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Review

Thyroid involvement in hepatitis C – Associated mixed cryoglobulinemia

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ABSTRACT

OBJECTIVE: The prevalence and clinical features of thyroid involvement in patients with hepatitis C virus-associated mixed cryoglobulinemia (MC+HCV) have been reviewed. DESIGN: A PubMed Medline search was conducted through December 2011 to identify all studies that reported thyroid involvement in MC+HCV patients. Reference lists of the papers initially detected were manually searched to identify additional relevant reports. Studies had to contain sufficient and clear information to be included. RESULTS: In MC+HCV patients, the following thyroid autoimmune abnormalities were significantly more frequent than in controls: high levels of serum anti-thyroperoxidase autoantibody (AbTPO); high levels of serum AbTPO and/or anti-thyroglobulin autoantibody; humoral and ultrasonographical signs of thyroid autoimmunity (35% *vs* 16%); prevalence of subclinical hypothyroidism (11% *vs* 2%). Also, the prevalence of papillary thyroid cancer has been found higher in MC+HCV patients than in controls, in particular in patients with autoimmune thyroiditis. The involvement of T helper 1 immunity and chemokine (C-X-C motif) ligand 10 (CXCL10) may be the pathogenetic basis of the association between MC+HCV and thyroid autoimmunity. CONCLUSION: These results show a high prevalence of thyroid disorders in patients with MC+HCV and point to the need for careful monitoring of thyroid function in these patients.

Key words: Autoimmunity, Chemokines, Cryoglobulinemia, Hepatitis C, Hypothyroidism, Thyroid neoplasms

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INTRODUCTION

Hepatitis C virus (HCV) is known to be responsible for both hepatic and extrahepatic diseases (HCV-related extrahepatic diseases = HCV-EHDs). The most important systemic HCV-EHDs are HCV-

related mixed cryoglobulinemia (MC+HCV) and lymphoproliferative disorders, while the most frequent and clinically important endocrine HCV-EHDs are thyroid disorders and type 2 diabetes mellitus (T2D).

To the best of our knowledge, no study has reviewed thyroid disorders in cryoglobulinemia. Here, a review of the literature about the association of MC+HCV and thyroid disorders is reported. A PubMed Medline search was conducted through December 2011 to identify all studies that reported thyroid involvement in MC+HCV patients. Reference lists of the papers initially detected were manually searched to identify additional relevant reports. Studies had to contain sufficient and clear information to be included.

Thyroid autoimmunity and HCV

Several studies have been conducted to evaluate the real prevalence of thyroid autoimmunity (AT) in HCV positive (HCV+) patients, these however reporting conflicting results (Table 1). From a meta-analysis of the literature, a significant association between HCV infection and AT and/or dysfunction has been reported.[1-3]

A large study investigated the prevalence of thyroid disorders in 630 consecutive patients with chronic hepatitis due to HCV infection (CHC) not treated with interferon (IFN)-α as compared with a control group of 389 subjects from an iodine-deficient area, another control group of 268 persons living in an area of iodine sufficiency and 86 patients with chronic hepatitis B. Patients with CHC were more likely to have hypothyroidism (13%), anti-thyroglobulin antibodies (AbTg) (17%) and anti-thyroperoxidase antibodies (AbTPO) (21%) than were any of the other groups.[4]

These results have recently been confirmed in a retrospective cohort study of users of the US Veterans Affairs health care facilities from 1997 to 2004, which included 146,394 HCV+ patients and 572,293 patients uninfected with HCV. The thyroiditis risk was significantly increased in HCV+ patients. This result is particularly interesting since 97% of HCV+ patients were men and it is well known that male gender implies a lower risk of thyroiditis than female gender.[5]

Thyroid disorders observed in HCV chronic infection[2,4] are associated with a higher risk of AT in the female gender and furthermore there is an increased risk of hypothyroidism in female AbTPO positive subjects.

