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The association of aneurysms related to arteriovenous fistulas and chronic hepatitis C virus infection in maintenance hemodialysis

İdame hemodiyaliz tedavisi gören hastalarda arteriyovenöz fistül anevrizmaları ile kronik hepatit C virüs enfeksiyonunun birlikteliği

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Background: This study aims to investigate a possible association of aneurysm of arteriovenous fistulas (AVFs) and chronic hepatitis C virus (HCV) infection in maintenance hemodialysis (HD) patients.

Methods: In this cross-sectional study, 179 HD patients with AVFs who were referred to Van Yüzüncü Yıl University Hospital between January 2010 and December 2010 were evaluated. Data including age, sex, duration of renal failure, number of operated fistulas, number of patients with aneurysmal fistulas and chronic HCV infection were recorded. Doppler ultrasonography was performed to determine AVF patency and aneurysm flow.

Results: Thirthy-three patients (group A) had aneurysm and 21 (group A1) of these patients had chronic HCV infection, while 12 (group A2) had no chronic HCV infection. Hundred and forty-six patients (group B) had no aneurysm. Of these patients, 15 (group B1) had chronic HCV infection, while 131 (group B2) had no chronic HCV infection. There were no statistical differences in age, sex, and duration of renal failure between the groups. The mean AVF flow was higher in group A1 (856±123 ml/min) compared to group A2 (560±98 ml/min) ($p<0.05$). The mean AVF flow was also higher in group B1 (536±54 ml/min) compared to group B2 (373±47 ml/min) ($p<0.05$). Criyoglobulinemia positivity was statistically significant in aneurysmal AVFs (group A1 and A2) than nonaneurysmal AVFs (group B1 and B2) ($p<0.001$).

Conclusion: Our results demonstrated that aneurysm of AVFs in maintenance HD patients was associated with chronic HCV infection.

Key words: Aneurysm; arteriovenous fistula; hepatitis C virus.

Amaç: Bu çalışmada idame hemodiyaliz (HD) tedavisi gören hastalarda arteriyovenöz fistüllerin (AVF) anevrizmaları ile hepatit C virus (HCV) enfeksiyonunun muhtemel birlikteliği araştırıldı.

Çalışma planı: Bu kesitsel çalışmada, Ocak 2010 - Aralık 2010 tarihleri arasında Van Yüzüncü Yıl Üniversite hastanesine yönlendirilen AVF'li 179 HD hastası değerlendirildi. Yaş, cinsiyet, renal yetmezlik süresi, ameliyat edilen fistül sayısı, anevrizmal fistülü olan hasta sayısı ve kronik HCV enfeksiyonu verileri kaydedildi. Arteriyovenöz fistül açıklığı ve anevrizmal akımı belirlemek için Dopler ultrasonografi yapıldı.

Bulgular: Otuz üç hastada (grup A) anevrizma vardı ve anevrizması olan 33 hastanın 21'inde (grup A1) kronik HCV enfeksiyonu varken, 12 hastada (grup A2) kronik HCV enfeksiyonu yoktu. Yüz kırk altı hastada (grup B) anevrizma yoktu. Bu hastaların 15'inde (grup B1) kronik HCV enfeksiyonu vardı, 131'inde (grup B2) kronik HCV enfeksiyonu yoktu. Gruplar arasında yaş, cinsiyet, renal yetmezlik açısından istatistiksel fark yoktu. Ortalama AVF akımı grup A1'de (856±123 ml/dk.) group A2'ye (560±98 ml/dk.) göre daha yüksek idi ($p<0.05$). Ortalama AVF akımı grup B1'de (536±54 ml/dk.) grup B2'ye (373±47 ml/dk.) göre daha yüksek idi ($p<0.05$). Kriyoglobulinemi pozitifliği anevrizmal AVF'lerde (grup A1 ve A2) anevrizmal olmayan AVF'lere (grup B1 ve B2) göre istatistiksel olarak anlamlı idi ($p<0.001$).

