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Case report

An autopsy case of eosinophilic coronary periarteritis with coronary arterial degeneration and repaired dissection

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ABSTRACT

Eosinophilic coronary periarteritis (ECPA) is a rare disease, almost exclusively diagnosed postmortem, characterized by a clinical course of vasospastic angina (VSA) attacks and histologically observed periarterial eosinophilic infiltration in the coronary arteries. Although the etiology of ECPA remains uncertain, its pathogenesis may be attributed to an allergic reaction. In addition, ECPA is often associated with spontaneous coronary artery dissection (SCAD); however, the pathogenesis underlying the link between inflammation and dissection remains unclear.

In the current case, a 45-year-old female experienced VSA attacks and succumbed to a fatal exacerbation of VSA approximately six years after the first onset of symptoms. Pathological examination at autopsy revealed periarterial eosinophilic infiltration in the coronary artery, suggesting ECPA. Characteristically, the pathological findings further showed localized SCAD with a repair response and deposition of a degenerative matrix in the tunica media. These findings may provide insights into the pathogenesis of ECPA.

This case highlights the importance of autopsy examinations for discussing and elucidating the pathophysiology of ECPA.

1. Introduction

Eosinophilic coronary periarteritis (ECPA) is characterized by vasospastic angina (VSA) of nocturnal and early morning onset. According to the accumulated literature, ECPA involves eosinophilic infiltration confined to the adventitia and periadventitial soft tissue of the epicardial coronary arteries, without evidence of systemic vasculitis.[1,2] Although the etiology of ECPA remains unclear, allergic- or immune-mediated mechanisms are believed to play a crucial role, considering the observed eosinophilic inflammation surrounding the coronary arteries.[2]

ECPA often coexists with spontaneous coronary artery dissection (SCAD) and predominantly affects females, with a reported male-to-female ratio of 1:14.[2] A case series on ECPA found that the coronary wall with eosinophilic inflammation exhibited no damage to either the medial smooth muscle or the internal elastic lamina.[1] Conversely, another case series reported that SCAD not only coexisted with ECPA but also with cystic medial necrosis (CMN), with at least some cases showing the simultaneous coexistence of both ECPA and CMN.[3] These findings suggest a potential link between ECPA, SCAD, and CMN pathogenesis.

Herein, we report a case in which a patient died suddenly following an exacerbated VSA episode and was diagnosed with ECPA at autopsy. This case revealed pathological findings of ECPA and was further characterized by localized SCAD with a repair reaction and CMN-like degeneration in the tunica media of the coronary wall.

The purpose of this case report was to discuss the pathogenesis of ECPA based on histopathological findings.

2. Case presentation

A 45-year-old female had been experiencing angina for approximately six years. Coronary angiography was not performed because echocardiography revealed no ischemic changes in the myocardium. Additionally, a 24-hr Holter electrocardiography did not detect ischemic changes, probably because no attacks occurred during the examination. The patient reported recurrent angina symptoms approximately once every six months, often occurring early in the morning and resolving

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with sublingual nitrate tablets.

She had received two doses of the coronavirus disease 2019 (COVID-19) vaccine, which was considered an mRNA vaccine, two years prior to her death. She had no history of asthma, and her blood tests showed no evidence of eosinophilia. The patient was a smoker and smoked 10–20 cigarettes daily. She was not taking any new medications, and her history of other allergic diseases was unknown.

Approximately one year before her death, she sought medical attention from her local doctor because of recurrent angina symptoms. At the time of consultation, the blood test showed no elevated creatine phosphokinase level (troponin levels were not examined). Electrocardiography did not reveal ischemic heart disease. However, the echocardiographic findings suggested myocarditis. Consequently, a polymerase chain reaction test for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was performed, yielding a positive result. Because the infectious agent was identified as SARS-CoV-2 and a diagnosis of COVID-19 was confirmed, no further investigations for myocarditis were undertaken. The patient complained of a persistent increase in the frequency of angina episodes following COVID-19 infection, albeit self-reported.

Approximately one year later, on the night of her death, the patient complained of “having an attack” and subsequently experienced cardiopulmonary arrest witnessed by her family. She was transported to the hospital, but resuscitation efforts were unsuccessful, and she was pronounced dead. At the hospital, the SARS-CoV-2 antigen test was negative.

