DOI: 10.7860/NJLM/2021/46316:2473

Original Article

Pathology Section

A Histopathological Study of Mast Cells in Atheromatous Lesions on Autopsy Specimens

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ABSTRACT

Introduction: Atherosclerosis is emerging as one of the leading causes of death globally. Role of mast cells in the development and progression of atherosclerosis has been proposed recently. Literature review has shown that few studies have demonstrated significant number of mast cells in atherosclerotic plaques and more at the site of plaque rupture. Whereas, few studies have not found any significant increase in number of mast cells in atherosclerotic plaques. The present study was undertaken to know whether mast cells are significantly increased in atherosclerotic lesions.

Aim: The aim of the study was to know the correlation between mast cells and various grades of atherosclerosis.

Materials and Methods: A cross-sectional histopathological study was conducted on 60 autopsy heart specimens (perinatal and paediatric heart specimens were excluded) from October 2010 to October 2012 in Department of Pathology, Bangalore Medical College and Research Institute. Sections were taken from the Right Coronary Artery (RCA) and Left Coronary Artery (LCA) and its branches, aorta and pulmonary artery and were examined under the microscope for atheromatous lesions. American Heart Association (AHA) grading of atherosclerosis was used to grade atherosclerosis. Special stains for mast cells, 2% aqueous toluidine blue stain was employed on the sections to demonstrate and quantify mast cells (per mm^2) in the arterial intima. The corresponding grade and number of mast cells were correlated.

Results: Of the total 360 arteries (includes all 6 arteries in each of the 60 cases) studied, 206 arteries showed atherosclerotic change. The most common artery involved was left anterior descending artery (in 57 cases i.e., 95%) followed by the left main coronary artery (in 48 cases i.e., 80%). Involvement of triple vessels (20 cases i.e., 33.3%) was most common, followed by four vessel involvement (18 cases i.e., 30%). Grade II (52 arteries i.e., 25.2%) atherosclerosis was most common, followed by grade IV (41 arteries i.e., 19.90%). Kruskal Wallis test showed significant difference in the median mast cells in various grades of atherosclerosis (p-value <0.05). Spearman's correlation co-efficient showed positive correlation between various grades and number of mast cells in most of the arteries (except Left Circumflex Artery (LCxA) showed negative correlation and no statistical data could be derived for pulmonary artery as only 3/60 arteries showed atherosclerosis).

Conclusion: The present study has demonstrated that mast cells are found in good number in atherosclerotic lesions of coronary arteries and also with the progression of atherosclerosis, the number of mast cells increased except in the LCxA. Identifying the cellular participants and molecular mediators of inflammation during atherogenesis may prove to be of immense help in the treatment of coronary heart diseases.

Keywords: Coronary artery disease, Heart, Myocardial infarction

INTRODUCTION

Atherosclerosis is emerging as one of the major causes of death worldwide. There has been a surge in the prevalence of atherosclerosis in urban and rural India in the past few decades as quoted by the epidemiologists [1]. The most accepted pathogenesis of atherogenesis is the response-to-injury hypothesis which states that atherosclerosis is a chronic inflammatory and healing response of the arterial wall to endothelial injury [2]. Researchers over the past few decades have implicated various etiological factors of atherosclerosis. The role of mast cells in the pathogenesis of atherosclerosis has been proposed recently [3-5]. Mast cells are well known for their participation in allergic inflammatory reactions. They contain numerous secretory granules in the cytoplasm which contain heparin, histamine and many proteases such as tryptase [6]. There are two schools of thought regarding the association of mast cell with atherosclerosis. Mast cells contribute to the development of atherosclerosis by virtue of producing various inflammatory mediators like histamine, prostaglandins, cytokines, chemokines, tryptase and chymase, all of which affect cellular proliferation, produce vascular inflammation and endothelial dysfunction leading to macrophage-foam cell formation, which is seen in the early lesions of atherosclerosis [3]. The other school of thought says there is no prolonged or transient activation of mast cells in acute coronary syndromes [7].

