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COVID-19 AND THE THYROID FUNCTION IN PATIENTS WITH HCV- ASSOCIATED HEPATOCELLULAR CARCINOMA

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Abstract

Context. COVID-19 is more than a respiratory infection, with deep implications regarding multiple systems and organs. Thyroid damage is frequent in COVID-19 and may overlap previous HCV or HCC associated diseases.

Objective. The objective of this study is to determine the effects of COVID-19 in patients with HCV associated HCC and thyroid comorbidities.

Design. We performed a retrospective study of the thyroid function tests and autoantibodies in patients with HCV-associated HCC prior and during COVID-19.

Subjects and Methods. We included 52 consecutive patients with HCV-associated HCC and documented thyroid disease, diagnosed with COVID -19 between April and October 2020. Serum values of thyroid-stimulating hormone, free T3, free T4, anti-thyroglobulin antibodies and anti-thyroid peroxydase antibodies were determined and compared to baseline levels.

Results. At baseline, 44 patients had positive antithyroid antibodies, 6 had hypothyroidism in substitution and 2 had hyperthyroidism under treatment. During COVID-19 we found an increase in serum values of antithyroid antibodies, and decreased levels of TSH, freeT3 and freeT4 levels. Specific therapies were discontinued in one patient with hyperthyroidism and 3 patients with hypothyroidism.

Conclusion. There is a significant impact of COVID-19 on the thyroid homeostasis; a long-term prognostic value for patients with HCC infected with COVID-19 required further extensive research.

Keywords: COVID-19, hepatitis C chronic infection, hepatocellular carcinoma, autoimmune thyroiditis, hypothyroidism, hyperthyroidism.

INTRODUCTION

The ongoing COVID-19 pandemic has proven to be an important opportunity for the study of immune and pathophysiologic processes involved in a multitude of diseases. The reaction of different organs and systems to the direct infection or to the induced systemic inflammatory response may help understand underlying mechanisms of specific diseases (1, 2).

Thyroid abnormalities have been associated with several viral infections, including hepatitis C virus (HCV) infection (3). It is already well-known that HCV is responsible for various extrahepatic manifestations, mediated by inflammatory or autoimmune mechanisms or even by direct infection of extrahepatic organs, such as the thyroid (4-7). Thyroid involvement is one of the most frequent endocrine disorders associated with HCV chronic infection. In this scenario, thyroid damage is determined by an increased inflammatory response (the result being autoimmune thyroiditis) (8) or by direct HCV infection (9).

Thyroid hormone signaling pathway is considered to be involved in the development and progression of various neoplastic lesions, including hepatocellular carcinoma (HCC) (10). The World Health Organization approximates that over 1 million individuals will die from liver cancer in 2030 (11). It is well known that among the risk factors for liver cancer, HCV is associated with a 15- to 20- fold increased risk for HCC (12). Moreover, metabolic risk factors for HCC development also play an important role. Thyroid hormones are involved in cellular growth and metabolism, and hypothyroidism has been associated with an increased HCC risk (13, 14).

After the recent emergence of the novel coronavirus, the similarities between HCV and SARS-CoV-2 have been intensely studied. One basic resemblance between the two viruses is that both are single-stranded RNA viruses. The exacerbated immune response, particularly from T helper2 lymphocytes, has been observed in HCV infection as well as in the previous

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SARS infections, resulting in immune-mediated tissue damage, alterations that are also suspected in COVID-19 (15). Also, both HCV and SARS-CoV enter the cells by using ion channels (viroporins); both viruses use proteins (such as p7 and E) that bond to viroporins (16). Another important similitude between the two viruses is the chloride channels impairment, thus interfering with many physiologic processes such as neuronal excitation, muscle contraction and transepithelial fluid transportation (17). Hypochloremia is frequently encountered in COVID-19, being associated with increased illness severity (18).

MATERIALS AND METHODS

This study aims to assess the effects of SARS-CoV-2 infection on thyroid diseases in patients with hepatocellular carcinoma and HCV chronic hepatitis. The research was approved by the local Ethics Committee. From May 2020 to December 2020, we performed a retrospective observational study on patients with cured HCV infection, hepatocellular carcinoma and documented thyroid disease who became infected with SARS CoV-2.