Postmortem blood examination revealed that the anti-SARS-CoV-2 antibody titer was elevated to 5120 U/ml, which was consistent with a prior COVID-19 infection or vaccination when considered alongside the antigen test results. Antineutrophil cytoplasmic antibody (ANCA) tests were negative for both MPO-ANCA and PR3-ANCA.

After inspection by the police, the suspicion of criminal, accidental, or poisoning death was eliminated, and the death was judged to be an internal sudden death. A post-mortem examination was performed at the Osaka Prefectural Medical Examiner’s Office to determine the cause of death as part of a public health investigation. Post-mortem CT confirmed no lethal damage to the vital organs based on radiologic findings, and a general autopsy was performed without craniotomy.

The patient, who was 170 cm tall and weighed 72 kg, showed autopsy findings consistent with a sudden death. The heart weighed 510 g, indicating a hypertrophic heart, with a left ventricular anterior wall thickness of 1.3 cm and a right ventricular wall of 0.5 cm. Although no macroscopic stenosis was observed in either the right or left coronary arteries, serial sections of the bilateral coronary arteries were sampled for a detailed examination of coronary pathology.

Histopathological examination revealed substantial eosinophil-predominant infiltration of inflammatory cells in the adventitia and peri-adventitial soft tissue in the entire right coronary artery (RCA) (Fig. 1A and B). Immunohistochemical analysis identified prominent tryptase-positive mast cell infiltrates in the same regions as the eosinophilic infiltration (Fig. 1C). In contrast, the left coronary artery (LCA) showed no infiltration of inflammatory cells, including eosinophils or mast cells, unlike the RCA (Fig. 2A). In both the RCA and LCA, segmental CMN-like degeneration was observed in the tunica media, accompanied by fibrous matrix deposition, edematous changes, and damage to smooth muscle fibers (Figs. 1D and 2B, C). These changes were associated with the fragmentation of the medial elastic fibers and internal elastic lamina. Alcian blue staining was positive at the sites of CMN-like degeneration and edematous fibrous matrix deposition, indicating that the deposited mucoid extracellular matrix comprised acid mucopolysaccharides (Fig. 1E).

The intima of the RCA and LCA exhibited eccentric fibrous thickening in most areas, with minimal eosinophilic infiltration.

In the RCA wall, areas of replacement fibrosis extended from the intima to the tunica media. In some of these fibrotic areas, immature granulation tissue and organized fibrotic tissue were detected, with ruptured external and internal elastic laminae (Fig. 1F). Fibrotic replacement was likely caused by an injury to these elastic laminae. Additionally, in another area of the RCA, the vasa vasorum appeared to transition from the adventitia to a dissociation-like fissure at the interface with the intima, where the endothelial lining was observed at the transition to the fissure (Fig. 1G). The superficial intima of these fissures exhibited marked fibrous thickening. These findings suggested an old, localized dissection with repair responses affecting the entire tunica media, rather than degeneration caused solely by vasospasm. However, there was no evidence of fresh or large coronary artery dissection or

