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Case Report

Mast Cell Density In The Heart Of Eosinophilic Coronary Periarteritis (ECPA): A Histochemical Study.

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Abstract

The mast cell counts in the adventitia of large subepicardial coronary arteries and in the myocardium of both the right and left ventricles were determined in a patient (age 40 years, male) with eosinophilic coronary periarteritis (ECPA) and a patient (age 66 years, male) without cardiac inflammation. A large number of mast cells (96.0/mm^2) were found with numerous eosinophils in the adventitia of the inflamed subepicardial coronary artery of patients with ECPA. On the other hand, in a patient (age 66 years, male) without coronary inflammation, the average mast cell count was normal (7.0±0.8 mast cell /mm^2).

The mast cell counts of the right and left myocardia of patients with ECPA were 13.6±4.2 mast cell / mm^2 and 13.8±2.0 mast cell /mm^2, respectively, and those of patients without coronary inflammation were 10.2±1.6 mast cell /mm^2 and 8.2±1.7 mast cell /mm^2, respectively. The mast cell counts in the myocardium of patients with ECPA was slightly greater than that in patients without coronary inflammation. These differences in numbers of mast cells between patients with ECPA and patients without inflammation were considered to be influenced by coronary artery inflammation. The mast cell counts in the coronary adventitia of patients with ECPA was approximately 14 times greater than that in patients without coronary artery infection. These findings indicate that the adventitial resident mast cells of the coronary arteries in patients with ECPA might transform into a new phenotype with the ability to recruit eosinophils from the blood. Coronary spasm in patients with ECPA could be induced by mediators released from transformed mast cells and recruited eosinophils. However, the precise mechanism of mast cell transformation remains to be elucidated.

Keywords: Eosinophilic coronary periarteritis (ECPA), spontaneous coronary artery dissection (SCAD), resident mast cell, mast cell density (number), mast cell phenotype.

INTRODUCTION

Eosinophilic coronary periarteritis (ECPA) is a rare disease leading to vasospastic angina (i.e., Prinzmetal's variant angina [1]) and sudden cardiac death (SCD) [2,3]. The characteristic clinical findings of this disease include: a) vasospastic angina normally occurring within 30 minutes, usually from the evening to the early morning; b) anginal attack usually occurring with circadian or circannual rhythm; c) electrocardiogram (ECG) findings showing ST segment elevation during an anginal attack; d) almost all patients experience SCD early in the morning; e) allergies or a history of allergies are difficult to identify in patients with this disease.

At autopsy, macroscopic findings of the heart include a) subepicardial large coronary arteries that are grayish-white in color, b) left ventricular hypertrophy, and c) small scar formation scattered in the left ventricular wall.

The histological findings include a) infiltration of numerous eosinophils with other inflammatory cells in the adventitia of large coronary arteries in the subepicardial artery; b) all 3 main coronary artery branches are affected, with the left anterior descending artery most frequently affected; c) the medial smooth muscle cells and both the internal and external elastic laminae of the affected coronary artery are well preserved; and d) fibrinoid necrosis or granulomas, as observed in poly arteritis nodosa (PN) or allergic granulomatous angiitis (AGA), are not identified.

On the other hand, in 1982, Robinowitz et al. [4] reported 8 autopsy cases of spontaneous coronary artery dissection (SCAD) and summarized the characteristic findings of these

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8 cases with a review of 46 cases in the literature. Two years later, Virmani et al. [5] added 3 more autopsy cases to the 8 cases reported by Robinowitz et al. [4]. The 11 autopsy cases of SCAD reported by Virmani et al. were all female and ranged in age from 26 to 47 years. Three of them presented in the postpartum period, and 9 died suddenly. The most common artery of dissection was the left coronary anterior descending artery (LAD). In the 11 patients, the dissection usually occurred in the outer third of the media. The characteristic histological finding was infiltration of the most prominent eosinophils limited to the adventitia of the dissected portion of the coronary arteries. This adventitial eosinophilic inflammation of the epicardial coronary arteries in SCAD patients is considered to be the same finding as that in ECPA patients.

In 2015, Mandal et al. [6] reported two autopsy cases of SCAD that histologically presented a dense band of inflammatory cells, including copious eosinophils within the adventitial and periadventitial tissues of the dissected coronary arteries, similar to the findings of the ECPA. They proposed the "mast cell hypothesis" on the etiology and pathogenesis of ECPA.

It is now generally accepted that mast cells have a functionally intimate relationship with eosinophils and that they cross-talk with each other in allergic reactions [7–12].

We investigated the distribution or density of mast cells in the heart of a patient with ECPA and, as a control, a patient (age, 66 years, male) without coronary inflammation. The mast cells in the adventitia of the subepicardial right and left coronary arteries and in the right and left ventricular myocardium were measured via immunohistochemistry for tryptase, which is known as a mediator contained in the secretory granules of mast cells.

MATERIALS AND METHODS

The materials used in this study were the right coronary artery of the heart obtained from an autopsy case reported as a typical case of ECPA (the 1st case of EPCA reported in 1989), and the left coronary artery of the heart obtained from a 66-year-old man who died of mesothelioma without cardiac problems. The tissues obtained from both patients were embedded in paraffin, and the paraffin sections were used for immunohistochemical staining of tryptase. Positive and negative controls were utilized. The antibody source was tryptase (mouse monoclonal, Cell Marque, Rocklin, CA).

RESULTS

The mast cell counts in the hearts of patients with ECPA and patients without cardiac problems were measured in the adventitia of the subepicardial large coronary arteries and in both ventricular myocardia.

