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Case Report

Systemic amyloidosis with amyloid goiter: An autopsy report

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ABSTRACT

Systemic amyloidosis is a rare but potentially lethal disease characterized by amyloid accumulation in all organs. Amyloid goiter is an extremely rare pathological lesion characterized by thyroid gland enlargement with fat deposition due to local or systemic amyloidosis. A 60 s woman with rheumatoid arthritis was found unconscious on her bed and declared dead after failed cardiopulmonary resuscitation. Postmortem computed tomography showed severe enlargement of the heart and thyroid glands, suggestive of cardiac hypertrophy and thyroidism. Histological examination revealed amorphous eosinophilic deposits with parenchymal cell destruction in all organs, including the heart and thyroid gland. Abnormal amorphous deposits in the tissues were positive for amyloid A as noted upon Congo red immunohistochemical staining and birefringence microscopy, confirming systemic amyloidosis with amyloid goiter. Serum biochemical analysis revealed increased levels of C-reactive protein; anti-cyclic citrullinated peptide antibody; creatinine kinase-myoglobin binding and *N*-terminal pro-brain natriuretic peptide; and thyroglobulin, free triiodothyronine, and free thyroxine, indicating systemic inflammation, active rheumatoid arthritis, heart failure, and destructive hyperthyroidism, respectively. These findings suggested that the cause of death was undiagnosed heart failure due to secondary systemic amyloid A (AA) amyloidosis related to rheumatoid arthritis. In addition, destructive hyperthyroidism caused by systemic AA amyloidosis may have also been one of the causes of death as indicated by cardiac overload. To the best of our knowledge, this is the first forensic autopsy report of cardiac amyloidosis with amyloid goiter. In conclusion, this autopsy report highlights the importance of increased awareness and early intervention for severe but treatable complications of systemic amyloidosis.

1. Introduction

Systemic amyloidosis is a rare disease characterized by amyloid accumulation in whole organs and parenchymal cell destruction [1]. Regardless of the etiology of systemic amyloidosis, cardiac amyloidosis and cardiac amyloid accumulation with myocardial cell destruction could lead to lethal cardiovascular events due to incident or aggravated heart failure, coronary artery disease, arrhythmia, cardiomyopathies, and myocarditis [2]. Therefore, early diagnosis and treatment of cardiac amyloidosis are important in patients with systemic amyloidosis. However, no gold standard diagnostic and therapeutic methods for cardiac amyloidosis have been developed owing to the rarity and variability in the severity of heterogeneous diseases. Thus, the prognosis of patients with cardiac amyloidosis remains poor [3,4].

Amyloid goiter is an extremely rare pathological change characterized by thyroid gland enlargement with fat deposition due to local or systemic amyloidosis [5]. In patients with amyloid goiter, hyperthyroidism or hypothyroidism can be induced by acute or chronic destructive amyloid accumulation in the thyroid gland [6]. It is well known that hyperthyroidism or hypothyroidism can lead to various cardiac injuries because dysregulation of thyroid hormone secretion induces pathological changes in cardiac function and structure due to impairment of the cardiac load and the renin-angiotensin-aldosterone axis [7]. However, to our best knowledge, no forensic autopsy report in which death resulted from amyloid cardiomyopathy with amyloid goiter secondary to amyloid A (AA) systemic amyloidosis has been reported to date [8].

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2. Case history

2.1. Clinical history

A 60 s woman was found unconscious on the bed by her husband. He immediately called an ambulance, and the paramedics arrived at the scene 6 min after the call and took her to the emergency hospital. However, she had cardiopulmonary arrest upon arrival at the hospital and died after failed cardiopulmonary resuscitation. The patient was diagnosed with rheumatoid arthritis (RA) 25 years before her death and was on regular physician follow-up. At 15 years before her death, she complained of stomach discomfort and was diagnosed with a gastric ulcer due to amyloidosis. However, since no medical records were retained, it is unknown if she was diagnosed with RA-associated gastric AA amyloidosis upon pathological analysis of biopsied samples. At 14 years before her death, she was diagnosed with renal failure due to amyloidosis and underwent dialysis. Thereafter, she had multiple bone fractures (e.g., thoracic and lumbar vertebrae), possibly due to osteoporosis caused by chronic renal failure and dialysis-related hypotension [9]. She also often experienced fall injuries during this time.

Several years before death, she underwent coronary artery stenting due to angina pectoris of unknown etiology and had been receiving steroid therapy for interstitial pneumonitis due to RA and secondary pulmonary hypertension. However, she stopped taking disease-modifying anti-rheumatic drugs (DMARDs) for RA during this time, probably to avoid adverse effects of anti-rheumatoid drugs for pneumonitis (e.g., methotrexate-associated pneumonitis) [10]. At 1 day before her death, she fell and had injuries in her head and right elbow and went to the emergency doctor. However, she was discharged home by the doctor because she had no fracture in her head and right elbow, and her general condition was good. On the morning of her death, she complained of drowsiness and loss of appetite and did not have breakfast. At 1 h before her death, her husband came to take care of her but found her unconscious on the bed.

She had been taking steroids for RA, aspirin and statins for coronary artery disease, prostacyclin agonists for pulmonary hypertension, and several dialysis treatment drugs (e.g., adrenergic receptor agonists for dialysis-related hypotension). Her husband reported that she did not drink alcohol and had no history of smoking. She had no family history of sudden unexpected death. The emergency physician indicated that postmortem computed tomography (CT) did not show bone fractures or intracranial hemorrhage in the patient (data not shown). A total blood count test of postmortem blood obtained by the emergency physician showed mildly elevated white blood cells, moderately reduced red blood cells, and mildly reduced platelet counts (Table 1).

