

Disease dependent qualitative and quantitative differences in the inflammatory response to ascites occurring in cirrhotics

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Abstract

AIM: To assess differing patterns and levels of ascitic fluid cytokine and growth factors exist between those with a high risk and low risk of spontaneous bacterial peritonitis (SBP).

METHODS: A total of 57 consecutive patients with ascites requiring a large volume paracentesis were studied. Their age, gender, specific underlying disease conditions were recorded after a review of their clinical records. Each underwent a routine assessment prior to their paracentesis consisting of a complete blood count, complete metabolic profile and prothrombin time/international normalized ratio (INR) determination. The ascitic fluid was cultured and a complete cell

count and albumin determination was obtained on the fluid. In addition, blood and ascitic fluid was assessed for the levels of interleukin interleukin (IL)-1A, IL-1B, IL-2, IL-4, IL-8, IL-10, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) utilizing the Randox Biochip platforms (Boston, MA). A serum-ascites gradient, for each cytokine and growth factor was calculated. The results are reported as mean \pm SEM between disease groups with statistical analysis consisting of the student *t*-test (two tailed) with a *P* value of 0.05 defining significance.

RESULTS: No clinically important demographic or biochemical differences between the 4 groups studied were evident. In contrast, marked difference in the cytokine and growth factors levels and pattern were evident between the 4 disease groups. Individuals with alcoholic cirrhosis had the highest levels of IL-1A, IL-1B, IL-4, IFN γ . Those with malignant disease had the highest levels of IL-2. Those with hepatitis C virus (HCV) associated cirrhosis had the highest value for IL-6, IL-8, IL-10, MCP-1 and VEGF. Those with cardiac disease had the highest level of TNF- α and EGF. The calculated serum-ascites gradients for the cardiac and malignant disease groups had a greater frequency of negative values signifying greater levels of IL-8, IL-10 and MCP-1 in ascites than did those with alcohol or HCV disease.

CONCLUSION: These data document important differences in the cytokine and growth factor levels in plasma, ascitic fluid and the calculated plasma - ascites fluid gradients in cirrhotics requiring a large volume paracentesis. These differences may be important in determining the risk for bacterial peritonitis.

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Key words: Ascites; Cirrhosis; Growth factors; Inflammation; Procalcitonin

Core tip: Previous studies have examined factors relative to the pathogenesis of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis of the liver. This study was designed to examine the role of cytokines in decompensated cirrhotics requiring a large-volume paracentesis for ascites management and to compare the biomarker responses present in both the plasma and ascitic fluid of cirrhotics of differing etiologies. Factors likely to represent protective cytokines associated with a reduced risk for SBP include epidermal growth factor, tumor necrosis factor- α , interleukin (IL)-1A, IL-8, and IL-10. Those more likely to be associated with potential for SBP include: IL-1B, IL-4, monocyte chemoattractant protein -1, and interfero- γ .

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INTRODUCTION

Large-volume ascites occurring in cirrhotic patients has been shown to manifest an inflammatory response characterized by increased levels of cytokines, interleukins and several growth factors^[1]. The pathophysiologic mechanisms responsible for the development of cirrhosis and ultimately decompensated cirrhosis vary as a function of the underlying hepatic disease^[2,3]. These differences in pathophysiology may be reflected in the cytokine, interleukin and growth factor induced response that occurs. Moreover, depending upon the site of inflammatory cell activation, differences in plasma and ascitic fluid levels of inducible cytokines and growth factors may exist. These differences may explain in part an increase rate of bacterial translocation and subsequent spontaneous bacterial peritonitis (SBP) development.

Previous studies have reported that cytokine characteristics of the Th1 response are increased in decompensated cirrhosis especially with infection^[4]. Interleukin (IL)-4 which is a major cytokine of the Th2 response was not significantly different between decompensated cirrhotic patients with infected or non-infected ascites^[4]. The current study was designed to confirm these findings and expanding it to study the role of growth factors in cirrhotics with non-infected ascites.