A.Mast cell count in the heart of a patient (40-year-old, male) with eosinophilic coronary periarteritis (ECPA)

1)Mast cell count in the adventitia of the inflamed subepicardial right coronary artery: 96.0±27.2 mast cell /mm^2(range 68 to 132 mast cell /mm^2 =96,0±27,2 mast cell /mm^2)
(**Fig 1-a, -b HE and Fig 1-c, -d Tryptase**)

A. 1) H-E and tryptase stain of the coronary artery and ventricular myocardium in a patient (age 40 years, male) with ECPA

Figure 1a. H-E stain of right coronary artery (1.0mm^2), Infiltration of numerous eosinophils with other inflammatory cells, ECPA case.

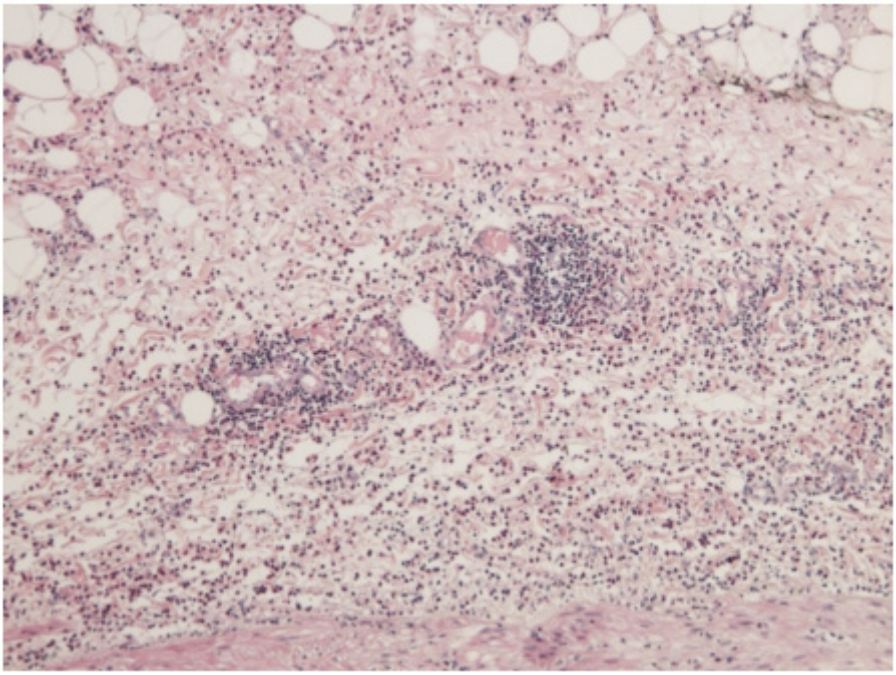


Figure 1b. Large magnification (0.25 mm^2) of Fig 1-a. Eosinophils are more distinct.

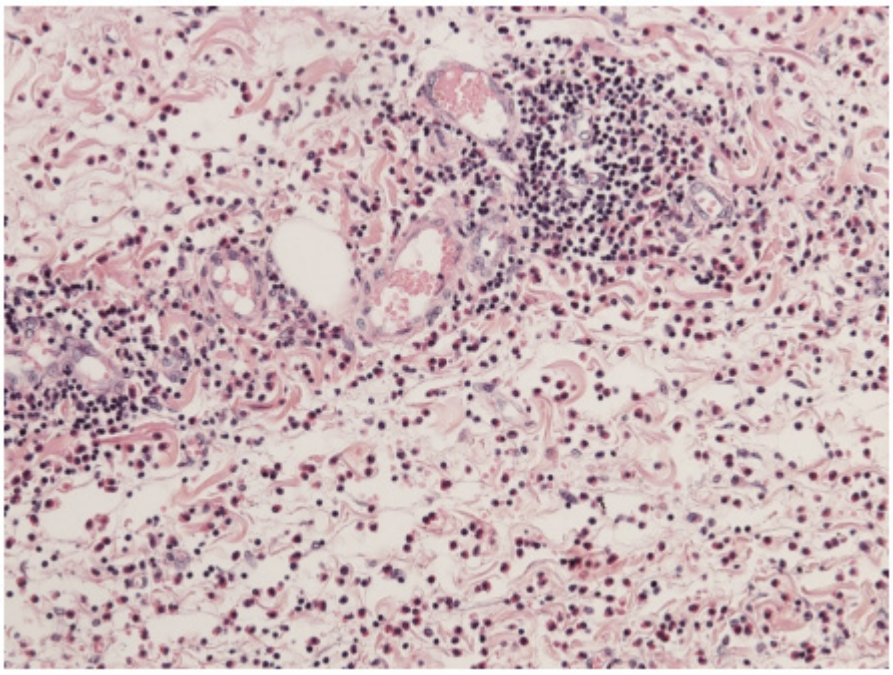


Figure 1c. Tryptase stain of r-coronary artery (0.10 mm^2). Many tryptase positive cells with numerous inflammatory cells, ECPA case.

