INTRODUCTION

Amyloidosis (AL) is an uncommon diagnosis at the time of autopsy; however, as cardiac AL is associated with arrhythmias, and, thus, the possibility for sudden death, decedents with this condition will be encountered by forensic pathologists. Although AL can occur as a primary disorder associated with multiple myeloma and plasma cell dyscrasias, hereditary forms and secondary forms also occur. Identification of the hereditary forms can have important implications for surviving family members. The diagnosis of cardiac AL at autopsy depends upon knowledge of this disease process, and its histologic appearance and various morphologic patterns, and, when necessary, through the use of supplemental histologic stains, as well as serologic, and, if necessary, genetic testing.

MATERIALS AND METHODS

All reports for autopsies conducted by the author in a 9-year period were reviewed retrospectively for the diagnosis of cardiac AL. Four cases were identified from 1128 autopsies.

RESULTS

Case 1

A male in his late 90s, who died as a result of urosepsis, with associated co-morbidities of severe coronary artery atherosclerosis, recent onset dementia following treated subdural hemorrhage, a pituitary adenoma, and aspiration pneumonia had, upon microscopic examination of the heart, cardiac AL identified in the left ventricular wall. The individual amyloid deposits were small in amount and characterized as wispy bands intermingled between cardiac myocytes or as small globular aggregates [Figures 1 and 2]. The heart weight was 396 g.

Case 2

A male in his mid-90s fell and broke his wrist at a nursing home, was treated in the hospital, and shortly after being returned to the nursing home, became unresponsive. His cause of death was certified as cardiac dysrhythmia due to cardiomegaly (heart weight of 589 g), with the acute stress associated with a fracture and his underlying moderate coronary artery atherosclerosis determined to be significant contributing factors. His co-morbidities included Hashimoto thyroiditis and dementia, with neuronal depopulation of the CA4 region of Ammon’s horn of the hippocampus identified upon microscopic examination. Upon microscopic examination of the heart, amyloid was identified in the wall of the left ventricle, with a similar description to that of Case 1.

Case 3

A male in his mid-50s was found unresponsive by his wife in their house. He had a history of recently diagnosed multiple myelomas and seronegative rheumatoid arthritis. At autopsy, the heart weighed 464 g, and the lungs had a combined weight...
of 2662 g. Upon palpation of the lungs, they were noted to have increased firmness diffusely throughout, and, the upper lobe of each lung had a sub pleural mass (8.0 and 4.0 cm). The heart had pale subendocardial myocardium and rough endocardial surfaces in the atria. Microscopically, the heart had large aggregates of smudgy, a cellular, and eosinophilic material, which was present in the atria and the cardiac valves as well as within the wall of the left ventricle. In the wall of the left ventricle, the deposits were predominantly subendocardial in distribution [Figure 3], corresponding to the pale myocardium noted grossly, and were not only confined to the vasculature (such as in Case 4 below). A Congo red stain revealed prominent apple-green birefringence upon polarization. Similar changes were noted in the atrioventricular nodal and pulmonary vasculature, and in the upper lobe masses noted grossly.

Case 4

A male in his mid-50s became unresponsive following an episode of diaphoresis, shortness of breath, and body aches.

At autopsy, the heart weighed 490 g. The myocardium had no gross lesions; however, the cardiac valves appeared rubbery in texture. Upon microscopic examination, vessels in the bone marrow, heart, pancreas, liver, kidney, spleen, and lung were noted to have thick, acellular, smudgy, eosinophilic walls. Within sections of the heart examined, nearly every intramyocardial coronary arterial branch had similar changes, some with near occlusion of the lumen [Figures 4 and 5]. The process focally extended into the adjacent myocardium between myocytes; however, the prominent pattern was that of vascular involvement. Congo red stains revealed the material to have an apple-green birefringence, although the amount of such staining was minimal when compared to Case 3. Associated with these changes was patchy interstitial fibrosis. Postmortem serologic testing for free light chains indicated a lambda concentration of 0.73 mg/dL, a kappa concentration of 44.00 mg/dL, and a kappa/lambda ratio of 60.27. Examination of the bone marrow did not reveal an apparent increase in the number of plasma cells; however, postmortem analysis was impaired by autolysis.

DISCUSSION

Amyloid represents the accumulation within organ parenchyma of a protein that has become folded into a $\beta$ pleated sheet [1]. Kholová and Niessen summarized the 19 proteins associated with AL; of these, eight involved the cardiovascular system: Immunoglobulin light chain, immunoglobulin heavy chain, serum amyloid A, $\beta$-2-microglobulin, transthyretin, atrial natriuretic factor, apolipoprotein A-I, and lactadherin [2]. Lactadherin and apolipoprotein A-I involve the aorta, and atrial natriuretic factor involves the atrium [2].

AL is an infrequent diagnosis at autopsy. Thornton reviewed the records from 11,586 autopsies and found that 81 had amyloid disease [3]. Of these 81 cases, in 31 cases the amyloid involved the heart. In 43/81 cases, the AL was determined to be primary (with three of these associated with multiple myelomas), and
in 39/81, the amyloid was secondary to bronchiectasis (most commonly), tuberculosis, sarcoidosis, syphilis, rheumatoid arthritis, systemic lupus erythematosus, or renal cell carcinoma. One patient had two possible secondary causes for amyloid disease. Senile cardiac AL was included as a primary cause of AL. Of 1128 cases, the author identified four with cardiac AL (0.355%, which is similar to Thornton’s incidence of 0.268%).