Thyroid dysfunctions (TD) in MC+HCV

Few studies have evaluated autoimmune thyroid disorders (AITD) in patients with cryoglobulinemia (Table 2). In a study by Codes et al,[6] 127 patients with positive anti-HCV results were evaluated, based on detectable ribonucleic acid (RNA)-HCV by reverse transcriptase-polymerase chain reaction (RT-PCR) of genotypes 1a, 1b and 3a. TD occurred in 7/30 (23.3%) of the patients infected by genotype 3 (p =

Table 1. Papers that evaluated the interrelationship between HCV infection and AT

Field of interest	Author	Main findings
Association between HCV infection and AT/or dysfunction	Pateron et al[1]	Increase of latent autoimmune thyroid diseases in patients with chronic hepatitis C
	Antonelli et al[2]	Significant increase of the prevalence has been observed both for thyroid autoimmune disorders (OR= 1.6, 95% confidence interval 1.4-1.9) as well as for hypothyroidism (OR= 2.9; confidence interval 2-4.1) in HCV-positive patients (with chronic hepatitis or HCVAb positivity)
	Antonelli et al[3]	Significant associations among chronic HCV infection, thyroid autoimmunity and hypothyroidism have been revealed. A high prevalence of thyroid cancer has been reported in HCV-positive patients. Chronic HCV infection could lead to the development of type 2 diabetes mellitus, possibly as a result of HCV-induced metabolic disturbances
	Antonelli et al[4]	Patients with CHC were more likely to have hypothyroidism (13%), AbTg (17%) and AbTPO (21%) than were controls
	Giordano et al[5]	Thyroiditis risk is significantly increased in male HCV+ with respect to uninfected patients

AbTg: anti-thyroglobulin antibody, AbTPO: anti-thyroperoxidase antibody, AT: thyroid autoimmunity, HCV: hepatitis C virus, CHC: patients with chronic hepatitis due to HCV infection, OR: odds ratio.

Table 2. Papers that evaluated the interrelationship among HCV infection, MC, TD and AITD

Field of interest	Author	Main findings
Association between HCV infection and development of TD and AITD	Giordano et al[5]	Thyroiditis risk is significantly increased in male HCV+ in comparison with uninfected patients
	Antonelli et al[15]	Higher prevalence of TSH, AbTg and AbTPO levels, and hypothyroidism in HCV+ patients (p <0.001 for all)
Association between MC+HCV and development of TD and AITD	Codes et al[6]	HCV+ patients, genotype 3, develop TD with a prevalence rate of 23.3% (p = 0.05) and MC in 38% of cases (p = 0.02)
	Zarebska-Michaluk et al[7]	HCV+ patients develop AITD with a prevalence rate of 16.2%, and MC in 37.1%
	Castellano et al[9]	Case report of hypothyroidism, hemolytic anemia and cryoglobulinemia in a patient with HCV infection
	Antonelli et al[10]	Higher prevalence of AITD in patients with MC+HCV, not only with respect to controls (AbTPO 28% *vs* 9%, p = 0.001; AbTPO and/or AbTg 31% *vs* 12%, p = 0.004; thyroid autoimmunity 35% *vs* 16%, p = 0.006; subclinical hypothyroidism 11% *vs* 2%, p = 0.038), but also with respect to HCV+ patients without cryoglobulinemia (AbTPO 28% *vs* 14%, p = 0.035)

AbTg: anti-thyroglobulin antibody, AbTPO: anti-thyroperoxidase antibody, AITD: autoimmune thyroid disorders, HCV: hepatitis C virus, HCV+: HCV positive patients, MC: mixed cryoglobulinemia, MC+HCV: HCV-related MC, TD: thyroid dysfunctions, TSH: thyroid-stimulating hormone.

0.05) and cryoglobulinemia was also more frequent in this group (5/13, 38%, p = 0.02).

