



Case Report

Fatal Dieulafoy lesion with IgG4-related disease: An autopsy case report



Masashi Miyao^{a,*}, Chihiro Kawai^c, Hirokazu Kotani^b, Hirozo Minami^a, Hitoshi Abiru^a, Hideki Hamayasu^a, Akira Yamamoto^c, Keiji Tamaki^a

^a Department of Forensic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

^b Department of Forensic Medicine and Sciences, Mie University Graduate School of Medicine, Mie, Japan

^c Center for Medical Education, Kyoto University Graduate School of Medicine, Kyoto, Japan

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ABSTRACT

Dieulafoy lesions are rare vascular malformations of the gastrointestinal tract; however, they can lead to fatal vascular bleeding. Immunoglobulin G4-related disease (IgG4-RD) is a rare systemic fibroinflammatory disease involving multiple organs, including the vasculature. To date, no autopsy reports of Dieulafoy lesions with IgG4-RD have been described in the literature. A 48-year-old man was found dead in his home with hematochezia. Postmortem computed tomography revealed high-density gastric contents and an enlarged iso-density area in the pancreas, indicating gastric hemorrhage and mass-forming lesions. Macroscopic and histological examinations revealed an ulcer of the body of the stomach with a large amount of hemorrhage from the enlarged artery in the submucosal layer, confirming the rupture of the Dieulafoy lesion. Moreover, lymphocyte infiltrations with increased IgG4 positive cells were found in the pancreas, thyroid gland, and arteries in non-ulcer regions of the stomach, suggesting IgG4-RD. Serum biochemical analysis showed elevated levels of inflammatory mediators, such as IgE, soluble-interleukin-2 receptor, and C-reactive protein. These findings suggest that systemic inflammation caused by IgG4-RD could, at least in part, contribute to the development of Dieulafoy lesions and fatal rupture of the lesion. This case report highlights the importance of autopsy research focusing on Dieulafoy lesions and IgG4-RD to promote awareness and a better understanding of the relationships between these treatable diseases to establish earlier and effective interventional strategies for better patient outcomes.

1. Introduction

Dieulafoy lesions are rare vascular malformations of the wall of the gastrointestinal tract [1]. They are most commonly found in the stomach and rupture of the abnormally enlarged arteries within the lesion can lead to life-threatening hemorrhage. Mortality due to the rupture of Dieulafoy lesions has been reported to be approximately 80%, although recent advances in endoscopic therapy have reduced mortality significantly to only 8% [1]. However, the true mortality resulting from lesion rupture may be underestimated due to the rarity of the disorder and a consequent lack of awareness by clinicians and the general population.

IgG4-related disease (IgG4-RD) is a rare autoimmune disease characterized by high serum levels of IgG4, mass-forming lesions in multiple organs such as a pancreas and a thyroid gland, and abundant tissue infiltration by IgG4-positive plasma cells [2]. Although the all-cause

mortality in patients with IgG4-RD has not been reported to be higher than that in the general population [3], it has been observed that IgG4-RD may involve systemic aortic/arterial inflammation and aneurysm formation, including abdominal aortic aneurysm [4]. To our best knowledge, no cases of fatal Dieulafoy lesions in the gastric artery associated with IgG4-RD have been reported in the literature. Here, we report an autopsy case in which death resulted from hemorrhage due to the rupture of a Dieulafoy lesion in a patient with IgG4-related disease.

2. Case history

2.1. Clinical history

A 48-year-old Japanese man was found lying unconscious on the floor of his home by his elder sister. She observed evidence of

Abbreviations: CD4, cluster of differentiation 4; CRP, C-reactive protein; CT, computed tomography; IgG4, immunoglobulin G4; IgG4-RD, immunoglobulin G4-related disease; H-FABP, heart-type fatty acid-binding protein; NSAIDs, nonsteroidal anti-inflammatory drugs; sIL2R, soluble-interleukin-2 receptor.

* Corresponding author at: Department of Forensic Medicine, Kyoto University Graduate School of Medicine, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.

E-mail address: miyaom@fp.med.kyoto-u.ac.jp (M. Miyao).