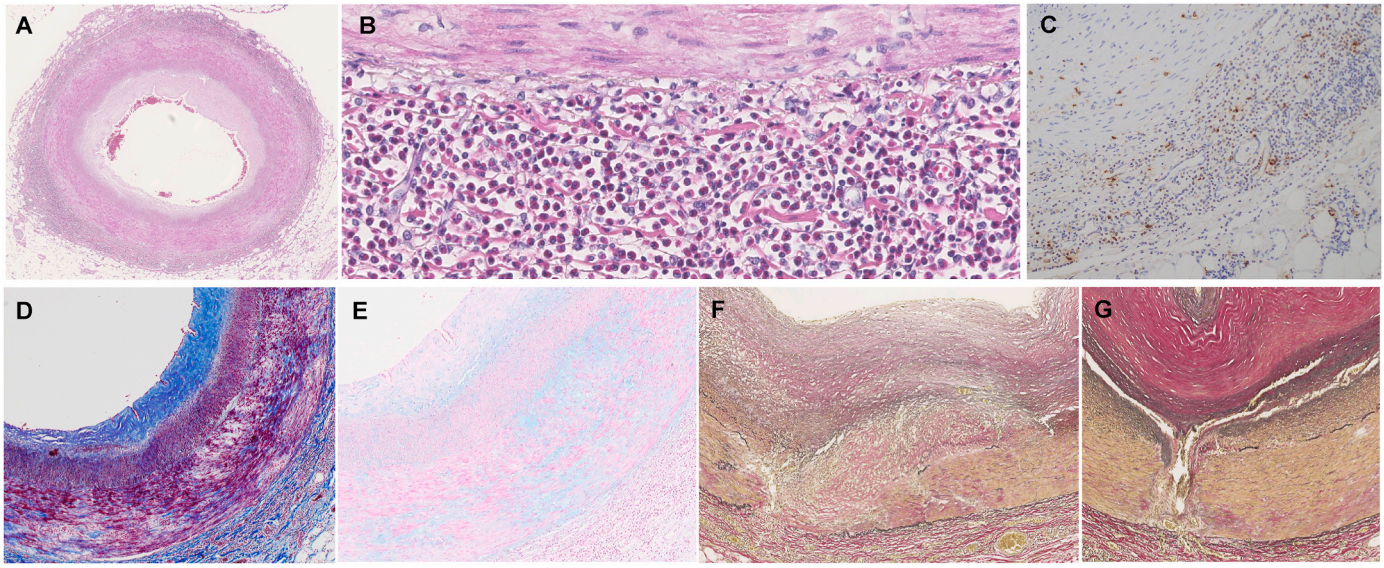

Fig. 1. Histopathological findings in the right coronary artery
(A, B) Hematoxylin and eosin staining, **(C)** immunohistochemistry for mast cell tryptase, **(D)** Masson’s trichrome staining, **(E)** Alcian blue staining, and **(F, G)** Elastica van Gieson staining.
(A, B) Eosinophil-predominant infiltration around RCA, **(C)** Mast cells infiltration positive for tryptase, **(D)** CMN-like degeneration in the tunica media, **(E)** Alcian blue positive of deposited degenerative matrix, **(F)** Replacement fibrosis from the intima to the tunica media, and **(G)** Vasa vasorum transitioning from the adventitia to the dissociation-like fissure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

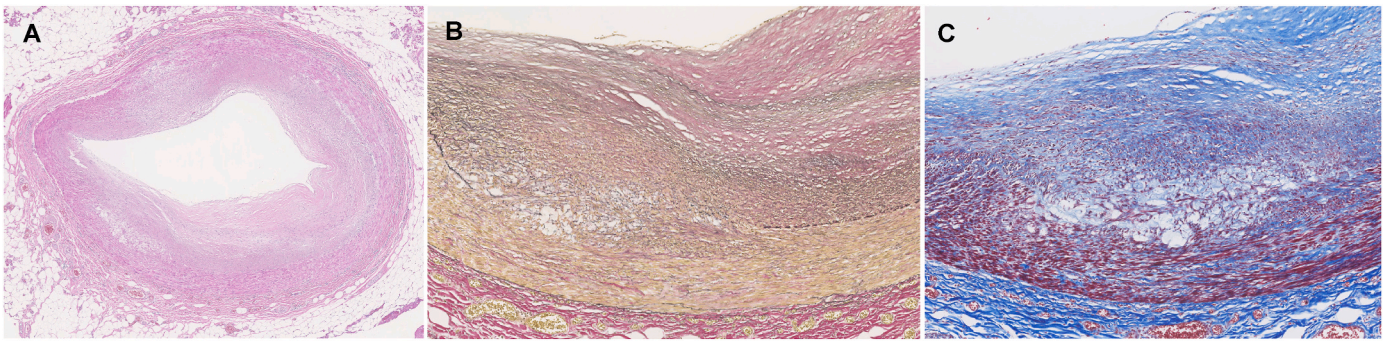

Fig. 2. Histopathological findings in the left coronary artery
(A) Hematoxylin and eosin staining, **(B)** Elastica van Gieson staining, and **(C)** Masson's trichrome staining.
(A) Fibrous thickening of the intima as in RCA, but no infiltration of inflammatory cells, including eosinophils, **(B, C)** CMN-like degeneration in the tunica media, accompanied by fibrous matrix deposition, edematous changes, fragmentation of elastic fibers, and damage to smooth muscle fibers.

luminal occlusion.

Both the RCA and LCA remained patent, with no signs of plaque disruption, fibrinoid necrosis, or granulomatous lesions.

