recently, a retrospective cohort study of users of US Veterans Affairs health care facilities, which included 146,394 CHC patients, and 572,293 controls, confirmed the thyroiditis risk was significantly increased in CHC patients [6].

Some studies evaluated autoimmune thyroid disorders (AITD) in MC + HCV patients. Codes et al. [7] studied 127 CHC patients. In CHC patients infected by genotype 3 ($P = 0.05$), thyroid dysfunction (TD) occurred in 23.3% and cryoglobulinemia in 38%. Zarebska-Michaluk et al. [8] studied 340 untreated CHC consecutive patients. Two hundred and ten patients with CHC (61.7%) presented at least 1 HCV-EHDs, including MC (37.1%) and AT (16.2%). Furthermore, anecdotal studies reported TD in MC + HCV patients [9,10].

More recently, a case–control prospective study has been conducted in 93 MC + HCV patients, matched by gender and age (+/− 2 years) to 93 CHC patients without MC and 93 HCV-negative controls. Thyroid autoimmune manifestations [AbTPO (28% vs. 9%), serum AbTPO and/or AbTg (31% vs. 12%), AT (35% vs. 16%)], and subclinical hypothyroidism (11% vs. 2%) were more frequent in MC + HCV patients than in HCV-negative controls, or in CHC patients (AbTPO, 28% vs. 14%) [11]. Increased circulating levels of AbTPO and increased risk of hypothyroidism in female gender and AbTPO-positive subjects characterized the pattern of thyroid disorders observed in MC + HCV patients [2,4].

To the best of our knowledge, no study has evaluated the incidence of thyroid disorders in cryoglobulinemia.

The aim of our study was to evaluate the incidence of new cases of clinical and subclinical TD in a wide group of MC + HCV patients.

2. Patients and methods

One hundred and fifty-one MC + HCV patients consecutively referred to the Internal Medicine or Rheumatology Units of the University of Pisa and Modena (from 1992 to 2011) underwent a thyroid evaluation.

The diagnosis of MC was based on the presence of serum mixed (IgG-IgM) cryoglobulins and the classical clinical triad (purpura, weakness, arthralgias), and the exclusion of other well-known systemic disorders, such as immuno-rheumatic, neoplastic, and infectious diseases [12,13].

HCV infection was systematically evaluated in all patients, who were excluded if they were HCV-negative.

MC + HCV patients were excluded from the study, if they had been previously treated with external radiotherapy in the region of the neck or mediastinum, or if they had had IFNalpha treatments.

Among the MC + HCV patients, those with subclinical or clinical hypothyroidism, subclinical hyperthyroidism or Graves' disesase, were excluded too. One hundred and twelve MC + HCV patients without TD were eligible for the longitudinal study. They were studied again, at least 1 year after the initial evaluation, one or more times. The median follow-up period from the initial evaluation was 67 months (range 12–191 months).

Each of the 112 MC + HCV patients eligible for the study was gender- and age-matched, one-to-one with a control group, without TD, of the background population from the same geographic area (northwest Tuscany) with a similar iodine intake (that is an important environmental risk factor for the appearance of thyroid autoimmune disorders) [14].

This control group was extracted from a larger sample of >2000 subjects in a population-based survey of thyroid disorders, who were initially studied in 1994 and subsequently reevaluated (by thyroid function, autoantibodies and ultrasonography) in 2002–2003 (see above). The median follow-up period from the initial evaluation was 97 months (range 87–112 months).

All 112 MC + HCV patients and controls were reevaluated, by (a) physical examination; (b) thyroid ultrasonography, as previously reported [15]; and (c) circulating free triiodothyronine (FT3) and free thyroxine (FT4) (AMERLEX-MAB FT3/FT4 Kit; Amersham, UK), thyroid-stimulating hormone (TSH) (reference range 0.3–3.6 μU/mL) (DiaSorin, USA), AbTPO, and AbTg antibodies (ICN Pharmaceuticals, USA; positivity >100 IU/mL).

If TD appeared during the follow-up, 112 MC + HCV patients were appropriately treated and excluded from a further evaluation.

The study was approved by the institutional ethic committee, and all subjects gave their informed written consent to participate.

Mean group values were compared using one-way ANOVA for normally distributed variables, otherwise by the Mann–Whitney U test. The χ^2 test was used to compare categorical variables. A logistic regression analysis was performed in MC + HCV patients including gender, age, smoking, TSH, AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as dependent variable.

3. Results

The clinical features of the 112 eligible MC + HCV patients are reported in Table 1.

The thyroid status of MC + HCV patients entering the longitudinal study and matched controls is reported in Table 2. The prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume <6 mL were higher in the MC + HCV group than in controls (Table 2), and TSH was slightly but significantly higher in MC + HCV patients. On the whole, indices of thyroid autoimmunity (AbTg, AbTPO, or ultrasonographic diagnosis of thyroiditis) were more frequent in MC + HCV than in controls.

At the last evaluation (after a median of 67 and 97 months, respectively, in MC + HCV patients and controls: $P < 0.01$, ANOVA), TSH levels and AbTPO titers were significantly higher in MC + HCV patients than in controls (Table 2). Subclinical hypothyroidism was more common in MC + HCV patients than in controls. The prevalence of subclinical hyperthyroidism was higher in MC + HCV patients than in controls. On the whole, the prevalence of TD (subclinical or clinical hypo- and hyperthyroidism) was significantly more frequent in MC + HCV patients (Table 2). The prevalence of subjects with positive AbTPO, thyroid

Table 1
Demographic and clinico-serological features of 112 MC + HCV patients.

Age (years)	62 ± 15
Men/Women	26/86
Disease duration with MC (years)	14 ± 10
Purpura	86%
Active vasculitis	41%
Weakness	99%
Arthralgias	92%
Arthritis	15%
Raynaud's phenomenon	47%
Sjogren's syndrome	44%
Peripheral neuropathy	77%
Renal involvement*	11%
Aminotransferases elevation and/or histologic activity†	85%
Cryocrit (%)	4.6 ± 9.2
CH50 (normal: 160–220 units)	114 ± 45
C3 (normal: 60–130 mg/dl)	79 ± 44
C4 (normal 20–55 mg/dl)	12 ± 7
Autoantibodies‡	34%

* Serum creatinine >1.5 mg/dl and/or proteinuria >0.5 g/24 h.
† Increase of the liver enzyme (alanine aminotransferase) and/or histological alterations.
‡ Presence of anti-nuclear and/or anti-mitochondrial and/or anti-smooth muscle and/or anti-extractable nuclear antigen autoantibodies.