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Case Report

Acute Myocardial Infarction due to Cardiac Allograft Vasculopathy: An Autopsy Report

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After the Organ Transplant Act was enforced in 2000, the criteria for the diagnosis of brain death have been legalized, and cardiac transplantation has become a promising treatment choice for patients with chronic heart disease. Even though more than hundreds of cases have been accumulated in the national registry and the survival rates are increasing, the compliance of long-term survivors may decrease paradoxically, which can hinder the efforts to enhance the quality of the registry. The patients who are lost from the doctor's surveillance and die outside hospitals should be appropriately examined to determine the cause of death so that the influence of their medical condition, if any, on their death could be revealed. Here, we report an autopsy case of a patient who died of a complication of chronic rejection after cardiac transplantation.

Key Words: Heart transplantation; Graft rejection; Coronary vessels; Cause of death; Myocardial infarction

Introduction

Cardiac transplantation has been established as a reliable treatment option for patients with various chronic heart diseases. In Korea, 1,319 cases of cardiac transplantation have been performed from 2000 to 2016, and more than 100 patients a year are currently operated [1,2]. With the development of surgical technique and immunosuppressant regimens, the prognosis of the recipients also has improved continuously. In the 2000s, the 5-year and 10-year survival rates were approximately 75% and 60% respectively in the western countries [3]. The long-term survival data in Korea also show compatible outcomes [4]. For the improvement of survival rate and quality of life, every cardiac recipient needs regular long-term follow-up with monitoring of acute and chronic complications such as graft rejection and side effects of drugs. Patient compliance is mandatory for these management approaches; however, it decreases over

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time with loss of alertness to their original disease.

Cardiac allograft vasculopathy (CAV), described as diffuse concentric narrowing of coronary arteries, can lead to intracoronary thrombosis, and even acute myocardial infarction and sudden death. The number of recipients who die due to CAV gradually increases during the first year of cardiac transplantation, and since then, its proportion among the causes of death in cardiac recipients maintains about 10% consistently [3]. Considering that the number of patients who are lost from medical surveillance system generally increases, these patients could be encountered in forensic practice without detailed medical records. They should be differentiated from the ordinary cases of acute cardiac death and diagnosed appropriately, not only for the benefit of the deceased and their bereaved family, but also for the treatment of other recipients and improvement of the national health system. To discuss these issues, we present here an autopsy case of a cardiac transplant recipient with multiple types of rejection including CAV followed by acute myocardial infarction.

Case Report

A 51-year-old man suddenly collapsed while drinking with his friends and died soon, despite resuscitation. His family reported that he had suffered from a cardiac arrest about 5 years ago and had undergone cardiac transplantation 2 years after the incident. He had visited the hospital every 2–3 months for regular follow-up and drug prescription, but did not do so for the past 7–8 months.

The victim had approximately 25-cm length of surgical scar on the midline of his chest. The epicardium was strongly adhered to the pericardium in its entire aspect. The heart, including the roots of the great vessels was resected, and it weighed 728 g. The great vessels and both atria had been sutured, joining the donor heart and recipient part by ordinary surgical techniques and there was no complication. The vascular walls of all three major coronary branches showed diffuse concentric thickening with severe stenosis in up to 80% of the lumen and yellowish discoloration in only focal areas, which was suggestive of CAV. In the cross section of the myocardium, a focal dark area due to ischemic necrosis was observed in the lateral wall of left ventricle. These gross findings are presented in Fig. 1.

Microscopic examination revealed intimal hyperplasia and intraluminal thrombosis in multiple coronary arteries. There was no definite evidence of atherosclerosis, such as foam cell or inflammatory cell collection, cholesterol cleft, and calcification. The dark area of the lateral wall of left ventricle noted in the gross examination showed diffuse myocyte necrosis, neutrophil infiltration, karyorrhexis, and interstitial edema. Mixed inflammatory cells infiltrating through the epicardial and intramyocardial vascular walls and myocardial interstitium could be diagnosed as severe acute cellular rejection (ACR). Moreover, C4d staining was positive in some intramyocardial capillaries, even though they were not adequate to satisfy the immunopathologic criteria of antibody-mediated rejection (AMR). These microscopic findings are presented in Figs. 2–4, according to the types of rejection they are related to.

