Eosinophilic Coronary Periarteritis: A New Type of Coronary Arteritis as a Cause of Vasospastic Angina and Sudden Death

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Abstract
Eosinophilic coronary periarteritis (ECPA) has been recently established as a new pathological entity and clinically showed a vasospastic angina and sudden cardiac death (SCD). The patients were relatively young (mainly 30 to 50 years old) and predominantly male. The characteristic clinical findings of this disease include: a) vasospastic angina (Prinzmetal’s variant angina) appearing usually from evening to early in the morning, b) all patients experienced SCD early in the morning, and c) allergy or history of allergy was hard to identify in the patients with this disease. Histological findings include: a) eosinophilic inflammatory infiltration limited to the adventitia and periadventitial soft issue is recognized in the epicardial large coronary arteries, b) all 3 main coronary artery branches are affected, with the left anterior descending artery most frequently affected, c) medial smooth muscle cells of the affected coronary artery and both internal and elastic laminae are well preserved, d) fibrinoid necrosis or granuloma as seen in polyarteritis nodosa or allergic granulomatous angina are not found in or around the inflammatory area, and e) no findings of any type of vasculitis in any other tissues or organs (i.e., localized or non-systemic periarteritis). Spontaneous coronary artery dissection (SCAD) is frequently accompanied by eosinophilic inflammatory infiltration limited to the adventitia and periadventitial soft issue in the dissected portion of the epicardial coronary arteries, i.e., same as the findings of ECPA, and the patients usually die suddenly.

Keywords: Eosinophilic coronary periarteritis (ECPA); Vasospastic angina (Prinzmetal variant angina); Sudden cardiac death (SCD); Spontaneous coronary artery dissection (SCAD)

Introduction
Sudden cardiac death (SCD) is a major cause of mortality in elderly individuals owing to a high prevalence of coronary heart disease, especially that of coronary arteriosclerosis. Primary vasculitis, such as polyarteritis nodosa (PAN) and allergic granulomatous angitis (AGA, or Churg-Strauss Syndrome, CSS), also affects the coronary arteries and occasionally induces cardiac arrest and SCD. However, the primary vasculitis is usually systemic, and almost all coronary vasculitis appears as a manifestation of systemic vasculitis [1]. Recently, a special type of coronary arteritis, eosinophilic coronary periarteritis (ECPA), clinically showing vasospastic angina (Prinzmetal’s variant angina [2]) and SCD was established as a new pathological entity by Kajihara et al., who found that ECPA is not a systemic vasculitis and appears predominantly in males [3]. Relatively younger patients are affected, mainly 30- to 50-year-olds, and the mortality rate from SCD is high.

The characteristic clinical findings of ECPA are: a) vasospastic angina (Prinzmetal’s variant angina) appearing mainly from evening to early in the morning, b) the patients die suddenly early in the morning, and c) few patients have an allergy or history of allergy. The histological findings include: a) eosinophilic inflammation limited to the adventitia and periadventitial soft issue appearing in the epicardial large coronary arteries; b) all 3 main coronary artery branches are affected, chiefly the left anterior descending (LAD) artery; c) medial smooth muscle cells and both internal and external elastic laminae are well preserved; d) fibrinoid necrosis or granuloma as seen in PAN or AGA is not found in or around the inflammatory area; and e) no type of vasculitis can be found in any other tissues or organs (i.e., localized or non-systemic periarteritis).

Robinowitz et al. [4] and Virmani et al. [5] reported their own autopsy cases of spontaneous coronary artery dissection (SCAD). They found that a) SCAD was most frequently seen as an acute coronary syndrome in females during the peripartum period, b) dissection of the coronary arterial wall appeared between the media and adventitia, and c) eosinophilic inflammatory infiltration was recognized in the adventitia of the dissected portion, findings similar to those of ECPA.

The diagnosis of ECPA is made almost exclusively at autopsy and is very difficult to make at the clinical examination stage. However, vasospastic angina appearing mainly from the evening to early in the morning (Prinzmetal’s variant angina) is the most important symptom of this disease.