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hematochezia, probably due to gastrointestinal bleeding. However, no trace of vomiting of blood (hematemesis or hemoptysis) was detected at the scene. She immediately called an ambulance, and the paramedics arrived at the scene six minutes after the call. However, it was apparent that the patient had already died as rigor mortis had begun throughout his body, and he was thus not taken to an emergency hospital.

At the age of 22 years, the patient had been diagnosed with autism spectrum disorder, hyperlipidemia, and hypertension. Although he had previously received medical treatment, five years before his death, he suddenly stopped going to the hospital without notice. During these five years, he had not received any treatment or taken any medication. Five days before his death, the patient complained of mild headache and fatigue. One day before death, he told his sister of a worsening headache. She advised him to see a physician, but he refused. The next day, she visited him to take care of him but found that he was dead.

As he had refused to take any medication, he did not treat his headache with nonsteroidal anti-inflammatory drugs (NSAIDs), a common risk for gastrointestinal bleeding. To the best of his sister's knowledge, he had never been diagnosed with diseases that could be directly responsible for gastrointestinal bleeding. His sister mentioned that he did not drink alcohol but had a history of daily smoking. He had no familial history of sudden unexpected death, hematopoietic disorders, or autoimmune diseases. He did not complain of symptoms of heart disease, such as chest pain, palpitation, and shortness of breath.

To determine the cause of death, a complete autopsy was performed two days after death.

2.2. Autopsy findings

Postmortem computed tomography (CT) revealed a slightly higher than normal density in the gastric contents suggesting upper gastrointestinal bleeding and a slightly enlarged iso-density area in the pancreatic tail (Fig. 1A, B). The visceral adipose tissue area calculated by CT was slightly increased to 140 cm² (clinical reference value, <100 cm²). The deceased was 168 cm tall and weighed 75.5 kg, with a body mass index of 26.8 kg/m², which falls in the range of mild obesity for his age in Japan. External examination of the whole body showed no signs of traumatic injuries (e.g. abrasions, bruises) or bleeding disorders (e.g. enlarged lymph nodes, jaundice). No signs of malformation such as arachnodactyly ("spider fingers"), which is a feature of Marfan syndrome that could be involved in aortic and arterial aneurysm development, were identified. Consistent with the clinical history and CT findings, the presence of a large amount of hematochezia, whitish changes in skin coloration, severely reduced lividity, and severely reduced congestion levels in several organs, including the liver and kidneys, suggested severe anemia owing to gastrointestinal bleeding.

Internal examination revealed bright-red hemorrhage (590 ml) in the gastrointestinal contents (all the contents were blood and blood clots) and an ulcer (1.5 × 1.0 cm) in the stomach showing evidence of the

rupture of an extremely enlarged artery (Fig. 2A, B), suggesting that the hemorrhaging had resulted from the rupture of a Dieulafoy lesion. The gastric contents included not only bright red-colored hemorrhages but also heterogeneous dark red and white blood clots, suggestive of repetitive hemorrhages (Fig. 2C). The pancreas was mildly enlarged even in the presence of severe anemia, as shown by a pancreas weight of 153 g (reference value, 107 ± 38 g) [5]. A homogeneous white-colored mass was found in the tail of the pancreas (Fig. 2D–F). The heart was severely hypertrophic, with a weight of 630 g (reference value, 370 ± 73 g). The amount of the blood in the heart was reduced to 100 ml (the mean blood volume of a 40–50 year old man is approximately 300–400 ml as reported in our institution). Although intermediate to severe atherosclerotic changes were found in the coronary arteries (50% in right coronary artery, 75% in left anterior descending artery, and 50% in circumflex artery), thoracic and abdominal aorta, and basilar arteries of the brain, no signs of infarctions, aneurysms, or ruptures were observed, except for the gastric artery. The liver weighed 1467 g (reference value, 1497 ± 341 g), and a mild yellowish (steatotic) change was observed. Macroscopically, the thyroid gland showed no pathological changes and weighed 21.2 g (reference value, 17.3 ± 5.5 g). No drugs, toxins, or alcohol were identified in the serum or urine by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Tests for hepatitis B and C viruses were negative. A screening test for cardiac injuries using a heart-type fatty acid-binding protein (H-FABP) was negative.