Inclusion criteria for the current study were:

- History of HCV infection, with sustained virologic response after direct-acting antiviral therapy (ombitasvir/ paritaprevir/ritonavir and dasabuvir or ledipasvir/ sofosbuvir);

- Documented thyroid impairment (autoimmune thyroiditis, hyperthyroidism or hypothyroidism) within 6 months prior to COVID-19;

- Documented hepatocellular carcinoma (without previous treatment) – either by computerized tomography (CT) scan or magnetic resonance imaging (MRI);

- Documented SARS-CoV-2 infection.

The exclusion criteria were:

- Other concomitant or previous malignant process;

- Co-infection with hepatitis B virus (HBV) or HIV;

- Modifications regarding the thyroid substitution therapy or antithyroid drugs within 6 months of the first visit;

Demographic and medical data were obtained from electronic source documents. Each patient was evaluated during COVID-19 infection by serum determination of: antithyroid antibodies (anti-thiroglobulin (antiTG), anti-thyroid peroxydase (ATPO)), thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3). TSH, fT3, fT4 and antiTG antibodies were determined using electrochemiluminescence assays (normal values between 0.27 and 4.2μUI/mL for TSH, between 2.2 and 4.4 pg/mL for fT3, between 12 and 22 pmol/L for fT4 and less than 115 IU/ml for antiTG). ATPO were determined using chemiluminescence with microparticles (normal values less than 34 IU/mL). The results were compared to the results obtained at the previous follow-up visit (within 6 months of current evaluation).

Data were analyzed using statistical software SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and we used mean +/- standard deviation to express numerical parameters. We performed ANOVA test to compare values at the three visits of evaluation (statistical significance was considered at a p-value less than 0.05).

RESULTS

The study included 52 patients, with a mean age of 53.57 years, female patients representing 57.70%. Baseline characteristics of the study group are presented in Table 1. Out of the 52 patients, 8 patients were under specific medication for the thyroid disease: 6 patients were receiving levothyroxine (mean dose of 53.4 mcg daily) for hypothyroidism, while 2 patients with hyperthyroidism were being treated with methimazole (mean dose 7.7mg daily).

According to the severity of the SARS-CoV-2 infection, 46 patients had mild respiratory infection, while 6 patients had a moderate COVID-19. The most frequent symptoms were: myalgia (46/52 patients), headache (40/52 patients), fatigue (39/52 patients), fever (31/52 patients), and digestive symptoms (27/52 patients).

When examining the patients during SARS-CoV-2 infection, increased levels of antithyroid antibodies were reported by comparison to the initial values. In patients with autoimmune thyroiditis, mean values of ATPO were 1217.7 ± 277IU/mL (*versus* 990.1 ± 446.7 IU/mL at baseline, p value 0.02) and mean values of antiTG were 588.2 ± 189.1 IU/mL (*versus* 345.2 ± 122.21 IU/mL at baseline, p value 0.01). In patients without autoimmune thyroiditis, ATPO levels increased to 127.9 ±29.8 IU/mL (*versus* 17.4 ± 6.3 IU/mL at baseline, p value <0.01) and antiTG values increased to 137.1 ± 41.9 IU/mL (*versus* 67.1 ± 19.7 IU/mL at baseline, p value 0.03). We also observed a significant decrease in TSH, fT3 and fT4 levels in patients with euthyroidism. The results are presented in Table 2.

Treatment was discontinued in 3 patients receiving levothyroxine and one patient receiving methimazole.

DISCUSSION

Our study reveals that COVID 19 significantly impacts levels of thyroid hormones and antithyroid antibodies in patients with hepatocellular carcinoma and thyroid disease. The thyroid gland shows an inflammatory response in sepsis, including "low triiodothyronine" syndrome (19), central hypothyroidism secondary to septic shock and hypophyseal hypoperfusion (20), inhibitory effects of proinflammatory cytokines (21). A decreased baseline thyroid function is an independent poor prognosis factor in patients with sepsis (22).

Our findings are consistent with these results as a decrease in TSH, fT3 and fT4 levels is clearly observed during COVID-19 infection. Several varieties of thyroid disease have been associated with COVID-19 infection. Subacute thyroiditis may develop as late as 36 days after COVID-19 typical symptoms (23). The incidence of subacute thyroiditis is increased in patients requiring intensive care, as opposed to patients managed on the medical ward (24).

High prevalence of thyrotoxicosis (20.2%) and hypothyroidism (5.2%) has been described in non- ICU patients (25). Our findings of low levels of thyroid hormones are consistent with those of a large multicenter trial including 621 patients (26). Overall, it is estimated that 13% to 64% of patients with COVID-19 develop thyroid dysfunction (27).