Zarebska-Michaluk et al[7] studied 340 consecutive patients (mean age: 42 years) with untreated CHC to assess the prevalence and predictive factors of extra-hepatic manifestation (EM) in Poland. Two hundred ten patients with CHC (61.7%) presented at least one EM, including MC (37.1%), thrombocytopenia (27.6%), AT (16.2%), dermatological disorders (4.1%) and T2D (4.1%). The authors conclude that in Poland the majority of patients with CHC have EM in conjunction with cryoglobulinemia, thrombocytopenia, AT, dermatological disorders and T2D.

Furthermore, anecdotal studies have reported TD in MC+HCV patients. For example, a case of hyperthyroidism due to the presence of "thyroid-stimulating immunoglobulins" and Graves' disease in a patient with MC (type II) was reported,[8] while Castellano et al[9] described a case of hypothyroidism, hemolytic anemia and cryoglobulinemia in a patient with HCV infection.

More recently, a case-control prospective study was conducted: 93 MC+HCV patients were matched by gender and age (+/- 2 years) to 93 patients with CHC without MC and 93 healthy (HCV-negative) controls from the local population. Serum AbTPO (28% *vs* 9%), serum AbTPO and/or AbTg (31% *vs* 12%), AT (35% *vs* 16%) and subclinical hypothyroidism (11% *vs* 2%) were significantly more frequent in MC+HCV patients than in HCV-negative controls. Serum AbTPO were also significantly more frequent in MC+HCV patients than in CHC controls (28% *vs* 14%). These results showed a higher prevalence of thyroid disorders in patients with MC+HCV in comparison with controls and with HCV+ patients without cryoglobulinemia.[10]

Thyroid disorders observed in MC+HCV infection[2,4] are associated with a higher risk of AT in the female gender and furthermore there is an increased risk of hypothyroidism in female AbTPO positive subjects (similarly to HCV+ patients without MC).

Thyroid cancer (TC)

A high prevalence of papillary thyroid cancer (PTC; Table 3) was first observed over a decade ago in 139 HCV+ patients (2.2%), while no case was observed in 835 control subjects, long-term residents of an iodine-deficient area.[11]

Subsequently, a case-control study reported that in patients undergoing surgery for PTC, the presence of HCV infection was significantly higher than in subjects undergoing surgery for benign disorders, particularly in women.[12]

More recently, 459 patients were screened with different types of cancer: 130 TC, 114 liver cancer, 41 multiple myeloma, 111 non-Hodgkin's lymphoma, 63 Hodgkin's disease, in comparison with a control group of 226 patients with no history of cancer.[13] Liver cancer [odds ratio (OR) 32.9, 95% confidence interval (95% CI) 16.5-65.4, $p < 0.0001$], multiple myeloma (OR 4.5, 95% CI 1.9-10.7, $p = 0.0004$) and B-cell non-Hodgkin's lymphoma (OR 3.7, 95% CI 1.9-7.4, $p = 0.0001$) showed greater risks. For Hodgkin's disease there was no significant association ($p = 0.3$), while a link was noted between HCV and TC (OR 2.8, 95% CI 1.2-6.3, $p = 0.01$).

However, the above reported retrospective cohort study of users of the US Veterans Affairs health care facilities did not confirm an increased risk of TC in HCV+ patients. This result is interesting; however, since 97% of HCV+ patients were men and male gender implies a lower risk of TC than female gender, it needs to be regarded with caution.[5]

A prospective study investigated prevalence and features of TC in 308 patients with CHC *vs* two gender- and age-matched control groups: 616 subjects from an iodine-deficient area and 616 subjects from an iodine-sufficient area. Among HCV+ patients, 6 patients with PTC were detected, while no case was observed in control 1 ($p = 0.001$) and only one case in control 2 ($p = 0.003$). In HCV+ patients, 83% with TC had evidence of AT *vs* 31% of the other HCV+ patients ($p = 0.02$).[14]