Sonuç: Sonuçlarımız idame HD tedavisi gören hastaların AVF anevrizmalarının kronik HCV enfeksiyonu ile olan müspet birlikteliğini gösterdi.

Anahtar sözcükler: Anevrizma; arteriyovenöz fistül; hepatit C virüsü.

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The long-term patency of arteriovenous fistulas (AVFs) is closely associated with the long-term survival of patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD).[1] Unfortunately long-term shunt function is limited in many of these patients, with the most common causes being acute thrombosis and shunt stenoses.[2] In addition, shunt dysfunction can result from the formation of an aneurysm,[3,4] which can lead to shunt failure due to thrombosis, infection, and acute rupture. Aneurysms occurs in 5-40% of all AVFs, and erosion of the covering skin and progressive growth expansion are regarded as indications for surgical correction for aneurysmal AVFs.[5-7] Furthermore, concomittant diseases and complications, such as hepatitis C virus (HCV) infection, are also important health issues which are related to maintenance HD patients.[8] The prevalance of anti-HCV seropositivity in patients undergoing regular HD ranges between 7-40%.[9] In addition, mixed cryoglobulinemia (MC) is the most frequent extrahepatic manifestation associated with HCV chronic infection, being detected in 50-60% of the HCV (+) patients.[10,11] Additionally, MC may be clinically asymptomatic or induce various kinds of immune complex (IC) vasculitis,[12,13] which are histologically characterized by a perivascular mononuclear cell infiltrate, with or without vessel wall necrosis that affects small-size veins and arterioles.[14] Mixed cryoglobulinemia is also characterized by the clonal expansion of rheumatoid factor (RF)-expressing B cells in the liver, lymph nodes, and peripheral blood, resulting in the presence of cryoglobulins in the circulation. Cryoglobulins are cold-insoluble immune complexes containing RF, polyclonal immunoglobulin G (IgG), and HCV ribonucleic acid (RNA) that precipitate and deposit on the vascular endothelium and affect organs such as the skin, kidneys, and peripheral nerves.[15,16] Clinical manifestations associated with MC range from the so-called "MC syndrome" (purpura, arthralgia, and asthenia) to more serious lesions with neurological and renal involvement. Shortly after the discovery of HCV in 1989, evidence became available that 80% of cryoglobulinemia vasculitis cases were associated with HCV infection. The primary role of HCV in the mechanism of cryoprecipitation is suggested mainly by its selective concentration in cryoglobulins.[17] Mixed cryoglobulinemia may manifest as small-vessel vasculitis, and it has been suggested that antibody (Ab) or sensitized T cells to HCV-containing endothelial cells may initiate the vasculitis process.

The aim of this study was to determine the possible relationship between aneurysmal AVFs and chronic HCV infection, especially in patients with MC.

PATIENTS AND METHODS

This study evaluated 179 patients with ESRD on regular HD treatment who had AVF and had been referred to a university hospital. The patient data, including age, gender, duration of renal failure, number of operated fistulas, and number of patients with aneurysmal fistulas was collected and documented. In addition, the pulsatile mass along with the radial and ulnar pulses were assessed, and the Allen test was used to make a definitive diagnosis. Color Doppler ultrasonography (USG) was performed to determine the characteristics of the AVFs and confirm the aneurysm. The serum samples of the patients were tested for anti-HCV antibody using an enzyme-linked immunosorbent assay II (ELISA-II) test, and those with a positive result underwent an HCV RNA test to determine whether there was a polymerase chain reaction (PCR). A positive PCR test indicated HCV infection.

