Review Article

Cryoglobulinemia and Inflammation in COVID-19 Infected Patients with Chronic Hepatitis C

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Abstract

We aim to observe the inflammatory s tatus i n p atients w ith h epatitis C associated cryoglobulinemia after COVID-19 infection. We evaluated 3 patients with hepatitis C associated cryoglobulinemia, 6 patients with hepatitis C and 16 patients without comorbidities with COVID-19 infection.

In lammatory markers were signi icantly increased in 2 patients with cryoglobulinemia, as opposed to patients without the associated condition, with or without hepatitis C. In the third patient the levels of C reactive protein and erythrocyte sedimentation rate were similar to HCV positive patients.

Keywords

COVID-19; Cryglobulinemia; Hepatitis

Introduction

The COVID-19 pandemic is in a constant state of development, bringing new daily challenges to medical professionals all around the world regarding treatment, prevention and complications.

It has also caused a clear and significant delay in the path of eliminating Hepatitis C Virus (HCV) infection, [1] with a major impact beyond field of hepatology, as HCV infection does pose as a threat only by itself, yet by its multiple extrahepatic complications, such as non-Hodgkin lymphoma [2] cryoglobulinemia, [3] diabetes [4] or rare associated conditions such as sarcoidosis. [5]

Cryoglobulins are immunoglobulins which have the property of reversibly precipitate forming a gel at temperatures of 37°C. [6]

Based on immunoglobulin composition, the Brouet classification shows 3 cryoglobulinemia sub types: Type I cryoglobulinaemia is associated with B cell lymphoproliferative disorders, while type II and type III mixed cryoglobulinemia are most commonly associated with systemic autoimmune diseases, lymphoproliferative disorders and chronic infections, such as hepatitis C virus infection. [6]

Type II and type III mixed cryoblobulinemia have mainly HCV infection as etiology with up to 90% of cases being caused by this virus.

Methods

The aim of this study is to observe the inflammatory status in patients with cryoglobulinemia associated HCV infection, compared to that of HCV infected patients without cryoglobulinemia and previously healthy individuals during and after COVID-19 infection.

From June 2020 to December 2020 we conducted an observational study enrolling patients with COVID-19 infection and HCV associated cryoglobulinemia, patients with COVID-19 and HCV infection without other complications and patients with COVID-19 infection and no comorbidities [Table 1].

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Table 1: Clinical and biological parameters on admission in patients with COVID-19 infection

	Patient 1 with cryoglobulinemia	Patient 2 with cryoglobulinemia	Patient 3 with cryoglobulinemia	Group II	Group III
				(N=6 patients)	(N=16 patients)
Mean age	36	42	45	51.87±12.25	48.23±21.93
Gender (male:female)	male	female	female	2:04	7:09
AST (N: 0-35 IU/mL)	118	92	67	72±21	58±16
ALT (N: 0-45 UI/mL)	143	83	71	79±32	61±19
GGT (N: 0-30 IU/L)	67	45	39	98±23	63±28
Creatinine (N: 0.7-1.2 mg/dL)	0.73	1.22	0.81	0.78±0.35	0.82±0.42
CRP (N: 0-3 mg/L)	218	152.5	89	116.7±32.6	102.1±18.2
ESR (N: 0-25 mm/h)	41	51	33	26.3±16.3	27.5±10.3
C3 (N: 90-180 mg-dL)	74	63	85	110.5±28.4	126±23
C4 (N: 10-40 mg/dL)	8	5	11	23.8±11.2	17.7±8.4

*ALT alanine aminotransferase AST aspartate aminotransferase, GGT gamma glutamyl transpeptidase, CRP C-reactive protein, ESR erythrocyte sedimentation rate

The diagnosis of COVID-19 infection was made by SARS-COV2 RNA detection via Reverse-Transcription Polymerase Chain Reaction (RT-PCT) from the upper respiratory tract (both nasal and pharyngeal swabs) using Cobas® SARS-COV2 test (Roche Diagnostics, F. Hoffmann–La Roche, Ltd, Basil, SW). Active HCV infection was diagnosed using positive antiHCV antibodies and values of HCV viremia quantitatively assessed by RT-PCR.

Exclusion criteria for this study were Hepatitis B or HIV co-infection, history of or ongoing autoimmune diseases, inflammatory bowel disease, present treatment with anti-inflammatories (steroidal or non-steroidal) or immune modulators.