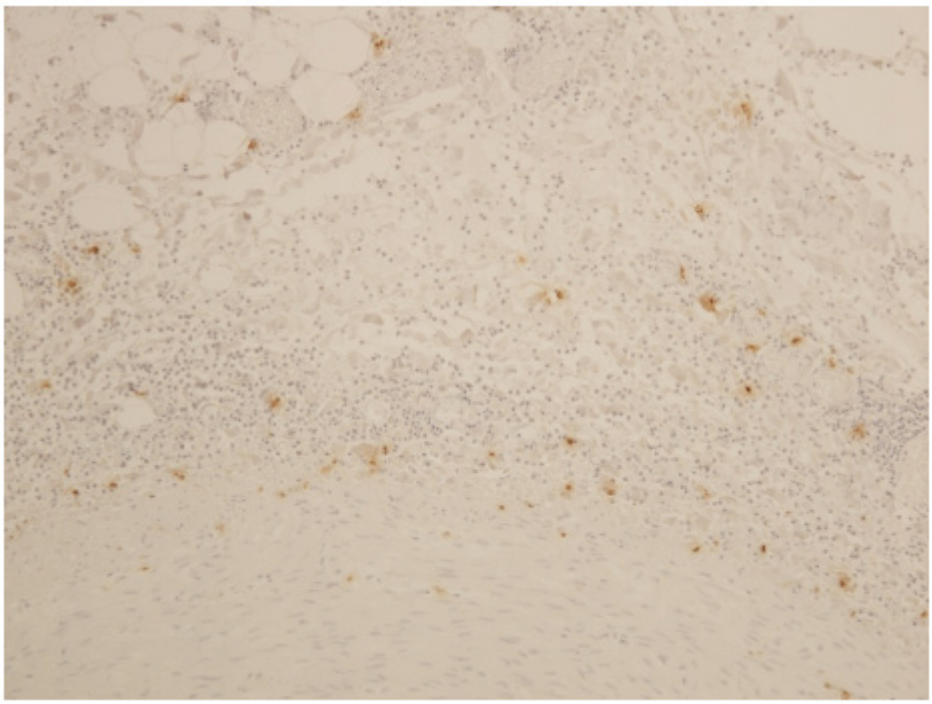
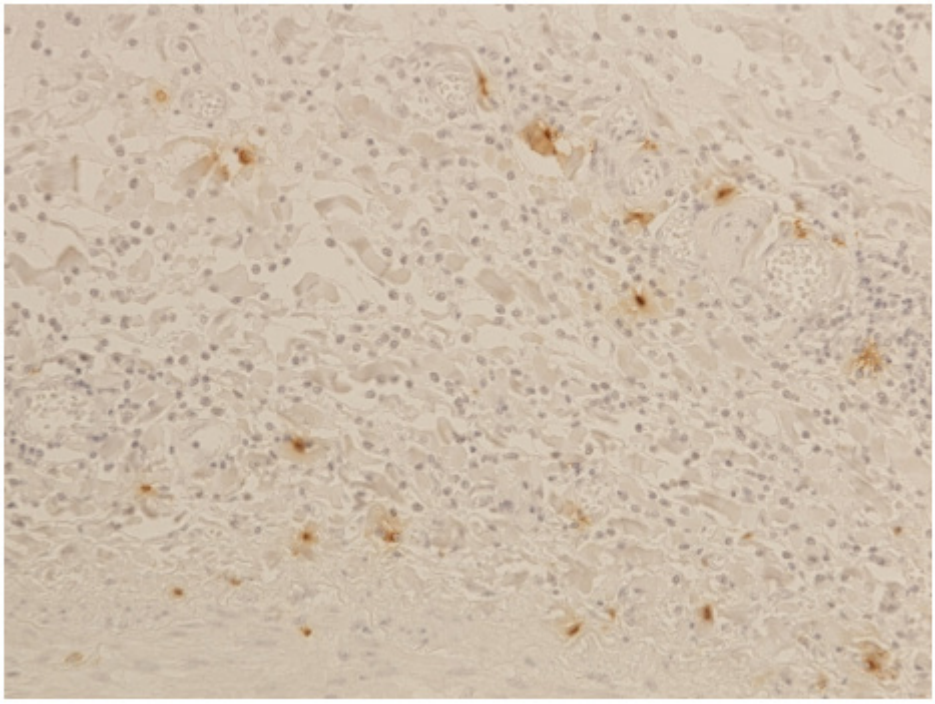


Figure 1d. Large magnification (0.25 mm^2) of Fig 1-c. Tryptase positive cells with other inflammatory cells are more distinct.



2) HE and Mast cell count in the right ventricular myocardium: 13,6±4.2 mast cell/mm^2 (range 8 to 20 mast cell /mm^2 = 13.6±4.2 mast cell/ mm^2), (**Fig 2-a HE, -b Tryptase**)

Figure 2a. H-E stain of r-ventricular wall of ECPA case. Infiltration of inflammatory cells is hardly seen in the peri-myocardial spaces (0.10 mm2)