Histological examination revealed that the ruptured artery in the stomach ulcer was located in the submucosal layer (Fig. 3A–E). The artery was profoundly enlarged (over 10-fold increase) compared with arteries in the submucosal layers of non-ulcerated areas (Fig. 3F), confirming that the ruptured artery was a Dieulafoy lesion [6]. Neutrophil accumulation and lymphocyte infiltration were observed in the lesion. Interestingly, several normally sized arteries in the non-ulcerated area also showed lymphocyte infiltration (the inset of Fig. 3F). Moreover, immunohistochemical staining for IgG4 (anti-IgG4 antibody, MA5-24862, Invitrogen/Thermo Fisher Scientific, Waltham, MA, USA) and IgG (anti-IgG antibody, ab109489, Abcam, Cambridge, MA, USA) showed an increased number of IgG4-positive cells (IgG4/IgG-positive cell ratio >40% and IgG4-positive plasma cells >10/high power field) in the area surrounding the arteries (Fig. 3G–I). Most of the IgG4-positive cells showed cartwheel appearance, which was suggestive of increased numbers of IgG4-producing plasma cells (Fig. 3H). Lymphocyte infiltration around the ulcer lesion was not associated with an increase in IgG4-positive cells (data not shown), possibly due to protein denaturation by the ulcer. Macroscopic examination of the whitish mass in the pancreas showed the presence of storiform fibrosis (swirling type of fibrosis) and obliterative phlebitis (fibrous venous obliteration), which are key features of IgG4-RD (Fig. 4A, B). In addition, substantial inflammatory changes with the destruction of parenchymal and ductal cells and an increased number of IgG4-positive cells were also observed

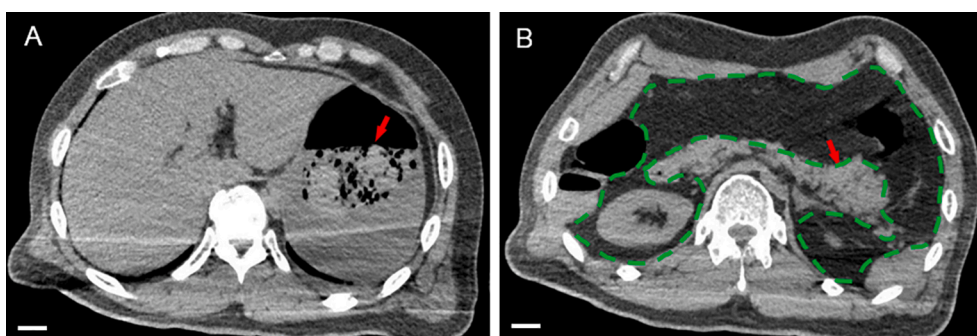


Fig. 1. Postmortem computed tomography images. (A) A coronal image of the upper abdomen shows slightly increased density of the gastric contents, suggestive of upper gastrointestinal bleeding (arrow). (B) A coronal image of the middle abdomen shows a slightly enlarged iso-density area in the pancreatic tail (arrow). Increased area of visceral adipose tissue (highlighted by a dotted line), a marker of visceral obesity, is shown. Bars represent 2 cm.