Our study included 25 patients 3 with HCV associated cryoglobulinemia (Group I), 6 patients with hepatitis C (Group II) and 16 patients without comorbidities (Group III), all of which had an active SARS-COV2 infection. All patients received supportive therapy, prophylactic low-molecular weight heparin and dexamethasone (8mg daily). None of the patients required antibiotic treatment. Also, none of the patients had received antiviral therapy for HCV chronic infection.

We monitored serum levels of transaminases, gama-glutamyltranspeptidase, serum creatinine, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), serum complement fractions C3 and C4 on admission, on discharge and at one-month follow-up.

Results

All subjects had mild or moderate forms of COVID-19 infection. None of the patients registered an oxygen saturation under 90% in ambient air, only 4 patients required non-invasive oxygen therapy in order to maintain a saturation of over 95%. We found increased inflammatory markers as well as low levels of complement fractions C3 and C4 in two of the patients with HCV associated cryoglobulinemia, compared to patients with HCV infection or previously healthy COVID-19 infected patients.

On admission, CRP and ESR values for patients associating cryoglobulinemia were slightly higher than those in patients with HCV infection alone. The values for those patients were significantly higher than those registered in the group consisting of previously healthy individuals ($p<0.01$, CI 95%) [Table 1].

During hospitalization, the male patient with cryoglobulinemia, 2 patients with HCV chronic hepatitis and one patient without comorbidities required non-invasive ventilation with low oxygen volumes by facial mask in order to maintain an oxygen saturation level over 95%.

At discharge, 2 of the cryoblobulinemia associated HCV patients maintained high values for CRP and ESR, together with low C3 and C4 levels and altered liver and renal function. Group II also records a slight improvement in inflammatory markers and liver and renal function while Group III continues having a significant improvement of all biological markers.

Lastly, at one-month follow-up, the 2 patients with altered liver and renal function, together with a still present inflammatory status have yet to reach normal values for CRP and ESR. The other patient associating cryoglobulinemia, together with patients from Group II presented with almost normal values for all biological markers. Patients from the third group, while having slightly elevated CRP values, register normal levels of ESR altogether with normal C3 and C4 levels, normal liver and renal function [Table 2].

Table 2: Clinical and biological parameters at discharge and one-month follow-up in patients with COVID-19 infection.

		Patient 1 with cryoglobulinemia	Patient 2 with cryoglobulinemia	Patient 3 with cryoglobulinemia	Group II	Group III
					(N=6 patients)	(N=16 patients)
Mean age		36	42	45	51.87±12.25	48.23±21.93
Gender (male:female)		male	female	female	2:04	7:09
AST	On discharge	107	88	61	69±20	55±18
(N: 0-35 IU/mL)	1 month	80	65	50	58±21	28±19
ALT	On discharge	137	80	68	76±30	59±21
(N: 0-45 UI/mL)	1 month	98	67	55	72±28	32±17
GGT	On discharge	66	42	37	88±25	60±24
(N: 0-30 IU/L)	1 month	52	40	33	60±24	29±13
Creatinine (N: 0.7-1.2 mg/dL)	On discharge	0.72	1.13	0.76	0.72±0.31	0.79±0.40
	1 month	0.69	1.02	0.71	0.70±0.28	0.75±0.20
CRP	On discharge	69	46.2	37	52.2±24.2	38.3±15.8
(N: 0-3 mg/L)	1 month	37	34	18	27±9.2	7.7±4.2
ESR	On discharge	39	50	29	22.7±11.8	24.6±10.2
(N: 0-25 mm/h)	1 month	39	50	29	20.7±6.5	15.7±5.3
C3	On discharge	78	69	88	118.7±30.4	129±27
(N: 90-180 mg-dL)	1 month	87	81	92	128.3±20.4	136±24
C4	On discharge	8	5	12	25.7±11.9	19.7±8.8
(N: 10-40 mg/dL)	1 month	8.5	5.3	13	27.3±12.2	28.7±9.3

*ALT alanine aminotransferase AST aspartate aminotransferase, GGT gamma glutamyl transpeptidase, CRP C-reactive protein, ESR erythrocyte sedimentation rate

