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CASE REPORT

CLINICAL CASE

Persistent Prothrombotic State in a Patient With Alström Syndrome

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ABSTRACT

We present the case of a patient with Alström syndrome who was found to have evidence of a prothrombotic state on autopsy after sudden cardiac death. To the best of our knowledge, this case of persistent prothrombotic milieu is the first described in a patient with Alström syndrome. (J Am Coll Cardiol Case Rep 2024;29:102215) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 58-year-old man was diagnosed with Alström syndrome in 2006 at the age of 42 years with confirmatory genetic testing. He was followed up regularly via the supraregional specialist multidisciplinary team from 2012, which consisted of a joint clinic that included input from inherited diseases, respiratory, cardiology, and clinical psychology. He remained stable for many years, but in 2021, he presented with worsening exertional dyspnea.

LEARNING OBJECTIVES

- To have a high index of suspicion for thrombus in patients with Alström syndrome. irrespective of anticoagulation status.
- To consider intensification of treatment regimen in patients with recurrent thrombotic phenomena despite conventional anticoagulation, though guidance on strategy is lacking.
- To consider screening for concurrent thrombophilia for exclusion purposes.

PAST MEDICAL HISTORY

The patient had the following disease manifestations of Alström syndrome: type 2 diabetes, hypertension, blindness, sensorineural hearing loss, chronic kidney disease, dyslipidemia and hypogonadism. Cardiac magnetic resonance (CMR) in 2012 showed a non-dilated left ventricle (LV) with a mildly impaired systolic function (ejection fraction [EF], 47%), hypokinetic anterior, lateral and inferior mid and apical LV segments, and extensive patchy late gadolinium enhancement (Figure 1). Computed tomography coronary angiography in the same year demonstrated coronary calcification but no luminal stenoses. In 2016, he experienced symptoms suggestive of transient ischemic attack and had an implantable loop recorder, which excluded pathological dysrhythmias over a 3-year period. In 2017, transthoracic echocardiography (TTE) identified an apical LV thrombus

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ABBREVIATIONS

CAD = coronary artery disease

CKD = chronic kidney disease

CMR = cardiac magnetic resonance imaging

CRTD = cardiac resynchronization therapy-defibrillator

CTCA = computed tomography coronary angiography

ILR = implantable loop recorder

LAD = left anterior descending

LGE = late gadolinium enhancement

LV = left ventricle

LVSD = left ventricular systolic dysfunction

MPA = main pulmonary artery

OM1 = first obtuse marginal branch

PM = post-mortem

RBBB = right bundle branch block

RCA = right coronary artery

RV = right ventricle

SCD = sudden cardiac death

TIA = transient ischemic attack

TTE = transthoracic echocardiogram

which necessitated lifelong anticoagulation with warfarin (Figure 2). Serial TTE and CMR showed regression of LV thrombus and stable albeit mildly impaired LV systolic function (EF, 50%). CMR in 2020 showed total resolution of LV thrombus; nonetheless, the patient was maintained on anticoagulation without interruption, with good compliance and therapeutic international normalized ratio (INR) levels throughout.

INVESTIGATIONS

Repeat TTE performed in 2021 noted deterioration in LV systolic function (EF, 32%) and recurrence of apical LV thrombus. A 12-lead electrocardiograph revealed new right bundle branch block with a QRS duration of 152 ms. The patient was initiated on guideline-directed medical therapy but repeat TTE showed persistence of severe LV systolic dysfunction with an EF of 35%.

MANAGEMENT

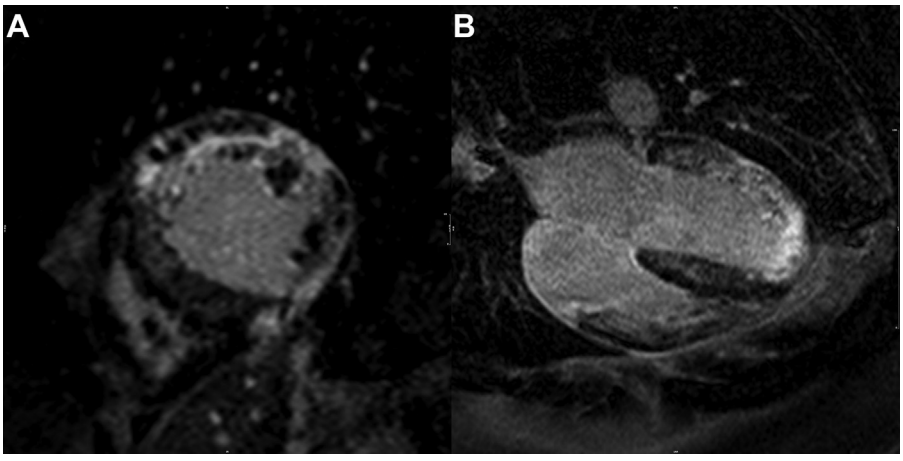
A referral was made to device multidisciplinary team in view of fulfilment of conventional criteria with subsequent listing for cardiac resynchronization therapy-defibrillator. A Medtronic Cobalt XT HF quadripolar single coil cardiac resynchronization therapy-defibrillator device (DTPA2QQ) was inserted with pacing mode set at DDD (lower rate of 50 beats/min) and tachycardia zones with monitoring to >150 beats/min and therapies at >200 beats/min. There were no immediate sequelae and he was discharged with provisions for home monitoring linked to the local ambulance service.