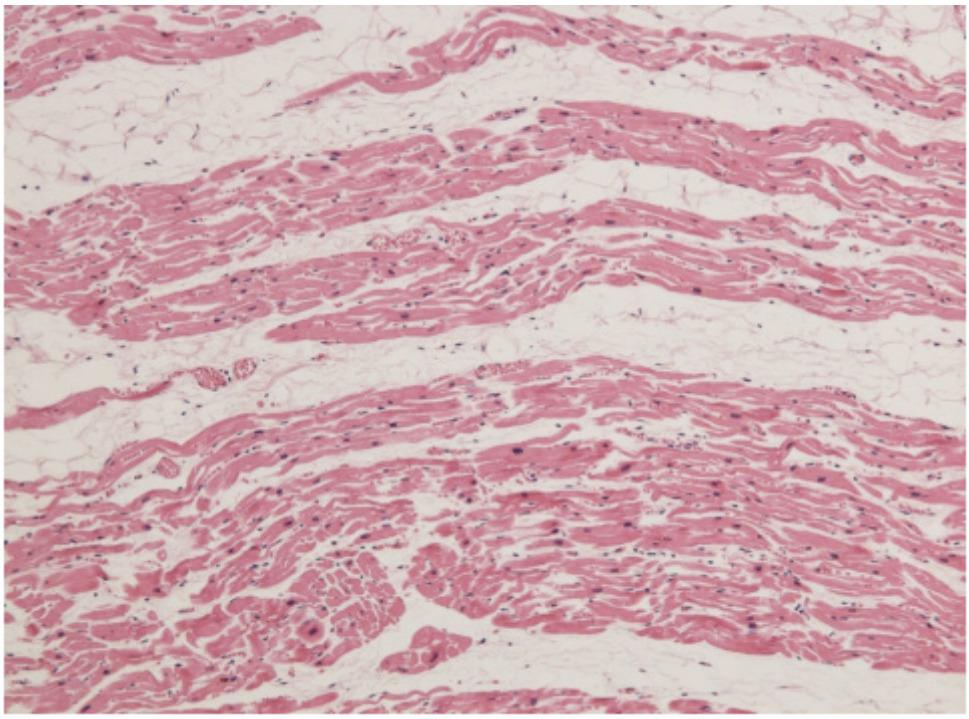
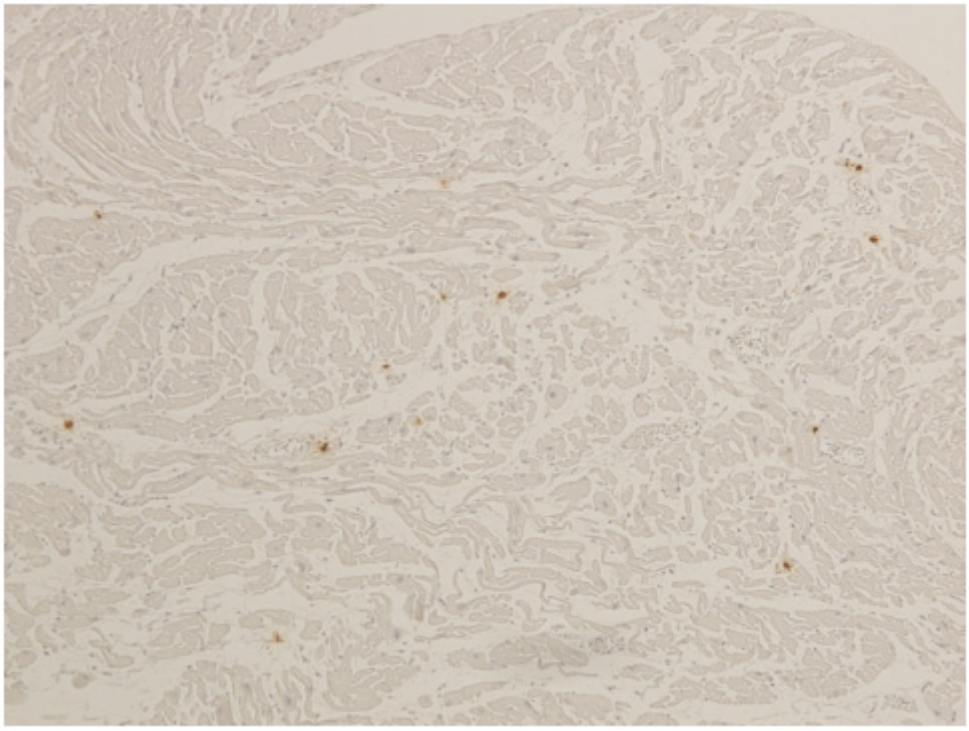


Figure 2b. Tryptase stain of r-ventricular wall of ECPA case (0.10 mm^2). Small number of tryptase positive cells are seen in the peri-myocardial spaces



3) HE and Mast cell count in the left ventricular myocardium: 13.8±2.0 mast cell /mm^2 (range 11 to 17 mast cell /mm^2 = 13.8±2.0 mast cell /mm^2), (**Fig 3-a HE, -b Tryptase**)

Figure 3a. H-E stain of l-ventricular wall of ECPA case (1.0mm^2). Inflammatory cells are hardly seen in the peri-vascular and peri-myocardial connective tissue.

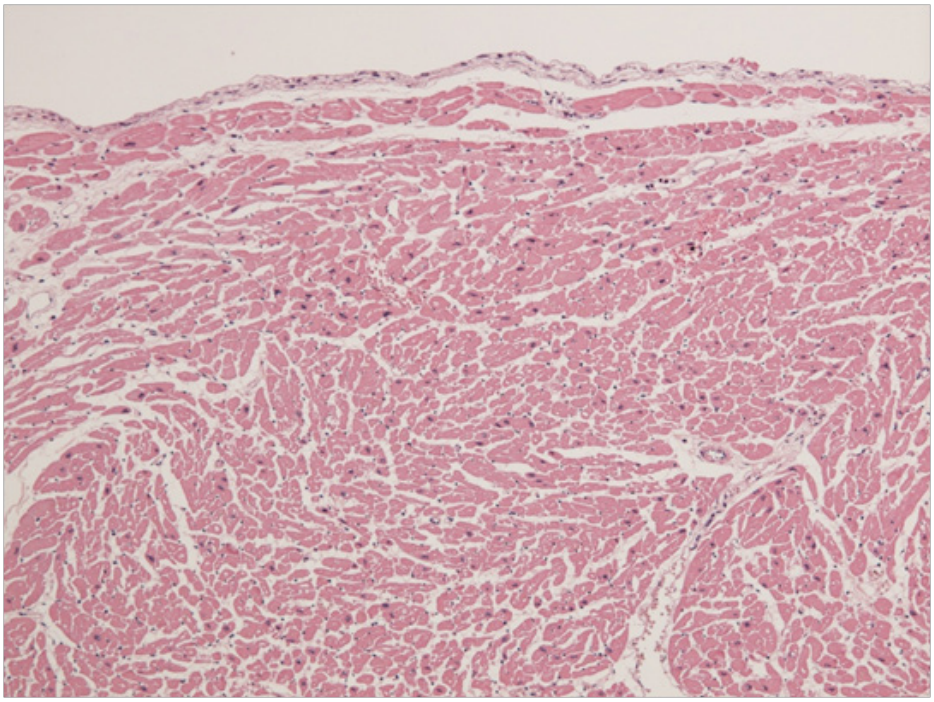
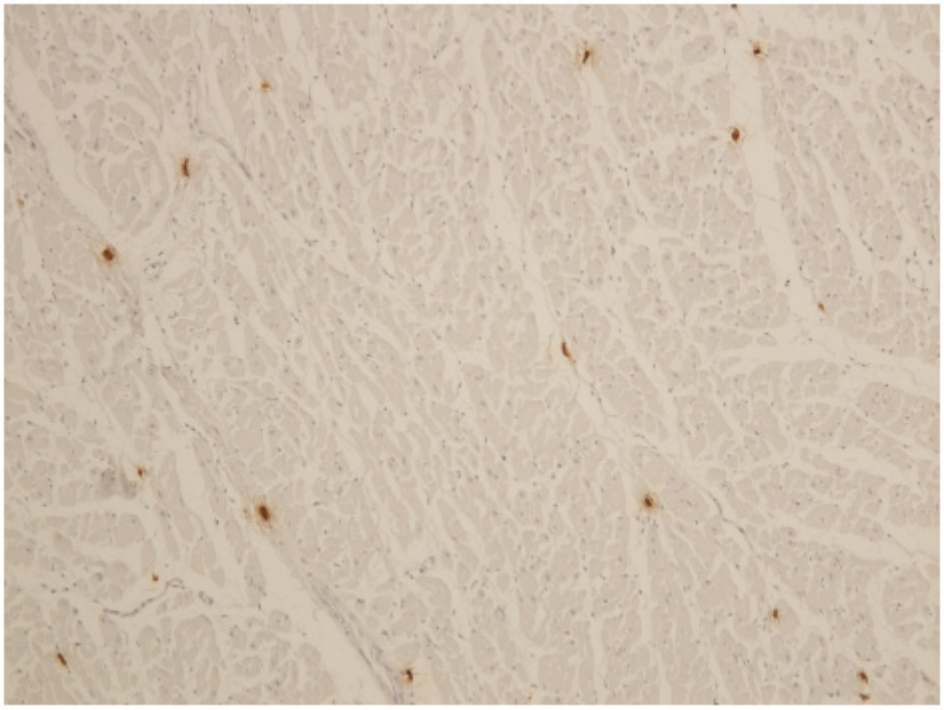