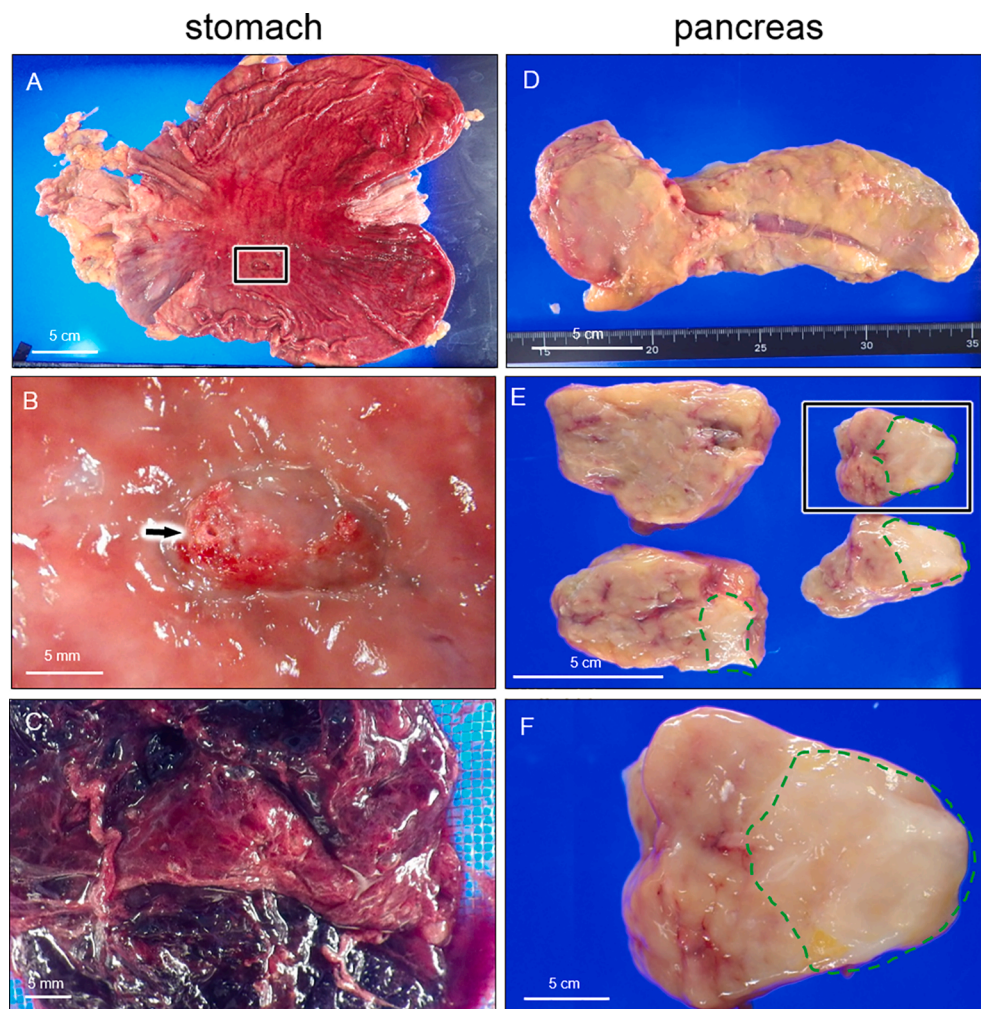


Fig. 2. Macroscopic findings of the stomach and pancreas. (A) Bright red-colored hemorrhages are visible in the gastric mucosa. (B) High magnification image highlighted by the black box in (A). The arrow indicates rupture of an abnormally enlarged artery in the ulcer lesion. (C) Abundant clots present in the gastric content. (D) Mildly enlarged pancreas. (E) Abnormal white-colored mass (highlighted by dotted line) is visible in the pancreatic tail. (F) High magnification image of boxed area in (E). The dotted line highlights the white-colored mass in the pancreatic tail.

(Fig. 4C–F). Although the thyroid gland showed no obvious pathological changes on macroscopic examination, similar lymphocyte infiltration, parenchymal cell destruction, and increased numbers of IgG4-positive cells were found (Fig. 4G–J). Consistent with the macroscopic observation of hemorrhages and clots in the gastric contents (Fig. 2C), substantial infiltration of hemosiderin-laden macrophages was seen in the lungs (Fig. 4K), again suggestive of repeated hemorrhaging. The bone marrow showed an increased tendency toward hematopoietic cell cellularity with a ratio of 70–90% (reference value in 40-year-old, 40–80%) (Fig. 4L). The heart showed hypertrophic changes with mild perivascular fibrosis, consistent with hypertensive heart disease; however, no signs of inherited cardiomyopathy or myocarditis were observed. A hyaline cap was visible in the kidney glomerulus which is a sign of diabetic nephropathy. No pathological changes were observed in the other organs. No signs of malignancy were found in any organ except for slight atypical changes in the parenchymal cells of the pancreas and thyroid gland, possibly due to inflammatory reactions.