Serum biochemical analysis of the blood showed severely reduced levels of albumin and glucose, and severely increased levels of creatinine and C-reactive protein, suggestive of renal failure and systemic inflammation (Table 2). Moreover, the levels of troponin-T, creatinine kinase, creatinine kinase-myoglobin binding, and *N*-terminal pro-brain natriuretic peptide, markers of cardiac injury and heart failure, were also significantly increased.

Her primary physician reported that she had nausea and vomiting after dialysis the day before her death, but these are well-known symptoms of chronic kidney disease and hemodynamic changes due to dialysis; therefore, the doctor did not perform cardiac functional analysis. In addition, no other noticeable signs were identified on physical examination or vital signs. The doctor did not believe that dialysis directly contributed to her death. The precise etiologies of cardiac injuries, RA, pulmonary diseases, medications, and fall injuries were unknown, as were their contributions to her death. Therefore, a complete forensic autopsy was performed 2 days after death.

Table 1
Complete blood count test.

Measurement	Data	Clinical reference value
White blood cell (10^9/L)	9.65	2.7–8.5
Red blood cell (10^{12}/L)	2.6	3.37–4.94
Hemoglobin (g/dL)	7.8	10.5–14.9
Platelet (10^9/L)	76	110–347

Table 2
Serum biochemical analysis.

Measurement	Data	Clinical reference value
Albumin (g/dL)	2.5	3.9–5.1
Creatinine (mg/dL)	3.26	0.46–0.78
Glucose (mg/dL)	4	78–110
CRP (mg/dL)	4.0	<0.2
Creatine kinase (mg/dL)	792	43–157
Creatine kinase-myoglobin binding (mg/dL)	75	5.0–16.0
Troponin-T (mg/dL)	1.180	<0.014
NT-pro-BNP (pg/mL)	35,000	<125
anti-CCP antibody (U/mL)	9.4	<4.5
Rheumatoid factor (IU/mL)	5	<15
SAA (mg/mL)	28.2	<8.0
Thyroglobulin (ng/dL)	129,000	<35.1
anti-thyroglobulin antibody (IU/mL)	16.5	<19.3
anti-TPO antibody (IU/mL)	2.0	<3.3
TSH (mIU/mL)	3.35	0.61–4.23
Free T3 (pg/dL)	11.7	2.52–4.06
Free T4 (ng/dL)	2.03	0.75–1.45

CRP, C-reactive protein; NT-pro-BNP, *N*-terminal pro-brain natriuretic peptide; anti-CCP antibody, anti-cyclic citrullinated peptide antibody; SAA, serum amyloid A peptide; anti-TPO antibody, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

2.2. Autopsy findings

Postmortem CT revealed a severely enlarged heart and thyroid gland with low-density parenchymal areas, a high-density area in the right coronary artery (consistent with stenting), pulmonary effusion, and severely atrophic kidneys (Fig. 1**A-D**). CT-based skeletal muscle index at the third lumber level (Fig. 1**E, F**), a marker of sarcopenia, was severely reduced to 13.2 cm^2/m^2 (clinical cutoff level: 29.6). Consistent with the CT interpretations of the emergency doctor, no fractures or signs of severe hemorrhage (e.g., intracranial hemorrhage) were identified.

The deceased was 156 cm tall and weighed 39.2 kg, with a body mass index of 16.1 kg/m^2 (severe emaciation). External examination showed multiple bruises (at most 20 × 6 cm in the right elbow) and abrasions (at most 4 × 1 cm) on the head, chest, right elbow, and right leg, probably worsened by aspirin treatment (data not shown). The neck was severely enlarged in the front region, suggesting thyroid gland disease (Fig. 2**A**). The right foot showed mild bunion (big toes), claw toes (second and fifth toes), callus (second toe), and hammer toes (second and third toes), all of which were compatible with RA (Fig. 2**B**). Consistent with the clinical history, mild whitish changes in skin coloration and moderately reduced lividity were found, suggesting moderate anemia.

Internal examination revealed severe cardiac hypertrophy and severe epicardial fat deposits, with a weight of 447 (314.4 ± 60.5 g), even in the severe emaciation state (Fig. 2**C**). Although intermediate-to-severe atherosclerotic changes were found in the coronary arteries with right coronary artery stenting, no signs of thrombus, aneurysms, or ruptures were observed. The horizontal heart section showed moderate cardiac hypertrophy and scattered yellowish discoloration in the right ventricle and the posterior wall of the left ventricle, suggestive of amyloidosis (Fig. 2**D**). The thyroid gland was severely enlarged with a heterogeneous yellowish color change, suggesting fat deposition with parenchymal destruction (Fig. 2**E**). In the lungs, slight emphysematous changes were identified in the apex regions; however, no typical signs of interstitial pneumonitis, such as honeycombing, were observed. Pericardial effusion (20 ml), pulmonary effusion (left: 72 ml; right: 120 ml), and abdominal ascites (small amount) were identified, possibly due to

