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Systemic mastocytosis associates with cardiovascular events despite lower plasma lipid levels

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ABSTRACT

Background and aims: Mast cells have been implicated in the development and progression of atherosclerosis in animal models and human autopsy studies. However, it is unknown whether long-term exposure to excess of mast cells is associated with cardiovascular disease (CVD) in humans. Our objective was to compare the prevalence of CVD and cardiovascular risk factors in patients with systemic mastocytosis (SM) and controls.

Methods: In 50 patients with SM and 50 age and sex matched controls, the history of CVD and presence of cardiovascular risk factors were assessed. Carotid ultrasound was performed to assess carotid intima-media thickness (C-IMT) and plaques presence.

Results: CVD events were more prevalent in SM patients compared to controls (20% *vs.* 6%, $p = 0.04$). The prevalence of C-IMT and carotid plaques was similar between patients with SM and controls. In multivariate analysis, CVD events were significantly associated with SM (OR 7.0 (95% CI 1.3–37.6), $p = 0.02$) and hypertension (OR 9.5 (95% CI 1.9–48.7), $p = 0.01$). The prevalence of diabetes, hypertension, obesity and smoking was similar between the two groups. Total cholesterol and LDL-C levels were significantly lower in SM patients than in the control group. (5.1 ± 1.1 *vs.* 5.9 ± 0.9 mmol/l, $p < 0.05$ and 2.9 ± 0.8 *vs.* 3.5 ± 0.7 mmol/l, $p < 0.05$, respectively).

Conclusions: Despite lower plasma total cholesterol and LDL-C, the prevalence of CVD is higher in patients with SM compared to healthy controls. Beyond the setting of SM, this study can be considered as a proof of concept study, indicating the contribution of mast cells to CVD in humans.

1. Introduction

Acute cardiovascular syndromes such as myocardial infarction and stroke are a major cause of morbidity and mortality worldwide, caused by the development of atherosclerosis in the arterial wall [1]. Inflammation, matrix degradation and lipid accumulation are generally considered key processes in atherosclerosis and the pathogenesis of atherosclerotic plaque rupture [2]. The mast cell, a prominent inflammatory cell type and a major effector cell in allergy and asthma, has also been associated with cardiovascular disease (CVD) [3]. In human pathology studies, it was established that mast cells accumulate both in the rupture-prone shoulder region of coronary atheromas [4,5] and in the perivascular tissue during atherosclerotic lesion progression [6–8]. Particularly, in advanced stages of atherosclerosis, the number of mast cells is high [5]. In experimental mouse models, activation of perivascular mast cells on the one hand promoted atherosclerotic plaque destabilization [9], while on the other hand, mast cell deficiency limited atherogenesis [10]. Together, these data suggest that mast cells, containing a large number of proteases and pro-inflammatory mediators, are causally linked to plaque destabilization and even rupture, underlining the importance of mast cells in CVD.

Systemic mastocytosis (SM) is a disease characterized by an accumulation of mast cells in one or more organs. Manifestations of the disease are largely provoked by the resultant increase in mast cell-derived mediators, which have a variety of local and systemic

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effects such as flushing and anaphylaxis. Diagnosis is based on a combination of major and minor criteria according to the World Health Organization's (WHO). If at least one major and one minor or at least three minor SM criteria are fulfilled, the diagnosis of SM is made [11]. SM is further divided into four distinct disorders: indolent systemic mastocytosis (ISM), SM with an associated hematologic neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). The most common form is indolent SM of which the smouldering SM is a subtype defined by the presence of organ involvement without organ dysfunction [12].

In view of the aforementioned effects of mast cell activation on atherogenesis and atherosclerotic plaque destabilization, we hypothesize that patients with SM have more advanced atherosclerosis and/or more adverse cardiovascular risk factors compared to subjects without SM. In this study, we thus aimed to compare the prevalence of CVD and cardiovascular risk factors in patients with SM and age- and sex-matched controls.