In the serum biochemical analysis, although the levels of IgG4 and IgG2, qualitative markers of IgG4-RD, were within normal ranges, those of IgE, C-reactive protein (CRP), and soluble-interleukin-2 receptor (sIL2R), quantitative markers for active IgG4-RD and systemic inflammatory changes were markedly increased, consistent with a diagnosis of active IgG4-RD (Table 1). We could not obtain sufficient blood to perform complete blood counts, including measurement of the hemoglobin level, due to the blood loss caused by the hemorrhages, and we prioritized serum analysis rather than complete blood tests for the evaluation of IgG4-RD and inflammation.

3. Discussion

Based on the clinical history and autopsy findings, we concluded that the cause of death was hemorrhagic shock resulting from the rupture of the Dieulafoy lesion in the stomach. As IgG4-RD has been reported to be associated with a higher incidence of systemic inflammatory arteritis including abdominal aortic aneurysm [7], we believe that IgG4-RD could, at least in part, have contributed to the development of the Dieulafoy lesion and his death.

Dieulafoy lesions are thought to be congenital vascular anomalies [8], therefore, medical treatments cannot fundamentally reduce their prevalence. However, due to advances in endoscopic therapy, mortality resulting from lesion rupture can be almost completely prevented, especially in the case of an early diagnosis [9]. In this case, we consider that, if he had gone to the hospital immediately after experiencing headache and fatigue, and had received endoscopic treatment, he may have survived, as the symptoms were likely secondary phenomena caused by anemia resulting from repeated hemorrhaging [10], as evidenced by the heterogeneous dark red and white blood clot in the gastric contents. Unfortunately, because the patient refused all medical interventions, he did not seek a diagnosis for his worsening symptoms and thus did not receive treatment and died.

Definitive diagnosis of IgG4-RD is challenging because of the unknown mechanisms underlying the disease and difficulties in differential diagnoses [11]. In this case, the patient had the overall radiological and macroscopic characteristics of IgG4-RD, and dense lymphocyte infiltrations with increased IgG4-positive cells were found in the thyroid