Some drugs, such as diphenhydramine and lidocaine, were found within the therapeutic range in the deceased's blood, but no immunosuppressant was detected. This absence of immunosuppressant in the blood appeared to be the cause of severe ACR. No other injury or disease was found in the autopsy. According to the above autopsy findings, the cause of his death was suspected to be acute myocardial infarction resulting from CAV, a chronic form of cardiac rejection.

Discussion

The mechanism of transplant rejection could be divided into cellular and humoral (antibody-mediated), but the actual manifestations are different among the transplanted organs. There are three types of cardiac transplant rejection, namely ACR, AMR, and CAV. As in the present case, it is not infrequent that a patient has more than one type of rejection simultaneously. The interaction and synergistic effect between the acute and chronic rejections during their development and progression are also well known these days [5,6].

ACR is primarily due to the T cell-mediated response of the recipient against the allograft tissue, while AMR is related to the complement system activation,

resulting in direct injury to the allograft tissue. Although the incidence and severity decrease over time, these types of acute rejection can occur any time after transplantation.

CAV is known to be the most critical factor in the long-term survival of both the recipient and the allograft. Although the International Society for Heart and Lung Transplantation proposed a clinical classification system of CAV based on coronary angiographic findings in 2010 [7], the initial concept of CAV was suggested based on pathologic findings, such as diffuse concentric intimal hyperplasia [6,8], different from atherosclerosis, which generally shows focal eccentric narrowing with yellowish plaques (and/or calcifications). CAV is one of the most common findings in a cardiac recipient, as it begins to appear in the first year of transplantation, and is found in about half of the recipients after 10 years [6]. Immunologic factors including inflammation, mismatching of histocompatibility leukocyte antigen, and endothelial activation, and non-immunologic factors like age, sex, smoking, and underlying condition of both donor and recipient are known to be related to the development of CAV. Previous or simultaneous existence of ACR, or AMR, or its degree is also known to have a positive relationship with CAV [4–6]. The heart of the deceased in this report also showed CAV and severe ACR at the same time.