FOLLOW-UP

The patient was subsequently reviewed via device clinic with exclusion of significant arrhythmias and effective biventricular pacing (95%). He remained clinically well with no overt symptoms of heart failure and euvolemic fluid status. Unfortunately, 83 days after device implantation, he was found unresponsive in his home and certified dead at scene.

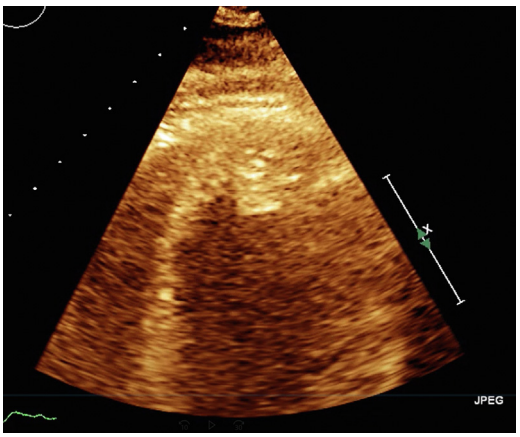
Owing to the unclear cause of demise, a post mortem (PM) examination was undertaken with consent from next of kin. This revealed mild to moderate asymmetrical biventricular hypertrophy with LV wall thickness of 2.2 cm and a right ventricle wall thickness of 1.0 cm (Figure 3A). There was near-circumferential subendocardial fibrous scarring of LV wall. The right atrial lead was ensheathed in thrombus (Figure 3B) with the presence of an adherent apical LV thrombus (Figure 3C). There was advanced coronary artery disease with the left anterior descending artery displaying 75% stenosis by diameter and first obtuse marginal branch (OM1) showing 90% to 99% stenosis by diameter. The mid right coronary artery similarly exhibited 50% to 75% localized, eccentric atheromatous encroachment. A review of the respiratory system showed presence of adherent laminated thrombus in the main pulmonary trunk and left main pulmonary artery (Figure 3D).

FIGURE 1 CMR Images



CMR images in short-axis (A) and long-axis (B) views showing extensive patchy late gadolinium enhancement. CMR = cardiac magnetic resonance.

FIGURE 2 TTE



TTE in zoomed apical 4 chamber view revealing presence of apical thrombus. TTE = transthoracic echocardiography.

Remote device interrogation excluded pathological arrhythmias at time of death. However, data were indicative of lead impedance and threshold alerts in the preceding period, suggesting ineffective electrical depolarization of the myocardium. The interim conclusion from the PM examination was that likely mode of death was cardiac dysrhythmia; the device was programmed to detect and respond to specific predefined parameters only and, therefore, could not cover all eventualities. The possibility of a respiratory arrest was raised but the pathologist felt that, on balance, sudden cardiac death was most likely given advanced cardiac manifestations.

DISCUSSION

Alström syndrome is an ultra-rare condition with estimated incidence of 1 in 500,000 to 1 in 1,000,000. It was first described in 1959[1] and is inherited in an autosomal recessive manner owing to mutations at various sites within the *ALMS1* gene, located on chromosome 2p13, with resultant abnormality of the ALMS1 protein found in primary cilia of centrosomes and basal bodies.[2] Underlying pathophysiological mechanisms are not fully elucidated, but animal studies suggest defects in ciliogenesis and function.[3] The ALMS1 protein has also been implicated in intracellular trafficking, regulation of cilia signaling pathways, and cellular differentiation.[4]