In the serological testing for cryoglobulins, serum preparation was performed at 37 °C to prevent premature immune complex precipitation. The serum was then stored at 4 °C for seven days, inspected daily for a precipitate, and spun in a Wintrobe tube (ATICO Medical Pvt. Ltd., Ambala, Haryana, India) for to calculate of the cryocrit, the percentage of cryoglobulin in the serum. A cryocrit ≥2% indicated a positive result. The cryocrit was then typed using immunofixation.[18] Some chronic HCV patients with MC may be HCV Ab+ yet have undetectable plasma HCV RNA.[19] In such cases, examining the cryocrit for HCV RNA is warranted. The patients in this study with HCV and MC had serum cryoglobulin levels of over 0.05 g/lt on at least two occasions and were positive for serum HCV RNA

Statistical analyses

Statistical tests were performed using the SPSS version 13 for Windows (SPSS Inc., Chicago, IL, USA) software program. Continous variables were expressed as mean ± standard deviation (SD), and either a chi-square test or Fisher's exact test was used for comparing percentages. In addition, Student's t-test was used to compare parametric measurements, and the Mann-Whitney U test was used to compare non-parametric measurements among the groups. A p-value of <0.05 was interpreted as being statistically significant.

RESULTS

Thirty-three of the 179 patients (18%) had an aneurysm (group A). Twenty-one of these 33 (63%) had chronic

HCV infection (group A1), but 12 (37%) did not (group A2). Furthermore, 146 patients (82%) had no aneurysm (group B), but 15 of these (10%) had chronic HCV infection (group B1). That left 131 patients (90 %) who had no chronic HCV infection (group B2). The clinical and demographic characteristics of the patients are given in Table 1. There were no significant differences with regard to age, body mass index (BMI), ESRD duration, renal function parameters, or serum glucose levels among the groups (p>0.05). However, the mean serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin, indirect bilirubin, and gamma globulin were higher in groups A1 and B1 than in groups A2 and B2, respectively (p<0.05) (Tables 1 and 2). Additionally, the mean serum levels of the RF were higher in groups A1 and B1 than in groups A2 and B2, respectively (p<0.05). Cryoglobulinemia positivity was also the highest in groups A1 (17/21 patients; 80%), and B1 (11/15 patients; 73%) than in groups A2 (1/12 patients; 0.08%) and B2 (13/131 patients; 0.09%). While the test for HCV RNA was positive for all of the patients in groups A1 (21/21 patients) and B1 (15/15 patients), none of the patients in groups A2 and group B2 tested positive. We also determined that the mean AVF flows of the patients in groups A1 and B1 were

Table 1. Aneurysm positive patients (n=33)

Variable	Aneurysm positive								
	Group A1 (HCV +)				Group A2 (HCV –)				
	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*
Groups	21	63			12	37			≤0.05
Age (years)			42±12	17-56			41±16	14-67	NS
Body mass index (kg/m^2)			20.3±2.4				21.6±2.6		NS
ESRD duration in years			13±6	1-14			14±5	1-13	NS
Opened AVF count			5.2±1.2	3-7			4.8±1.1	2-7	NS
Last functional AVF duration in months			18±12	7-31			21±16	11-41	NS
Mean AVF flow (ml/min)			856±123	517-1569			560±98	432-986	≤0.05
Hypertension	7	33			5	41			NS
Diabetes mellitus	5	23			6	50			NS
Hyperlipidemia	8	38			4	33			NS
Smoking	7	33			5	41			NS
Hormone use	0	0			0	0			NS
Cancer	0	0			0	0			NS
Creatinine (mg/dL)			3.2±1.2				3.3±1.1		NS
Blood urea nitrogen (mg/dL)			67±19				66±18		NS
Glucose (mg/dL)			127±59				132±57		NS
Aspartate transaminase (IU/L)			57±26				19±6		≤0.05
Alanine transaminase (IU/L)			43±17				11±5		≤0.05
Alkaline phosphatase (IU/L)			364±176				231±151		≤0.05
Total bilirubin (mg/dL)			1.3±0.2				1.2±0.2		NS
Indirect bilirubin (mg/dL)			0.3±0.02				0.1±0.01		≤0.05
Hemoglobin (g/dL)			7±2				9±2		≤0.05
Hematocrit (%)			25±6				27±7		≤0.05
White blood cell (K/mm^3)			4761±1786				5198±1832		≤0.05
Platelet (Thousand K/mm^3)			153±43				215±72		≤0.05
C-reactive protein (mg/L)			6.4±2.8				5.8±1.9		≤0.05
Total cholesterol (mg/dL)			258±89				271±94		NS
Low-density lipoprotein (mg/dL)			117±42				109±38		≤0.05
High-density lipoprotein (mg/dL)			46±17				58±23		≤0.05
Gamma globulin (gr/dL)			5.7±1.8				1.1±0.2		≤0.05
Rhemotoid factor (IU/ml)			38±7				13±3		≤0.05
Criyoglobulinemia positivity	17	80			1	0.08			≤0.05
HCV-RNA positivity	21	100			0	0			≤0.05

