Case Report

Arrhythmia Storm in Cardiac Amyloidosis Secondary to Neglected Psoriatic Arthritis: A Case Report

Melly Susanti[1], MD; Ivana Purnama Dewi[1], MD; Agus Subagjo[1*], MD; Yuliasih[2], PhD;

ABSTRACT

Systemic AA amyloidosis is a rare infiltrative disease representing a complication of chronic inflammatory disorders. Cardiac involvement is extremely rare and is associated with a poor prognosis. Early recognition is imperative as appropriate measures and treatment of the underlying disease may prevent death from refractory heart failure and fatal arrhythmias.

Case Report: A 53-year-old male patient with psoriatic arthritis presented with heart failure and nephrotic syndrome. Electrocardiography revealed a first-degree atrioventricular block, low-voltage QRS complexes, and a prolonged QT interval. Echocardiography revealed a hypertrophic left ventricle with normal systolic function and signs of diastolic dysfunction, as well as right ventricular dysfunction and mild pericardial effusion. An abdominal fat pad punch biopsy confirmed amyloidosis deposition. A 24-hour Holter study recorded self-terminated polymorphic ventricular arrhythmias. Immunosuppressive, anti-inflammatory, antiarrhythmic, and heart failure agents were promptly instituted, which proved ineffective.

Conclusions: Significant cardiac involvement in systemic AA amyloidosis is infrequent and complicated by fatal arrhythmias not described before. This report highlights the significance of the early recognition and aggressive control of the inflammatory response. ***(Iranian Heart Journal 2022; 23(2): 120-129)***

KEYWORDS: Amyloidosis, Psoriatic arthritis, Polymorphic ventricular arrhythmia

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Airlangga University – Dr. Soetomo General Hospital, Surabaya, Indonesia.
[2] Department of Internal Medicine, Faculty of Medicine, Airlangga University – Dr. Soetomo General Hospital, Surabaya, Indonesia.

*** Corresponding Author:** Agus Subagjo, MD; Department of Cardiology and Vascular Medicine, Faculty of Medicine, Airlangga University – Dr. Soetomo General Hospital, Surabaya, Indonesia.
Email: agussubagjospjp@gmail.com **Tel:** +62 811 3490 69

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AA amyloidosis is a heterogeneous group of disorders related to the extracellular deposition of abnormal protein metabolism, in which misfolded protein precursors deposit with proteoglycans and serum amyloid P protein.[1] Systemic AA amyloidosis may complicate any chronic inflammatory disorder. One of them is psoriatic arthritis, a chronic, immune-mediated, inflammatory arthropathy that presents inflammation of the joints and entheses, including those of the axial skeleton.[1,2] Amyloid fibrils are derived from a hepatic acute-phase reactant, serum amyloid A protein, an apolipoprotein constituent of high-density lipoprotein.[1] Cardiac involvement in AA amyloidosis is rare, reported only in about 0 to 2% of the affected subjects.[3,4] To the best of our knowledge, cardiac involvement in systemic AA amyloidosis complicated by polymorphic ventricular tachycardia has not been reported in the literature.

Case Report

A 53-year-old man with a history of hypertension presented with shortness of breath and whole-body edema to our emergency department. His shortness of breath had begun approximately 1 month before presentation with dyspnea on exertion, which gradually progressed. His medical history was unremarkable. There was no family history of heart failure or sudden cardiac death. On arrival at our hospital, the patient complained of mild dyspnea at rest and marked dyspnea on exertion. He described stable 3-pillow orthopnea for the preceding month and denied any cough, chest discomfort, and palpitations. However, he complained of back pain and stiffness, which had worsened over 1 year.

On physical examination, the patient was ill-appearing and afebrile with a blood pressure of 89/60 mm Hg, a heart rate of 74 beats per minute, a respiratory rate of 25 breaths per minute, and an oxygen saturation level of 99% on 3 liters of nasal cannula oxygen. A cardiovascular examination revealed an elevated jugular venous pressure at 12 cm with positive hepatojugular reflux, a regular rate, and a regular rhythm with an audible third heart sound and no murmurs. On lung examination, he had bilateral rales at the bases. His abdomen was tense and distended to palpation. The liver was palpable 2 fingerbreadths below the right costal margin. A prominent fluid wave was appreciated. He had pitting edema on the extremities. There was an asymmetrically impaired range of motion of the hip, the knee, the shoulder, and the wrist joints. Nail plate thickening and crumbling were observed on his right second and third fingers. The Classification Criteria for Psoriatic Arthritis score was 4 points.

