RESEARCH ARTICLE

Stasis dermatitis: A skin manifestation of poor prognosis in patients with heart failure

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Abstract

Background: The relationship between stasis dermatitis (SD), clinical factors, and heart failure (HF) outcomes in outpatients has not been previously assessed.

Methods: This observational cross-sectional study evaluated 324 patients admitted to the HF outpatient clinic. A total of 158 HF outpatients (100 males and 58 females) were enrolled in the study and were divided into two groups depending on whether they were diagnosed with SD within six months before attending the outpatient clinic. Forty-one patients (26 %) diagnosed with SD in the preceding six months were designated group 1, and 117 (74 %) not diagnosed were designated group 2.

Results: Diabetes mellitus (DM) (OR =5.473, p <0.001), chronic obstructive pulmonary disease (COPD) (OR =2.623, p =0.039), and increased systolic pulmonary artery pressure (SPAP) (OR =1.061, p =0.001) values were independently associated with SD in multivariate logistic regression analysis. During the follow-up of 12 ± 4 months, no significant difference was documented between group 1 and group 2 regarding the death ratio (17 % vs. 19 %, p =0.991). In the multivariate Cox proportional-hazards model with a stepwise forward method, the presence of SD diagnosis [hazard ratio (HR) =2.933, 95 % Confidence Interval (CI): 1.660-5.181, p <0.001] and coronary artery disease (CAD) (HR=2.492, 95%CI: 1.238-5.018, p= 0.011) remained independently associated with the risk of HF-related hospitalization.

Conclusion: SD was found, for the first time, to be independently associated with DM, COPD, and increased SPAP values and determined as an independent predictor for HF-related hospitalization.HIPPOKRATIA 2022, 26 (1):13-18.

Keywords: Chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hospitalization, stasis dermatitis, systolic pulmonary artery pressure

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Introduction

Stasis dermatitis (SD) is a common dermatological condition characterized by eczematous plaques on the lower extremities, especially in the medial malleolus. Although it is called dermatitis, the basis of its etiopathogenesis is increased venous pressure and decreased blood flow, primarily due to cardiovascular pathologies. In the early stage, progressive skin inflammation triggered by the disturbance in blood flow causes itching, scaling, and erythema in the affected areas. In addition, hemosiderin-charged macrophages and the extravasation of erythrocyte elements due to the increase in hemodynamic pressure induce a hyperpigmented appearance in the skin. Especially in cases that develop due to venous insufficiency, varicose veins often accompany this appearance[1,2].

In advanced stages, white fibrotic lesions, also known as atrophie blanche, appear on the skin due to fibrosis. Furthermore, lipodermatosclerosis, a kind of panniculitis, develops in the affected leg induced by fibrosis. The ankle thinning seen in lipodermatosclerosis due to sclerosis is described as the inverted champagne glass appearance. When the underlying pathology is not corrected, ulcers occur even in mild traumas such as scratching[3].

In patients with heart failure (HF), raising in peripheral venous pressure reflects an increase in central venous pressure, and venous congestion that develops depending on this is often observed[4]. SD, which can also be seen in HF patients, can be associated with increased peripheral venous pressure in these patients. Although SD is a common comorbidity in HF patients in daily practice, there was no study evaluating the factors associated with SD in HF patients. In our study, we aimed to assess the SD observed in HF patients and its relationship with the prognosis of HF.

Methods

In this observational cross-sectional cohort study, we evaluated consecutive patients admitted to the HF outpatient clinic at our center between June 2012 and June 2013. Patients' medical records were assessed concern-

ing their demographic characteristics (age, gender), body mass index (BMI), comorbidities [hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD)], laboratory data, clinical features [functional capacity class: The New York Heart Association classification (NYHA), 12-lead resting electrocardiogram, echocardiographic data, and recent therapy method] and were recorded. Eligible patients should have been diagnosed with SD within six months before attending the HF outpatient clinic. They were assessed by reviewing their hospital medical records and notes of their follow-up appointments.