Categorization of AL is important as it allows for an organized understanding of the various conditions responsible for this pathologic finding. Although Thornton grouped AL into primary and secondary forms [3], other authors use different categories, extracting conditions from either primary or secondary and grouping them individually. In their review, Kholová and Niessen [2] list four categories of AL: Primary, secondary, hereditary, and age-related. Hassan et al. [4], in addition to those four categories of AL, list a fifth, hemodialysis-associated. Khan and Falk [1] list five types of AL and the protein and diseases each is associated with. These five types include (1) AL (monoclonal immunoglobulin light chain) associated with plasma cell dyscrasias and multiple myeloma, (2) AA (amyloid A protein), associated with rheumatoid arthritis, tuberculosis, and familial mediterranean fever, (3) Familial types (with ATTR having transthyretin, ApoA-I having apolipoprotein A-I, and AfiB having fibrinogen A-αL), (4) Aβ2M (β2 microglobulin) associated with chronic hemodialysis, and (5) Aβ (beta protein) associated with Alzheimer’s disease. Mutated transthyretin is a common protein found in hereditary AL while normal transthyretin is a common protein found in age-related AL [4].

Based upon their review of the literature, Kholová and Niessen [2] describe that secondary and hereditary forms rarely involve the heart, or, in the case of hereditary forms, only late in the course of the disease. However, Banypersad et al. [5] indicate that cardiac involvement in hereditary forms of AL can be under-diagnosed, and often attributed to another disease such as hypertension. Cardiac AL can involve the atria, ventricles, and valves. Atrial AL is very common with increasing age, with the condition present in around 80% of people above the age of 70 years who are autopsied [5].

The mechanism of death of cardiac AL can include arrhythmias [2], thus, being in the purview of forensic pathologists, and thus the need for such physicians to understand the classification of AL. In the four deaths listed above, the two cases found in men in their 90s most likely represent age-related AL, being microscopic in nature, and with no other underlying cause of the AL identified. No immunohistochemical stains or serologic or genetic testing were utilized, however. Case 3 and 4 represent AL associated with multiple myelomas and a likely plasma cell dyscrasia, respectively. In Case 4, the morphologic pattern, being nearly entirely confined to intramyocardial vessels, is relatively unique.

Patients with prominent involvement of the intramural coronary artery branches are reported [6]; however, this condition appears to be rarely diagnosed at the time of autopsy. Morin et al. [7] presented the case of a 60-year-old male who died as the result of cardiac AL affecting the walls of the coronary arterial branches, but with none in the myocardium. The underlying cause was AL, with lambda light chains the accumulated protein. In their abstract, the authors indicate that isolated intramural vessel involvement is rarely seen and that there have been no reported cases of such a condition causing sudden death, except their own. Although the authors describe “sections” of myocardium, the number of sections is not indicated, and thus, the isolated involvement of the intramyocardial coronary arterial branches may be relative. Also, the authors did not sample the bone marrow, which may have provided a source for the elevated lambda light chains. However, Petersen et al. [8] reported the death of a 68-year-old man, who had “marked diffuse involvement of medium and small intramural coronary
arteries and a number of veins by medial and perivascular amyloid deposits was associated with similarly marked luminal compromise.” The decedent also has severe coronary artery atherosclerosis and a healed transmural myocardial infarct. Morin et al. [7] did cite Petersen et al. [8], but it was only in relation to how common cardiac involvement occurs in AL patients. Given that the individual described by Petersen et al. [8] also had severe coronary artery atherosclerosis, the cause of death may not be solely cardiac AL. Thus, Case 4 presented above would represent either the second or third such case of intramyocardial vascular, cardiac AL presenting with sudden death. The individual described in Case 4 did not have severe coronary artery atherosclerosis.

The diagnosis of not just the AL, but also its underlying cause at autopsy can be important. To facilitate this process, Garibaldi and Zaas [9] suggest an algorithm for the diagnosis of cardiac AL. Of relevance to a forensic pathologist, if the heart displays AL, and an M protein was detected, and the bone marrow biopsy is concordant with the M protein, the likely diagnosis is AL. If there is discordance, or no M protein is detected, special stains and genetic testing are recommended to separate between AL, senile (with ATTR protein), secondary (with AA protein) or familial (with ATTR protein mutations). Kholová and Niessen [2] indicate that there are commercially available antibodies against kappa light chain, lambda light chain, AA amyloid, β2 microglobulin, atrial natriuretic peptide, and transthyretin. Another possible testing procedure to identify the specific type of amyloid protein is laser capture microdissection which can obtain small samples for analyzation via mass spectrometry [5].

CONCLUSION

Cardiac AL is an uncommon diagnosis at autopsy, but one which can present itself to a forensic pathologist, via the sudden and unexpected death of an individual. Identifying the condition through knowledge of its histologic appearance and morphologic patterns, and establishing the underlying cause for its presence, is important, and, when pursued in an organized fashion, very possible.

Ethical Standards

As the submitted paper does not involve human’s subject research, Institutional Review Board approval is not required. The paper is a retrospective review of material gathered in the normal course of an autopsy performed by the author, and all unique identifying information has been withheld.

REFERENCES