2. Patients and methods

2.1. Study population

The Immunology department of the Erasmus Medical Center treats a large cohort of patients with SM as expertise center on mastocytosis, as recently described by Hermans et al. [12] Subjects were enrolled between April 2014 and July 2015. SM patients were invited to participate in the study. Subjects for the control group were collected by asking the SM patients to bring another person not diagnosed with SM, preferably of the same age and sex. If a patient was not able to bring a subject for the control group, the investigators provided a subject through advertisement in the hospital. Inclusion criterion for all subjects was age older than 18 years. An additional inclusion criterion, solely for the SM patients, was having met the WHO criteria for the diagnosis of SM. The study complied with the Declaration of Helsinki and written informed consent for the use of clinical data and for blood storage was obtained from all subjects. The study was approved by the Medical Ethics Committee of the Erasmus MC (MEC-2013-556).

2.2. Data collection

We acquired clinical data by using a standard questionnaire, comprising medical history, including history of cardiovascular events and cardiovascular risk factors. Moreover, information on medication use was obtained. Blood pressure, length and weight were measured in all subjects. Smoking was defined as both previous and current smoking.

Overnight fasting blood samples were collected for measurement of fasting glucose and lipid profile total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apolipoprotein-AI (ApoA-I), apolipoprotein-B (ApoB), lipoprotein(a) (Lp(a)), which were determined using the standard laboratory techniques. Untreated LDL-C levels before statin use were retrieved. If this information was not available, untreated LDL-C was calculated using the conversion factor for statin and dosage being used [13,14].

Carotid intima-media thickness (C-IMT) and the presence of carotid plaques were assessed using the Panasonic Cardio Health Station as described by Bos et al. [15] Plaques were scored as present or absent. In this study, C-IMT indicates the mean of the left and right mean C-IMT.

Cardiovascular disease (CVD) events were defined as coronary heart disease (CHD) classified by myocardial infarction, resuscitated cardiac arrest and angina pectoris followed or not by coronary revascularization, cerebrovascular events and/or the presence of peripheral arterial vascular disease.

Cerebrovascular events were defined by history of stroke and transient ischemic attacks. Peripheral vascular disease was defined by symptoms of claudication diagnosed by a vascular surgeon and/or revascularization of the peripheral vasculature.

2.3. Statistical analysis

Statistical analysis was conducted using SPSS, version 21. Results are presented as mean ± standard deviation (S.D.). Categorical variables were compared using Pearson's Chi-square. Continuous variables were compared using Student's *t*-test when normally distributed; the Mann-Whitney *U* test was used when variables were not normally distributed. Logistic regression analysis was used to evaluate the association between CVD and the known cardiovascular risk indicators such as age, sex, body mass index, smoking, hypertension, untreated LDL-C levels and diabetes mellitus. Linear regression analysis was applied to evaluate the association between C-IMT and the aforementioned potentially confounding cardiovascular risk factors. The association between SM and C-IMT was evaluated by use of a linear regression model, the association between SM and CVD events and plaques by use of a logistic regression model. Results were considered statistically significant if the corresponding *p*-value was <0.05.

3. Results

The demographic and clinical data are shown in Table 1. We enrolled 50 patients with SM and 50 controls. The mean age was similar in the two groups (60 ± 11 years in the SM group and 59 ± 10 years in the control group, $p = 0.86$). Sex was equally distributed in both groups. The other baseline characteristics were also similar in the two groups.

Within the group of patients with SM, most patients had indolent SM, 1 had smouldering SM and 2 had SM with an associated hematologic neoplasm, i.e. chronic myelomonocytic leukemia (CMMoL) and acute myeloid leukemia (AML).

3.1. Cardiovascular disease

Carotid ultrasound showed that the prevalence of carotid artery plaques and C-IMT was similar between patients with SM compared to controls (54% *vs.* 38%, $p = 0.11$ and 0.65 ± 0.11 mm *vs.* 0.64 ± 0.13 mm, $p = 0.65$ respectively). In 77% of all cases with CVD events, plaques were present. Despite the lack of differences in C-IMT, CVD events were more prevalent in patients with SM compared to controls (20% *vs.* 6%, $p = 0.04$). The CVD events consisted mainly of CHD (10% in SM patients and 4% in controls) and cerebrovascular events (10% and 2% respectively). Two subjects in the SM group had had 2 types of CVD events (Table 1).

In multivariable regression analyses, CVD events were significantly associated with SM ($p = 0.02$) and hypertension ($p = 0.01$) (Table 2).