A 12-lead electrocardiogram (ECG) revealed sinus rhythm with a rate of 70 beats per minute, a first-degree atrioventricular (AV) block, low-voltage QRS complexes in all leads, a prolonged QT interval (QT/QTc 520/562 ms), and an rS pattern in the precordial leads (Fig. 1A). Laboratory parameters at admission documented multiorgan dysfunction (urea=63 mg/dL, creatinine=2.58 mg/dL, creatinine clearance by Cockcroft–Gault=34 mL/min, uric acid=11.4 mg/dL, alanine aminotransferase=45 U/L, and aspartate aminotransferase=138 U/L). Additionally, serum electrolytes were within the normal limits, rheumatoid factors and antinuclear factors were negative, the erythrocyte sedimentation rate was 70 mm/h, and C-reactive protein was 7 mg/dL. Moreover, the fasting lipid profile showed increased levels of total cholesterol (281 mg/dL) and low-density lipoprotein (254 mg/dL). A 24-hour urine collection showed 3.5 g of protein. Urinalysis revealed +3 protein, +2 erythrocyte, and ≥300 mg/g albumin-to-creatinine ratio, indicating massive proteinuria. Serum protein electrophoresis revealed a polyclonal gammopathy pattern (Fig. 1B). Chest posteroanterior film revealed cardiomegaly and pleural effusion (Fig. 1C). A pelvic radiograph showed bilateral sacroiliitis (New York criteria grade III) (Fig. 1D). Lateral plain radiography of the thoracic spine demonstrated spondylitis (Fig. 1E).

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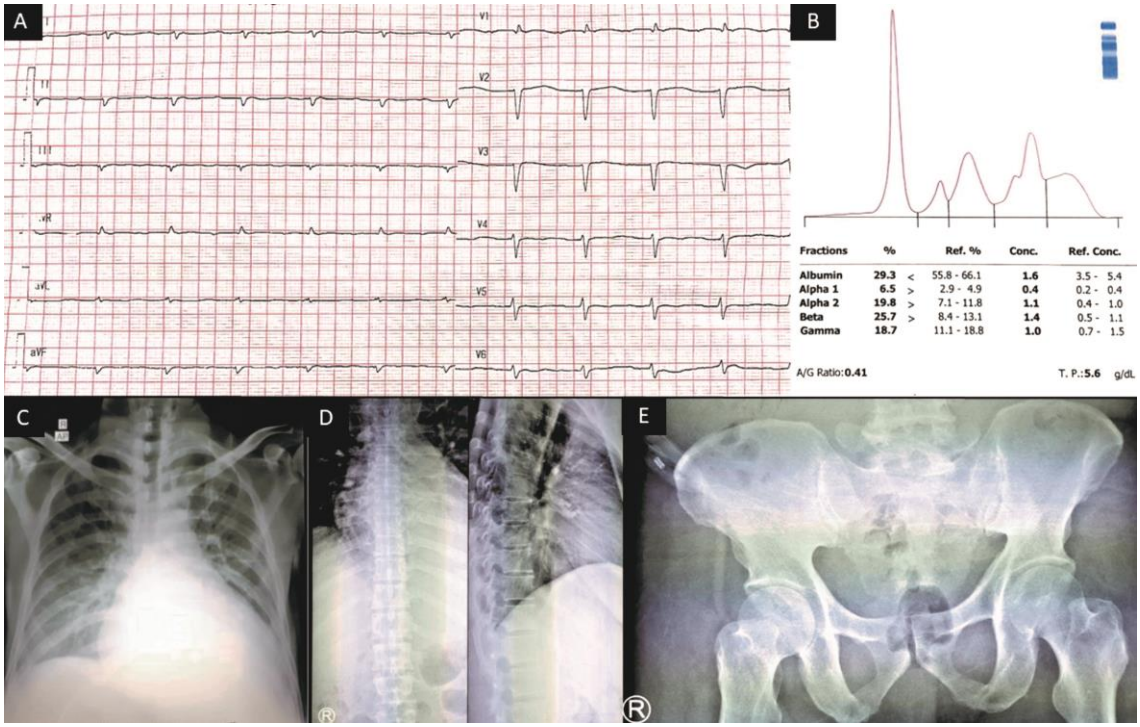