The results of various studies on the association of mast cells with atherosclerosis have been variable. To the best of the knowledge, the data on role of mast cells in atherosclerosis in Indian population is very meagre. Hence, the present study was undertaken to throw more light on role of mast cells in atherosclerosis so that it can open up a new platform in the management of atherosclerosis by targeting these mast cells and its mediators.

Hence, the objectives of the present study were

1) To study the distribution of mast cells in different grades of atherosclerotic lesions {as per the American Heart Association (AHA) grading of atherosclerosis}
2) To study the distribution of mast cells in atheromatous lesions of various blood vessels (coronary arteries and its branches, aorta, pulmonary artery)
3) To study the correlation between mast cells and various grades of atheromatous lesions.

MATERIALS AND METHODS

A cross-sectional study was done on heart specimens obtained from autopsies performed at the Department of Forensic Medicine, Victoria

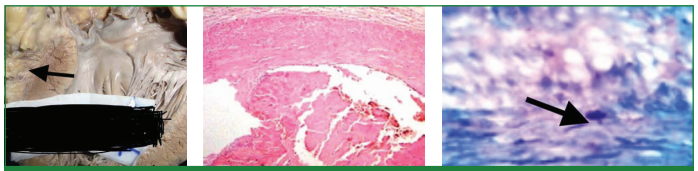
and Bowring Hospital, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India from October 2010 to October 2012. Institutional Ethics Committee approval was obtained before the commencement of the study (BMC/PGs/185/2011-12). Sixty heart specimens received during the study period were included in the study by applying inclusion and exclusion criteria.

Inclusion criteria: Only those heart specimens that were proved to be atheromatous by histopathological examination were included.

Exclusion criteria: Autolysed specimens, heart specimens that did not show atheromatous lesions on histopathological examination and perinatal and paediatric heart specimens were excluded from the study.

The postmortem examination was done after obtaining consent from next of kin in case of medical autopsy and requisition from the Police/ Department of Forensic Medicine in medico-legal autopsies and the cause of death was ascertained. The hearts were weighed and fixed in 10% buffered formalin solution. Measurements of the right ventricular wall, left ventricular wall, inter-ventricular septa and stump of aorta were taken. Circumference of mitral, tricuspid, pulmonary and aortic valve was noted. Coronary arteries were dissected along the flow of blood. LCA and its branches Left Anterior Descending artery (LAD) and LCxA and RCA were dissected longitudinally and then sectioned by multiple closely spaced cuts with a scalpel to examine for any atherosclerotic plaques, thrombus, narrowing of the lumen and calcification. Tissue bits were taken from LCA, LAD, LCxA, and RCA from gross atherosclerotic lesions as well as suspicious lesions for the microscopic assessment of atherosclerosis. [Table/Fig-1] shows the narrowing of LAD artery by atheromatous plaque.

Sections for aorta and pulmonary artery were given from plaques. After processing, the sections were stained with haematoxylin and eosin stain and examined microscopically for atheromatous lesions. [Table/Fig-2] demonstrates disruption of fibrous cap with accompanying surface thrombus (Type VIc of AHA). Special stains for mast cells-2% aqueous Toluidine blue stain was employed on the sections to demonstrate and quantify mast cells at the site of the atheromatous lesion [Table/Fig-3]. Microscopic grading of atherosclerosis was done using the modified AHA classification of atherosclerosis [Table/Fig-4] [8].



[Table/Fig-1]: Narrowing of LAD artery (arrow) by atheromatous plaque.
[Table/Fig-2]: Atheromatous plaque with superimposed thrombus-grade VI atherosclerosis (H&E,10X).
[Table/Fig-3]: Degranulated mast cell in tunica intima (Toluidine blue, 40X). (Images from left to right)