There were no significant associations between SM and plaque presence ($p = 0.22$) and C-IMT ($p = 0.57$). In addition, no other variable except age was associated with C-IMT ($p < 0.001$) (Table 3).

The mean tryptase concentration was somewhat higher in the group of SM patients with CVD events in comparison to SM patients without CVD (79.4 ± 83.5 μg/L *vs.* 54.2 ± 59 μg/L respectively, $p = 0.273$).

3.2. Cardiovascular risk factors

The prevalence of diabetes, hypertension, obesity and smoking did not differ between patients with SM and controls.

Table 1
Baseline characteristics.

Characteristics	SM (n = 50)	Controls (n = 50)	*p*-value
Age, mean ± SD (y)	60 ± 11	59 ± 10	0.86
Male (n, %)	25 (50)	25 (50)	1.00
BMI, mean ± SD (kg/m^2)	27 ± 4	27 ± 5	0.90
Waist, mean ± SD (cm)	97 ± 11	96 ± 14	0.70
Systolic blood pressure, mean ± SD (mmHg)	146 ± 20	146 ± 21	0.93
Diastolic blood pressure, mean ± SD (mmHg)	86 ± 10	89 ± 12	0.15
Diabetes (n, %)[a]	5 (10)	1 (2)	0.09
Fasting blood glucose, mean ± SD (mmol/L)	5.6 ± 1.3	5.4 ± 0.7	0.44
Hypertension (n, %)[b]	17 (34)	14 (28)	0.52
Hypercholesterolaemia (n, %)[c]	12 (24)	9 (18)	0.46
Statin medication (n, %)	10 (20)	7 (14)	0.42
Smoking (n, %)[d]	27 (54)	27 (54)	1.00
Plaques (n, %)	27 (54)	19 (38)	0.11
IMT, mean ± SD (mm)	0.65 ± 0.11	0.64 ± 0.13	0.65
Cardiovascular disease events (n, %)[e]	**10 (20)**	**3 (6)**	**0.04**
Cerebrovascular events (n, %)	5 (10)	1 (2)	0.09
Peripheral arterial disease (n, %)	2 (4)	0 (0)	0.15
Coronary heart disease (CHD) events (n, %)[f]	5 (10)	2 (4)	0.24

[a] Diabetes is defined by the use of anti-diabetic medication.
[b] Hypertension is defined by the use of anti-hypertensive medication.
[c] Hypercholesterolaemia is defined by the use of statins and/or reported presence of hypercholesterolaemia.
[d] Smoking includes both previous and current smoking.
[e] Cardiovascular disease includes cerebrovascular and coronary heart disease events and peripheral arterial disease. All patients used aspirin 80–100 mg per day.
[f] Coronary heart disease events include myocardial infarction and coronary interventions.

Table 2
Multivariable regression analyses with CVD as dependent variable.

Variable	OR (95% CI)	*p*-value
Age	1.0 (0.9–1.1)	0.73
Male	1.6 (0.4–7.1)	0.54
BMI	1.0 (0.8–1.3)	0.90
Hypertension	9.5 (1.9–48.7)	0.01
Smoking	1.3 (0.3–5.7)	0.72
Diabetes	0.22 (0.2–3.4)	0.28
LDL-cholesterol without statin[a]	1.6 (0.7–3.7)	0.28
Systemic mastocytosis	7.0 (1.3–37.6)	0.02

[a] LDL-cholesterol without statin are based on untreated LDL-C levels or calculated with the conversion factor for the statin being used.

Table 3
Multivariable regression analyses with plaques and C-IMT as dependent variables.[a]

Variable	Plaques		C-IMT	
	OR (95% CI)	*p*-value	Beta (β)	*p*-value
Age	1.0 (1.0–1.1)	0.09	0.61	<0.001
Male	1.0 (0.4–2.6)	0.97	-0.08	0.39
BMI	1.0 (0.9–1.1)	0.49	0.11	0.19
Hypertension	2.6 (0.9–7.5)	0.08	-0.03	0.75
Smoking	1.1 (0.4–2.7)	0.89	0.06	0.45
Diabetes	0.0 (0.0 -.)	0.99	-0.08	0.38
LDL-cholesterol without statin	1.1 (0.7–1.1)	0.77	-0.02	0.78
Systemic mastocytosis	1.8 (0.7–4.7)	0.22	0.05	0.57

[a] In the multivariable linear regression analyses of C-IMT the adjusted $R^2 = 0.333$.