Figure 1: Twelve-lead electrocardiography recording (A) reveals sinus rhythm with a rate of 70 beats per minute, a prolonged PR interval (280 ms), low-voltage QRS complexes in the limb (≤0.5 mV) and precordial (≤1.0 mV) leads, a prolonged QT interval (QT/QTc=520/562 ms), and an rS pattern in the precordial leads. Serum protein electrophoresis (B) reveals markedly decreased albumin levels, with an increased level of α-2 and β, as well as a broad diffuse γ band. The chest radiograph (C) demonstrates cardiomegaly and pleural effusion. The anteroposterior pelvic radiograph (D) shows sclerosis on both sides of the joint and the widening of the joint space. (Left) The lateral radiograph of the spine (E) shows squaring of the anterior vertebral bodies and longitudinal ligament calcification (syndesmophytes).

A 2D transthoracic echocardiogram performed on hospital day 2 revealed a normal left ventricular (LV) systolic function (ejection fraction=55%) and cavity with evidence of fine granular appearance and hypertrophic myocardium (septal thickness=15 mm, posterior wall thickness=17 mm, and LV mass index 133.61 g/m^2). A restrictive filling pattern of the LV was documented (Fig. 2C). The right atria were moderately dilated. There was mild mitral regurgitation (Fig. 2B), moderate tricuspid regurgitation, and mild pericardial effusion. Additionally, 2D speckle-tracking echocardiography (GE Healthcare) was performed. Longitudinal strain (LS) measurements were performed offline using automated software (EchoPAC, version 202, Advanced Analysis Technologies; GE Healthcare). The LV endocardium was manually identified using 3 standard apical views, and tissue speckles were automatically detected, tracked frame by frame throughout the cardiac cycle. The patient had a lower global LS value (−8.5). The majority of the segments in the basal and mid-ventricular regions had reduced LS, with relative apical sparing (Fig. 2D).

The clinical course was characterized by rapid deterioration. Drugs for heart failure were up-titrated to the maximum tolerated dose. Given the AV block and concern of profound hypotension with inadequate response to any vasopressor, angiotensin-converting enzyme inhibitors and beta-blockers were avoided.

Concerning all previous findings and the clinical course, restrictive cardiomyopathy secondary to AA amyloidosis with neglected psoriatic arthritis was suspected. We performed a fine-needle aspiration biopsy from the abdominal fat pad, but the result was inconclusive. Given the high clinical suspicion of cardiac amyloidosis, an abdominal fat pad punch biopsy was performed, which revealed amyloid deposition with Congo red staining (Fig. 3B). Thus, the fine-needle aspiration biopsy failed to confirm amyloidosis in our case. A diagnosis of AA amyloidosis with cardiac and possible renal involvement was established.

In coordination with the rheumatologist, immunosuppressive therapy (leflunomide 20 mg once daily) and an anti-inflammatory agent (sulfasalazine 500 mg twice daily) were initiated. Financial aspects limited the use of TNFα-inhibitors in this patient. All heart failure symptoms improved, mainly after 7 days of treatment.