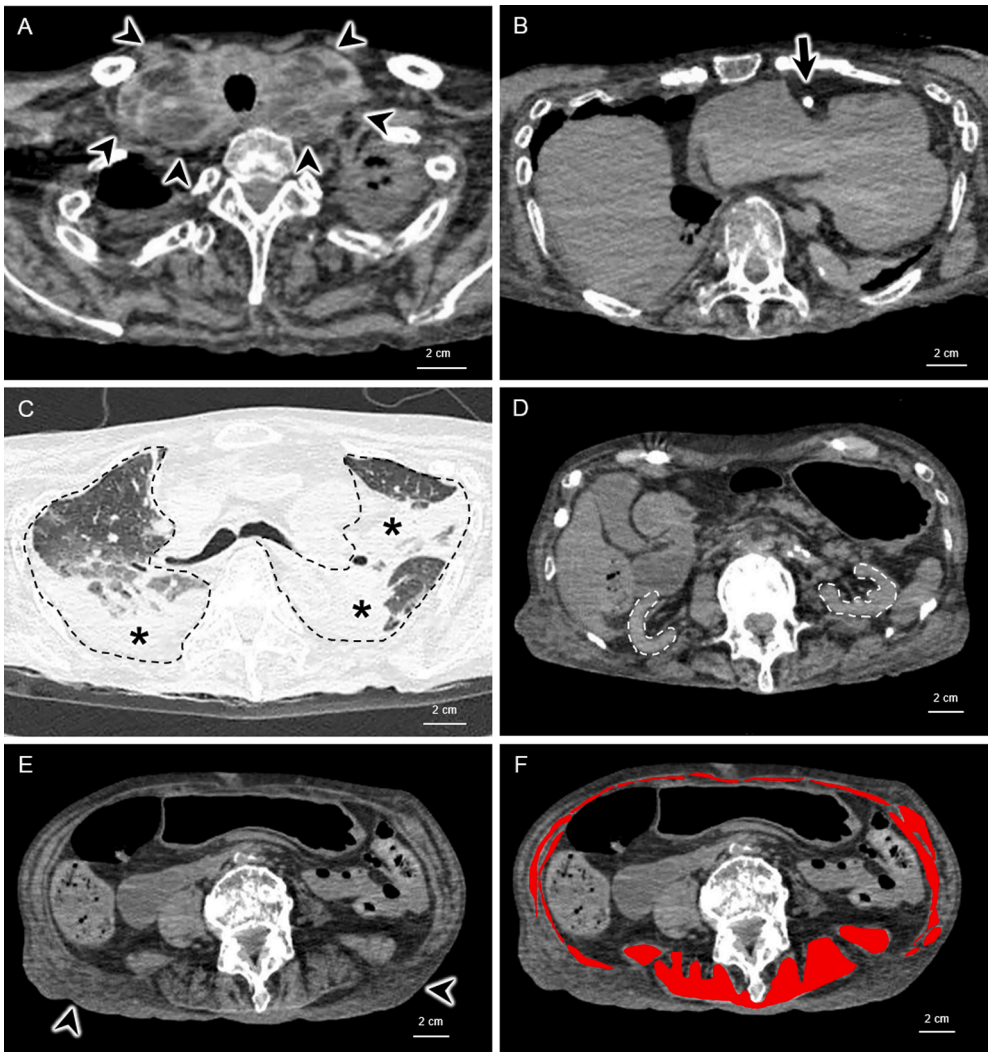

Fig. 1. Computed tomography findings. (A) Severely enlarged thyroid gland (arrowhead). Heterogeneous low-density lesions are seen in the internal area of both lobes. (B) Clear circular high-density area in the right coronary artery, suggestive of stent (arrow). (C) Lung area (dotted lines). Pulmonary and pleural effusion (asterisks). No obvious signs of interstitial lung disease such as ground-glass opacities or honeycomb are identified. (D) Severely atrophic kidneys (dotted lines). (E, F) Horizontal area at the level of the third lumber is shown. Arrowheads highlight subcutaneous heterogeneous high-density area, suggestive of subcutaneous edema (E). Red area highlights severely reduced skeletal muscle area (F). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

heart failure (effusion due to increased pressure of capillaries owing to ineffective pumping of blood) or severe emaciation (effusion by reduced osmotic pressure to vessels from tissues owing to hypoalbuminemia). A small amount of salicylic acid, a metabolite of aspirin, was detected in the serum; however, no toxins or alcohols were identified in the serum or urine by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Tests for hepatitis B and C were negative. A screening test for cardiac injuries using heart-type fatty acid-binding protein was positive.

Histological examination of the heart and thyroid revealed amorphous deposits with parenchymal cell destruction, suggestive of systemic amyloidosis (Figs. 3, 4). The deposits were positive for amyloid A as noted upon Congo red staining and birefringence microscopy, which confirmed amyloidosis. The positivity of the Congo red-stained area was abolished after permanganic acid treatment (data not shown) [11], suggesting AA amyloidosis rather than amyloid light chain (AL) amyloidosis. Immunohistochemical staining of the deposits for amyloid A (anti-amyloid A antibody, x100, M0759, Agilent Technologies, Santa Clara, CA, USA) was positive, whereas that for β2-microglobulin (anti-beta-2-microglobulin antibody, x400, A0072, Agilent Technologies, Santa Clara, CA, USA), a marker for Aβ2 amyloidosis (dialysis-related amyloidosis), were negative, confirming AA amyloidosis (most probably due to RA). Notably, peripheral regions that stained positive with Congo red and unstained cytoplasm of cardiomyocytes were highly birefringent when viewed under polarized light (Fig. 3**G, J**). Furthermore, the total area of apple-green colored deposits shown via birefringence microscopy were larger than the deposits stained positive with Congo red when viewed without polarized light (data not shown). The apple-green colored deposits seen under polarized light were not only present in the ventricular wall, but were also found in the cardiac conduction system such as sinoatrial node, a sinoatrial artery, and a right coronary artery (Fig. 3**H, I, K, L**). In the thyroid, clusters of mature adipocytes replacing the thyroid tissue, which is a characteristic histological feature of amyloid goiter [12], were observed (Fig. 4**A-G**). Interestingly, small deposits stained positive with Congo red were found primarily around the mature adipocytes, whereas large deposits were found around destructed parenchymal cells (Fig. 4**G**). In contrast to the differences observed in the staining patterns in the heart, apple-green colored deposits in the thyroid gland were smaller than the deposits stained positive with Congo red, as viewed without polarized light (Fig. 4**H, I**). In addition, dense areas in the thyroid stained positive with Congo red showed little to no correlated apple-green birefringence. Other organs, such as the kidneys, lungs, and pancreas, also showed AA deposition with parenchymal cell destruction (Fig. 4**A-I**), suggestive of a highly active state of systemic AA amyloidosis (see Fig. 5).