The aim of this investigation was: (1) to identify and quantitate the plasma and ascitic fluid biomarkers of inflammation in decompensated cirrhotics requiring a large-volume paracentesis for ascites management and (2) to compare and contrast the biomarker responses present in both the plasma and ascitic fluid of cirrhotics of

differing etiologies.

MATERIALS AND METHODS

Subjects

A total of 57 consecutive cirrhotics requiring a large-volume paracentesis for clinical reasons were studied. Their age, gender and the specific disease etiology for their cirrhosis was determined by a review of their clinical records and, when necessary additional clinical testing procedures. Four distinct etiologic groups of cirrhotics were identified and the cytokine levels were compared between groups in an effort to examine the role of the etiologic factor responsible for cirrhosis in each subgroup.

Inclusion and exclusion criteria

Inclusion criteria: (1) cirrhosis documented by imaging (either an abnormal CT or US) or liver biopsy; (2) ascites requiring a large volume paracentesis because of tense ascites and failure to control the ascites with diuretics (furosemide and spironolactone); and (3) willingness to undergo a large volume paracentesis and sign an informed written consent documenting their participation and allowing for the additional studies required as a result of their participation.

Exclusion criteria: (1) no evidence for cirrhosis; (2) no ascites or adequate ascites control with diuretics; and (3) unwillingness to participate and sign an informed written consent.

Investigations

Each subject had the following routine laboratory studies determined: complete blood count, complete metabolic profile consisting of blood urea nitrogen, creatinine, glucose, total bilirubin, alkaline phosphatase, aspartate and alanine aminotransferases, total protein, albumin, and prothrombin time/INR. Each patient had a calculated Child-Turcotte-Pugh (CTP) score and the following studies were obtained on their ascitic fluid: cell counts for red blood cells, white blood cells and differential, albumin and ascitic fluid cultures. In addition to these routine measures, the plasma and ascitic fluid of each subject was assayed for a panel of biomarkers of inflammation to include the following: procalcitonin, IL-1A, IL-1B, IL-2, IL-4, IL-8, IL-10, monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF). Procalcitonin was assayed utilizing the BioMerieux Vidas assay (Lombard, Illinois). The interleukins, inflammatory cytokines and growth factors were assayed utilizing Randox Biochip assay Platforms (Boston, Massachusetts). All results were compared to that of a normal human plasma panel utilized as a control sample which was obtained commercially from Bioreclamation, LLC (Liverpool, NY, United States). In addition, the levels of the analytes

Table 1 Characteristics of the 57 subjects' studies and of procalcitonin cytokines, and growth factors in plasma (mean \pm SEM)

Parameter	ETOH	HCV	Malignancy	Cardiac
<i>n</i>	25	20	8	4
Male/female	18/7	14/6	5/3	2/2
CTP score	9.1 \pm 0.2	8.2 \pm 0.1	8.1 \pm 0.1	8.1 \pm 0.1
Laboratory tests				
Creatinine (mg/dL)	1.2 \pm 0.1	1.1 \pm 0.1	1.2 \pm 0.3	1.3 \pm 0.2
Prothrombin time (s)	14.0 \pm 0.4	13.8 \pm 1.0	13.6 \pm 0.2	12.5 \pm 0.2
Total bilirubin (mg/dL)	1.4 \pm 0.1	1.2 \pm 0.2	1.4 \pm 0.2	1.9 \pm 0.3
Albumin (g/dL)	3.1 \pm 0.2	3.2 \pm 0.2	3.0 \pm 0.4	3.2 \pm 0.3
PCT	0.375 \pm 0.215	0.440 \pm 0.230	0.954 \pm 0.242	0.092 \pm 0.70
IL-1A	0.26 \pm 0.146	0.160 \pm 0.070	0.182 \pm 0.106	0.135 \pm 0.065
IL-1B	4.710 \pm 2.252	1.747 \pm 0.800	1.982 \pm 0.106	1.610 \pm 0.990
IL-2	2.498 \pm 1.333	1.203 \pm 0.548	2.690 \pm 1.905	1.025 \pm 0.375
IL-4	3.157 \pm 1.429	2.580 \pm 1.005	1.508 \pm 0.422	1.430 \pm 0.090
IL-6	83.791 \pm 47.204	164.430 \pm 70.891	105.392 \pm 60.511	129.700 \pm 112.500
IL-8	92.790 \pm 44.935	334.513 \pm 184.222	104.165 \pm 61.670	16.415 \pm 6.815
IL-10	1.335 \pm 0.454	1.620 \pm 0.779	1.117 \pm 0.297	1.415 \pm 0.615
MCP-1	111.139 \pm 17.746	326.407 \pm 137.768	116.052 \pm 32.101	88.350 \pm 35.150
IFN γ	1.148 \pm 0.650	0.303 \pm 0.058	0.712 \pm 0.201	0.725 \pm 0.525
TNF- α	3.887 \pm 1.218	5.843 \pm 2.248	4.805 \pm 1.304	13.600 \pm 11.80
EGF	37.451 \pm 11.642	92.453 \pm 42.231	70.690 \pm 36.431	126.00 \pm 35.150
VEGF	11.658 \pm 4.419	194.347 \pm 130.788	20.523 \pm 7.739	41.470 \pm 32.870