Like other coronary artery diseases, CAV can be a

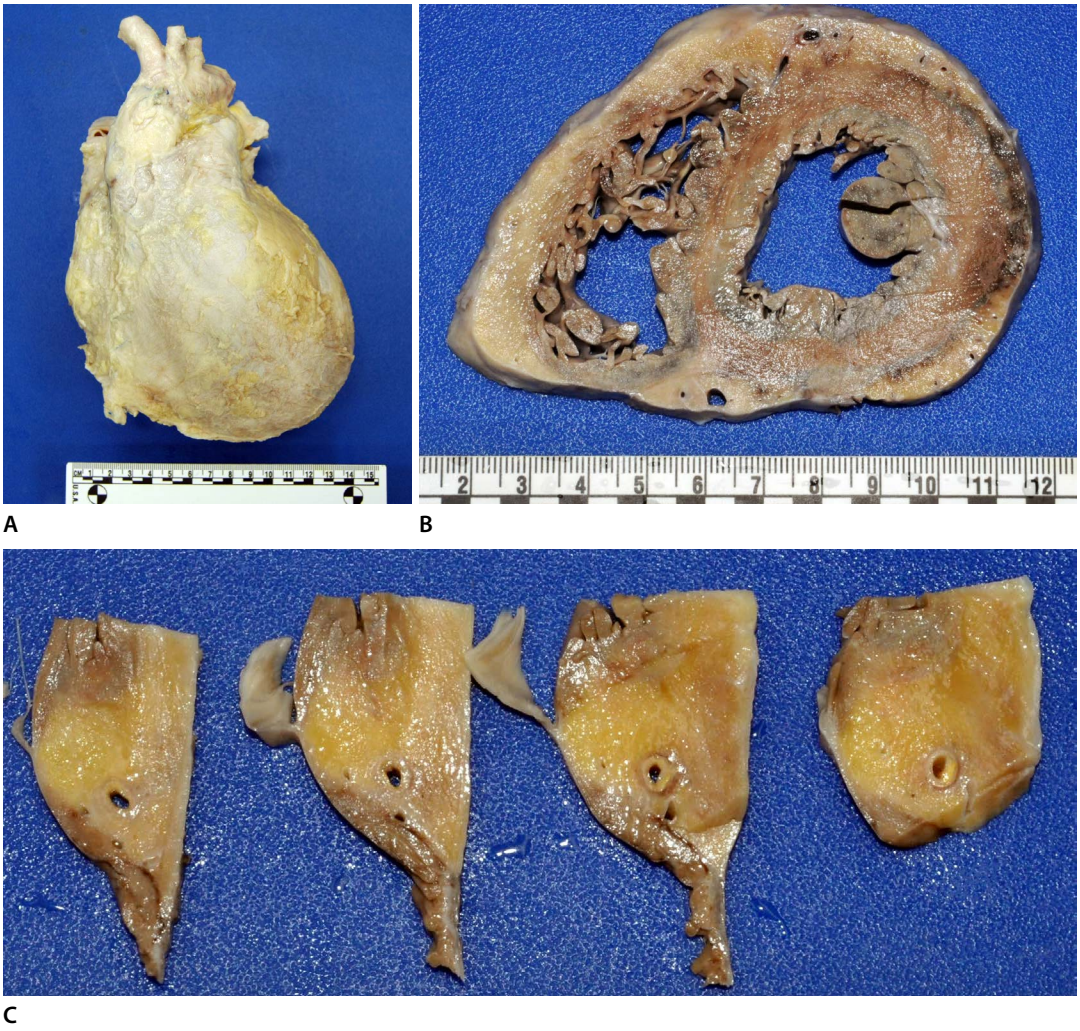

Fig. 1. Gross findings of formalin-fixed heart and coronary arteries of the deceased. (**A**) The heart is enlarged and the entire epicardium is adhered to the pericardial sac. (**B**) Cross section of the lateral wall of left ventricle shows focal discoloration which implies ischemic necrosis. (**C**) In the serial section of major coronary arteries, the lumens are narrowed due to diffuse concentric wall thickening (left circumflex artery).

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cause of arrhythmia, myocardial infarction, and sudden cardiac death. However, the patient with CAV does not feel any chest pain that could be a warning sign, whether typical or not, because the donor heart has been denervated during transplantation and separated from the recipient's nerve system. Unfortunately, there is still no standardized prevention or treatment option for CAV, whereas the main target of an immunosuppressant is acute rejection [4,6]. It emphasizes the importance of high level of suspicion for CAV with regular monitoring using echocardiography. Moreover, even after CAV is diagnosed, revascularization is indicated in a few restricted groups because of the nature of CAV, diffuse involvement to multiple coronary branches. Most of remaining cases require timely re-transplantation. Recently, the data for long-term prognosis of cardiac transplantation have been accumulated in Korea, and some of them that have been published [4,9] show comparable or even better outcomes than international results [4]. Additionally, the Korean Organ Transplant Registry, established in 2014, integrated pre- and post-transplantation data, with the aim of "standardization, research, and planning of patient care" [2]. For successful maintenance of the registry, the included patients