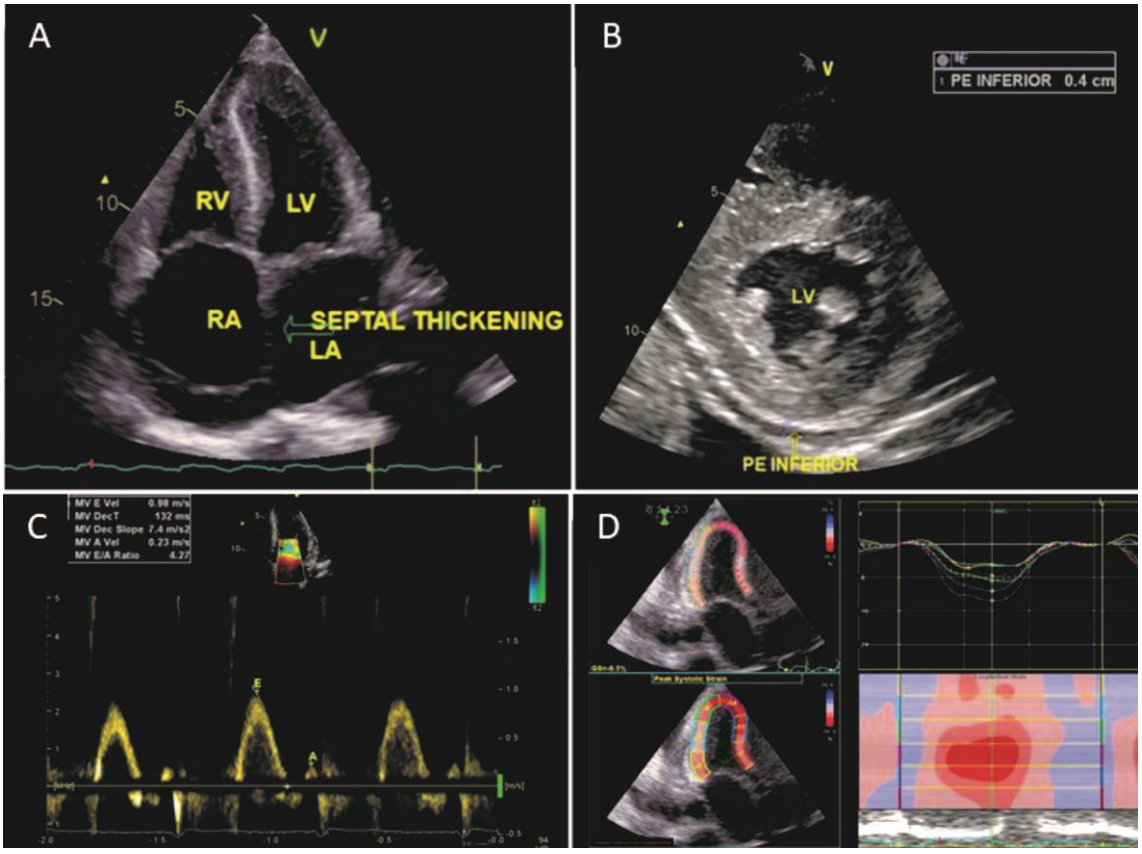

Figure 2: Echocardiography in the apical 4-chamber view (A) and short-axis view (B) demonstrates the granular sparkling appearance of the hypertrophic myocardium. The LV wall is thickened with a homogenous texture of the interatrial septum, mitral, and tricuspid leaflets. The RV free wall is also thickened. There is a mild inferior PE.

RA, Right atrium; LA, Left atrium; RV, Right ventricle; LV, Left ventricle; PE, Pericardial effusion

The image presents the apical 4-chamber view in the pulsed-wave Doppler measurement of the transmitral flow (C) with features of restrictive filling (ie, increased E velocity, reduced A velocity [E/A ratio=4.27], and shortened deceleration time). Speckle-tracking echocardiography of longitudinal strain demonstrates a distinctive apical sparing pattern. The global strain of the left ventricle is -8,5%.

Red, Normal strain values; Pink, Reduced value; Light pink, Severely reduced values

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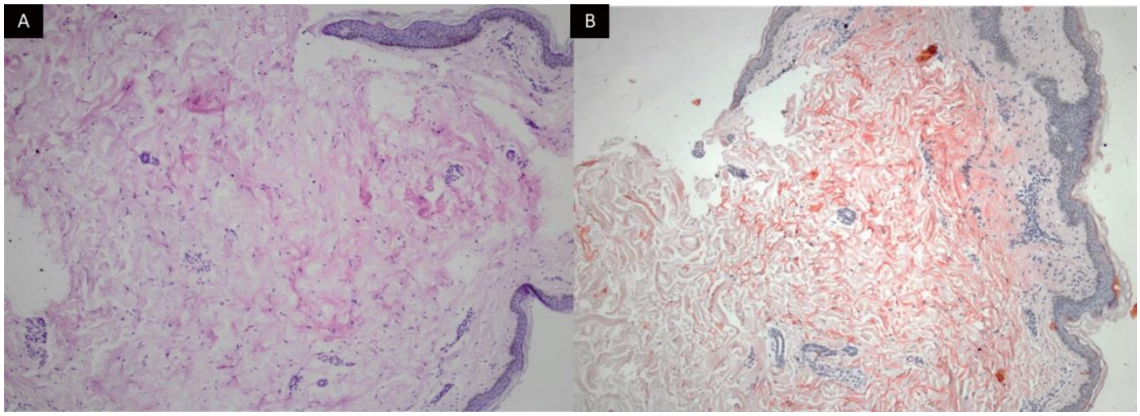