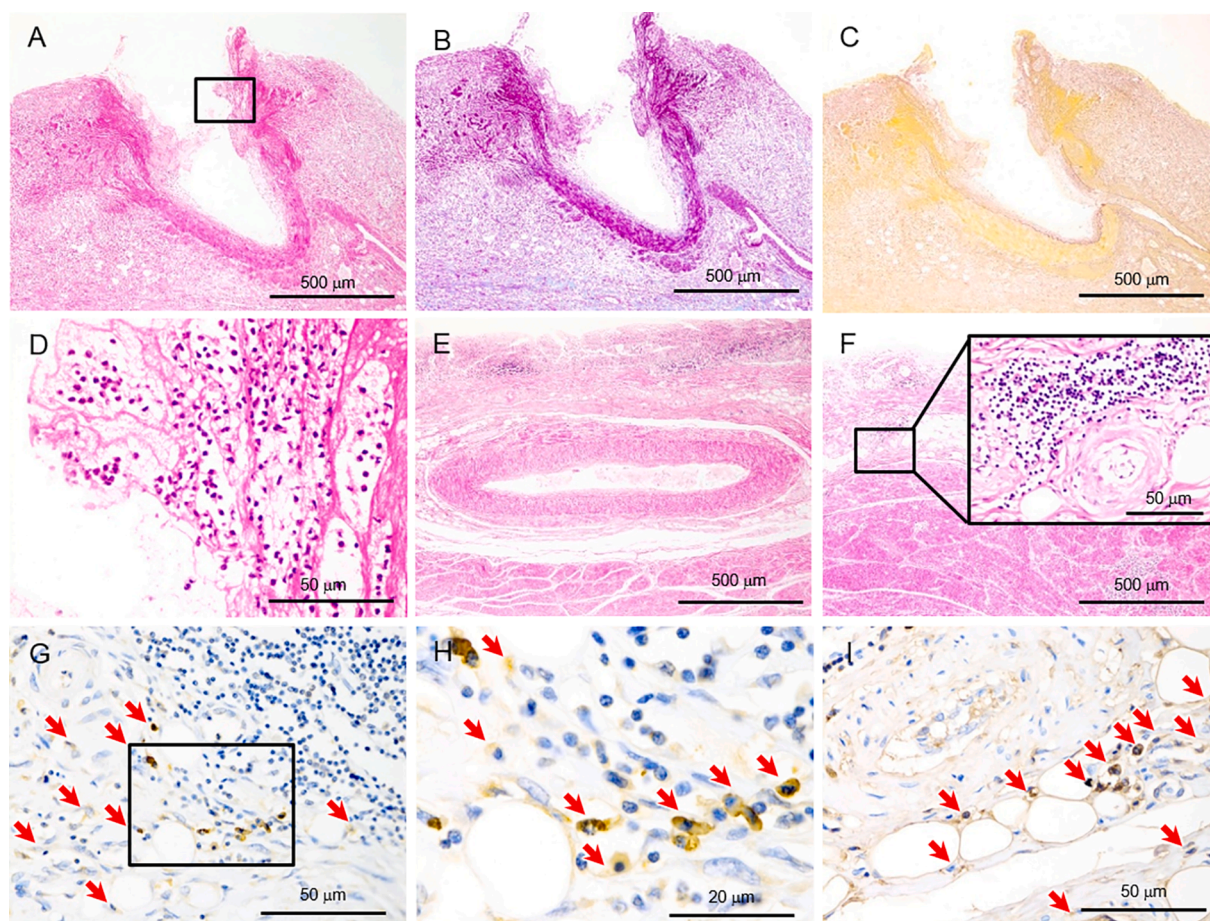


Fig. 3. Histological findings of the stomach. (A) Hematoxylin and eosin stained section showing rupture of an extremely enlarged artery in the submucosal layer of the stomach. (B) Azan-stained serial section of (A). (C) Elastica van Gieson-stained serial section of (A). No sign of heritable elastic fiber disease is visible. (D) High magnification image (the boxed area of [A]) showing massive neutrophil infiltration with fibrin deposition. (E) Non-ruptured area of the enlarged artery in the submucosal layer. (F) Normal-sized artery in the submucosal layer showing mild lymphocyte infiltration in the interstitial area. The inset represents the high magnification image of the boxed area. (G) Immunohistological staining for IgG4 in the serial section of (F) showing increased number of IgG4 positive cells (shown by red arrows). (H) High magnification image of the boxed area in (G). (I) Immunohistological staining of the submucosal layer for IgG.

and pancreas. Notably, storiform fibrosis and obliterative phlebitis, typical features of IgG4-RD, were found in the pancreas. In addition, we also found that histological evidence of IgG4-positive plasma cell infiltration such as IgG4/IgG-positive cell ratio $>40\%$ and IgG4-positive plasma cells $>10/\text{high power field}$. This case showed normal serum IgG4 levels; however, it has been reported that up to 40% of IgG4-RD patients show normal or low serum IgG4 levels and we, therefore, considered that normal serum IgG4 levels were not exclusionary [12]. Other diseases such as malignant tumors (e.g., lymphoma) and benign diseases (e.g., sarcoidosis) were not considered as no supporting findings for these diseases. Based on the current diagnostic guidelines for the disease in Japan, we believe that the patient had IgG4-RD [11].

Although Dieulafoy lesions are thought to be congenital anomalies, several acquired modifiable factors, such as cardiac diseases (including arrhythmia, coronary artery disease) and hypertension, have been reported as risks for rupture of the lesions [13]. IgG4-RD could also be risk for rupture of the lesion because IgG4-RD can affect arterial wall thickening and luminal dilatation through systemic vascular inflammation [14]. Therefore, we believe that IgG4-RD could, at least in part, have contributed to the patient's development of the Dieulafoy lesion and his death. Although the pathogenic mechanisms underlying the initiation of the disease remain largely unknown, it has been found that autoreactive B cells and aberrant CD4+ T cells contribute to inflammation and fibrosis, leading to the subsequent multiple organ dysfunction seen in IgG4-RD [12]. Patients with allergic conditions with