Figure 3b. Tryptase stain of l-ventricular wall of ECPA case (0.10 mm^2). Small number of tryptase positive cells are seen in the peri-myocardial spaces.



B. H-E and Mast cell count in the heart of a patient (66-year-old, male) without cardiac problems

1)Mast cell count in the adventitia of the subepicardial left coronary Artery: 7.0±0.8 mast cell /mm^2 (range 6 to 8/mm^2 = 7.0±0.8 mast cell /mm^2) (**Fig 4-a HE, -b Tryptase**)

Figure 4a. H-E-stain of left coronary artery and adventitial tissue of a patient without coronary inflammation (1.0mm^2). Inflammatory cells are hardly seen in the perivascular and adventitial connective tissue.

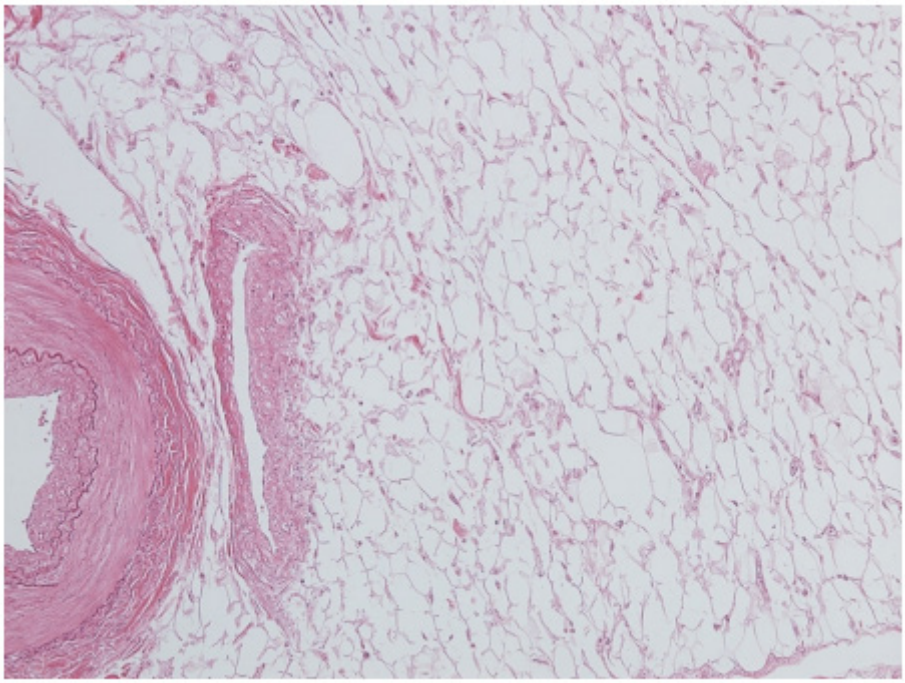
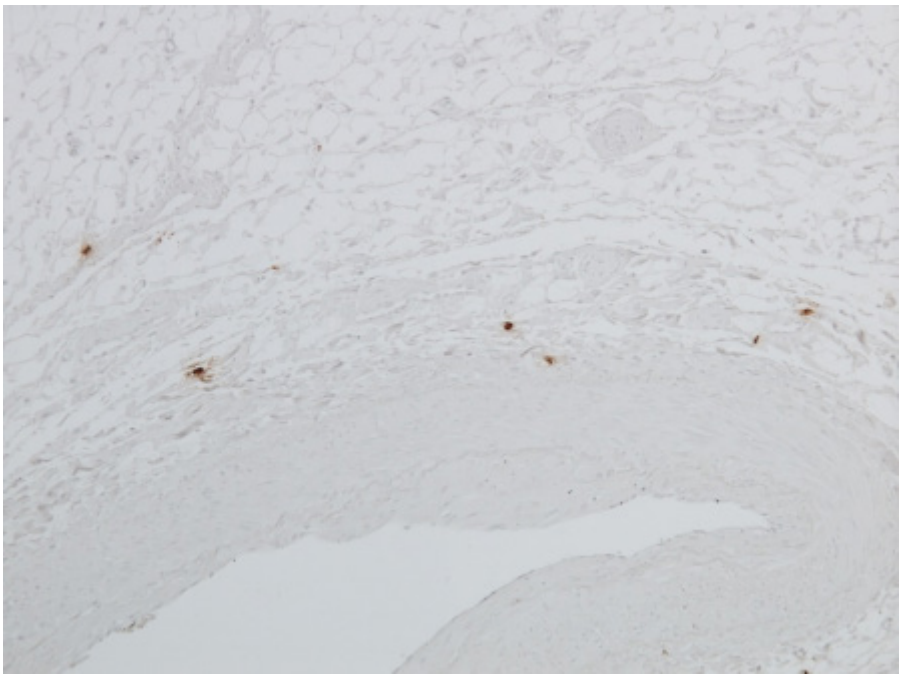


Figure 4b. Tryptase-stain of left coronary artery and adventitial connective tissue of a patient without inflammation (0.10 mm^2). Small number of tryptase positive cells are seen in the peri-arterial and adventitial tissue.