Serum biochemical analysis using the cardiac blood obtained on autopsy showed active RA as evidence by increased anti-cyclic citrullinated peptide antibody level, but negative for rheumatoid factor; active systemic AA amyloidosis as evidenced by increased serum amyloid A peptide (SAA) level; and destructive hyperthyroidism as evidenced by increased levels of thyroglobulin, free triiodothyronine (T3), and free thyroxine (T4) with a normal thyroid-stimulating hormone (TSH) level.

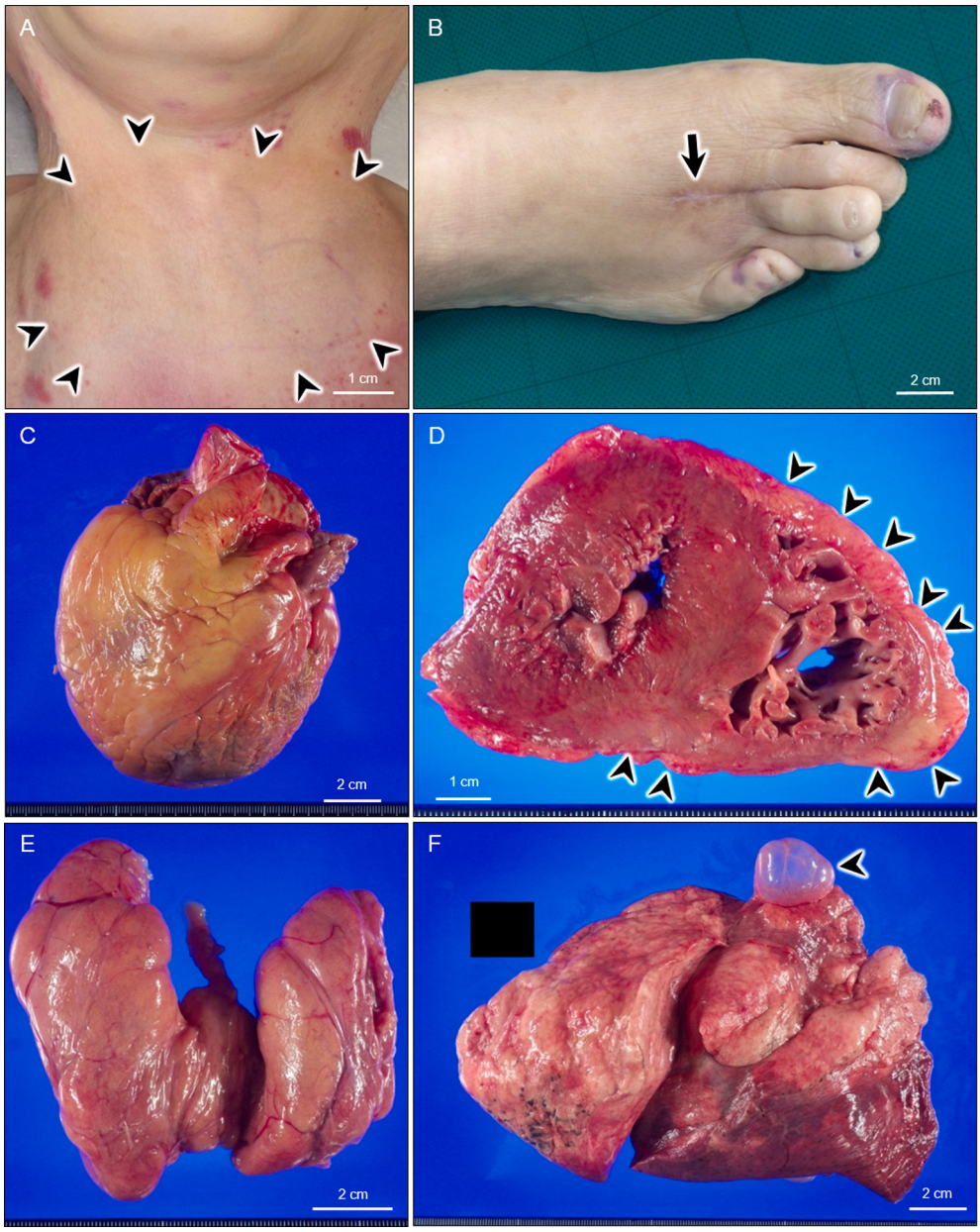

Fig. 2. Macroscopic findings. (A) Front of neck is severely enlarged (highlighted by arrowheads). (B) Right foot shows mild bunion (big toe), claw toes (second and fifth toes), callus (second toe), and hammer toes (second and third toes). A surgical scar is highlighted (arrow). Small bruises in toes are noted. (C) Heart shows severely hypertrophy with epicardial fat deposition. (D) Horizontal section of the heart shows severely hypertrophic wall in both the left and right ventricles. Yellowish lesions are highlighted (arrowheads). (E) The thyroid gland shows severe enlargement with heterogeneous yellowish discoloration. (F) The right lung has a bulla in the middle lobe (arrowhead). No signs suggestive of interstitial pneumonitis such as honeycombing are observed.

However, no suggestive signs of autoimmune thyroiditis, such as Hashimoto's disease and Basedow disease (negative for anti-thyroglobulin and anti-thyroid peroxidase antibodies) were observed (Table 2). In the lung, no signs of interstitial pneumonitis (e.g., interstitial inflammatory infiltrations with/without granulomas and signs of diffuse alveolar damage) were found [10].