In the myocardial wall, extensive fibrous thickening of the endocardium was observed, with a few eosinophils and interstitial fibrosis of the myocardium in the subendocardial region (Fig. 3A and B). Fibrous thickening of the endocardium and a few eosinophils may indicate a history of endomyocarditis. Additionally, small interstitial or perivascular fibrosis in the subendocardial myocardium was compatible with previous ischemic changes caused by vasospasms of the small coronary arteries (Fig. 3C). Myocardial degeneration in the apical myocardium was indicative of focal myocardial fiber damage caused by RCA vasospasms (Fig. 3D). Cardiac hypertrophy may have occurred due to compensatory mechanisms following ischemic and inflammatory changes. However, there was no evidence of fresh infarction, active myocarditis, or microvascular changes.

In addition to the heart, the thymus, thyroid, and spleen were examined histologically; however, these organs displayed no evidence of systemic vasculitis such as fibrinoid necrosis, granulomatous lesions, or other arterial wall degeneration.

The mapping between each panel of the figure and the above histological findings is shown in Table 1.

Table 1
Histopathological findings.

Right coronary artery (Fig. 1)	(A), (B)	Eosinophil-predominant infiltration of inflammatory cells in the adventitia and peri-adventitia (HE)
	(C)	Tryptase-positive mast cell infiltrates in the same regions as the eosinophilic infiltration (IHC)
	(D)	Segmental CMN-like degeneration in the tunica media, accompanied by fibrous matrix deposition, edematous changes, and damage to smooth muscle fibers (MT)
	(E)	Deposition of mucoid extracellular matrix comprised acid mucopolysaccharides at the sites of CMN-like degeneration (Ab)
	(F)	Replacement fibrosis from the intima to the tunica media with ruptured external and internal elastic laminae (EvG)
	(G)	Vasa vasorum transitioning from the adventitia to a dissociation-like fissure with endothelial lining, and superficial intima with marked fibrous thickening (EvG)
Left coronary artery (Fig. 2)	(A)	No infiltration of inflammatory cells, including eosinophils or mast cells, unlike RCA (HE)
	(B), (C)	Segmental CMN-like degeneration in the tunica media, like RCA (B, EvG; C, MT)
Myocardium (Fig. 3)	(A)	Extensive fibrous thickening of the endocardium (HE)
	(B)	A few eosinophils and interstitial fibrosis in the subendocardial region (HE)
	(C)	Small interstitial or perivascular fibrosis in the subendocardial myocardium (HE)
	(D)	Apical myocardial degeneration, indicative of focal myocardial fiber damage (MT)

HE, Hematoxylin and eosin staining; IHC, Immunohistochemistry staining; MT, Masson's trichrome staining; Ab, Alcian blue staining; EvG, Elastica van Gieson staining; RCA, Right coronary artery.

3. Discussion

Although prominent eosinophilic infiltration was observed exclusively around the RCA in the current case, this finding aligns with the histopathological features of ECPA, as eosinophilic infiltration reportedly impacts only a single coronary artery in some cases of ECPA.[1] Additionally, the clinical course suggesting VSA, as well as the prominent infiltration of tryptase-positive mast cells at the site of eosinophil infiltration, strongly supported the diagnosis of ECPA.[1,2,4] Furthermore, the characteristic coronary pathology findings in this case of ECPA were

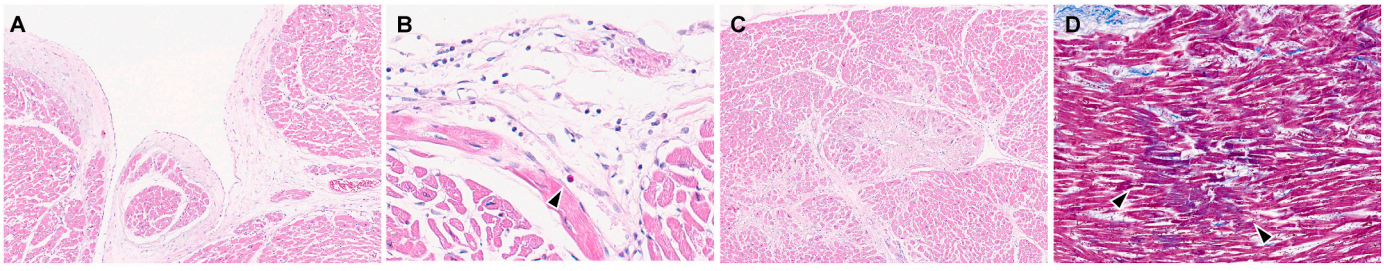

Fig. 3. Histopathological findings of the myocardium
(A, B, C) Hematoxylin and eosin staining and **(D)** Masson's trichrome staining.
(A) Thin fibrous thickening of the endocardium, **(B)** A few eosinophils in the endocardium (arrowhead), **(C)** Small interstitial or perivascular fibrosis in the subendocardial region, and **(D)** Myocardial degeneration in the apex, indicated by areas of Masson's trichrome staining discoloration (arrowhead).