2) Mast cell count in the right ventricular myocardium: 10.2±1.6 mast cell /mm^2(range 8 to 12 mast cell /mm^2 = 10.2±1.6 mast cell /mm^2) (**Fig 5-a HE, -b Tryptase**).

Figure 5a. HE-stain of r-ventricular wall of a patient without coronary inflammation (1.0mm^2).Inflammatory cells are hardly seen in the perivascular and peri-myocardial spaces.

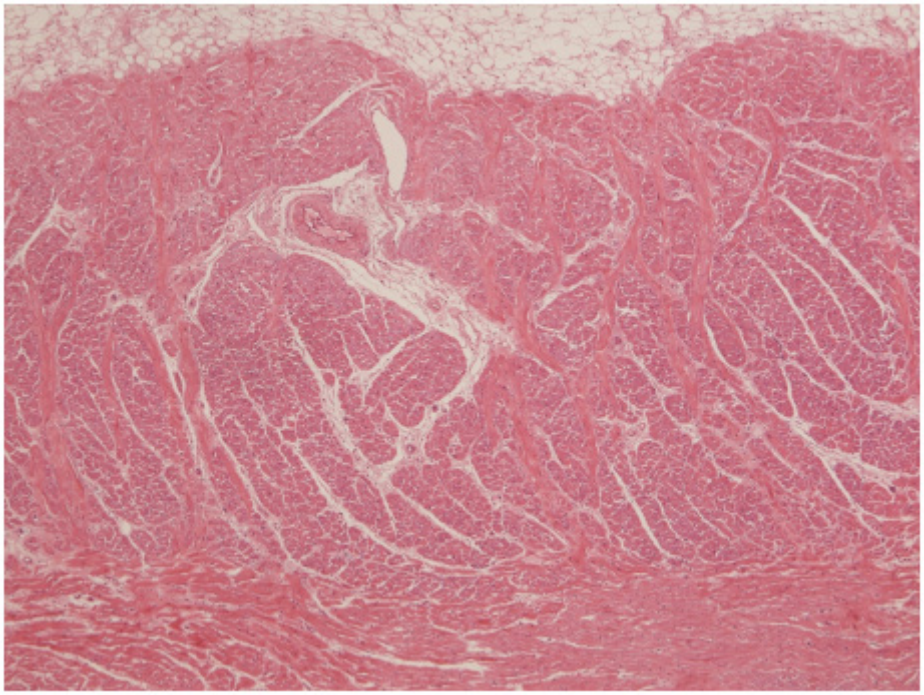
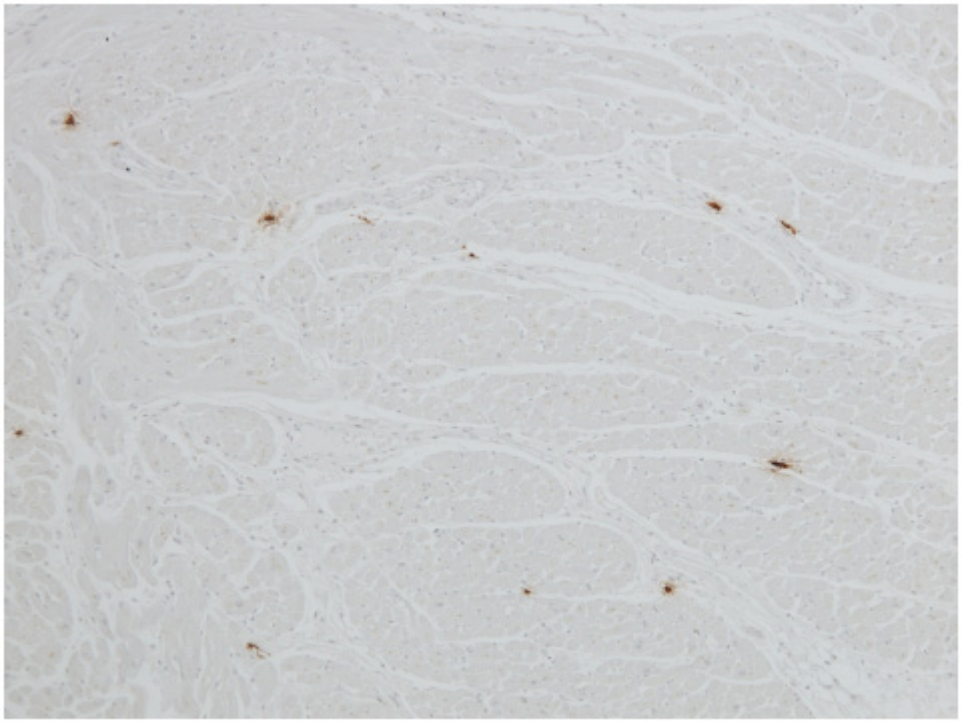


Figure 5b. Tryptase stain of r-ventricular wall of a patient without coronary inflammation (1.0mm^2). Small number of tryptase positive cells are seen in the peri-myocardial and peri-vascular spaces,



3) Mast cell count in the left ventricular myocardium: 8.2±1.7/mm^2 (range 5 to 10 mast cell /mm^2 = 8.2±1.7 mast cell /mm^2) (**Fig 6-a HE, -b Tryptase**)

Figure 6a. H-E stain of l-ventricular wall of a patient without coronary inflammation (1.0mm^2).Inflammatory cells are hardly seen in the perivascular and peri-myocardial Connective tissues.