elevated serum IgE levels, as in this case, activated B cells and CD4+ T cells are also known to induce not only the production of anti-inflammatory factors such as IgG4 but also inflammatory mediators such as sIL2R and CRP and apoptotic factors [4,15]. The inflammatory and apoptotic mediators secreted by the autoreactive B cells and CD4+ T cells could lead to the damage and destruction of target cells, including the endothelial cells, vascular smooth muscle cells, and parenchymal cells present in the Dieulafoy lesion, thyroid, and pancreas, as seen in this case. In parallel with the inflammatory and apoptotic responses, fibroblasts may also be activated, resulting in fibrogenesis, such as the storiform fibrosis and obliterative phlebitis of the pancreas seen in the present case. Thereafter, the elevated levels of inflammation caused by IgG4-RD (IgG4-related arteritis) could contribute to arterial stenosis, dilation, calcification, and wall thickening since some of these pathological changes could improve following steroid therapy [16]. Eventually, these arterial injuries owing to the IgG4-related arteritis could directly and/or indirectly result in the rupture of the Dieulafoy lesion in this case. Therefore, we believe that IgG4-related arteritis could have contributed to his death. Further studies, such as case series, autopsy studies, are warranted to clarify the association between these treatable diseases. When a forensic pathologist encounter a case with gastrointestinal bleeding, a complete autopsy with histopathological examinations should be performed to better understand the mechanisms of the hemorrhages including Dieulafoy lesion and IgG4-RD.