The prevalence of TC was also investigated in a series of 94 unselected MC+HCV patients in comparison with a gender- and age-matched control group obtained from a sample of the general population (470 subjects). The prevalence of thyroid nodules was higher in control subjects than in MC patients (65.3% *vs* 54.8%), albeit not significantly. In the MC series, two patients with PTC were found, while no case was observed among controls ($p = 0.001$, χ^2 *P* value); lymphocytic infiltration was observed in the thyroid tissue in both MC patients with PTC.[15]

Recently, other studies have confirmed an association between AT and TC.[16] Accordingly, features of AT were observed more frequently in HCV+ patients than in controls, suggesting that AT may be a predisposing condition for TC.[14] The finding of an increased prevalence of TC in HCV+ patients is clinically relevant since about 15-30% of these patients may show an aggressive disease difficult to treat.[17]

Of interest, thyroid autoimmunity and chronic thyroiditis have been regarded as preneoplastic conditions. Okayasu et al[18] found that the prevalence of lymphocytic infiltrates, which are indicative of autoimmune thyroiditis, was significantly higher in patients with PTC than in patients with adenomatous goiter or follicular adenoma.

Table 3. Papers that evaluated the interrelationship among HCV infection, MC and thyroid cancer

Field of interest	Author	Main findings
Association between HCV and development of thyroid cancer	Antonelli et al[11]	HCV+ patients develop papillary thyroid cancer with a prevalence rate of 2.2% *vs* 0% among controls
	Montella et al[12]	In patients undergoing surgery for papillary thyroid cancer, the presence of HCV infection is significantly higher than that observed in subjects undergoing surgery for benign disorders, particularly in women
	Montella et al[13]	An association between thyroid cancer and HCV infection is noted with OR 2.8, 95% CI 1.2-6.3, $p = 0.01$
	Giordano et al[5]	No association
	Antonelli et al[14]	Higher prevalence of papillary thyroid cancer in HCV+ patients, in particular in the presence of thyroid autoimmunity
Association between MC+HCV and development of thyroid cancer	Antonelli et al[15]	Higher prevalence of papillary thyroid cancer in MC patients *vs* controls ($p = 0.001$, χ^2 *P* value; $p = 0.02$, Fisher's exact test). In MC patients with papillary thyroid cancer there is evidence of lymphocytic infiltration in the thyroid tissue

95% CI: 95% confidence interval, HCV: hepatitis C virus, HCV+: HCV positive patients, MC: mixed cryoglobulinemia, MC+HCV: HCV-related MC, OR: odds ratio.

These findings have recently been confirmed in a study that found patients with a high titer of thyroid autoantibodies showed a higher frequency of PTC (9.3%) compared to patients with a low titer or negative thyroid autoantibodies (about 6.5%) and also presented higher serum TSH (median 1.16 *vs* 0.75 μU/ml).[16]

In our HCV-related mixed cryoglobulinemia patient series both patients with PTC had lymphocytic infiltration of the thyroid.[15] Features of thyroid autoimmunity were observed more frequently in HCV+ patients than in controls, indicating that thyroid autoimmunity may be a predisposing condition for thyroid papillary cancer.[15]

An oncogenic role for HCV has been demonstrated in the case of hepatocellular carcinoma complicating chronic HCV infection, with or without cirrhosis as an intermediate.[19] As HCV is an RNA virus that cannot be integrated in the host genome, its oncogenic potential must be exerted through indirect mechanisms.[19]

What mechanisms transduce the HCV oncogenic potential in TC remain to be investigated; however, the association between TC and AT in MC+HCV patients points to a possible link between these disorders.