HCV: Hepatitis C virus; SD: Standard deviation; ESRD: End-stage renal disease; AVF: Arteriovenous fistula; RNA: Ribonucleic acid; NS: Not significant.

Table 2. Aneurysm-negative patients (n=146)

Variable	Aneurysm negative								
	Group B1 (HCV +)				Group B2 (HCV –)				
	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*
Groups	15	10.3			131	89.7			≤0.05
Age (years)			42±13	14-72			43±12	10-69	≤0.05
Gender									
Males	7	46			64	48			≤0.05
Females	8	54			67	52			≤0.05
Body mass index (kg/m^2)			21.1±1.3				21.2±1.2		NS
ESRD duration in years			14±4	2-12			15±5	2-11	NS
Opened AVF count			3.8±1.1	2-5			3.6±0.8	2-5	NS
Last functional AVF duration in months			24±16	11-45			28±14	10-41	NS
Mean AVF flow (ml/min)			536±54	247-911			373±47	232-538	≤0.05
Hypertension	8	53			67	51			≤0.05
Diabetes mellitus	6	40			56	43			≤0.05
Hyperlipidemia	7	46			54	41			≤0.05
Smoking	6	40			58	44			≤0.05
Hormone use	0	0			0	0			NS
Cancer	0	0			0	0			NS
Creatinine (mg/dL)			3.1±1.2				3.3±1.3		NS
Blood urea nitrogen (mg/dL)			63±14				68±16		NS
Glucose (mg/dL)			131±64				129±47		NS
Aspartate transaminase (IU/L)			61±29				8±0.3		≤0.05
Alanine transaminase (IU/L)			39±17				6±0.2		≤0.05
Alkaline phosphatase (IU/L)			372±123				184±96		≤0.05
Total bilirubin (mg/dL)			1.7±0.4				0.6±0.02		≤0.05
Indirect bilirubin (mg/dL)			0.7±0.42				0.1±0.01		≤0.05
Hemoglobin (g/dL)			8±3				11±4		≤0.05
Hematocrit (%)			26±9				30±7		≤0.05
White blood cell (K/mm^3)			3894±1346				6354±1936		≤0.05
Platelet (Thousand K/mm^3)			187±49				248±87		≤0.05
C-reactive protein (mg/L)			9.3±5.8				3.7±1.2		≤0.05
Total cholesterol (mg/dL)			224±76				221±54		NS
Low-density lipoprotein (mg/dL)			127±52				89±43		≤0.05
High-density lipoprotein (mg/dL)			39±21				51±33		≤0.05
Gama globulin (gr/dL)			4.9±1.4				1.3±0.3		≤0.05
Rhemotoid factor (IU/ml)			29±7				12±3		≤0.05
Criyoglobulinemia positivity	11	73			13	0.09			≤0.05
HCV-RNA positivity	15	100			0	0			≤0.05

HCV: Hepatitis C virus; SD: Standard deviation; ESRD: End-stage renal disease; AVF: Arteriovenous fistula; RNA: Ribonucleic acid; NS: Not significant.

higher than those in groups A2 and B2 respectively ($p<0.05$).