We also considered that cardiac disease (e.g. cardiac hypertrophy,

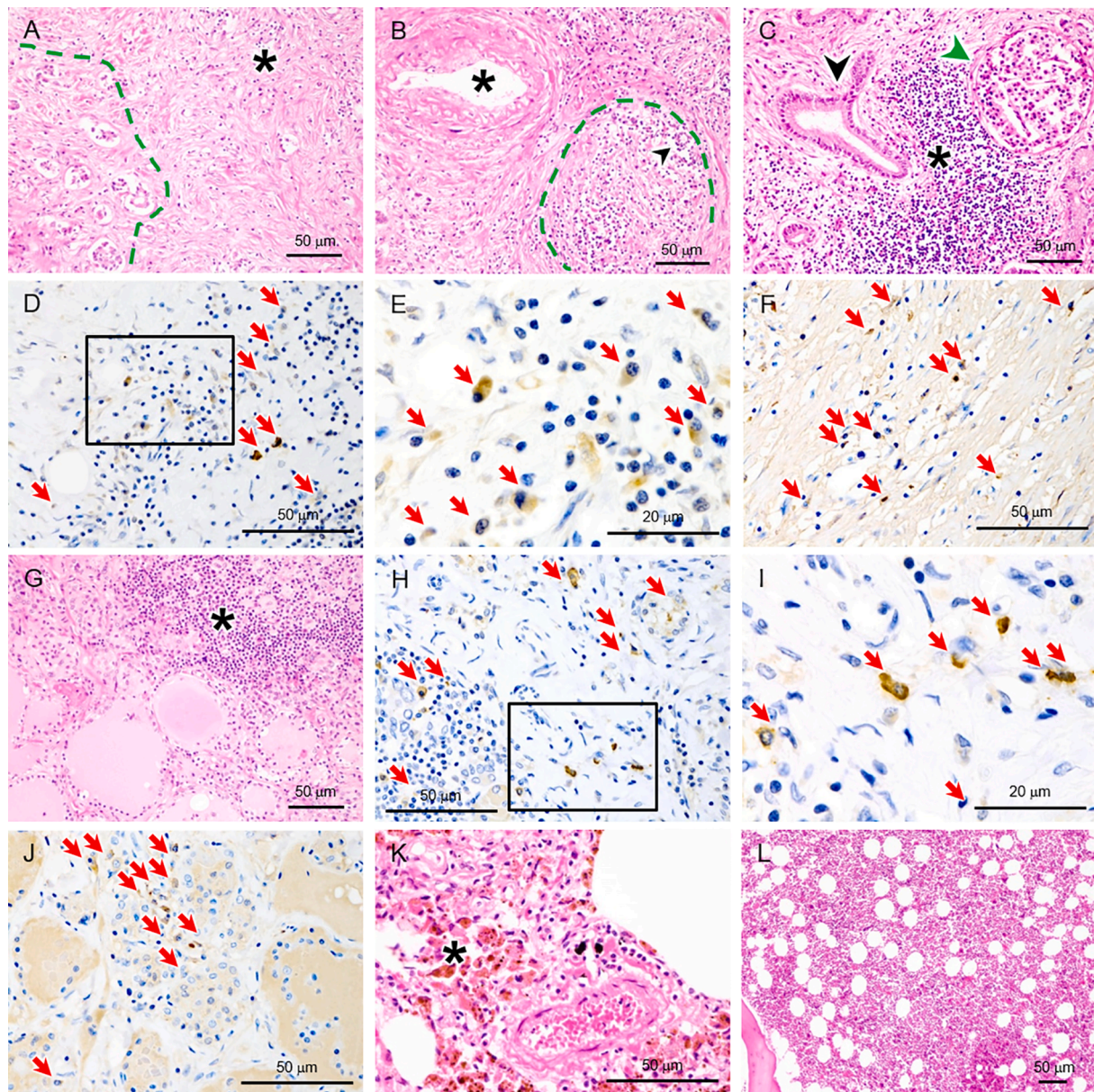


Fig. 4. Histological findings of the pancreas, thyroid gland, lung, and bone marrow. (A) Pancreas showing presence of storiform fibrosis (highlighted by the asterisk). Destroyed parenchymal cells with lymphocyte infiltration are visible in the left area. (B) The dotted line highlights the area of obliterative phlebitis, the lumen of the vein is completely obliterated (shown by the arrowhead), and the asterisk indicates a relatively intact artery located parallel to the vein. (C) Massive lymphocyte infiltration (shown by the asterisk), tortuous ducts (shown by the black arrowhead), and the complete absence of parenchymal cells with a relatively intact islet of Langerhans (shown by the green arrowhead) are shown. (D) Immunohistological staining of the pancreas for IgG4. Red arrows indicate the IgG4-positive cells. (E) High magnification image of the boxed area in (D). (F) Immunohistological staining of the pancreas for IgG. (G) Thyroid gland showing massive lymphocyte infiltration with destroyed parenchymal cells. (H) Immunohistological staining of the thyroid for IgG4. Red arrows indicate IgG4-positive cells. (I) High magnification image of the boxed area in (H). (J) Immunohistological staining of the thyroid for IgG. (K) Lung section showing hemosiderin-laden macrophage infiltration (shown by the asterisk). (L) Bone marrow section showing increased cellularity of the hematopoietic cells.

Table 1
Serum biochemical analysis.

Measurement	Data	Clinical reference value
IgG4 (mg/dl)	39.1	4.8–105
IgG2 (mg/dl)	290	239–838
IgE (IU/ml)	234	<173
CRP (mg/dl)	0.942	<0.14
sIL2R (U/ml)	2620	157–474

IgG4, immunoglobulin G4; IgG2, immunoglobulin G2, IgE, immunoglobulin E; CRP, C-reactive protein; sIL2R, soluble-interleukin-2 receptor.

coronary artery stenosis, arrhythmia) could contribute to his death even though the screening test of H-FABP was negative since he had suggestive autopsy signs of the disease, and concomitant cardiovascular disease had been reported to be one of the major predictors of mortality in the patients with Dieulafoy lesion [13]. In addition, we considered that the postmortem serum H-FABP level could be false negative since the leakage of H-FABP from the cardiomyocytes into the serum following cardiac injury could be theoretically reduced by the post-mortem time [17] and loss of blood volume owing to the hemorrhage.

In conclusion, to our best knowledge, this is the first autopsy case report of a Dieulafoy lesion associated with IgG4-RD. An autopsy case report with a detailed history and histological examinations could lead

to increased awareness and thus early treatment of this rare lesion to improve patient prognosis. Further autopsy studies are needed to clarify the precise relationship between Dieulafoy lesions and IgG4-RD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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