Materials and Methods
Our group has personally studied 7 autopsy cases (case nos. 1-7) of ECPA as shown in Table 1 (which includes 4 additional published cases). In our 7 autopsy cases, the heart was fixed in 10% formalin solution, and then the major epicardial coronary arteries were serially cut into about 5 mm long segments. They were then dehydrated in alcohol and embedded in paraffin. Paraffin sections of each coronary artery were stained with Hematoxylin and Eosin, PAS,
Masson’s trichrome, and Elastica-van Gieson stains. In case no. 1, the infiltrating inflammatory cells, especially eosinophils, were identified by electron microscopy. The myocardium was examined grossly and microscopically for evidence of acute or healed myocardial infarction. Other organs such as the lungs, liver, kidneys, gastrointestinal tract, and pancreas were also examined in the same way as those of the heart.

Results

The age of our 7 autopsy cases ranged from 19 to 47 years (mean age, 35.71 years), and the male:female ratio was 6:1. Two of the patients had a past clinical history of asthma, and 1 had a past history of hypereosinophilia. All of these patients had complained of anginal pain (variant angina) occurring early in the morning and all had died suddenly.

Heart weight in these 7 autopsy cases ranged from 220 g to 400 g (mean weight, 352.86 g), and each heart was slightly hypertrophied. The affected main coronary arteries in the subepicardial region were macroscopically grayish-white in color and elastically hard as shown in Figure 1.

At histological examination, dense inflammatory infiltration, mainly that of eosinophils, was observed in the adventitia and periadventitial soft tissue of the large coronary arteries located in the epicardial region (Figures 2a and b). Inflammatory changes were present in all 3 coronary arteries, LAD, left circumflex (LCX), and right coronary artery (RCA), in 4 cases, in 2 coronary arteries (LAD and RCA) in 1 case, and only in the LAD in 2 cases. Infiltrating eosinophils were identified by electron microscopy (Figure 3). The intima of the affected coronary arteries usually showed slight fibrous thickening. The internal and external elastic laminae and medial smooth muscle cells were well preserved (Figure 4). No inflammatory changes were observed in the intramural coronary vessels. In all cases, no type of arteritis or vasculitis could be identified in the vessels of other tissues and organs. SCAD was not found in any of our cases.

Congestion was usually seen in the lungs and liver in all of our reported cases. In case no. 3, the lungs showed typical findings of bronchial asthma, such as hypersecretion of bronchial epithelium, hypertrophy of bronchial smooth muscle cells, and eosinophilic infiltration of the bronchial mucosa. The bone marrow in this case was hyperplastic, mainly with a proliferation of eosinophils. A small number of eosinophils were scattered in the spleen, thymus, and in several lymph nodes.

Four reported cases from the literature are also shown in Table 1. Patient age in these additional cases ranged from 28 to 70 years old, with a male:female ratio of 2:2. Hearts weighed from 340 g to 385 g. The affected coronary arteries included the LAD (3 cases), RCA (1 case), and LCX (1 case). Microscopic findings were almost the same as those of our reported cases.

Discussion

Almost all of the patients with ECPA presented in this report clinically showed anginal pain for several weeks or years. Chest discomfort or anginal pain mainly occurred between the evening and the early morning (Prinzmetal’s variant angina), and the patients died suddenly in the early morning. In all cases, except for our cases no. 3 and 6, there was no history of bronchial asthma or drug allergy. Our case no. 3 also had a past history of hypereosinophilia.

At autopsy, the distinctive macroscopic findings of our cases were found mainly in the heart, especially in the epicardial coronary arteries (from the main stem to their large branches), which were grayish white in color and elastically hard. At histological examination, severe inflammatory infiltration, mainly by eosinophils, was localized in the adventitia and periadventitial soft tissue of the epicardial coronary arteries, whereas the intima and media were usually free from inflammatory change. Internal and external elastic laminae and medial smooth muscle cells were well preserved. Fibrinoid necrosis or granulomatous inflammation as seen in PAN or AGA could not be found in the inflamed areas, and no type of vasculitis could be found in any other tissues or organs.