The inclusion criteria specified consecutive HF patients who attended the HF outpatient clinic between June 2013 and June 2014, and their follow-up notes (routinely filled in all HF patients following their consent) could be reached. According to the exclusion criteria, we did not enroll in the study individuals under the age of 18, patients with known lower extremity venous insufficiency (primary or secondary to previous venous vascular surgery), patients with lower extremity venous thrombosis, patients with signs of dermatitis other than SD on the lower extremities, patients with severely impaired functional capacity (patients who cannot even do daily tasks such as going to the toilet), patients with comorbidities other than HF that may lead to SD (patients with a history of malignancy, or cirrhotic hepatic disease), and patients with signs of acute decompensation at presentation. As suggested by existing guidelines[5,6], the diagnosis of decompensation was based on a combination of recently deteriorated HF symptoms and signs.

HF-related hospitalization or mortality was selected as the endpoint of the study. Hospitalization requirement for HF is defined as the presence of severe HF clinical signs or symptoms requiring administration of at least 40 mg intravenous furosemide within two hours of admission, either in a ward or intensive care unit lasting more than three days. We followed all patients for an average of 12 ± 4 months from the date of admission from the outpatient clinic regarding the development of the endpoints.

Experienced echocardiographers performed all examinations utilizing the Vivid 7 system with 2.5-5 Mhz probes (GE Medical System, Horten, Norway). In line with the most recent guidelines[5], we calculated the ejection fraction (EF) using the modified Simpson method and estimated the chamber sizes. We calculated the systolic pulmonary artery pressure (SPAP) using the peak velocity of tricuspid regurgitation and estimated right atrial pressure[6].

The study was approved by the Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision No: 2020-01/06, date: 15/01/2020).

Statistical analysis

For categorical variables, data are presented as numbers and percentages, for continuous variables as means ± standard deviation, and for skewed continuous variables, tested using the Kolmogorov-Smirnov test, as medians with (min-max) range. For categorical variables, depending on data distribution, the chi-square or Fisher's exact test was utilized to compare patients' groups. For continuous variables, the independent samples t-test was used for normally distributed, and when the distribution was skewed, the Mann-Whitney U test was used. We performed the Spearman correlation to examine the relationships between the variables. We considered p-values <0.05 statistically significant (Table 1, Table 2). We used a multivariate logistic regression model with the stepwise forward method to identify independent parameters associated with SD (Table 3). In addition, univariate analysis was used to measure the relationship of variables to HF-related hospitalization. The factors significant in univariate analysis were then analyzed in the multivariate Cox proportional hazards model to determine the independent prognostic factor (Table 4). All statistical procedures were performed using SPSS for Windows, Version 14.0. (SPSS Inc., Chicago, IL, USA).

Results

We evaluated 324 patients admitted to the HF outpatient clinic, and 158 met the inclusion criteria and were enrolled in the study. There were 100 males and 58 females (male/female ratio: 2/1.16) with mean age of 66 ± 12 years and mean EF of 31 ± 8 %. The patients were divided into two groups depending on whether they were diagnosed with SD within six months before attending the outpatient clinic. Forty-one patients (26 %) diagnosed with SD in the preceding six months were designated group 1, and 117 patients (74 %) not diagnosed were designated group 2. Table 1 compares the two groups in terms of basic clinical features, echocardiographic parameters, and laboratory parameters. Significantly more patients with DM and COPD were included in group 1 than in group 2 (73 % vs. 33 %, p <0.001; 42 % vs. 21 %, p =0.021, respectively). Patients in group 1 had a higher mean left atrial (LA) diameter and higher SPAP than the patients in group 2 (48 ± 7 vs. 45 ± 6, p =0.009; 55 ± 14 vs. 44 ± 13, p <0.001, respectively).

DM, COPD, and increased SPAP values were associated with SD independently of other variables, as exhibited in multivariate logistic regression analysis, which included age, gender, BMI, and parameters statistically different between patients diagnosed with and without SD (Table 3). No significant difference was found in the HF-related treatment of patients diagnosed and not diagnosed with SD (Table 2). Twenty-nine patients (18 %) succumbed at 12 ± 4 months of follow-up, but there was no significant difference in mortality between groups 1 and 2 (17 % vs. 19 %, p =0.991). In the same follow-up period, 58 patients (37 %) were hospitalized due to HF, and hospitalization was more frequent in group 1 than in group 2 patients (71 % vs. 25 %, p <0.001) (Table 2).