No significant difference between any of these groups $P > 0.05$. HCV: Hepatitis C virus; PCT: Procalcitonin cytokines; IL: Interleukin; MCP-1: Monocyte chemotactic protein-1; IFN- γ : Interferon- γ ; TNF- α : Tumor necrosis factor- α ; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor.

present in plasma were compared against those in the patients' ascitic fluid. Plasma- Ascites gradients were calculated for each analyte and the mean for each disease group was calculated.

Human research approval

The IRB of Cook County Health and Hospital System approved this study prior to its initiation. Each subject signed an informed written consent before their participation in the study. Moreover, the Cook County Health and Hospital System funded the study in its entirety.

Statistical analysis

The mean and standard error of the mean for each parameter was determined and the differences between the means of the various disease groups studied were calculated utilizing the students *t*-test. A *P* value < 0.05 was considered to be significant.

RESULTS

The characteristics of the 57 subjects studied are shown in Table 1. No clinically important differences between the 4 disease groups studied were evident. In contrast, the procalcitonin levels in plasma varied substantially between groups with the greatest values being present in the group with malignancy (Table 1). The lowest procalcitonin values were seen in those with cardiac cirrhosis. The alcoholic and hepatitis C positive groups had plasma procalcitonin levels that were midway between these two extremes (Table 1).

The ascitic fluid procalcitonin levels mirrored the plasma levels with the greatest values being found in the group with malignancy and the lowest levels being pres-

ent in those with cardiac disease. Again the other two groups had values midway between these two extremes (Table 2). Interestingly, however the alcoholic subgroup had an ascitic fluid procalcitonin value that was greater than that of the hepatitis C positive subgroup such that the relative position of the procalcitonin level in the two subgroups was reversed as compared to that found in plasma (Tables 1 and 2).

The cytokine and growth factor values varied markedly between groups for each parameter studied (Tables 3 and 4). The mean levels of the various factors measured in plasma aligned from the highest to the lowest for each disease group is reported in Table 3. Individuals with alcoholic liver disease had the highest IL-1a, IL-1b, IL-4 and interferon gamma levels. Individuals with malignant the liver disease had the highest values for IL-2. Those with hepatitis C had the highest levels IL-6, IL-8, IL-10, MCP-1 and VEGF.