DISCUSSION

In this study, we assessed the relationship between chronic HCV infection, cryoglobulinemia positivity, and the flows of aneurysmatic and non-aneurysmatic fistulas in HD patients and found a correlation between the higher AVF flows and HCV RNA positivity and cryoglobulinemia. Arteriovenous fistulas are known to be associated with various complications, such as steal syndrome, arm edema, thrombosis, and aneurysms.[20] The most common late complication of AVF is the development of an aneurysm, which is usually a true aneurysm.[21] Hepatitis C virus infection is a catastrophic problem in ESRD patients,[22] with the prevalence of HCV among ESRD patients varying between 5 and 85% worldwide.[23] This virus is responsible for both hepatic and extrahepatic diseases because of the

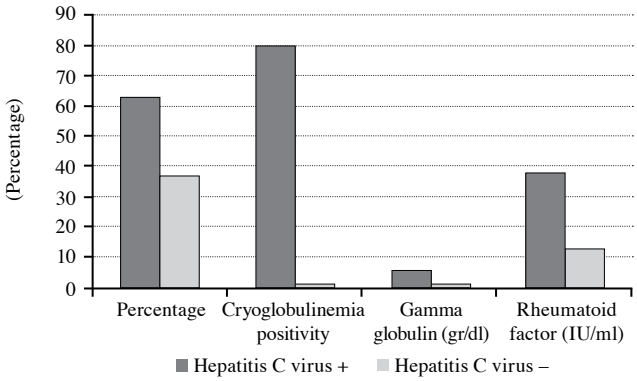

Figure 1. Aneurysm-positive patients. Hepatitis C virus and cryoglobulinemia. Positivity, gamma globulin, and rheumatoid factor levels.

possibility of infecting not only hepatic but also extrahepatic cells and its ability to remain in the host.[24,25] The most documented extrahepatic manifestation related to HCV infections is MC.[11,26,27]

Shichi et al.[28] found that anti-HCV antibodies have been reported in 10.6% of patients with hypertrophic cardiomyopathy and 6.3% of those affected by dilatative cardiomyopathy, which is much higher that the rate attributed to the controls (2.4%). In addition, Ishizaka et al.[29] determined that there was a significantly higher prevalence of aortic atherosclerosis in patients with HCV infection, which is noteworthy and found that this association was mostly evident in cases involving active viral replication.[30] Furthermore, the high prevalence of antibodies to HCV connected with higher concentrations of HCV RNA genomic sequences in cryoglobulins suggests a correlation between MC and HCV infection and strongly supports the view that this virus plays a key role in causing vascular damage.[31,32] However, it is not clear whether this damage has an effect on AVFs with aneurysmal transformation. According to our results, the aneurysmal transformation of AVFs was higher in the HCV-infected patients, which led to the hypothesis that HCV RNA particles and/or cryoglobulinemia may disrupt the endothelial cells of fistulas in infected patients (Figures 1 and 2). Furthermore, in a 10-year follow-up of clinical studies comprised of 53 patients, Janicki et al.[33] determined that five (9.4%) developed an aneurysm. In addition, Eugster et al.,[34] followed 38 patients for 10 years, measuring their brachial artery diameters, and found an average increase of 1 cm at the end of this period. In addition, two of the patients (5.3%) developed an aneurysm. In another large study, Gharbi et al.[35] followed 422 patients opened 684 fistula for 39 months and have found that 11% developed aneurysm. Aneurysmal dilatation of AVFs is a known phenomenon that has not been thouroughly investigated.[36,37] The mechanisms underlying the dilatation are thought to be stress, high blood flow, and interference with the function of the vasa vasorum. Our study provided first-time evidence that the overflow of AVFs, both with or without aneurysms, can be seen in HD patients with HCV infection and that HCV infection and/or cryoglobulinemia, along with stress and vasa vasorum dysfunction, may play a role in the aneurysmal dilatation of fistulas (Figure 3).