localized dissection with a repair response and deposition of the degenerative matrix in the tunica media, indicating segmental CMN. These findings were consistent with the diagnosis of spontaneous coronary artery local dissection (localized SCAD) associated with adventitial eosinophilic inflammation or ECPA with localized dissection. The lack of a histological assessment of the aorta, lungs, and kidneys to exclude systemic vasculitis was a limitation of the pathological assessment in this case. However, the differential diagnosis of some typical vasculitis syndromes was excluded based on the lack of elevated ANCA levels in blood tests and histological assessment of the other organs sampled; therefore, the diagnosis of ECPA was considered appropriate. The dissection and degeneration of the tunica media observed in the present case were not described as characteristics of ECPA, as proposed by Kajihara et al.[1,2] However, Robinowitz et al. reported a series of SCAD cases in which adventitial eosinophilic infiltration and SCAD coexisted, and the assumption that some degeneration may occur in the tunica media is reasonable.[3] Indeed, according to that case series, ECPA coexisted with CMN in at least 7 of 46 cases of SCAD, suggesting a potential synergism between ECPA and CMN as a pathological etiology of SCAD.

The histopathological characteristics of this case included the observation that eosinophilic infiltration was confined to the RCA despite degeneration and destruction of the tunica media evident in the bilateral coronary arteries. This finding suggests that medial degeneration is not a result of ECPA. Even in the recently reported case of SCAD with ECPA and medial smooth muscle degeneration, it is speculated that this medial degeneration appears to have little association with eosinophilic inflammation and may be a non-inflammatory degeneration preceding dissection, as in fibromuscular dysplasia.[5] In this study, the temporal correlation between ECPA and medial degeneration is not discussed. However, in our case, medial degeneration may precede ECPA temporally, suggesting that medial degeneration is associated with the pathogenesis of both ECPA and SCAD. In addition, the replacement of fibrosis and granulation from the intima to the media observed in this case was atypical for a reparative response to dissection, considering that SCAD usually occurs at the adventitial-medial interface.[1,3] Differential diagnoses for such fibrous replacement may include inflammatory reactions resulting from a previous stage of arteritis, such as Kawasaki disease, and other less common arteritis, such as giant cell arteritis, Takayasu arteritis, and IgG4-related disease. This finding is also consistent with the reparative reaction resulting from damage following CMN-like degeneration in the tunica media. The scarring of the damage may indicate that medial degeneration has been progressing over a long period, developing from the early stages of the patient's history, and is consistent with the hypothesis that CMN-like degeneration is the most prior pathologic change.

The term "cystic medial necrosis" or "cystic degeneration" is now also referred to as "mucoid extracellular matrix accumulation (MEMA)".[6] MEMA is the primary pathologic substrate in hereditary connective tissue diseases, such as Marfan syndrome and Ehlers-Danlos syndrome, as well as non-inflammatory diseases of arteries such as fibromuscular dysplasia. Also, it can occur as a secondary phenomenon in many other pathological arterial conditions, including aging, smoking, hypertension, and pregnancy.[6] Therefore, MEMA, i.e., CMN-like degeneration, is a non-specific histological condition that describes the degeneration rather than the etiology. The association between disease categories with medial degeneration and eosinophilic inflammation is not common. However, considering that the process of degenerative matrix production has many different underlying causes, the hypothesis that eosinophilic inflammation may be induced by the degenerative matrix depending on its antigenic properties cannot be excluded.

Considering the pathophysiology of this case, although the patient had no documented allergic symptoms in the clinical course, the prominent infiltration of tryptase-positive mast cells at the site of eosinophil infiltration suggests an allergic pathogenesis. Furthermore, the clinical presentation strongly aligns with VSA, and such pathophysiology suggests the possibility of allergy-associated acute coronary syndrome, also known as Kounis syndrome.[7] Although it remains unclear whether the eosinophilic infiltration of ECPA is caused by allergic pathogenesis, the potential association between ECPA and Kounis syndrome has been suggested previously.[4,8] Thus, the histological findings in this case may also provide further evidence linking the pathogenesis of Kounis syndrome to ECPA.