Data regarding COVID-19 infection in patients with documented thyroid disease is scarce. Some authors report the recurrence of Graves' disease during infection, after several years of compensated thyroid

Table 1. Baseline characteristics of the study group

Total: 52 patients	Baseline characteristics
Mean age	53.57 ± 19.08 years
Gender distribution	Female: 36 patients Male: 22 patients
Mean time-lapse after SVR	13.8 ± 6.2 months
Type of thyroid disease	Autoimmune thyroiditis: 44 patients Hyperthyroidism: 2 patients Hypothyroidism: 6 patients
ATPO (N <34 IU/mL)	With autoimmune thyroiditis (44 patients): 990.1 ± 446.7 Without autoimmune thyroiditis (8 patients): 17.4 ± 6.3
antiTG (N< 115 IU/mL)	With autoimmune thyroiditis (44 patients): 345.2 ± 122.21 Without autoimmune thyroiditis (8 patients): 67.1 ± 19.7
TSH (N: 0.27- 4.2μUI/mL)	Euthyroidism: 3.45 ± 1.22 Hypothyroidism (under levothyroxine): 3.05 ± 0.63 Hyperthyroidism (under methimazole): 3.15 ± 1.17
fT3 (N: 2.2- 4.4 pg/mL)	Euthyroidism: 2.48 ± 1.53 Hypothyroidism (under levothyroxine): 3.77 ± 0.81 Hyperthyroidism (under methimazole): 2.88 ± 1.09
fT4 (N: 12- 22 pmol/L)	Euthyroidism: 18.52 ± 2.89 Hypothyroidism (under levothyroxine): 19.13 ± 5.22 Hyperthyroidism (under methimazole): 16.26 ± 3.23

*SVR sustained virologic response after HCV infection.

Table 2. Evolution of TSH, fT3 and fT4 in patients with euthyroidism and dysthyroidism in COVID-19 infection

		Baseline (<6 months)	During COVID-19	P value
TSH (μUI/mL)	Euthyroidism	3.45 ± 1.22	2.62 ± 1.15	**0.02**
	Hypothyroidism	3.05 ± 0.63	1.74 ±0.87	na
	Hyperthyroidism	3.15 ± 1.17	2.82 ±0.83	na
fT3 (pg/mL)	Euthyroidism	2.48 ± 1.53	1.76±0.64	**0.04**
	Hypothyroidism	3.77 ± 0.81	2.65±0.78	na
	Hyperthyroidism	2.88 ± 1.09	1.94±0.71	na
fT4 (pmol/L)	Euthyroidism	18.52 ± 2.89	13.31±2.73	**0.01**
	Hypothyroidism	19.13 ± 5.22	15.64±4.88	na
	Hyperthyroidism	16.26 ± 3.23	11.59±3.52	na

*na- statistical analysis was not performed due to the low number of patients (2 patients with hyperthyroidism and 6 patients with hypothyroidism).

function (28). To our knowledge, none of the articles published analyze the impact of COVID-19 on patients with HCV- induced thyroid disease, although this is a frequently encountered condition. Furthermore, the impact of COVID-19 on the thyroid function in patients with HCC can have a significant prognostic value. Thyroid disfunction has been associated with increased prevalence of HCC in susceptible patients (29) and poor outcomes (30). In recent years, the development of direct-acting antiviral agents, obtaining very high cure rates for HCV, is considered to reduce the risk of hepatic (cirrhosis, HCC) and extrahepatic (autoimmune, malignant) complications of this infection (31). Pre-existing HCV- associated thyroid conditions appear to persist despite antiviral therapy, in lower rates than during the interferon era (32, 33).

Our study shows that COVID-19 infection significantly alters thyroid hormones and auto-antibodies in patients with HCV associated hepatocellular carcinoma. The extent of these alterations could reach the requirement for change in substitution therapies or antithyroid drugs.

This research has several limitations: we did not include patients with severe COVID-19 infection, we did not take into account the use and impact of corticoid therapy. Also, an increased follow-up period would be required to estimate the long-term impact of COVID-19 on the thyroid function and on the prognosis of patients with HCC.

In conclusion, we strongly argue in favor of attentively monitoring thyroid hormones levels in patients with COVID-19 infection. The long-term outcomes of these patients, particularly patients with malignant conditions are to be determined.

Conflict of interest

The authors declare that they have no conflict of interest.

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