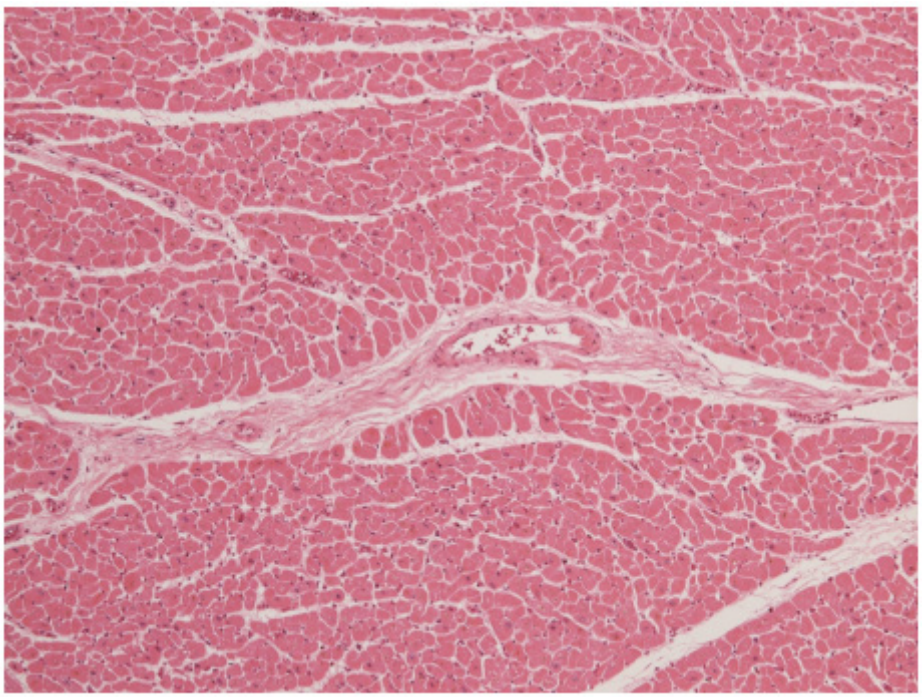
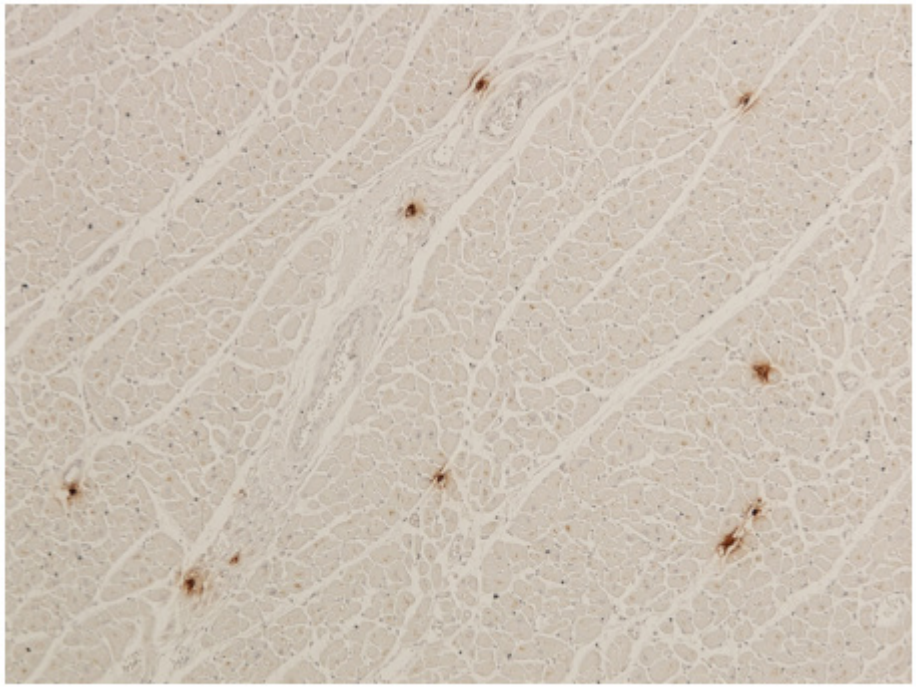


Figure 6b. Tryptase stain of l-ventricular wall of a patient without coronary inflammation (1.0mm^2). Small number of tryptase positive cells are seen in the peri-myocardial s and peri-vascular connective tissues.



As shown in **Fig. 1-a and 1-b**, a large number of eosinophils infiltrated with many lymphocytes and other leukocytes in the adventitia of the right subepicardial large coronary artery of patients with ECPA. The mast cells were identified via immunohistochemical staining of tryptase and are shown in **Fig. 1-c and -d**. The mast cell count in the adventitia of the inflamed coronary artery was markedly greater (96.0±27.2 mast cell /mm^2) than that in the noninflamed coronary adventitia (7.0/±0.8 mast cell/mm^2) (**Fig. 4-b**) of patients without coronary inflammation.

The right and left ventricular myocardia of patients with ECPA and patients without coronary infection were free from inflammatory cell infiltration (**Figs 2a, 3a, 5a and 6a**). The mast cell counts of both ventricles in patients with ECPA and without inflammation were not high, while a few mast cells were usually situated in perivascular connective tissue and between myocardial cells. In patients with ECPA, the mast cell count in the myocardia was slightly greater than that in patients without inflammation.