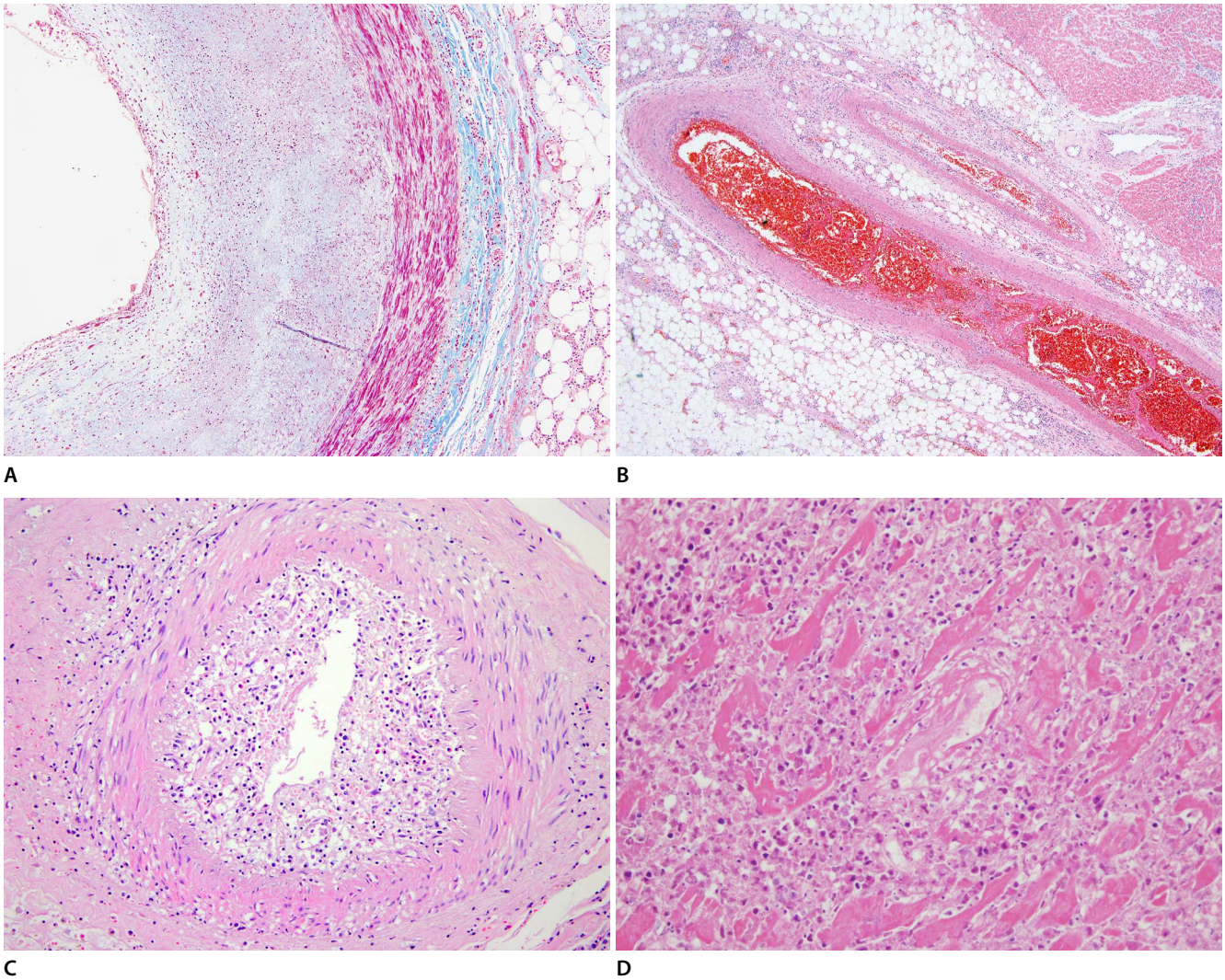
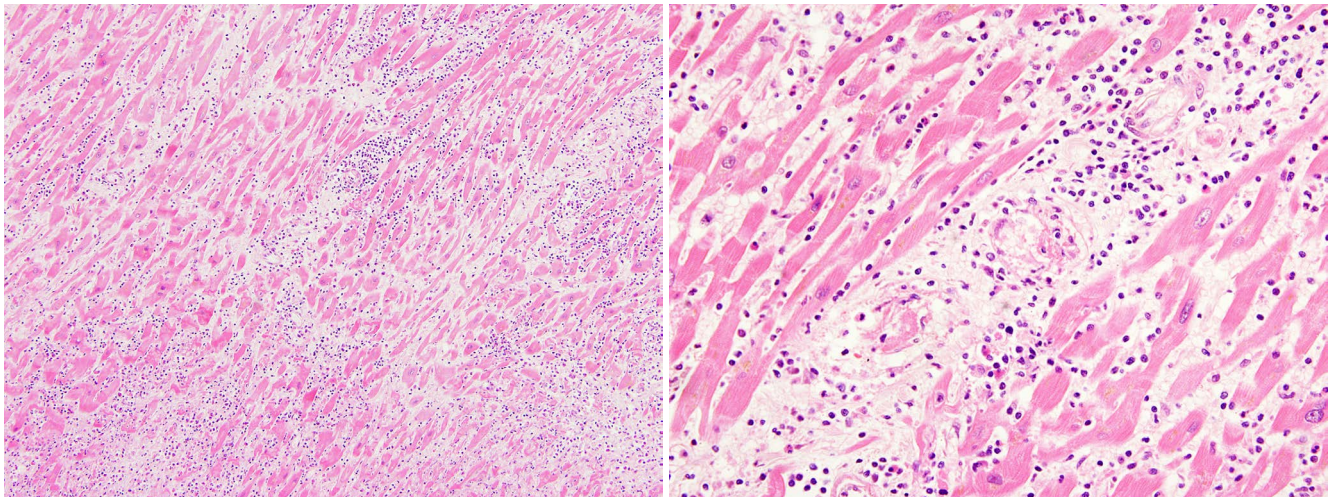