Discussion

The COVID-19 pandemic has greatly increased awareness regarding the importance of the inflammatory response associated with viral infections. The systemic response triggered by SARS-CoV-2 suggests similarities to the HCV infection and its impact on multiple organs and systems, with potential life threatening consequences. One of the most important comorbidities associated with HCV chronic infection is the presence of cryoglobulinemia, with a significant impact on renal and vascular functions. [7-9] Studies have shown a tendency for HCV patients to develop B cell non Hodgkin lymphoma, as well as other abnormal B cell proliferations. Moreover, it is well known that HCV induced cryoglobulinemia is defined by such aberrant B cell proliferations and that B cell expansions can be found in the liver tissue as well as the peripheral blood of cryoblobulinemic HCV patients. [7] Although other chronic infections, such as HBV infection or HIV infection are also associated with B cell expansion, HCV infection is of higher prevalence and it is mainly consisting of benign stimulation and proliferation. [7]

Another important element that plays a role in the pathogenesis of mixed cryoglobulinemia is the complement. Complement proteins are synthetized by macrophages and hepatocytes, lower levels of serum complement having been reported in HCV patients. [7] While C3 and C4 fractions are found in low quantities in cryoprecipitates, C1q finds itself in higher amounts, which may suggest that the binding activity is highly related to the pathogenic pathway of cryoglobulinemia. Adding to that, the HCV core protein also binds to the C1q fraction of the complement, affecting both T and B cell activity. The mechanism by with SARS COV-2 virus promotes an exaggerated immune response are still under analysis. Some studies show that once the virus enters the body and into the targeted cells it firstly generates an innate or adaptive immune response, leading to interferon production, however the innate immune response appears to be impaired due to non-structural proteins of the SARS-COV2 virus. [8] On the other hand, humoral response appears to be similar to that against other coronavirus infections, leading to IgG and IgM production by the B cells. Titers of both IgM and IgG antibodies were significantly higher in severe patients. In addition to this, patients requiring

intensive care presented with levels of cytokines, such as IL-2, IL-7, IL-10, etc. as well as a higher percentage of $CD14^+$ and $CD16^+$ inflammatory monocytes. These cells also contribute to the cytokine storm by secreting MCP1, IP-10 and MIP1α. It is believed that multiple viral structural and nonstructural proteins antagonize interferon response, facilitating viral replication which leads to the release of pyroptosis products, further inducing aberrant inflammatory responses. [8]

When facing pathogens, the complement system is the first to react, however, the role of the complement in SARS COV-2 infection is under debate, several studies suggesting that the coronavirus infection involves multiple complement pathways. [9] The SARS-COV2 virus is known to have many similarities with the SARS-COVvirus, hence researchers are trying to implement what they already know about the SARS-COV virus in the process of learning about the pathogenesis of the COVID-19 infection. Studies regarding SARS-COV show that activating the C3 component of the complement, accompanied by high levels of C5a leads to a more severe form of acute respiratory distress syndrome in subjects with SARS-COV infection. On the other hand, those with C3 deficiency had lower levels of cytokines, chemokines, and decreased lung infiltration. This leads to believe that complement activation could also favor a more severe form of pulmonary pathology in SARS-COV2 patients. [10]

Case reports of severe COVID-19 infected patients show increased levels of plasma C5a and sC5b-9, as well as high deposits of C5b-9 and C4d in the lung capillaries of deceased patients. C5 inhibitors have been used in clinical trials which resulted in immediate clinical improvement of the patients. However, C5 inhibition may not suppress all complement pathways, which may lead to excessive complement activation. C3 inhibition has proved to be a more efficient therapeutic choice, as it has a broader inhibitory effect. [11] Lower complement levels mean less aggressive clinical manifestations with less occurrence of acute respiratory distress syndrome. [9,11]

Very few cases of SARS-COV 2 infection in patients with cryoglobulinemia have been described. One case report presents a 62 years old patient with chronic lymphocytic leukemia and cryoglobulinemic glomerulonephritis who developed severe COVID-19 infection, with a favourable outcome after ICU admission. [12-15] The authors report a CRP level of 65 mg/L; in our patients with cryoglobulinemia we found significantly higher values.

Conclusion

While the SARS-COV2 infection has a negative impact on both liver and kidney functions as well as on the inflammatory status of HCV infected patients, the association of mixed cryoglobulinemia poses an additional threat to said patients, implying a more severe form of COVID-19 infection, as well as a longer, slower and more difficult recovery.

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