IFN-α in MC

IFN-α therapy for hepatitis C is associated with a high prevalence of TD. IFN-α is the main therapeutic agent for patients with CHC. Studies show that 2.5-20% of patients with CHC develop TD while on IFN-α therapy.[20] Although the etiology is not clear, research suggests that IFN-α induces an autoimmune reaction that leads to the development of anti-thyroid antibodies and subsequent TD.[20] The frequency of pre-treatment thyroid disorders, the induction of thyroid antibodies and the development of TD during IFN-α therapy are all reduced in patients with chronic hepatitis B compared with patients with CHC.[4,20] This finding implies that prevalence of thyroid disorders in IFN-α treated patients with CHC is due not only to the effect of the drug *per se*, but to the action of the drug on an immunological background that is predisposed to the development of TD, such as the predisposition to AT in HCV+ patients.

Thyroid disorders associated with IFN-α therapy include hypothyroidism (the most common), autoimmune primary hypothyroidism, Graves' hyperthyroidism and destructive thyroiditis.

TD resolves within 6 months of ending treatment in ~50% of patients; however, persistent TD requires specific treatment for hypothyroidism or Graves' hyperthyroidism. Regular follow-up tests should also be performed at 3-6 month intervals during treatment.

A recent paper has further evaluated the effect on IFN-α therapy on the thyroid in patients with CHC.[21]

No study has as yet evaluated prospectively the effect of IFN-α on thyroid function in patients with MC+HCV and only anecdotal reports are available in the literature.

Papo et al[22] reported the case of a 40-year-old woman treated with IFN-α for the management of essential cryoglobulinemia. Goiter enlargement was noticed after one year of IFN-α therapy. Free triiodothyronine and free thyroxine serum values, measured by radioimmunoassay, were apparently elevated, thus contrasting with clinical euthyroidism and normal thyroid-stimulating hormone (TSH) values. High serum levels of antithyroid hormone antibodies were found in the patients' serum via a radiolabeled hormone immunoprecipitation assay. AbTg and AbTPO titers were also elevated and paralleled antithyroid hormone antibodies. Clinical status and TSH levels remained normal after cessation of IFN-α therapy, while thyroid hormones values and anti-thyroid hormone antibody levels progressively normalized. This was the first report of anti-thyroid hormone antibodies induced by IFN-α.

Mazzaro et al[23] reported two patients treated with alpha 2b-IFN who developed hypothyroidism.

Since MC+HCV patients have a higher prevalence of AT than HCV+ patients without MC, and consequently MC+HCV are more prone to the development of TD during IFN-α therapy, prospective studies in the field are needed.

Pathogenesis

The pattern of thyroid disorders observed in HCV infection is characterized by the presence of increased circulating levels of AbTPO and increased risk of hypothyroidism in AbTPO positive subjects.[2] This pattern is similar to that observed in IFN-α treated patients

too.[24] An increased expression of interferon-gamma (IFN-γ), and IFN-γ inducible chemokines,[25] especially chemokine (C-X-C motif) ligand 10 (CXCL10), has been shown in hepatocytes and in lymphocytes of HCV infected patients, directly related to the degree of inflammation and with an increase of IFN-γ and CXCL10 circulating levels.[24]

Moreover, non-structural 5A protein and core proteins, alone or acting via the synergistic effect of cytokines, such as IFN-γ and tumor necrosis factor-alpha (TNF-α), are able to upregulate CXCL10 and CXCL9 gene expression and secretion in cultured human hepatocyte-derived cells.[26] Therefore, CXCL10-produced HCV-infected hepatocytes could play a key role in regulating T-cell trafficking into a T helper (Th) 1-type inflammatory site, such as the liver during chronic HCV infection, recruiting Th1 lymphocytes.[27-29] It has been shown that high CXCL10 levels are present in patients with AT, especially in the presence of hypothyroidism, and an involvement of Th1 immune response in the induction of AT,[30] Graves' disease and Graves' ophthalmopathy has been demonstrated.[27-29] Furthermore, the presence of HCV in the thyroid of chronically infected patients has been documented.[31,32]