Figure 3: The slide of the abdominal fat pad punch biopsy shows amyloid deposition: (A) H & E staining and (B) Congo red staining; original magnification x400.

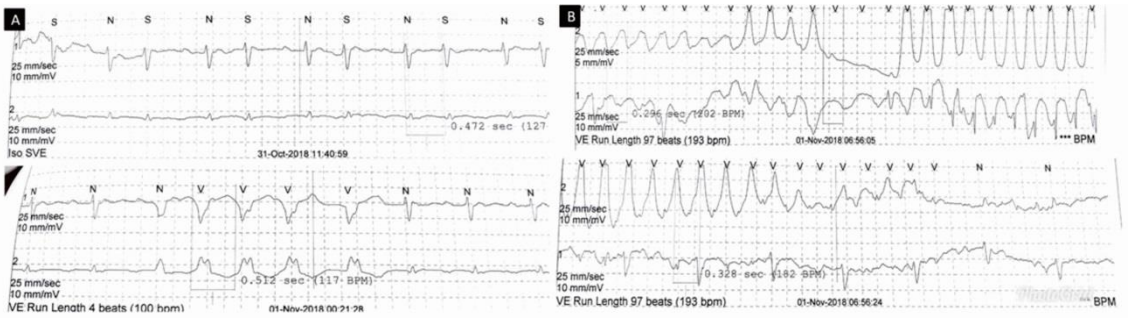

Figure 4: The 24-hour Holter study documents infrequent premature ventricular contractions. The image shows an episode of nonsustained ventricular tachycardia and Torsade de Pointes. The image illustrates infrequent premature atrial contractions with an episode of bigeminy. The baseline rhythm is sinus with a first-degree atrioventricular block and a prolonged QT interval (QTc 537 ms). Symptoms appeared during the episode of Torsade de Pointes.

On the 20th hospital day, the patient experienced the first episode of syncope. He regained consciousness within a few seconds without any prodromal symptoms before the event. Serum electrolytes were within the normal limit (magnesium=2.4 mg/dL and potassium=4.1 mEq/L). A 24-hour Holter monitoring study was performed, and it revealed 372 premature atrial contractions, 65 premature ventricular contractions, and 1 run of nonsustained polymorphic ventricular tachycardia lasting up to 96 beats in duration (Fig. 4). Symptoms appeared during the episode of polymorphic ventricular tachycardia. An intravenous bolus of magnesium sulfate (2 g) was given, and amiodarone was avoided due to QT-interval prolongation and profound hypotension. Despite the maximally tolerable dose of an antiarrhythmic drug (bisoprolol fumarate 7.5 mg daily) for arrhythmia prevention, syncopal attacks persisted with documented malignant arrhythmias.

The combined therapy of immunosuppressive, anti-inflammatory, heart failure, and antiarrhythmic drugs failed to reverse the course of the multiorgan failure and the refractory malignant arrhythmia. The patient died 33 days after the admission.

DISCUSSION

During the 20th century, AA amyloidosis has become less common, and the contribution of AA amyloid to large series

of amyloidosis has gradually decreased. The median age for AA amyloidosis is between 55 and 60 years.[5] The prognosis of untreated patients is poor as noticed in older studies, with median survival ranging from 3 to 4 years for AA amyloidosis.[6] Chronic inflammation resulting from rheumatic, autoimmune, and infectious diseases is associated with organ tissue deposition of the acute-phase reactant serum amyloid A protein. The process is triggered by circulating tumor necrosis factors, interleukins, and transcription factors, which upregulate the gene expression of the amyloid protein.[7]

Restrictive cardiomyopathy is the hallmark finding in cardiac amyloidosis, and it results from the interstitial deposits of amyloid fibrils. Once infiltrated, the myocardium becomes firm and noncompliant.[7] Clinically, this condition manifests itself as progressive diastolic dysfunction, elevated LV filling pressure, and heart failure with a preserved ejection fraction, as was the case in our patient.