Table 4 shows the result of the univariate analysis comparing those with and without HF-related hospitalization during the follow-up period. In the univariate anal-

Table 1: Baseline clinical characteristics, laboratory, and echocardiographic parameters of the 158 heart failure outpatients regarding stasis dermatitis diagnosis within six months preceding admission. Group 1 included patients with and group 2 without stasis dermatitis.

Characteristics	Group 1 SD (+) (n = 41)	Group 2 SD (-) (n =117)	P
Age (years)	66 ± 12	66 ± 12	0.924
Female (%)	12 (29 %)	46 (39 %)	0.251
Body mass index	28 ± 5	28 ± 4	0.953
NYHA functional class III-IV (%)	26 (65 %)	65 (57 %)	0.486
Hypertension (%)	21 (53 %)	50 (44 %)	0.324
Diabetes Mellitus (%)	30 (73 %)	38 (33 %)	**<0.001**
Coronary Artery Disease(%)	20 (50 %)	71 (46 %)	0.266
COPD (%)	17 (42 %)	25 (21 %)	**0.021**
Heart rate	80 ± 16	81 ± 17	0.931
Atrial Fibrillation (%)	15 (37 %)	30 (26 %)	0.256
Labaratory parameters			
Glucose (mg/dl)	134 (56-384)	109 (76-385)	**0.016**
BUN (mg/dl)	43 (16-99)	37 (10-250)	0.151
Creatinine (mg/dl)	1.3 (0.5-4.0)	1.2 (0.6-4.8)	0.089
Sodium (mmol/L)	136 ± 5	138 ± 5	0.084
Hemoglobin(g/dl)	12.7 ± 1.9	12.4 ± 1.8	0.322
Echocardiographic parameters			
LA diameter (mm)	48 ± 7	45 ± 6	**0.009**
LV diastolic diameter (mm)	59 ± 8	58 ± 7	0.550
Ejection Fraction (%)	30 ± 8	31 ± 8	0.312
sPAP (mmHg)	55 ± 14	44 ± 13	**<0.001**

Values are means ± standard deviation, number of patients with percentage in brackets, or medians with range in brackets. SD: stasis dermatitis, NYHA: New York heart association, COPD: chronic obstructive pulmonary disease, BUN: blood urea nitrogen, LA: left atrium, LV: left ventricle, sPAP: systolic pulmonary artery pressure.

Table 2: Medications and clinical outcomes of the patients stasis regarding dermatitis diagnosis within six months preceding admission to heart failure outpatient clinic.

	Group 1 SD (+) (n =41)	Group SD (-) (n =117)	p
HF-related medications (n=148)			
Usage of ACEI/ARB (%)	26 (72%)	81 (72%)	1.000
Usage of MRA (%)	21 (58%)	55(49%)	0.440
Usage of Beta Blocker (%)	27 (75%)	97 (87%)	0.166
Usage of Digoxin (%)	10 (28%)	29 (26%)	0.995
Usage of Diuretics (%)	30 (83%)	97 (87%)	0.830
Clinical outcomes			
HF-related hospitalization (%)	29 (71%)	29 (25%)	**<0.001**
Cardiovascular death (%)	7 (17%)	22 (19%)	0.991

SD: stasis dermatitis, HF: heart failure, ACEI: angiotensinogen converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist.

ysis, patients diagnosed with SD were more likely to have HF-related hospitalization (hazard ratio (HR) =2.827, 95 % Confidence Interval (CI): 1.689-4.731, p <0.001). Furthermore, advanced age, CAD, HT, high blood urea nitrogen (BUN), and glucose levels were recorded in patients with HF-related hospitalization. A Multivariate Cox proportional-hazards model with a stepwise forward method was performed by including variables found to be statistically significant at p <0.250 level in the univariate analysis and the variables found to be significantly different between those diagnosed with and without SD. The presence of SD diagnosis (HR =2.933, 95 % CI: 1.660-5.181, p <0.001) and CAD (HR =2.492, 95 % CI: 1.238-5.018, p =0.011) remained independently associated with the risk of HF-related hospitalization (Table 4).