Various arteries (RCA, LCA (main), LAD, LCxA, Aorta and Pulmonary) in each case were analysed for the grade of atherosclerosis and the corresponding Toluidine blue stained slides were examined to count the number of mast cells in the intima of the artery/mm^2. Normally, in arterial intima only few mast cells are present (on average 1 mast cell/mm^2) while a five-fold higher value (on average 5 mast cells/ mm^2) has been reported in fatty streaks [5]. The arterial wall from the endothelial surface to the luminal margin of the media was considered as the intima of artery while counting the mast cells. In advanced atherosclerotic lesion, where the internal elastic lamina was unclear or absent, mast cells located on the luminal side of atheromatous plaques were counted.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) 22.0 version was used for the analysis of the data. As the data was not normally distributed non parametric test Kruskal Wallis test was applied to see the median difference in mast cells in various grades of atherosclerosis in each of the six arteries. Spearman's correlation co-efficient had been calculated to analyse the correlation between grades and number of mast cells. The p-value <0.05 was considered to be statisticaly significant.

Types	Description
Type I	Intimal thickening with focal accumulation of monocyte/macrophage/ T-lymphocyte aggregates
Type II	Intimal foam cell macrophage aggregates in linear streaks commonly noted as fatty streak.
Type III	Pre-Atheroma: Intimal focal or diffuse extra-cellular lipid deposition and intimal smooth muscle cell proliferation with occasional lipid deposition
Type IV	Atheroma: The initial accumulation of confluent lipid core formation with accompanied smooth muscle cell proliferation and with distinct fibrocollagenous cap formation.
Type Va	Fibroatheroma: Formation of a fibro-atheromatous lesion which is a high-risk category featuring distinct lipid gruel separated by either thin or thick fibro-collagenous cap
Type Vb	Calcific: The dystrophic calcific specks/dense calcific deposits in the lipid core with collagenised intimal matrix
Type Vc	Fibrotic: The intimal lipid core may be partly or completely replaced by the exuberant accumulation of fibro- collagenous stroma with smooth muscle cells
Type VIa	The fibrous cap disruption in places leading to lipid core extrusion with or without superficial thrombus in the early stage
Type VIb	Disruption of fibrous cap, associated with surface haemorrhage along with lipid core extrusion
Type VIc	Disruption of fibrous cap with accompanying thrombus on the surface
Type VIabc	A combinatorial feature, which includes disruption of cap with surface thrombus

[Table/Fig-4]: AHA categorisation of atherosclerosis based on changes in the arterial intima [8].

RESULTS

Majority of cases were in the age group of 21-30 years and 41-50 years (13 cases i.e., 21.7% in each) followed by 31-40 years (12 cases i.e., 20%), 17-20 years (7 cases i.e., 11.7%), 51-60 years and 61-70 years (6 cases i.e., 10.1%) in each and >70 years (3 cases i.e., 5.1%). Males accounted for 90% (n=54 cases) and females 10.0% (n=6 cases). Cause of death was not known in 17 cases (28.3%), sudden death accounted for 15 cases (25.0%) and death due to coronary artery disease accounted for 8 cases (13.3%). Death due to other cardiovascular diseases, road traffic accidents, suicide, electrocution and snake bite accounted for the remaining 20 cases (33.3%). The weight of the heart was normal in 36 cases (60%) and the size of the heart was normal in 42 cases (70%). Of the total 360 arteries (includes all 6 arteries in each of the 60 cases) studied, 206 arteries showed atherosclerotic change and 154 arteries did not show atherosclerotic change. The most common artery involved was LAD artery (57 cases i.e., 95%) followed by others [Table/Fig-5]. Involvement of triple vessels (20 cases i.e., 33.3%) was most common followed by four vessels involvement (18 cases i.e., 30%), double vessel involvement (10 cases i.e., 16.6%), five vessels involvement (7 cases i.e.,11.6%), single vessel involvement (3 cases i.e., 5%) and all six vessel involvement (2 cases i.e., 3.3%). Incidence of grade II atherosclerosis (52 arteries i.e., 25.2%) was most common [Table/Fig-6].

Arteries involved	Number of cases (60)	% of cases
Left coronary artery	48	80
Left anterior descending artery	57	95
Left circumflex artery	38	63.3
Right coronary artery	42	70
Aorta	18	30
Pulmonary artery	3	5

[Table/Fig-5]: Incidence of atherosclerosis in various arteries.