Serum protein electrophoresis revealed a polyclonal gammopathy pattern, which might suggest an infectious or inflammatory reactive process,[8] with the latter being more likely to have happened in our patient. Moreover, the typical appearance of the ECG in cardiac amyloidosis was seen in our patient. Indeed, it was our first clue of cardiac amyloidosis. There were low-voltage QRS complexes in all the leads with poor R-wave progression in the precordial leads. The inverse correlation between increased ventricular mass and reduced ECG voltage is unique to infiltrative cardiomyopathy.[9]

AA amyloidosis rarely produces clinically apparent heart disease, and it is reported only in about 0 to 2% of the affected subjects.[3,4] While cardiac involvement with ventricular arrhythmia has been reported in other systemic amyloidosis conditions, it has never been reported in AA amyloidosis, to our best knowledge. Hence, its mechanism is still unknown. Moreover, a recent large population study emphasized the association between psoriasis and an increased risk of arrhythmia development, independent of classic cardiovascular risk factors. The study indicates that psoriatic arthritis was associated with a greater risk of arrhythmia, suggesting that inflammation may be an important key to pathogenesis. The exact cause of arrhythmias cannot be determined given that both the infiltration process by amyloid and inflammation due to psoriatic arthritis may induce arrhythmias.[10] Rapid ventricular rates can cause a precipitous drop in cardiac output, manifesting in syncope. Patients with cardiac amyloidosis are associated with QT prolongation.[11] We posit that the extensive deposition of amyloids in the myocardium might be the key behind the progression in the QTc length with subsequent arrhythmias. Finally, there are insufficient data and recommendations on implantable cardioverter-defibrillator (ICD) therapy in AA amyloidosis.

Echocardiography plays an essential role as a noninvasive test to diagnose cardiac amyloidosis. Increased LV wall thickness with evidence of diastolic dysfunction is the earliest echocardiographic abnormality. Right ventricular diastolic dysfunction can occur with a spectrum of correct ventricular filling abnormalities, and the restrictive filling pattern is seen only in the advanced stages of the disease.[12] There are many echocardiographic features in cardiac amyloidosis, and the combination of several features helps differentiate it from other diagnoses. Interatrial septum thickening has been very specific for amyloids in the latter stage of the disease, with 100% specificity.[13] Our patient demonstrated the classic echocardiographic features of cardiac amyloidosis, which commonly present only in the latter stages of the disease. Amyloid

cardiomyopathy is associated with dissociation between short- and long-axis systolic function. Speckle-tracking echocardiography shows impairment in longitudinal contractility even when the LV ejection fraction is within the normal range. A relative apical sparing pattern with a marked reduction in LS of all segments in basal and mid-ventricular wall regions is typical and is rarely seen in other diseases.[14,15] Global longitudinal strain (GLS) permits the quantification of LV function with greater sensitivity than the ejection fraction. The greater sensitivity of GLS over the ejection fraction has suggested that it is useful as an earlier marker of change for many cardiomyopathies.[16] Our patient demonstrated reduced GLS with the relative preservation of apical LS.

Cardiovascular magnetic resonance imaging is helpful for diagnosis since it can noninvasively provide evidence of strongly suggestive cardiac involvement in amyloidosis, with a sensitivity of 93% and specificity of 87%, by the presence of global subendocardial late gadolinium enhancement.[17] Limitations include cost, lack of wide availability, and the contraindication of gadolinium use in patients with moderately-to-severely impaired renal function, as seen in our patient.