In 1977, Ahronheim reported a case of sudden unexpected death of a 23-year-old woman in her 8th month of pregnancy [6]. She had complained of nausea and retrosternal pain early in the morning and was dead on arrival at the hospital. There was no history of asthma or hypereosinophilia. At autopsy, a dense inflammatory infiltration consisting of neutrophils, eosinophils, lymphocytes, and occasional histiocytes was found in the adventitia of the epicardial LAD coronary artery with mixed thrombus in the vascular lumen. No changes were evident in the myocardium, the intramural coronary branches, or thoracic aorta and Ahronheim diagnosed this type of coronary inflammation as an isolated coronary periarteritis. Eighteen years earlier, in 1959, he had reported a case of a 41-year-old woman who died suddenly after coronary artery dissection [7]. At autopsy, the adventitia of the dissected coronary artery had shown dense...
inflammatory infiltration including eosinophils. Because of these findings of periarterial inflammation in both cases, he considered that these two cases might be identified as the same entity, an isolated coronary periarteritis different from other forms of inflammatory coronary disease, and that the periarterial inflammation might be related to the occurrence of coronary artery dissection or aneurysm.

In 1989, Kajihara et al. [8] reported the first case of ECPA. In the same year, Lie and Bayardo reported the case of a 39-year-old man who had complained of intermittent chest pain during the preceding week and was found dead in the morning in his living room (sudden unexpected death) [9]. At autopsy, inflammatory cell infiltration was found most intensely in the adventitia and outer media and less profusely in the intima of the epicardial coronary arteries. In addition, a small number of eosinophils, were seen in the subendocardial layer of the left ventricle. Tissue eosinophilia was observed in the spleen. They considered that this type of isolated eosinophilic coronary arteritis was a limited form of CSS. The autopsy findings of our case no. 3 are quite similar to those of this case reported by Lie and Bayardo. The eosinophilic infiltration of the coronary arteries in both of these cases occurred mostly in the adventitia and periadventitial regions. Although a small number of eosinophils had infiltrated into the intima, both the outer and inner elastic laminae were well preserved in our cases. Neither fibrinoid necrosis such as that seen in PAN nor allergic granulomatous angiitis (AGA or CSS) could be found either in our cases or the case of Lie and Bayardo. On the basis of these coronary artery findings, the eosinophilic inflammation mainly in the adventitia of the coronary arteries could be considered as ECPA.

In 2005, Taira et al. reported an autopsy case of a 52-year-old man who had no history of asthma or of any other allergic diseases [10]. He showed symptoms of Prinzmetal-type variant angina and died after sudden cardiac arrest. At autopsy, the main stem of the right coronary artery 5 mm distal from the ostium was elastically hard and grayish-white in cross-section. On histological examination of this vascular lesion, dense eosinophilic infiltration was observed in the adventitia and periadventitial tissue, indicating eosinophilic periarteritis. No other type of vasculitis could be found in other organs or tissues. These findings are similar to those of the first case of ECPA reported in 1989 [8]. As a result, they considered isolated ECPA to be a new disease entity rather than a variant form of AGA or CSS, as reported by Lie and Bayardo [9].

Moreover, Ak et al. reported a case of coronary artery bypass...
descending artery; LCX, left coronary circumflex artery; LMC, left main coronary artery; RCA, right coronary artery

Tissue Eo., tissue eosinophilia; SCAD, spontaneous coronary artery dissection; N.D., not described; N.D.#, heart weight from 280 to 340 g; LAD, left coronary anterior

Pub. year, publication year; [ ], reference number; Hypereo., hypereosinophilia; SCD, sudden cardiac death; HW, heart weight; ECPA, eosinophilic coronary periarteritis; Tissue Eo., tissue eosinophilia; SCAD, spontaneous coronary artery dissection; N.D., not described; N.D.#, heart weight from 280 to 340 g; LAD, left coronary anterior descending artery; LCX, left coronary circumflex artery; LMC, left main coronary artery; RCA, right coronary artery