The mean values for the ascitic fluid levels of the same 12 factors aligned from the highest to the lowest is presented in Table 4. The cardiac group had the greatest values for 5 of the 12 factors measured followed by the alcoholic group with 3 and the other 2 groups with 2 each. The malignancy group at the lowest value for 5 factors followed by the cardiac group with 3 and the other 2 groups with 2 each. Because of the variability in the measured values, the groups did not differ statistically, but when one examines the mean values per se considerable differences are seen between the various groups with mean plasma values ranging from 1.5-20 times the values of the lowest value for each parameter (Table 4). Similarly, when one examines the mean values in the ascitic fluid, the range of values for a given factor between groups ranged from 1.3-10 times the value

Table 2 Procalcitonin, cytokines and growth factors in the ascitic fluid (mean ± SEM)

	ETOH	HCV	Malignancy	Cardiac
<i>n</i>	25	20	8	4
PCT	0.221 ± 0.129	0.125 ± 0.115	0.647 ± 0.497	0.043 ± 0.033
IL-1A	0.168 ± 0.042	0.200 ± 0.058	0.153 ± 0.052	0.700 ± 0.400
IL-1B	7.479 ± 4.813	4.3 ± 1.193	4.900 ± 1.021	5.000 ± 0.300
IL-2	1.368 ± 1.628	0.667 ± 0.067	1.990 ± 1.044	0.650 ± 0.050
IL-4	9.268 ± 1.628	15.833 ± 4.932	6.533 ± 0.984	10.555 ± 4.85
IL-6	687.177 ± 30.115	807.764 ± 0.867	707.525 ± 54.339	790.05 ± 39.750
IL-8	338.015 ± 91.838	329.567 ± 91.926	229.200 ± 105.057	718.25 ± 80.150
IL-10	74.686 ± 39.663	15.200 ± 3.5	9.043 ± 3.876	76.500 ± 44.700
MCP-1	919.608 ± 41.636	537.600 ± 88.357	576.728 ± 206.393	421.900 ± 82.6
IFN-γ	2.114 ± 0.671	0.467 ± 0.267	1.488 ± 0.838	0.2 ± 0.1
TNF-α	22.818 ± 8.882	30.433 ± 20.055	9.672 ± 1.786	70.950 ± 61.750
EGF	1.318 ± 0.345	0.967 ± 0.167	2.407 ± 0.465	4.9 ± 3.4
VEGF	54.383 ± 12.143	129.733 ± 63.589	689.12 ± 499.836	119.450 ± 117.950

No significant difference between any of these groups *P* > 0.05. HCV: Hepatitis C virus; PCT: Procalcitonin cytokines; IL: Interleukin; MCP-1: Monocyte chemotactic protein-1; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor.

Table 3 Mean levels of the plasma factors aligned from the highest to the lowest for each disease group

Highest values → Lowest values				
IL-1A	ETOH	Malignancy	HCV	Cardiac
	0.260	0.182	0.160	0.135
IL-1B	ETOH	Malignancy	HCV	Cardiac
	4.710	1.082	1.747	1.61
IL-2	Malignancy	ETOH	HCV	Cardiac
	2.690	2.498	1.203	1.025
IL-4	ETOH	HCV	Malignancy	Cardiac
	3.157	2.580	1.508	1.43
IL-6	HCV	Cardiac	Malignancy	ETOH
	164.430	129.700	109.392	83.791
IL-8	HCV	Malignancy	ETOH	Cardiac
	334.513	104.265	92.790	16.415
IL-10	HCV	Cardiac	ETOH	Malignancy
	1.620	1.415	1.335	1.117
MCP-1	HCV	Malignancy	ETOH	Cardiac
	326.407	116.052	111.130	88.35
IFN-γ	ETOH	Cardiac	Malignancy	HCV
	1.148	0.725	0.712	0.303
TNF-α	Cardiac	HCV	Malignancy	ETOH
	13.600	5.843	4.805	3.887
EGF	Cardiac	HCV	Malignancy	ETOH
	126.000	92.453	70.690	37.451
VEGF	HCV	Cardiac	Malignancy	ETOH
	194.347	41.470	20.523	11.658

HCV: Hepatitis C virus; IL: Interleukin; MCP-1: Monocyte chemotactic protein-1; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor.

of the lowest value (Table 5). The plasma-ascitic fluid gradients for each parameter were determined and are reported in (Table 5). A positive value for the plasma-ascitic fluid gradient identifies those factors wherein the plasma level was greater than the ascitic fluid level. In contrast, a negative value for the plasma-ascitic fluid gradient identifies those factors wherein the greater value was present in the ascitic fluid. A positive value suggests that the cytokine assayed arose from a systemic response while a negative value suggests that the response arose primarily in the abdominal cavity and that either a peritoneal or mesenteric origin for the cytokine.