Findings of Kruskal Wallis test to find the median mast cells in various grades of atherosclerosis in each of the arteries is presented in

Grade of atherosclerosis	Number of arteries	% of arteries
I	10	4.8
II	52	25.2
III	28	13.59
IV	41	19.90
V	39	18.93
VI	36	17.47

[Table/Fig-6]: Incidence of various grades of atherosclerosis in the arteries.

[Table/Fig-7]. No statistical data could be derived on pulmonary artery as only 3/60 cases showed atherosclerosis (1 case each in grade I, grade II and grade III). In the remaining arteries, significant difference in the median mast cells in various grades of atherosclerosis was seen (p-value <0.05). Spearman's correlation co-efficient showed positive correlation between grades and number of mast cells in LCA, left anterior descending artery, RCA and aorta. Thus, implicating that with the progression of atherosclerosis the number of mast cells increased.

[9,10]. Certain pathological and functional changes in the arteries can be assessed by measuring circulating markers of biological processes and by using non invasive imaging and functional techniques. These methods are expensive and not feasible for assessing atherosclerosis in the rural and urban population. On the other hand, an autopsy has proved to be a very efficient and economic method for assessing atherosclerosis. The current study was conducted on autopsied heart specimens of cases died due to various causes to know the presence of atherosclerotic lesions of the coronary arteries and assess whether mast cells have any association with atherosclerosis and do they significantly contribute to the progression of atherosclerosis. In the present study, the age range of the cases was from 21 years to more than 70 years. Majority of cases were in the age group of 21-30 years and 41-50 years (13 cases i.e., 21.7% in each).

The age distribution of cases in the present study is similar to that of the study done by Garg M et al., {majority of cases were in the age group of 31-40 years (27.0%) and 21-30 (28 cases i.e., 24.3%)} [11]. The premature incidence of coronary heart disease

		Grades of atherosclerosis																						χ_2 value and p-value
		Grade I				Grade II				Grade III				Grade IV				Grade V				Grade VI				
Art	U	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	
E	12	1	-	-	-	7	2.14± 1.34	2	1.0	7	3.28± 1.38	3	2.7	12	4.25± 0.75	4	0.7	13	4.76± 1.09	5.0	1.0	8	5.25± 1.28	5	2.7	19.64 and 0.001
F	3	1	-	-	-	11	1.90± 0.70	2	1.0	3	3.66± 0.57	4	-	11	4.18± 0.87	4	1.0	14	5.42± 1.39	5.5	1.2	17	5.0± 1.22	5	2	33.623 and <0.001
G	22	4	1.50± 0.57	1.5	1	9	1.55± 0.72	1	1.0	12	3.0± 0.60	3	0.0	7	3.71± 1.11	3	1.0	5	5.00± 1.00	5.0	2.0	1	-	-	-	28.340 and <0.001
H	18	-	-	-	-	10	2.10± 0.73	2	1.2	5	3.60± 1.51	4	3	11	4.27± 0.90	4	1.0	6	4.33± 0.81	4.5	1.2	10	5.20± 1.39	5	2	22.173 and <0.001
I	42	3	-	-	-	14	1.71± 0.46	2	1.0	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	7.617 and 0.022
J	57	1	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

[Table/Fig-7]: Mast cells in various grades of atherosclerosis in each of the arteries.
Art-artery: U-Number of arteries uninvolved by atherosclerosis; E-Left coronary artery; χ^2: Chi square; F-Left anterior descending artery; A-Number of arteries showing atherosclerosis; G-Left circumflex artery; B-Mean±Standard deviation; H-Right coronary artery; C-Median; I-Aorta; D-Interquartile range; J-Pulmonary artery
Test applied: kruskal wallis; In certain grades of atherosclerosis where <3 arteries were involved, the SPSS 22.0 version software did not calculate the mean mast cells, standard deviation, median and interquartile range; p-value <0.05 statisticaly significant; LC-DCP are the grades of atherosclerosis

There was negative correlation between grades and number of mast cells in LCxA. Spearman's correlation co-efficient could not be applied for pulmonary artery [Table/Fig-8].