3. Discussion

Based on the collective clinical histories and autopsy findings, we concluded that the cause of death was heart failure resulting from systemic AA amyloidosis with amyloid goiter. Given that in Japan, most patients with systemic AA amyloidosis have been reported to have RA [13], and the patient in the current study had active RA, we believe that the systemic AA amyloidosis was secondary to RA. In addition, the patient also had amyloid goiter with elevation of serum thyroid hormone levels, and secondary amyloid goiter with RA has been reported to be a potential risk factor for impaired thyroid hormone secretion [6]. We believe that the amyloid goiter could be indirectly involved in her death.

We conclude that the cause of death was heart failure resulting from amyloidosis. The patient was diagnosed with amyloidosis, and macroscopic and histological examinations of the heart clearly showed supportive signs of amyloidosis, such as scattered yellowish discoloration in the cardiac wall and amorphous- and Congo red-positive deposits with cardiomyocyte destruction. The present case had signs of other diseases that could induce heart failure, including coronary artery disease and hypertensive heart disease. However, we considered that these features had smaller contributions to her death than had amyloidosis and even secondary changes due to cardiac amyloidosis. This is because cardiac amyloidosis has been demonstrated to induce various cardiac injuries, such as heart failure, cardiac hypertrophy, aortic calcification, tachy- and bradyarrhythmias, and hypotension [14]. In support of this, the patient in the present case clearly showed severe amyloid depositions in the cardiac conduction system including the sinoatrial node, the sinoatrial artery, and the right coronary artery. Therefore, fatal or non-fatal arrhythmia could be a secondary change due to cardiac amyloidosis. In addition to the pathological changes in the heart, this patient also had amyloid goiter, which could be indirectly involved in her health. From