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grafting (CABG) of the internal thoracic artery and saphenous vein (SV) in in 2009 [11]. The patient was a 60-year-old woman who had undergone triple-vessel CABG 5 years before: left internal thoracic artery (LITA) to the LAD and SV to the RCA and CXA. She had no history of asthma or any other allergic diseases. She was re-admitted due to angina after exertion 3 years after the first operation. Coronary angiography showed diffuse narrowing of the distal half of the grafted LITA and an 80% proximal stenosis of the SV graft to the RCA. Two-vessel repeat CABG was performed by using a SV graft to the mid-LAD and a SV graft to the distal RCA. Histopathologic examination of the resected LITA graft revealed diffuse inflammatory infiltration with a large number of eosinophils and scattered lymphocytes and plasma cells throughout the adventitial and periadventitial tissues (same findings as in ECPA). The upper half of the graft LITA revealed normal histology except for mild to moderate fibrous intimal hyperplasia. The microscopic findings of the grafted SV were consistent with those of vein graft atherosclerosis. These findings indicate that eosinophilic infiltration limited to the arterial adventitia and periadventitial tissue of epicardial coronary arteries might have an intimate relation to local tissue factors involving vascular structures, mechanical factors, and/or nerve innervations. Recently, Arena et al. [12] and Omalu et al. [13] reported an additional two cases (a 70-year-old man and 54-year-old woman, respectively) of isolated eosinophilic coronary arteritis, quite similar to the first case reported in 1989.

Of particular interest is the fact that adventitial eosinophilic inflammation was frequently observed in the adventitia of dissected lesions of SCAD. In 1982, Robinowitz et al. reported 8 autopsy cases of SCAD and summarized the characteristic findings of these cases along with a review of 46 cases in the literature [4]. Two years later, Virmani et al. added 3 more autopsy cases to the 8 cases of Robinowitz et al. and reviewed 50 cases in the literature [5].

The 11 autopsy cases reported by Virmani et al. were all of woman who ranged in age from 26 to 47 years. Three had presented in the postpartum period and 9 had died suddenly. Systemic hypertension had been documented in only 2 cases. The heart weight was nearly normal, ranging from 240 g to 350 g, and the most commonly dissected artery was the LAD, occurring in 10 of the 11 cases. Histological examinations of the coronary artery dissections were made in the outer media of the artery but rarely in the mid-portion of the media. In all 11 cases, focal inflammatory infiltration, most prominently by eosinophils, was revealed in the adventitia of the dissected coronary arteries. The eosinophilic inflammation of the epicardial coronary arteries appearing in SCAD is considered to be the same finding as that in ECPA.

In the 50 autopsy cases of SCAD in the literature, as reported by Virmani et al., 42 (84%) were of women, 13 in the postpartum period, 2 in the third trimester, and 1 taking oral contraceptives. Sudden death was the most common outcome, occurring in 34 (64%) cases. Inflammatory infiltrates consisting of eosinophils in the adventitia of the vessels were described in 21 of the 32 patients in whom an inflammatory response was mentioned. All 21 of these patients were women. Cystic medial necrosis of the coronary arterial wall was described in 1 of the 10 male and 17 of the 40 female cases.

In relation to the results described above, Robinowitz et al. and Virmani et al. considered that the cause of the adventitial eosinophilic infiltration might be hypersensitivity or allergy. However, none of their 11 patients nor the 50 patients in the literature had any history of allergy. Moreover, no type of vasculitis was found in any other tissues or organs. Although the cause of eosinophilic infiltration limited to the adventitia of the epicardial coronary arteries is not known, they considered that infiltrating eosinophils containing lytic enzymes, and major basic protein might play an important role in the development of coronary arterial dissection.

After the report of Virmani et al., 15 cases of eosinophilic coronary periarteritis with SCAD were reported in the literature from 1987 to 2011 (Table 2 [14-22]). The case reported by Hunsaker et al. was of a 57-year-old woman who had a lifelong history of allergies to numerous agents, but no asthma or hypereosinophilia [15]. They considered that the eosinophilic inflammation limited to the adventitia of the epicardial coronary arteries was a special form (limited variant) of CSS. In contrast, Siegel and Koponen supposed that the eosinophilic inflammation of the epicardial coronary arteries was a special form (limited variant) of SCAD. In all 21 patients, the cause of eosinophilic inflammation limited to the adventitia of the epicardial coronary arteries was considered to be the same finding as that in ECPA.