Artery	r-value	p-value
Left coronary artery	0.626	<0.001
Left anterior descending artery	0.666	<0.001
Left circumflex artery	-0.423	0.001
Right coronary artery	0.696	<0.001
Aorta	0.661	0.003
Pulmonary artery	-	-

[Table/Fig-8]: Spearman's correlation co-efficient-correlation between atherosclerotic grades and mast cells in varoius arteries.
p-value <0.05 statisticaly significant

DISCUSSION

Atherosclerosis of the coronary arteries and myocardial infarction are the most commonly encountered cardiac diseases in autopsies. Atherosclerosis progresses asymptomatically for decades before manifesting clinically as coronary heart diseases and acute coronary syndromes. It begins in early life and progresses in stages from the deposition of foamy macrophages to the formation of fatty streaks, fibrous plaques, calcium deposits and complicated lesions ranging from plaque disruption to haemorrhage and thrombosis in Indians could be probably attributed to thrombotic factors like low fruit/vegetable intake, smoking, etc., and atherosclerotic factors like high-fat diet, hypertension and dyslipidaemia [12]. In both the studies, the current study and study by Garg M et al., males were more frequently affected than females [11]. The difference in the sex ratio could be due to lesser sample size in the present study and also could be due to differences in the geographical distribution. In the current study, death due to unknown cause (17 cases i.e., 28.3%) was most commonly observed, followed by sudden death (15 cases i.e., 25.0%). As compared to the study done by Thej MJ et al., in which road traffic accidents (46%) was the most common cause, followed by suicidal poisoning (37.1%) [13]. Atherosclerosis being a chronic disease with a multifactorial causation phenomenon, the cause of death has a negligible role in explaining the difference in the degree of atherosclerosis [13].

The incidence of atherosclerosis was highest in left anterior descending artery similar to that observed by various other authors [Table/Fig-9] [11,13,14]. Local haemodynamic and anatomic differences of LCA and RCA may be responsible for the left coronary system to be more predisposed to atherosclerosis development [15,16]. Left anterior descending artery has twice the torsion of RCA which may aid in generating helical flow patterns and promote atherosclerosis progression [16-19]. Also, the more frequent branching of the LCA as compared to the RCA renders

Studies	Sample size	Arteries involved					
		LCA	LAD	LCx	RCA	Aorta	Pulmonary artery
Current study	60	48 (80%)	57 (95%)	38 (63.3%)	42 (70%)	18 (30%)	3 (5%)
Garg M et al., [11]	115	-	38%	34%	35%	-	-
Yazdi SAT et al., [14]	80	-	60%	42.5%	50%	-	-
Thej MJ et al., [13] (In this study, the incidence of advanced lesion is quoted)	113	23 (20.35%)	31 (27.4%)		21 (18.5%)	Ascending aorta-23 (20.3%) Thoracic aorta-32 (28.3%) Abdominal aorta-41 (36.2%)	-

[Table/Fig-9]: Comparision of distribution of various arteries involved in current study with other authors [11,13,14].
LCA: Left coronary artery; LAD: Left anterior descending artery; LCx: Left circumflex artery; RCA: Right coronary artery

a disturbed flow in the respective regions, thus creating a more atherogenic environment in the LCA [20].

In the current study, triple vessel involvement was most common (33.33%) followed by the involvement of four vessels (30%). This is in concordance with a study done by Garg M et al., which also showed triple vessel involvement to be most common (44.4%) [11]. The incidence of grade II atherosclerosis was highest in present study (25.2%), followed by grade IV and V as compared to that of study by Garg M et al., which showed grade III to be more common (30.9%), and next in frequency was atheroma (27.3%) [11]. The differences observed in the incidence of grades of atherosclerosis among the studies could be due to differences in the sample size, lifestyle of the sample studied, the aggravating factors causing death and the time gap between the development and progression of atherosclerotic lesion and death.