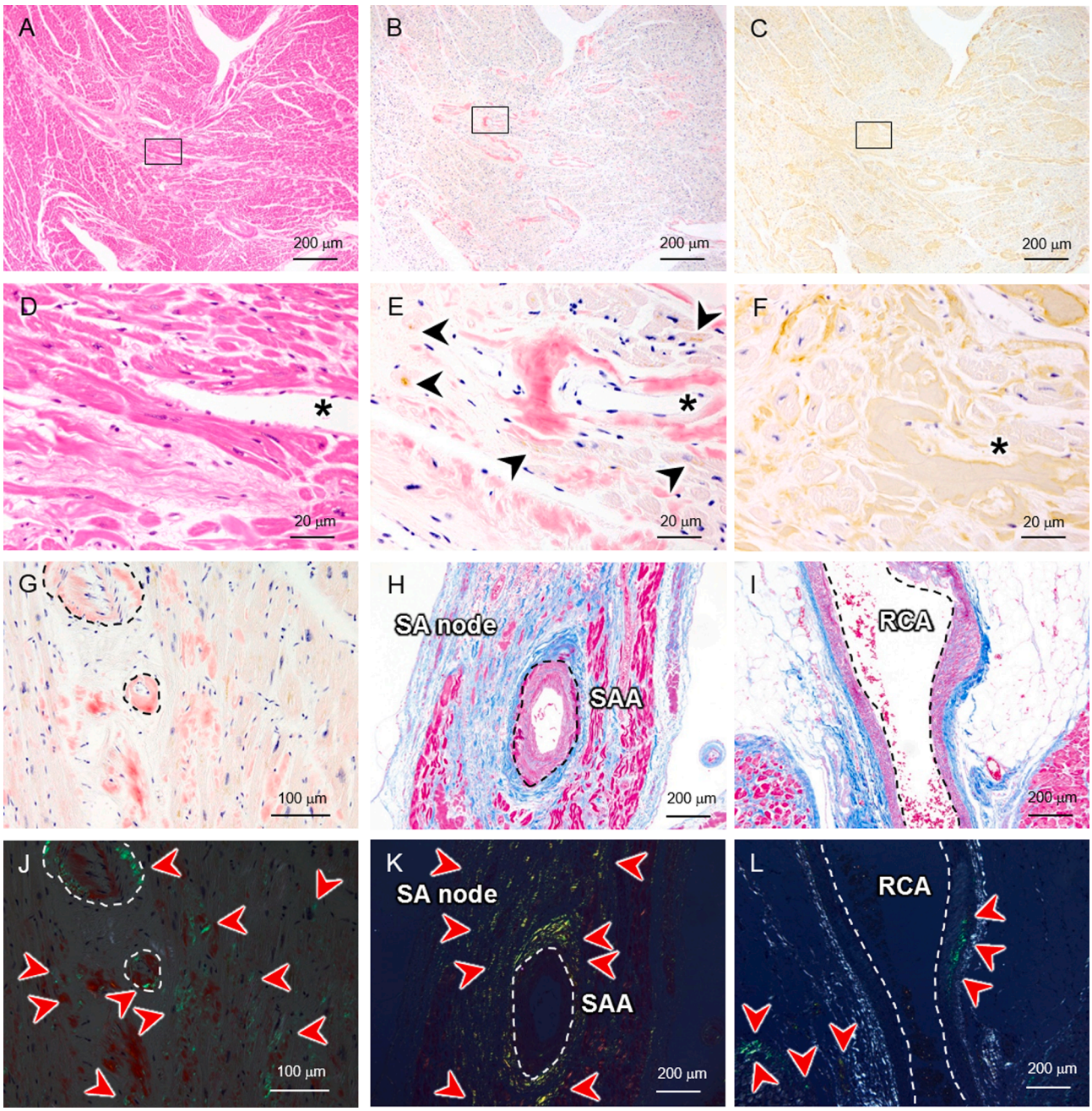

Fig. 3. Histological examination of heart tissue. (A, B, C) H&E-, Congo red-, and anti-amyloid A immuno-stained serial sections of the heart showing parenchymal cell destruction with amorphous deposits mainly around the vessels. Amorphous, eosinophilic deposits of the H&E-stained section (A) are Congo red-positive pink materials (B). The Congo red-positive materials also stain positively on immunohistological staining for amyloid A (C). (D–F) High magnification images of boxed area in each staining section of A–C. The same blood vessel are highlighted as asterisks. Black arrowheads indicate brownish colored-lipofuscin accumulations in the cardiomyocytes (E). (G–I) Congo red-, and Azan-stained sections of the left ventricular wall, sinoatrial (SA) node, sinoatrial artery (SAA), and right coronary artery (RCA) are shown. (J-L) Birefringence microscopic images of Congo red-stained sections (G-I). Dotted lines highlight the same arteries in images (G-I). Red arrowheads indicate apple-green colored deposits. Peripheral regions of Congo red-stained areas and Congo red-unstained cytoplasm of cardiomyocytes were highly birefringent under polarized light (apple-green color). White colored areas are made by nonspecific auto-fluorescence light. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

another point of view, we considered that severe hypoglycemia and the consequent arrhythmia from hypoglycemia could be partially involved in her death. Because hypoglycemia can be secondarily induced by low calorie intake due to heart failure, renal failure, or dialysis [15].

Amyloid goiter is an extremely rare lesion, especially secondary systemic amyloidosis related to RA [16]. To the best of our knowledge, no forensic autopsy case of systemic AA amyloidosis with amyloid goiter has been reported in the literature. Autopsy of the thyroid gland in the present case showed severe fat deposition with parenchymal cell destruction, which is a characteristic feature of amyloid goiter. However, it should be noted that the fatty infiltrations seen in the patient in the present case could be a pre-existing lesion, most likely a thyroid lipomatosis, as patients with thyroid lipomatosis have been reported to have RA or amyloidosis [17]. We speculate that the fatty infiltrations were most likely a secondary change due to destructive amyloid AA deposition. This is evidenced by small deposits stained positive with