Effective treatment will retard and prevent further deposition of amyloids, but the potential effect of treatment will be dependent on the extent of disease progression at the time of diagnosis. Thus, the early diagnosis of amyloid heart disease is of utmost importance, influencing further management of the patients.[18] A biopsy of an involved organ is the diagnostic gold standard. However, a clinically suspected site (eg, the kidney, the liver, or the heart) is an invasive procedure, and significant complications such as bleeding are a potential risk. Both biopsies of the rectum and abdominal fat aspiration are frequently used to detect systemic amyloidosis in patients with signs or symptoms of the disease.[19] In our index case, systemic amyloidosis could be confirmed by abdominal fat pad punch biopsy, while fine-needle aspiration biopsy failed to reveal amyloid deposition. Thus, a negative fine-needle subcutaneous fat pad biopsy does not exclude systemic amyloidosis. This finding demonstrates one of few clinical situations where the usefulness of punch biopsies can be relevant. Amyloid deposition in abdominal fat tissue is seen exclusively in the setting of systemic amyloidosis. The specificity of this test, provided that the staining procedure is performed correctly, approaches 100%. Sensitivity values vary greatly, from 52% to 88%. This wide range might be attributable to the amount of fat tissue, differences in experience with the staining and scoring of biopsy specimens, characteristics of the patients, the size of the study group, and the type of systemic amyloidosis.[19] The definitive diagnosis of cardiac amyloidosis is established with an endomyocardial biopsy or a positive noncardiac biopsy with classical cardiovascular magnetic resonance imaging or ECG findings, clinical, and conventional echocardiographic findings.[20]

Treatment for AA amyloidosis is aimed at decreasing serum amyloid A serum levels into the low-normal range (<4 mg/L).[21] If the serum amyloid A concentration can be maintained at less than 10 mg/L, survival at 10 years could reach 90%. Nevertheless, with serum amyloid A concentrations exceeding 10 mg/L, the survival rate might be as low as 40%.[22] The only way to achieve the target value of serum amyloid A is by the complete suppression or eradication of the underlying chronic inflammatory disease. Diuretics are the mainstay of therapy to control volume overload. However, they should be administered

cautiously since patients with restrictive cardiomyopathy rely on high ventricular filling pressure to maintain cardiac output. Accordingly, excessive diuresis can lead to a marked reduction in filling pressure and severe hypotension. Digoxin administration should be used cautiously since it binds to amyloid fibrils, resulting in a higher risk of toxicity, despite therapeutic serum digoxin levels.[23]

Our patient showed manifestations of amyloid deposition primarily in the heart and the kidneys, which are uncommon forms of the presentation of AA amyloidosis. Our patient presented with the classic findings of nephrotic syndrome (ie, severe edema, hypercholesterolemia, and massive proteinuria). As seen in our patient, the presence of rapidly progressed heart and renal failure with characteristic features of ECG should prompt further evaluation with noninvasive modalities such as echocardiography with speckle tracking and tissue biopsies to confirm infiltrative cardiomyopathy. This is highly suggestive that the natural course of cardiac amyloidosis is often unpredictable and can be aggressive at times if left undiagnosed and untreated.

Of note, there were some limitations in our report. Due to a paucity of facilities, we could not perform immune-histochemical testing to confirm AA amyloidosis and serum amyloid A concentration measurements to guide anti-inflammatory treatment. As previously mentioned, there was no cardiac magnetic resonance imaging in our center.

CONCLUSIONS

We encountered the atypical presentation of AA amyloidosis with cardiac involvement characterized by a syndrome of syncope, prolonged QTc, and recurrent polymorphic ventricular tachycardias, underscoring the need to consider chronic inflammatory disorder as a cause of cardiac amyloidosis. To our knowledge, a combination of the long QT interval and polymorphic ventricular tachycardias has not been previously reported in association with AA amyloid heart disease. Our case points out the usefulness of abdominal fat pad punch biopsies given that fat aspiration by needle could not confirm the presence of amyloid deposition. The effectiveness of treatment depends on timely diagnosis. Our patient gained no profit from improved treatment. He died from disease progression in the first months after diagnosis with advanced disease at presentation, multiorgan failure, and fatal malignant ventricular arrhythmias.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' Contributions

MS and AS made substantial contributions to the conception and the design of the manuscript and were major contributors to the writing of the manuscript. IPD edited the manuscript for publications. All the authors participated in drafting the manuscript. AS and Y revised the manuscript critically. All the authors read and approved the final version of the manuscript.

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Consent for Publication

Written informed consent was taken from the patient for the use of medical data for academic and research purposes, including publication.

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