Discussion

This is the first study to detect that SD is independently associated with DM, COPD, and high SPAP levels in ambulatory HF patients. Furthermore, we demonstrated that SD diagnosis is independently associated with the increased risk of HF-related hospitalization in HF outpatients.

The increase in venous pressure, mainly responsible for developing skin lesions, has primarily been associated with the failure of venous valves[2]. However, it is known that the factor primarily responsible for venous congestion, and therefore an increase in venous pressure in the lower extremities in patients with HF, is the increased intracardiac filling pressures, not a primary failure of the venous valves[7]. A long-term high level of peripheral venous pressure, seen as a reflection of increased intracardiac filling pressures, may be responsible for the developing SD lesions that we often encounter in daily practice in patients with HF.

When we searched the literature, we were still look-

Table 3: Multivariate logistic regression analysis for predicting stasis dermatitis including age, gender, Body mass index, and also variables found to be significantly different between groups in Table 1 (Diabetes Mellitus, chronic obstructive pulmonary disease, glucose levels, left atrium diameter, systolic pulmonary artery pressure).

Variables	p	OR	(95 % CI)
Diabetes Mellitus	<0.001	5.473	2.225-13.462
COPD	0.039	2.623	1.049-6.561
sPAP	0.001	1.061	1.025-1.098

SD: stasis dermatitis, CI: Confidence interval; OR: Odds ratio, COPD: chronic obstructive pulmonary disease, sPAP: systolic pulmonary artery pressure.

Table 4: Univariate and multivariate cox regression analysis for predicting heart failure-related hospitalization. All the variables from Table 1 were examined, and only those significant at p <0.250 level and also variables found to be significantly different between groups in Table 1, are shown in univariate analysis. Multivariate cox regression included all the variables in univariate analysis with the stepwise forward method.

	Univariate			Multivariate		
Variables	**p**	**HR**	**(95 % CI)**	**p**	**HR**	**(95 % CI)**
Presence of SD diagnosis	**<0.001**	2.827	1.689-4.731	**<0.001**	2.933	1.660-5.181
Coronary artery disease	**0.045**	1.712	1.012-2.895	**0.011**	2.492	1.238-5.018
Hypertension	**0.034**	1.753	1.042-2.946			
Diabetes Mellitus	0.157	1.471	0.862-2.510			
COPD	0.914	1.033	0.573-1.862			
Age	**0.036**	1.032	1.002-1.063			
NYHA Classes III-IV	0.083	1.639	0.938-2.864			
Glucose levels	**0.016**	1.004	1.001-1.007			
BUN levels	**0.005**	1.008	1.002-1.014			
Creatinine levels	0.202	1.260	0.883-1.799			
LA diameter	0.343	1.022	0.977-1.068			
sPAP	0.129	1.015	0.996-1.035			
LV diastolic diameter	0.193	1.024	0.988-1.061			

SD: stasis dermatitis, HF: heart failure, CI: confidence interval; HR: hazard ratio, COPD: chronic obstructive pulmonary disease, NYHA: New York heart association, BUN: blood urea nitrogen, sPAP: systolic pulmonary artery pressure, LA: left atrium, LV: left ventricle abbreviations in Table 1.