DISCUSSION

This study extends the finding of an earlier study evaluating cytokine, and growth factor levels in the plasma and ascitic fluid of cirrhotics^[1]. In both studies, the inflammatory cytokines IL-4, IL-6, IL-8, IL-10, TNF-α and MCP-1 have been shown to be increased in both the ascitic fluid and plasma of cirrhotics with large volume ascites. The present study performed in a completely different and slightly larger patient population extends the earlier study by documenting differences in the cytokine profiles based on the individuals underlying disease etiol-

Table 4 Mean values of the various factors in the ascitic fluid aligned from the highest to the lowest

Highest values → Lowest values				
IL-1A	Cardiac	HCV	ETOH	Malignancy
	0.700	0.200	0.168	0.153
IL-1B	ETOH	Cardiac	Malignancy	HCV
	7.479	5.000	4.900	4.300
IL-2	Malignancy	ETOH	HCV	Cardiac
	1.990	1.368	0.667	0.650
IL-4	HCV	Cardiac	ETOH	Malignancy
	15.833	10.555	9.268	6.533
IL-6	HCV	Cardiac	Malignancy	ETOH
	807.764	790.050	707.525	687.177
IL-8	Cardiac	ETOH	HCV	Malignancy
	718.250	338.015	329.567	229.200
IL-10	Cardiac	ETOH	HCV	Malignancy
	76.500	74.686	15.200	9.043
MCP-1	ETOH	Malignancy	HCV	Cardiac
	919.608	576.728	537.600	421.900
IFN- γ	ETOH	Malignancy	HCV	Cardiac
	2.114	1.488	0.467	0.200
TNF- α	Cardiac	HCV	ETOH	Malignancy
	70.950	30.433	22.818	9.672
EGF	Cardiac	Malignancy	ETOH	HCV
	4.900	2.407	1.318	0.967
VEGF	Malignancy	HCV	Cardiac	ETOH
	689.120	129.733	119.456	54.383

HCV: Hepatitis C virus; IL: Interleukin; MCP-1: Monocyte chemotactic protein-1; IFN- γ : Interferon- γ ; TNF- α : Tumor necrosis factor- α ; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor.

Table 5 Mean plasma- ascitic cytokine gradients segregated by disease etiology

	HCV	ETOH	Malignancy	Cardiac
IL-1A	-0.040	0.092	0.029	-0.565
IL-1B	-2.553	-2.769	1977.100	-3.390
IL-2	0.540	1.530	0.700	0.875
IL-4	-13.253	-6.111	-5.025	-9.125
IL-6	-643.337	-603.386	-602.133	-639.35
IL-8	-5.054	-245.225	-125.035	-701.835
IL-10	-13.580	-73.331	-7.926	-75.085
MCP-1	-201.193	-303.469	-460.673	-333.35
IFN- γ	-0.164	-0.966	-0.776	0.525
TNF- α	-24.590	-18.931	-4.777	57.050
EGF	96.486	36.176	-68.283	121.100
VEGF	64.614	-42.725	-668.649	-77.980

No significant difference between any of these groups $P > 0.05$. HCV: Hepatitis C virus; IL: Interleukin; MCP-1: Monocyte chemotactic protein-1; IFN- γ : Interferon- γ ; TNF- α : Tumor necrosis factor- α ; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor.

ogy for the cirrhosis^[1]. The current data suggests therefore that the pathophysiologic responses to the various hepatic disease etiologies in some way may determine, at least in part, the innate immune responses that occur and account for the differences in the cytokine and growth factor levels in the ascitic fluid and plasma^[2,3]. The IL-6 and MCP-1 levels were universally increased in all four cirrhotic groups. VEGF levels were increased most markedly in those with malignancy and to a lesser degree in those with cardiac and alcohol induced disease. Individuals with cirrhosis due to hepatitis C had the lowest VEGF levels. In contrast, the hepatitis C positive group had the greatest levels of IL-4 present in both plasma and ascitic fluid.