It is a fact that all 11 cases of ECPA with SCAD reported by Virmani

| Case No. | Author (Pub. year) | Age | Sex | Clinical findings | Autopsy findings | Tissue Eo. | SCAD |
|----------|-------------------|-----|-----|------------------|-----------------|-----------|------|
| 1        | Dowling (1987)    | 27  | F   | Asthma, Hypereo. | SCD 290 g       | RCA (-) (+) | (+)  |
| 2        | Hunsaker (1992)   | 57  | F   | Allergy          | 430 g (++)      | LAD (-) (+) | (-)  |
| 3        | Siegel (1994)     | 36  | F   | Angina           | 300 g (++)      | LAD (-) (+) | (+)  |
| 4        | Bateman-1(1995)   | 34  | F   | Angina           | 280 g (++)      | LAD (-) (+) | (+)  |
| 5        | Bateman-2(1995)   | 40  | F   | Angina           | N.D. (++)       | LAD (-) (+) | (-)  |
| 6        | Basso-1 (1996)    | 43  | F   | Angina           | N.D.# (+)       | LAD N.D. (+)| (+)  |
| 7        | Basso-2 (1996)    | 50  | F   | Angina           | N.D.# (+)       | LAD N.D. (+)| (+)  |
| 8        | Basso-3 (1996)    | 48  | F   | Angina           | N.D.# (+)       | LAD, LCX N.D. (+)| (+) |
| 9        | Basso-4 (1996)    | 37  | F   | Angina           | N.D.# (+)       | LMC (-) (+)| (+)  |
| 10       | Salmo (2002)      | 55  | F   | Angina           | 360 g (+)       | LAD (-) (+) | (+)  |
| 11       | Lepper (2005)     | 43  | F   | Angina           | 470 g (++)      | LAD, LCX, RCA (+) | (-) |
| 12       | Sloukas-1 (2009)  | 43  | M   | Angina           | N.D. (+)        | LAD (-) (+) | (+)  |
| 13       | Sloukas-2 (2009)  | 39  | F   | Angina           | 327 g (++)      | LAD (-) (+) | (+)  |
| 14       | Fengping (2011)   | 53  | F   | Angina           | 235 g (++)      | LAD (-) (+) | (+)  |
| 15       | Omalu (2011)      | 64  | F   | Angina           | 330 g (+)       | LAD (-) (+) | (+)  |

Table 2: Reported cases of eosinophilic coronary periarteritis with spontaneous coronary artery dissection.
et al. and all but 1 of 15 cases in our review of the literature from 1987 to 2011 (Table 2) were of women. However, as shown in Table 1, all but 3 of 11 cases of ECPA without SCAD were of men. Although the etiology and pathogenesis of the coronary artery dissection are still unknown, it might be that female sex hormones play an important role in the appearance of the coronary artery dissection. As described above, the characteristic clinical and histological findings of ECPA were clearly different from those of PAN and AGA (CSS). Moreover, ECPA was frequently accompanied by SCAD, particularly in women.

We believe that many more cases of ECPA will be discovered by microscopic examination of coronary arteries at autopsy in cases of vasospastic angina (Prinzmetal’s variant angina) and sudden unexpected death, even when there is no obvious macroscopic evidence of coronary disease. The pathogenesis of ECPA remains unknown, although an allergic or immune-mediated mechanism might play an important role in the presence of eosinophilic inflammation around the vasa vasorum of the coronary arteries.

The diagnosis of ECPA has been made almost exclusively at autopsy and was very difficult to make during the clinical examination stage. However, vasospastic angina appearing mainly from the evening to early in the morning (Prinzmetal’s vasospastic angina) will be the most important symptom of this disease. When a patient presents with symptoms of Prinzmetal’s vasospastic angina, it could be supposed that the epicardial coronary arteries might be inflamed as the result of ECPA.

The treatment of this disease is still not established. Depending on the degree of eosinophilic inflammation of the coronary arteries, steroid therapy might be useful. This type of coronary inflammation might be an important disease entity not only in clinical cardiology but also in clinical pathology and forensic medicine.

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