DISCUSSION

Mast cells are important cells of the immune system and arise from bone marrow-derived pluripotent progenitor cells that circulate in the blood and finally reside in connective tissues or mucosal tissues [9–12]. The mast cell phenotype in a tissue is controlled by its location and differentiation under the influence of various tissue microenvironmental conditions, which include mainly stem cell factor (SCF) and other cytokines [13, 14]. Historically, mast cells (MC_s) were classified into 2 subtypes according to tryptic enzyme expression levels. MC_s that produce the enzymes tryptase and chymase (MC_{TC}) and that contain tryptase but not chymase (MC_T). MC_{TC} are prominent in connective tissue, whereas MC_T are found in the mucosa [15–18].

In 1995, Patella et al. [19] isolated and purified human heart mast cells ($HHMC_s$), human lung mast cells ($HLMC_s$), and human skin mast cells ($HSMC_s$) and reported that the phenotype of $HHMC_s$ was different from that of $HLMC_s$ and $HSMC_s$.

Recently, Frossi et al. [20] reported that the mast cell phenotype was more variable and was dependent on the tissue residing in organs, such as the skin, lung, intestine, pancreas and kidney. Many investigators have reported that mast cells reside in the human heart, coronary arteries, and myocardium in relation to myocardial infarction or atherosclerosis and that the number of resident mast cells increases with several cardiac injuries.

In 1990, Stary [21] reported normal and atherosclerotic lesions in the coronary arteries of 691 subjects of <40 years of age and reported that mast cells in the normal coronary artery intima were rare, but mast cells in the intima were accompanied by the development of atherosclerosis. The number of adventitial mast cells in the intima was at least 10.

In 1995, Laine et al. [22] reported an article about the association between myocardial infarction and mast cells in the adventitia of the infarct-related coronary artery and noted that a significantly greater number of mast cells were present in the adventitia backing ruptured plaques (98±40 mast cells/mm^2, mean±SD) than in the adventitia backing

nonruptured plaques (41±12 mast cells/mm^2; p<0.001) or backing the normal intima (19±8 mast cells/mm^2; p<0.001). Even in the normal segments of the infarct-related coronary artery, the mast cell density was greater (2-fold) than that in the corresponding segments of the control arteries. Based on these findings, they concluded that the entire adventitial layer of the infarct-related coronary artery was affected by an inflammatory process.

In our study of patients with ECPA, the adventitial mast cell count of the subepicardial large coronary artery was 96.0±27.2 mast cell /mm^2, and the right and left ventricular must cell counts were 13.6±4.2 mast cell / mm^2 and 13.8±2.0 mast cell /mm^2, respectively. As a control heart of a patient without coronary inflammation (age 66 years, male), the adventitial mast cell count of the subepicardial large coronary artery was 7.0±0.8 mast cell /mm^2, and the right and left ventricular mast cell counts were 10.2±1.6 mast cell /mm^2 and 8.2±1.7 mast cell /mm^2, respectively.

The increased number of mast cells in the adventitia of the coronary arteries of patients with ECPA was almost the same as that in the infarct-related coronary artery of Laine's case (myocardial infarction), whereas the infiltration of eosinophils was not described in Laine's report.

ECPA is a type I hypersensitivity (allergic) disease (i.e., immunoglobulin E [IgE]-mediated disease), characterized by mast cell activation and the infiltration of eosinophils with other inflammatory cells. In our previous study, adventitial eosinophilic inflammation appeared not only in a single coronary artery (mostly the LAD) but also in two coronary arteries (LAD, RC) or all three coronary arteries (LAD, RC and LCX). These findings suggest that the activation or transition to a new phenotype of resident mast cells in the adventitia of coronary arteries might not be uniform but rather be localized or segmental.

There are some reports concerning the immunological mechanism by which mast cells and eosinophils cross-talk with soluble mediators released by both cell types and affect each other [7–14]. These findings suggest that resident mast cells in the adventitia of coronary arteries are activated, assume a new phenotype to recruit eosinophils from the bloodstream, and ultimately result in the onset of an allergic reaction, such as IgE-mediated (type I hypersensitivity) disease.

Wong et al. [8] reported that the mast cell-specific protease chymase can induce eosinophil infiltration into the inflammatory site, and some investigators suggest that genetic, environmental, and immunological aspects are likely involved.

In recent years, considerable information has been obtained from the study of high-affinity receptor for IgE (FcεRI) and the dysregulation of mast cell function in the context of physiological consequences [23]. However, the exact etiology and pathogenesis of ECPA are not yet understood.

In 1964, Fernex and Sternby [24] studied mast cell counts of the human myocardium via a large number of autopsy series and reported that the mast cell count in the left ventricular myocardium ranged between 0.1 and 11.5 per mm^2. The cases with <1 mast cell per mm2 were said to have "few mast cells", cases with 1–3 mast cells per mm^2 were said to have "normal mast cell counts", and cases with more than 3 mast cells per mm^2 were said to have a "large number of mast cells" in their myocardium.

In our study, there were more than 3 mast cells in the right and left myocardia of the heart with ECPA and without cardiac inflammation per mm^2, which is considered to be a "large number of mast cells", as proposed by Fernex and Sternby. The mast cell counts in both the right and left myocardia of patients with ECPA were slightly greater (13.6±4.2 mast cell / mm^2 and 13.8±2.0 mast cell /mm^2, respectively) than those (10.2±1.6 mast cell /mm^2 and 8.2±1.7 mast cell /mm^2, respectively) in the myocardium of patients without coronary infection. These differences in myocardial mast cell density (number) between patients with ECPA and without cardiac problems were considered to result from the influence of coronary artery inflammation.

With respect to the role of resident mast cells in the myocardium, it is now generally accepted that mast cells store and release several cytokines, some of which have been implicated in the activation of matrix metalloproteinases and in the fibrotic process [25–31]. Increased numbers of mast cells have been reported in explanted human hearts with dilated cardiomyopathy and in animal models of experimentally induced hypertension, myocardial infarction and chronic cardiac volume overload, and play a major role in the adverse remodeling underlying these cardiovascular disorders.

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