If this case is indicative of Kounis syndrome, further exploration of potential allergens is warranted. Given the potential relationship between ECPA and medial degeneration with mucoid extracellular matrix deposition, it can be hypothesized that allergic eosinophilic infiltration is a response to the degenerative matrix in the coronary artery, as discussed above. It should be noted that the patient was a current smoker, and smoking might have contributed to the exacerbation of medial degeneration and coronary inflammation.[6] Considering that the allergic reaction was localized to the coronary artery wall, it is plausible that systemic allergic symptoms were absent during the patient's clinical course. The absence of a response to the degenerative matrix deposited in the LCA could be attributed to qualitative or quantitative variations in degeneration or deposition, influencing the severity of the reactions. There are some limitations to this speculation. First, in this case report, we have merely hypothesized the association between medial degeneration and eosinophilic inflammation. Whether certain types of mucoid extracellular matrix can induce eosinophilic inflammation requires further biological verification. Second, the degenerative matrix of the coronary stroma was observed in a relatively young patient in this case, and, therefore, genetic mutations encoding connective tissue genes should be considered in the differential diagnosis as an essential etiology of medial degeneration. The limitation of the pathological assessment in this case was that genetic testing for connective tissue disorders or inherited vasculopathies was not performed, and further biological research on similar cases is desirable in the future.

Another characteristic of the clinical course in this case was an increased frequency of angina episodes following the COVID-19 infection, suggesting a possible association between COVID-19 and Kounis syndrome.[9] Incidentally, it cannot be ruled out that there may be a possible link to vaccination. However, the vaccination was performed one year prior to the COVID-19 infection; therefore, the relationship between angina attacks and vaccination remains unclear based on the temporal association. Notably, VSA with an allergy-like etiology occurring shortly after SARS-CoV-2 detection has been reported, suggesting Kounis syndrome.[10] Meanwhile, in the current case, active reinfection with COVID-19 was ruled out by antigen testing and pathological findings at the time of the fatal attack; thus, the pathophysiology was not a simple immediate allergic reaction to a viral antigen. Given the possibility that the potential allergen is the degenerative matrix deposited in the tunica media, the SARS-CoV-2 antigen may have triggered a cross-allergic reaction in the degenerative matrix. However, one limitation of this hypothesis is the lack of evidence beyond a temporal association. Additional biological evidence regarding the antigenic properties of the SARS-CoV-2 antigen and mucoid extracellular matrix should be obtained in the future.

4. Conclusion

In the current case, the clinical course and histopathological findings suggest a diagnosis of ECPA. This case is characterized by findings of eosinophilic inflammation in the RCA and localized SCAD with a repair reaction, along with the deposition of CMN-like degenerative matrix in the tunica media of both coronary walls. The distribution of pathological changes, that is, eosinophilic inflammation, dissection, and degenerative matrix, suggests that CMN-like degeneration may have been a prior etiology of ECPA in this case, and both pathologies may have acted synergistically to induce SCAD.

The limitations of the pathological speculation in this case include the unknown genetic mechanism underlying tunica media degeneration,

the antigenic properties of the degenerative matrix, which appears to be the essential cause of ECPA, and the unclear relationship between degeneration and VSA. Further studies on similar cases are needed to elucidate these mechanisms and improve our understanding.

Ethical approval and informed consent

The study was conducted in accordance with the Declaration of Helsinki 2013. Our institution did not require ethical approval for this case report. This case report was retrospective in nature and did not include any studies involving living human participants. This article contains no personal or identifiable information; thus, the identity of the deceased is completely confidential. For these reasons, informed consent was not required.

Author contributions

H.Y. was the main autopsy operator, performed the histological examinations, and drafted the original manuscript. Y.I. and K.H. performed the histological examinations and advised on the pathological analyses. E.M. and other authors contributed substantially to the revision of the manuscript.

All authors approved the submitted version of the manuscript, agreed to be personally accountable for the authors' contributions, and ensured that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, were appropriately investigated and resolved, as documented in the literature.

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Declaration of conflicting interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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