Levels of total cholesterol and LDL-C were significantly lower in the SM patients than in the control group (5.1 ± 1.1 *vs.* 5.9 ± 0.9 mmol/L, $p < 0.001$ and 2.9 ± 0.8 *vs.* 3.5 ± 0.7 mmol/L, $p < 0.001$, respectively, Fig. 1A). SM patients used statins more frequently, yet untreated LDL-C levels were significantly lower in the SM patient group compared to controls (3.2 ± 0.8 *vs.* 3.7 ± 0.8 mmol/L, $p = 0.01$). Levels of ApoA-I and ApoB were significantly lower in the SM patients compared to the control group (1.6 ± 0.4 *vs.* 1.9 ± 0.3 mmol/L, $p < 0.001$, and 0.9 ± 0.2 *vs.* 1.1 ± 0.2 g/L, $p = 0.02$ respectively, Fig. 1B). Concentrations of HDL-C, TG and Lp(a) were similar in the two groups (Fig. 1A and B).

The mean tryptase concentration was not associated with LDL-C levels in patients with SM ($p = 0.08$).

4. Discussion

In the present study, we showed that patients with SM compared to healthy age- and sex-matched controls had a higher prevalence of cardiovascular events despite lower plasma lipid levels.

Acute cardiovascular events usually arise from rupture of an atherosclerotic plaque, and mast cells have been shown to accumulate in the rupture prone shoulder regions of the plaques [5]. In experimental animal models, the activation of perivascular mast cells promote plaque destabilization [9], and it was shown in human carotid endarterectomy specimen that intraplaque mast cell numbers positively correlated with disease progression and destabilization [16]. The mast cell was actually the only inflammatory cell type predictive for the incidence of future cardiovascular events. Kupreishvili et al. recently showed, in a human pathology study, the presence of mast cells in the intima and media of both stable and unstable atherosclerotic coronary lesions after myocardial infarction. Mast cells were significantly increased in the media of unstable plaques in patients who experienced a myocardial infarction 5–14 days earlier [17]. These findings suggest that mast cells present in coronary lesions may contribute to the onset of myocardial infarction through plaque destabilization.

Our study showed that the incidence of CVD events is higher in patients with SM, and thus with increased mast cell numbers, compared to that in a matched control group, hence also suggesting that mast cells contribute to atherosclerotic plaque destabilization.

In line with the findings from our study, Broesby-Olsen et al. showed that within a nationwide population-based cohort, SM patients had an increased risk of stroke, as well as a non-significant increase in risk of myocardial infarction, with hazard ratios between 1 and 2 [18].

To our knowledge, we are the first to observe reduced plasma total cholesterol, LDL-C, ApoA-I and ApoB levels in patients with SM compared to controls. Mast cells have previously been reported to inhibit the functionality of HDL-C in reverse cholesterol transport