We also demonstrated that aneurysmal AVFs and HCF infection were more predominant in males, with group B1 having more males than the other groups. In addition, the duration of functional AVF was shorter in groups A1 and B1 than in groups A1 and A2, and the opening AVF counts were also higher in

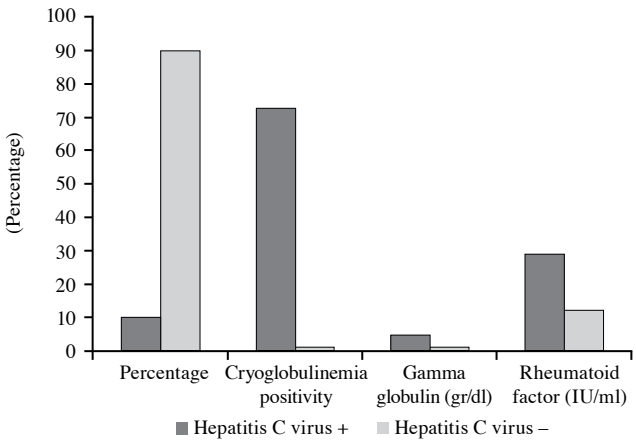

Figure 2. Aneurysm-negative patients. Hepatitis C virus and cryoglobulinemia positivity, gamma globulin, and rheumatoid factor levels.

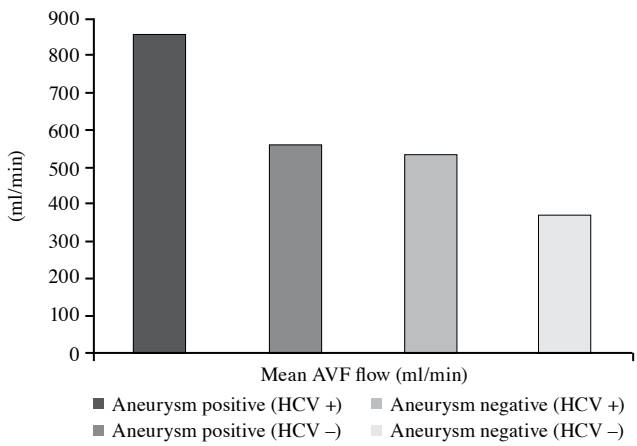

Figure 3. Mean arteriovenous fistula flow (ml/min) by groups. HCV: Hepatitis C virus; AVF: Arteriovenous fistula.

the same patients. Our results also led to speculation that HCV infection has deteriorating effects on AVF patency; however, the precise mechanisms by which this occurs needs to be researched further. Moreover, the serum levels of gamma globulin were higher in groups A1 and B1. Interestingly, Arase et al.[31] found that the gamma globulin levels were higher in HCV patients with extrahepatic manifestations. We also determined that the mean value of RF was higher in the HCV (+) patients that made up groups A1 and B1 and that chronic inflammation due to this infection may provide a possible explanation for the laboratory abnormalities in our study population.

To our knowledge, no other study in the literature has identified a link between AVF aneuryms and chronic HCV infection, but our results showed a strong correlation, leading us to postulate that AVF aneurysms are one of the deterioriating effects of HCV infection and cryoglobulinemia in the vascular endothelium. As Arase et al.[31] and Kırış et al.[32] discovered, the high prevalence of antibodies in relation to HCV along with the higher concentration of HCV RNA genomic sequences in cryoglobulins suggests a close relationship between MC and HCV infection and supports the view that this virus plays a key role in causing vascular damage.

A limitation of our study was that it was cross-sectional and not prospective in nature. It would be interesting to assess AVF flows in HD patients along with the changes in the status of HCV and cryoglobulinemia via a long-term follow-up study and to also analyze the possible relationship of these flows with the clinical aneurysmatic fistulas in chronic renal failure patients over time.

Conclusion

Our data showed a correlation between HD patients with HCV infection who have increased levels of AVF flows and cryoglobulinemia. However, further prospective, randomized, controlled studies are needed to determine the possible beneficial effects of anti-HCV therapy on AVF flow abnormalities among HD patients.

Declaration of conflicting interests

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