ing for a study that examined the development of SD in patients with HF. However, our study found that 26 % of HF outpatients had been diagnosed with SD within the preceding six months. A higher COPD rate in patients diagnosed with SD was consistent with our results on echocardiographic outcomes of the right heart in this group of patients. It is known that SPAP values increase in COPD patients due to the increase in right ventricular afterload. This increase in right ventricular afterload may lead to worse ventricular function and increased venous pressure[8]. In the group of patients with SD from all HF patients in our study, the ratio of patients with COPD and the mean SPAP, which indicates that the right ventricle is more affected due to COPD, were higher than in patients without SD. In addition, the average left atrium (LA) diameter, a parameter that can be considered an indicator of the long-term course of left ventricular (LV) diastolic functions and filling pressures, was found to be significantly higher in the patient group with SD[9]. It is known that SPAP and LA diameters can be considered echocardiographic reflections of cardiac filling pressures[10,11]. COPD, which we found to be associated with the diagnosis of SD independently of other variables, and SPAP values, which were found to be higher at the time of echocardiography, can be considered an indicator of long-term high ventricular filling pressures, leading to high central and peripheral venous pressure. Given the process of developing SD lesions, it is evident that extravasation is caused by long-term high venous pressures rather than instant or short-term increases in venous pressure. In our study, patients who had lately attended the outpatient clinic and did not have decompensated HF or SD at the time of admission were considered. We considered those diagnosed with SD in the preceding six months before their outpatient attendance might represent patients whose venous pressures were high for a long time due to increased cardiac filling pressures. As a result of our study, we came across echocardiographic findings that may be compatible with this idea in patients diagnosed with SD. Hence, patients with COPD and high SPAP values, which we found to be independently associated with SD, may represent a group with a poorer prognosis and chronically high central and peripheral venous pressure.

It is known that cardiac filling pressures keep fluctuating in patients with HF, and such high pressures are associated with a poor prognosis[12-15]. However, since precise measurements of these pressures can be invasive, they cannot be used in daily practice for follow-up and treatment. In the literature, studies exist regarding the contribution of following up intracardiac pressures with implanted devices in treatment and prognosis[16,17]. In the

current study, we speculated that SD might be a clinical reflection of high cardiac filling and venous pressures, which continue for a long time. Echocardiographic outcomes such as higher LA diameter averages, higher SPAP averages in the group of patients with SD, and the presence of SD diagnosis found to be independently associated with HF-related hospitalization, an essential indicator for HF prognosis, do support our speculation. If our study is supported by more extensive studies, including invasive hemodynamic data, such as cardiac filling pressures, it may allow the diagnosis of SD to be used as a cutaneous finding of HF and as a contributor to follow-up prognosis and treatment regulation. Although no studies evaluating the relationship of SD with HF exist in the literature, when other studies on SD are reviewed, obesity, female gender, and advanced age are identified as risk factors for SD development[2]. However, our study found no significant difference in gender, age, and BMI averages in HF patients diagnosed with and without SD.

Consistent with the study of Ozlu et al[18], which evaluated skin diseases in diabetic patients, the incidence rate of DM was higher in our patients with SD than in those without SD. In addition, DM was found to be associated with SD independent of factors such as age, gender, BMI, and other variables in the multivariate analysis of our study. Although no other studies have evaluated the direct DM-SD relationship, it is known that DM affects the skin through various mechanisms. In addition to direct skin damage caused by hyperglycemia, the advanced glycation end products (AGEs) induced by hyperglycemia have been associated with various skin lesions in diabetic patients[19-21]. Consistent with this information, the average blood sugar levels were higher in the group of patients with SD in our study. In addition, since a small recent study has shown that venous compliance decreases and transvenous protein escape increases in diabetic patients, the significantly higher rate of diabetic patients in the group of SD patients in our study may be an interesting new research topic[22].

There are some limitations regarding our study. Patient's medical information was obtained at the time of admission to the outpatient HF clinic, their medical history for the diagnosis of venous insufficiency and SD was obtained from hospital records, and deficiencies (information on the clinical stage and treatment of SD) in hospital records may have affected our study results. However, LA diameter, SPAP dimension, and echocardiographic reflection requiring invasive measurement can be considered a limitation. Another limitation is that the six-minute walk test was not performed on the patients. The functional capacity of the patients was determined according to the NYHA classification. In addition, our study did not include patients with severely impaired functional capacity (patients who cannot even do daily tasks such as going to the toilet) and acute decompensation findings.

In conclusion, for the first time in the literature, the association of SD with clinical and echocardiographic findings in HF patients was evaluated, and SD was found to be independently associated with DM, COPD, and increased SPAP values. It was also identified as an independent predictor for HF-related hospitalization. Further research evaluating the relationship of SD with invasively measured intracardiac pressure values in HF patients will allow us to obtain valuable results. If supported by large-scale multicenter studies, SD can be used as a cutaneous indicator of poor prognosis in HF patients.

Conflict of interest

The authors declare no conflicts of interest.

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