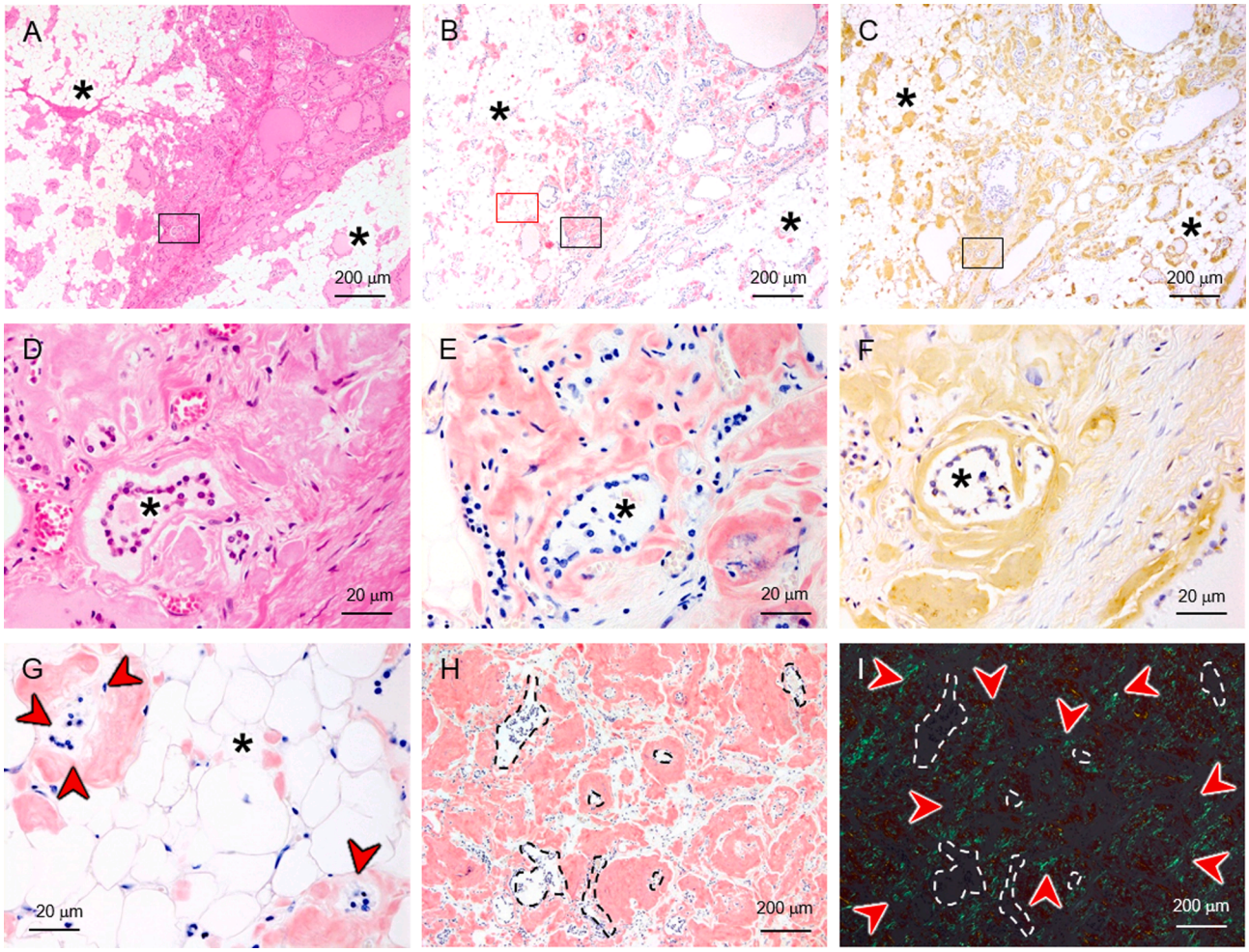

Fig. 4. Histological examination of the thyroid gland. (A, B, C) H&E-, Congo red-, and anti-amyloid A-immuno-stained serial sections of the thyroid are shown. H&E-stained sections showing severe fat depositions with parenchymal cell destruction. Diffuse amorphous, eosinophilic deposits in the H&E section (A) are Congo red-positive pink materials (B). The Congo red-positive materials also stain positively on immunohistological staining for amyloid A (C). (D-F) High-magnification images of black boxed area in each staining section of (A-C). The same colloid with severely destructed parenchymal cells are highlighted by asterisks. (G) A high-magnification image of red boxed area in (B). Red arrowheads indicate Congo red-positive deposits with parenchymal cell destruction. Asterisks highlight small Congo red-positive deposits in the degenerated fatty areas. (H, I) A section of thyroid gland stained with Congo red and the corresponding birefringence microscopy image. Dotted lines highlight the same parenchymal cells. Red arrowheads highlight apple-green colored deposits. Peripheral regions of Congo red-stained areas and Congo red-unstained area were highly birefringent under polarized light (apple-green color), while dense Congo red-stained area demonstrated little to no birefringence. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Congo red being found primarily around the mature adipocytes, while large deposits were found around destructed parenchymal cells, suggestive of active destruction of parenchymal cells as opposed to adipocytes by amyloid depositions. Future studies are required to clarify whether amyloidosis and thyroid lipomatosis are related, or simply coincident diseases. In support of our hypothesis, postmortem serum analysis in the present case showed highly elevated thyroglobulin, suggestive of severe thyroid parenchymal destruction. Despite severe elevation of serum thyroglobulin level, thyroid hormones free T3 and T4 showed only mild elevation. Theoretically, serum TSH levels should be decreased because of the negative feedback from elevated levels of free T3 and T4. However, the TSH levels were relatively in the upper normal range. We considered that the long clinical course and slow accumulation of the AA amyloid in the thyroid resulted in limited parenchymal cell destruction. There could be no sufficient parenchymal area to destruct in the thyroid. Regardless of etiology, it has been demonstrated that hyperthyroidism induces cardiac overload through two different pathways: (1) acute and direct elevation of systemic vascular resistance and (2) chronic excessive activation of the renin-angiotensin-aldosterone axis [7]. Cardiac overload due to hyperthyroidism can result in tachycardia, exercise intolerance, and dyspnea. Exercise intolerance can induce respiratory and skeletal muscle weakness, as observed in this patient. These abnormal changes caused by chronic hyperthyroidism can directly or indirectly lead to heart failure. Therefore, we considered that amyloid goiter could be, at least in part, involved in her death through the aggravation of heart failure by chronic hyperthyroidism. However, thyroid function is not impaired in most amyloid goiter patients, even if a hypothyroid or hyperthyroid state is detected in a minority of cases, as demonstrated by a systematic review that analyzed 30 cases from 127 publications [5]. We considered that the thyroid function in the present case could have fluctuated from euthyroidism to hypo- or hyperthyroidism because of the balance between the disease activities of amyloid goiter and RA and the steroid therapy [6]. Further autopsy studies are warranted to better understand the relationship between amyloid goiters and cardiac death.

Most systemic amyloidosis cases can be categorized as AL or AA amyloidosis. Other types of amyloidosis include transthyretin amyloidosis and dialysis-related amyloidosis (β2-microglobulin amyloidosis [Aβ2M]) [18]. This autopsy case clearly showed AA amyloid-positive amorphous deposits with parenchymal cell destruction in all the