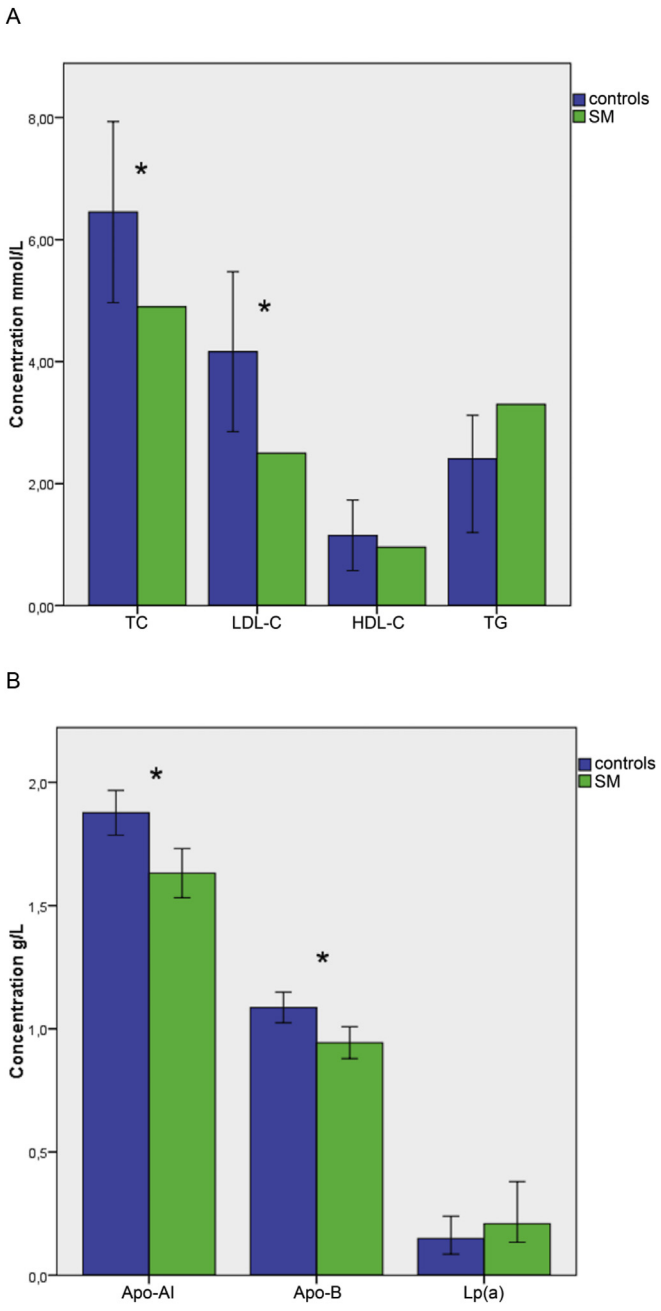

Fig. 1. Lipid profiles in patients with systemic mastocytosis and controls.
(A) TC, total cholesterol; TG, triglycerides, LDL-C; low-density lipoprotein-cholesterol without statin; HDL-C = high-density lipoprotein. (B) ApoA-I, apolipoprotein-AI; ApoB, apolipoprotein-B; Lp(a), lipoprotein(a). Results are presented as mean ± SD, except for TG and Lp(a), which are presented as median (IQR). Error bars represent 95% CI. $p < 0.05$ is considered statistically significant and is represented by an asterisk (*).

due to the release of the proteases chymase and tryptase [19]. Recently, it was established that chymase cleaves ApoA-I resulting in loss of its anti-inflammatory functions [20]. Moreover, cathepsin G, another protease released from mast cells, has been reported to degrade LDL, reducing LDL-C and ApoB levels [21]. Excessive mast cell protease activity in SM patients may be, at least in part, responsible for the altered apolipoprotein profile observed. Despite the "beneficial" lipid levels, which would suggest limited atherosclerotic lesion development in carotids of SM patients, lesion incidence was not different between the groups. The incidence of cardiovascular events was even higher in the SM group, suggesting that plaque stability was reduced in SM patients. We have previously established that chymase is one of the key players in mast cell-induced plaque destabilization [22], and tryptase has also been associated with plaque instability. Our findings support this hypothesis and suggest that mast cells contribute significantly to plaque destabilization.

Although the number of patients and cardiovascular events may seem small, the strength of our study is the complete cardiovascular phenotyping in a substantial population of patients with SM, considering the rareness of disease. This study can, thus, be regarded as an important pilot, which justifies the initiation of further research, preferably a prospective long-term follow-up study of a large cohort of SM patients and matched controls to further investigate the risk of cardiovascular disease in these patients.

4.1. Conclusions

We found a significantly higher prevalence of CVD events and lower plasma lipid levels in patients with SM compared to a control group. To our knowledge, this is the first study to investigate the prevalence of cardiovascular disease in relation with cardiovascular risk factors among patients with SM, supporting the evidence that mast cells contribute to atherosclerosis and CVD events in patients with SM and implying the pathogenicity of mast cells via plaque destabilization. In clinical context, cardiovascular screening in patients with SM seems warranted. Furthermore, we believe that these results reach beyond the setting of SM and can be considered as a proof of concept study, which unifies and strengthens insights learned from experimental atherosclerosis studies, reinforcing the concept of the contribution of mast cells to cardiovascular diseases in humans.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Roeters van Lennep and Indhirajanti had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Roeters van Lennep, Indhirajanti, Van Daele and Bot designed and performed research, analyzed data and wrote the article; Bos and Mulder contributed in the acquisition of data.

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