The finding of an increase in VEGF levels in cirrhotics with malignancy is interesting but not particularly surprising as malignant disorders are known to be associated with increased VEGF levels^[5,6]. The increase of VEGF levels in cardiac and alcohol induced liver disease is surprising and differs markedly from that seen in those with hepatitis C. This observation is consistent with the data reported in other studies wherein increased organ remodeling has been observed in individuals with cardiac and alcohol related disease but not so in those with hepatitis C virus^[2,3].

These data also support the role of the peritoneal based immune response in the pathogenesis of both bacterial translocations spontaneous bacterial peritoni-

tis^[1,7-14]. More specifically, they are consistent with the clinical observations that spontaneous bacterial peritonitis occurs less frequently in patients with cardiac and malignant ascites as contrasted to those with alcoholic liver disease and chronic viral induced liver disease.

As shown in Table 4, cardiac disease associated ascites has the highest ascitic fluid levels of IL-1A, IL-8, IL-10, TNF- α , and EGF. Conversely, the cardiac disease associated ascites has the lowest levels of IL-2 and MCP-1. Those with malignancy associated ascites have the highest levels of IL-2 and VEGF and the lowest levels of IL-1A, IL-4, IL-8, IL-10, and TNF- α .

The present findings for these two distinct etiologic groups suggest that the ascitic fluid immune response manifested in the ascitic fluid may account in some way for the lower rate of spontaneous bacterial peritonitis in individuals with ascites due to these two unique causes of cirrhosis.

Factors likely to represent protective cytokines associated with a reduced risk for SBP include EGF, TNF- α , IL-1A, IL-8, and IL-10. Those are more likely to be associated with potential for SBP include: IL-1B, IL-4, MCP-1, and IFN- γ (Table 4).

The data shown in Table 5 consisting of the serum-ascites gradient enables one to determine whether the primary source of the measured factor arose from the vascular space or the peritoneal cavity. Specifically, those with the positive value identify a primary vascular source of the measured factor while a negative value identifies these factors having their origin in the peritoneal cavity.

In summary, the present data suggest the well-recognized factors that include a reduced plasma oncotic pressure, increased splanchnic venous congestion and pressure, increased vascular permeability and an overwhelmed lymphatic mechanism for removing ascitic fluid account substantially for the development of clinical ascites. They suggest that unique immune related responses that differ between various hepatic disease states may also contribute to the development of ascites and the likelihood of developing spontaneous bacterial peritonitis. Further, these data suggest further that a better understanding of the different immune response characteristics present in cirrhotics of different etiologies may enable disease specific modulation of the immune response in each and thereby contribute to the development of improved therapies that control not only to the development of ascites but also overall disease progression.

COMMENTS

Background

Large-volume ascites occurring in cirrhotic patients has been shown to manifest an inflammatory response characterized by increased levels of cytokines, interleukins and several growth factors. The pathophysiologic mechanisms responsible for the development of cirrhosis and ultimately decompensated cirrhosis vary as a function of the underlying hepatic disease.

Research frontiers

This study extends the finding of an earlier study evaluating cytokine, and growth factor levels in the plasma and ascitic fluid of cirrhotics.

Innovations and breakthroughs

The current data suggests therefore that the pathophysiologic responses to the various hepatic disease etiologies in some way may determine, at least in part, the innate immune responses that occur and account for the differences in the cytokine and growth factor levels in the ascitic fluid and plasma.

Applications

The authors suggest that unique immune related responses that differ between various hepatic disease states may also contribute to the development of ascites and the likelihood of developing spontaneous bacterial peritonitis.

Peer review

The authors performed plasma and ascitic cytokines among various etiologies of cirrhosis.

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