In order to explore HCV-thyroid interactions at a cellular level, it was evaluated whether a human thyroid cell line (ML1, that shows robust surface expression of the major HCV receptor CD81) could be infected with HCV *in vitro*. It was demonstrated that HCV can infect human thyroid cells *in vitro*, suggesting that HCV infection of thyrocytes may play a role in the association between chronic HCV infection and thyroid autoimmunity.[33]

In agreement with the aforementioned, it could be speculated that HCV thyroid infection acts by upregulating CXCL10 gene expression and secretion in thyrocytes, recruiting Th1 lymphocytes, that secrete IFN-γ and TNF-α, which further induce CXCL10 secretion by thyrocytes, in this way perpetuating the immune cascade that leads to the appearance of AITD in genetically predisposed subjects.

This hypothesis has been confirmed by one study that evaluated serum levels of CXCL10, and of the prototype Th2 chemokine (C-C motif) ligand 2 (CCL2), in MC patients, and showed that CXCL10, but not CCL2, is significantly higher in the presence of AT, *vs* patients without thyroiditis. These findings indicate that the Th1 CXCL10 chemokine is specifically linked with the appearance of AT in these patients.[34]

CXCL10 and CCL2 serum levels were assayed in 60 patients with MC, in 45 patients with "MC with AT" (MC+AT) and in controls [60 without (called "control 1") and 45 with (called "control 2") AT]. CXCL10 was significantly higher in control 2 than in control 1 ($p < 0.001$) and in MC than in control 1. Moreover, CXCL10 chemokine levels were higher in MC+AT than in controls 1 and 2 and in MC ($p = 0.002$). A high CXCL10 level (> mean ± Standard Deviation [SD] control 1; >167 pg/mL) was present in 7% control 1, 21% control 2, 49% MC and 78% MC+AT ($p < 0.0001$). CCL2 serum levels were significantly higher in MC and in MC+AT than in control 1 or in control 2 ($p < 0.01$). A high CCL2 level (> mean ± SD control 1; >730 pg/mL) was present in 2% control 1, 1% control 2, 18% MC and 21% MC+AT ($p < 0.0001$).[34]

Among the proinflammatory cytokines, in MC+HCV patients interleukin (IL)1-β and TNF-α were not associated with the presence of AT, while IL-6 was slightly but significantly increased in AT patients.[35-37]

On the whole, the abovementioned data underline the importance of the activation of Th1 immunity in the immunopathogenesis of AT in patients with MC+HCV.

CONCLUSION

A high prevalence of AITD and hypothyroidism has been shown in HCV chronic infection. MC+HCV patients have a higher prevalence of both AITD and TD than HCV+ patients without cryoglobulinemia. Female gender is a risk factor for the development of AT in MC+HCV patients, while risk factors for hypothyroidism are female gender and the presence of circulating AbTPO. These data suggest that MC+HCV patients, in particular in the case of female patients, should be screened for TSH and AbTPO at the first evaluation. A careful follow-up of thyroid function by annual TSH determination in female MC+HCV patients in the presence of circulating AbTPO should be conducted.

IFN-α therapy is a well known risk for the development of AT and dysfunctions in HCV+ patients. As MC+HCV patients have a higher prevalence of AT than HCV+ patients without MC, and consequently MC+HCV are more prone to the development of TD during IFN-α therapy, prospective studies in the field are needed. However, TSH and AbTPO should be evaluated before the start of IFN-α therapy, and at least every three months during IFN-α administration. In patients who develop a thyroid dysfunction, the appropriate therapy should be administered and thyroid function should be monitored at least every three months during the first year after the end of IFN-α.

While other studies are needed to definitely confirm the association between TC and MC+HCV, the data available in the literature are sufficient to point to the need for careful thyroid monitoring by ultrasonography in these patients at the first evaluation. In female patients, in particular in the presence of AT, thyroid ultrasonography could be repeated every two years.

DECLARATION OF INTEREST

The authors have nothing to declare.

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