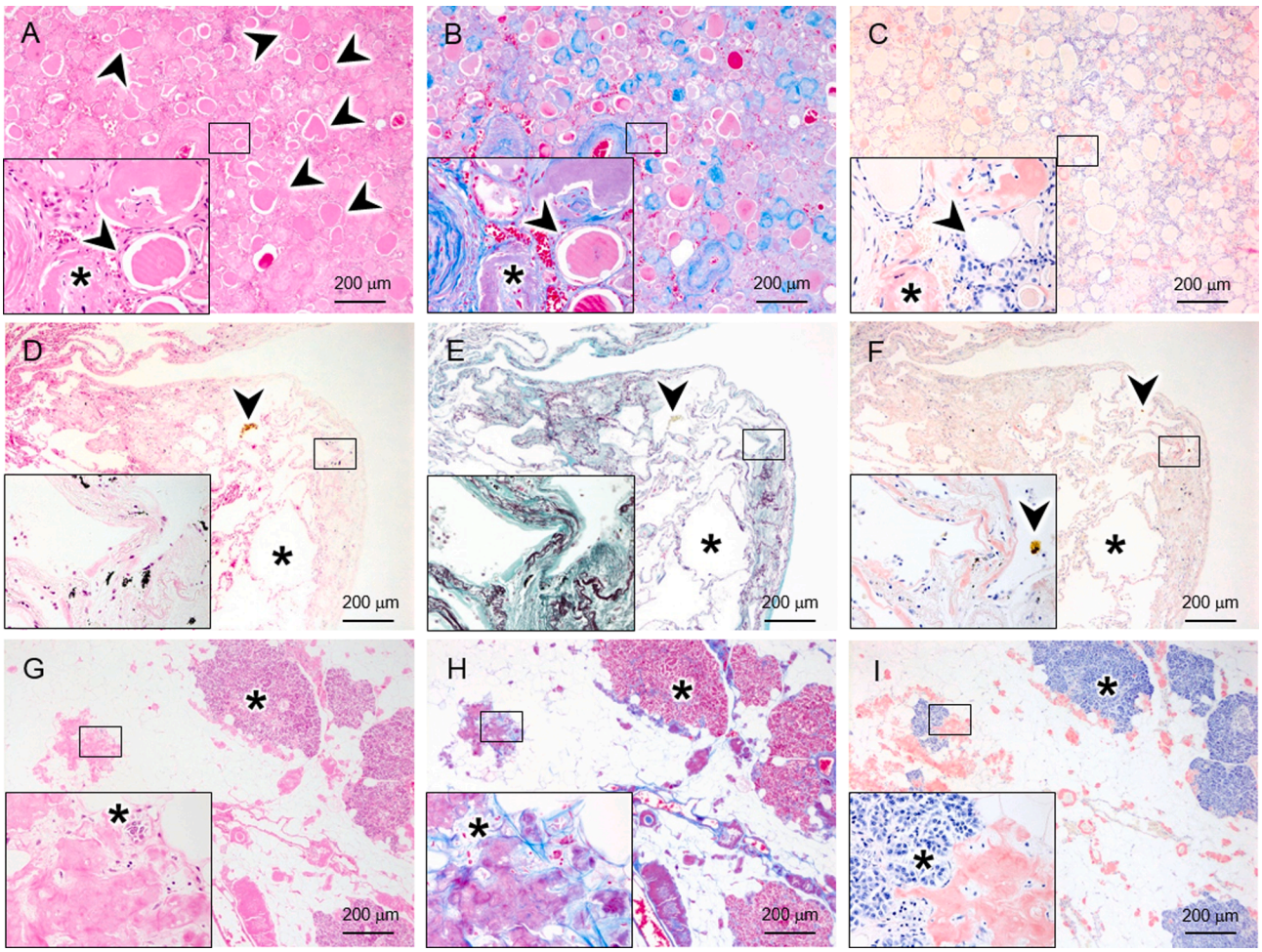

Fig. 5. Histological findings of the kidney, lung, and pancreas. (A, B, C) H&E-, Azan-, and Congo red-stained serial sections of the kidney showing severe glomerular sclerosis in almost all glomerulus. Amorphous, eosinophilic deposits in the H&E-stained section (A) are Congo red-positive pink materials (C). High-magnification images of the boxed areas are shown as insets. The same glomerulus with severe parenchymal cell destruction is highlighted with asterisks. Hyaline casts with degenerated tubular epithelial cells are highlighted with arrowheads. (D–F) H&E-, Elastica Masson-, and Congo red-stained serial sections of the lung showing slightly emphysematous changes highlighted by asterisks. Amorphous, eosinophilic deposits in the H&E stained section (D) are Congo red-positive pink materials (F). High-magnification images of the boxed areas are shown as insets. Hemosiderin-laden macrophages are highlighted by arrowheads. (G–I) H&E-, Azan-, and Congo red-stained serial sections of the pancreas showing severe fat depositions with parenchymal cell destruction (asterisks). Amorphous, eosinophilic deposits are shown. High-magnification images of the boxed areas are shown as insets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

organs. Other types of systemic amyloidosis were ruled out because there were no supportive findings. As mentioned above, we believe that systemic amyloidosis with amyloid goiter may have occurred secondary to RA. In general, cardiac injuries by AA amyloidosis have been reported as less severe compared to those of AL or transthyretin amyloidosis, most likely due to improved treatment for RA with biological agents [19]. However, the patient was not diagnosed with RA-associated systemic AA amyloidosis over a period of at least 10 years. We consider several reasons for the underdiagnosis of systemic AA amyloidosis with rheumatoid arthritis. One of the reasons could be due to the diagnosis of "interstitial pneumonitis." DMARDs are known to be a major risk factor for aggravation of pneumonitis (e.g., methotrexate-associated pneumonitis) [10]; therefore, clinicians could not aggressively treat RA using DMARDs [20]. The second reason could be the history of changing physicians several time. She moved or changed her primary physician at least 10 times since she was first diagnosed with RA. The pulmonary disease specialists could not properly interpret her pulmonary symptoms and/or pulmonary X-ray and CT images because of insufficient or sometimes overabundant medical histories. A third reason could be dialysis. It is well known that long term dialysis is a major risk for systemic amyloidosis (Aβ2M). Therefore, the nephrologist might have considered that systemic amyloidosis was secondary to dialysis. However, the doctors did not manage the "dialysis-related amyloidosis" because the withdrawal of dialysis meant her death. Therefore, physicians treating collagen disease cannot focus on aggressive treatment for RA. We considered that if she was sufficiently treated with high doses of steroids and DMARDs, she may have survived. This is because reduced serum SAA levels from amelioration of AA amyloid deposits to whole organs can subsequently improve systemic amyloidosis progression, including of cardiac amyloidosis and amyloid goiter. Clinicians who follow patients with amyloidosis complicated with RA should consider a regular serum SAA screening test to prevent rare but potentially lethal complications of AA amyloidosis, such as cardiac amyloidosis and amyloid goiter. When forensic pathologists encounter amyloidosis-suspected cases, they should consider histological examinations using Congo red staining in the presence or absence of potassium permanganate for screening AA or AL amyloidosis.

In conclusion, to the best of our knowledge, this is the first forensic autopsy case report of undiagnosed cardiac amyloidosis with amyloid goiter related to RA. An autopsy case report with a detailed history and histological examinations could lead to a better understanding of the causes of death in patients with amyloidosis and increase awareness on

these rare but treatable diseases and improve patient outcomes. Further autopsy studies are needed to clarify the contribution of amyloidosis to death.

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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