It is seen that in this study, as the grade of atherosclerosis advanced from grade I to VI the median number of mast cells increased with grade V and VI being associated with maximum number of mast cells (except in LCxA which did not show increase in median mast cells with increasing grades of atherosclerosis). It is in concordance with the study done by Kovanen PT et al., [21]. They demonstrated a dramatic increase in activated mast cells at the erosion or rupture sites of coronary atheromas. At the immediate site of erosion or rupture, mast cells amounted to 6% of all nucleated cells. Thus, mast cells were seen in significant numbers in atherosclerotic coronary arteries (except in LCxA) in our study and as well in study done by Kovanen PT et al., [21]. Similarly, Jeziorska M et al., in their study on 250 atherosclerotic lesions using immunohistochemical staining for mast cell tryptase and chymase demonstrated extensive mast cell activation by diffuse extracellular tryptase staining in advanced atherosclerotic plaques complicated by fissure, haemorrhage and thrombus formation [22].

Van Haelst PL et al., did an invivo study on blood samples of 37 patients suspected of acute myocardial infarction or unstable angina. Mast cell tryptase levels were determined. Fourteen controls were taken and their tryptase levels were also evaluated. It was found that there was no significant difference in levels of mast cell tryptase between the patients and control (6.964.0 vs. 7.964.6) and concluded that serum level of tryptase is not elevated in patients with acute coronary syndromes [7]. Neovascularisation was observed in three cases of grade VI atherosclerosis in tunica media at the site of plaque disruption in the present study which was also observed by Purushothaman KR and colleagues in their study [4]. They demonstrated increased neovascularisation in the ruptured plaques (AHA VI) and increased neovascularisation as an independent predictor of plaque rupture (p=0.0001) when comparing the features of plaque vulnerability in the human aortic atherosclerosis. Metzler B and Xu Q in their study on role of mast cells have explained the possible mechanism by which activated mast cells mediate atherosclerosis. The activated mast cells secrete certain mediators like histamine, tryptase, and chymase which may mediate or modulate atherogenesis [23].

The other explanation for mast cell mediated atherogenesis is the mast cell enzyme chymases proteolytically modifies Low-Density Lipoprotein (LDL) into copper oxidised-LDL to promote foam cell formation [24]. Tryptases, a mast cell enzyme degrades high density lipoprotein and block its function as an acceptor of cellular cholesterol [25]. Thus, mast cells by various mechanisms described above play a role in the progression of atherosclerosis, plaque destabilisation and rupture. The apparent relevance of mast cells in atherosclerosis progression warrants further study and also opens the way to promising new therapies in the prevention of acute coronary syndromes.

Limitation(s)

Though with the available resources the authors have elucidated increased mast cells in atheromatous lesions, present study faced certain limitations. The major being lack of a direct, experimental test in the prospective model in animals/humans and lack of demonstration of degranulated mast cells by immunohistochemistry.

CONCLUSION(S)

Autopsy is the best possible way to study human atherosclerotic lesions. This study highlights the importance of cardiovascular risk factors screening from early ages. It adds valuable data to the literature regarding the morphology of atherosclerotic lesions. Though the study involved only a small number of cases, most of the observations correlated with many similar studies. To conclude, present study has demonstrated that mast cells are found in good number in atherosclerotic lesions of coronary arteries and also with the progression of atherosclerosis the number of mast cells increased except in the LCxA. Identifying the cellular participants and molecular mediators of inflammation during atherogenesis may prove to be of immense help in the treatment of coronary heart diseases. Further studies can be done using mast cell tryptase immunohistochemical marker to demonstrate the mast cells in atherosclerotic lesions.

Acknowledgement

The author wish to thank the alma mater and head of department for having permitted us to perform this study and also thank all the laboratory staff who helped us during study period.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 27, 2020
- Manual Googling: Oct 10, 2020
- iThenticate Software: Feb 10, 2021 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 25, 2020**
Date of Peer Review: **Sep 04, 2020**
Date of Acceptance: **Dec 23, 2020**
Date of Publishing: **Apr 01, 2021**