Fig. 2. Microscopic findings of cardiac allograft vasculopathy and related myocardial infarction. (**A**) The cross-section of the coronary artery shows intimal hyperplasia with inflammatory cell infiltration (Masson-Trichrome stain, ×100). Intraluminal thrombosis (**B**, H&E stain, ×40) and arteritis (**C**, H&E stain, ×200) observed in subcoronary branches. (**D**) The ischemic area shows extensive myocyte necrosis and karyorrhexis (H&E stain, ×400).



A B

Fig. 3. Microscopic findings of acute cellular rejection. Dense infiltration of mixed inflammatory cells is observed in myocardial interstitium, which is mainly composed of lymphocytes and monocytes, accompanied by myocyte injury and intramyocardial vasculitis (**A**, H&E stain, ×100; **B**, H&E stain, ×400).

should be monitored for a long time to get adequate prognostic data. Especially, when a patient dies, the cause of death should be determined accurately by an expert, which would be mandatory for the assessment of morbidity and mortality of the registry. However, under the death management system of Korea, which does not obligate detailed examination by an impartial third party for any natural death, most of the cases of deaths outside hospital could be lost from the registry. It could be a reason for the relatively low mortality rate attributed to CAV in Korea [9]. The deceased in this report also could have been, like other victims of ordinary natural deaths, dismissed without knowing the relationship between his death and cardiac transplant, if autopsy had not been performed.

To minimize loss of the data, medical history of the deceased should be carefully collected during postmortem inspection, and thorough pathologic examination should be performed during autopsy. A lot of information could be obtained even from routine gross examination and standard hematoxylin and eosin staining method. Attention of the medical examiner would be the most momentous factor for securing valuable information.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

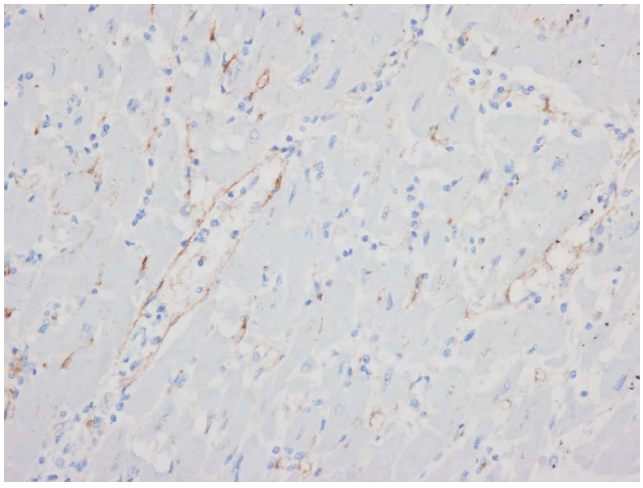


Fig. 4. Microscopic findings of antibody-mediated rejection. Some myocardial capillaries are positively stained with C4d stain (×400).

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