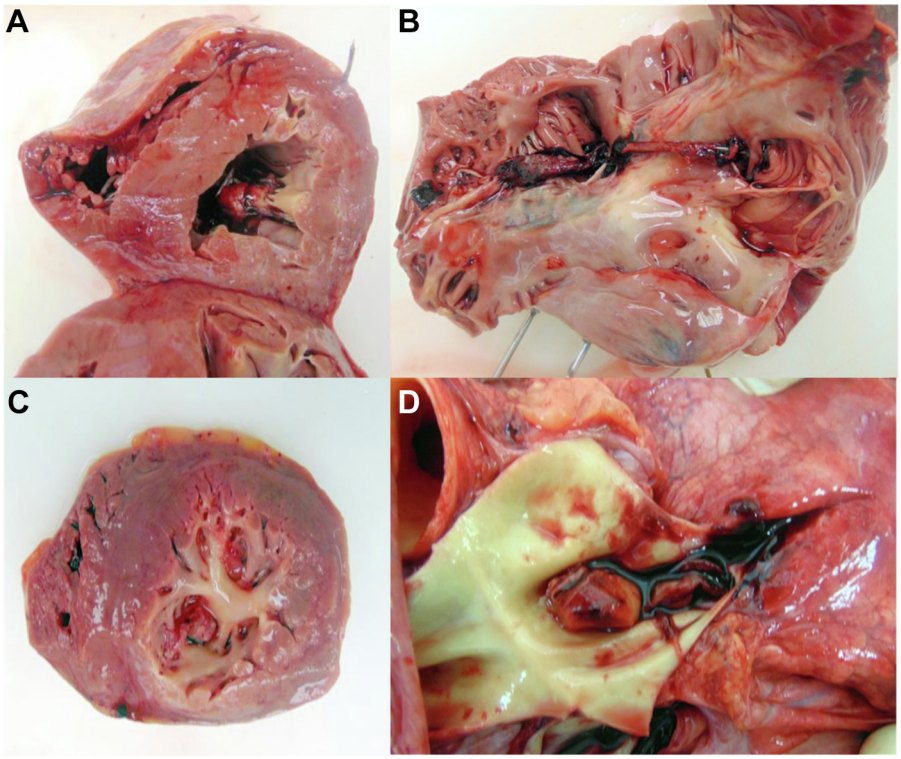
The expression and onset of clinical features is variable, including among siblings.[5] Classically, cone-rod dystrophy and secondary nystagmus develops in infancy resulting in blindness in the majority by the second decade of life, as seen in this case. Obesity, sensorineural hearing loss, insulin resistance, renal dysfunction and hepatic disease ranging from steatosis to cirrhosis are all seen in the later stages.[6] Cardiac complications are common with risk of cardiomyopathy in approximately 60%.[7]

Along with progressive hepatic and renal failure, cardiac failure is often the primary mode of death.[8] It is postulated that severe hyperinsulinemia results in erratic metabolism, leading to dysfunctional physiology in larger arteries with secondary myocardial hypertrophy, cardiomyopathy, and LV systolic dysfunction.[9] Accelerated coronary artery disease is also common in view of associated comorbidities. Prognosis is poor owing to disease distribution and severity of organ involvement with patients rarely exceeding fifth decade of life.[3] In this case, there was the presence of moderate cardiomegaly, severe coronary disease, and compensated cardiac insufficiency. He was, therefore, deemed susceptible to pathological dysrhythmias.

Despite conventional anticoagulation within the therapeutic range, there was extensive, adherent thrombus within pulmonary and cardiac vasculature with adherence to pacing leads that had developed semiacutely when considering the timing of device implantation. This finding is suggestive of a persistent prothrombotic milieu. Because our patient survived longer than predicted, it is plausible that thrombotic propensity increases with age and is concurrent with disease progression, or it may instead reflect temporal impact of established comorbidities. Thrombogenesis secondary to concurrent SARS-CoV-2 was considered; however, there was no history of suggestive symptoms. Formal viral sampling at time of PM was, therefore, not performed, although the possibility of severe relapsing hypercoagulability owing to rebound inflammatory flares in the absence of persistent viraemia cannot be excluded fully and has been reported previously.[10] A thrombophilia screen could also have been explored but no relevant family history existed and occurrence of LV thrombus was in the presence of known predisposition (ie, stasis secondary to regional wall dysfunction). A higher target INR was considered at time of LV thrombus recurrence; however, the patient was already on concurrent antiplatelet and also deemed a high fall risk given known visual impairment. Moreover, there are no compelling data to suggest that a higher INR is more effective in those with recurrent thrombus.[11]

No therapies are presently available to prevent or abrogate complications arising from Alström syndrome. An individualized approach using a

FIGURE 3 Post-mortem Examination of the Heart



(A) Transverse midseptal slice of the left ventricle showing concentric hypertrophy. (B) Right atrium/ventricle opened along the lateral border, revealing pacing lead ensheathed in thrombus. (C) Transverse slice of left ventricle showing thrombus at apex of left ventricle. (D) Main pulmonary trunk opened anteriorly, showing thrombus occluding the origin of the left pulmonary artery.

multidisciplinary team framework is broadly advocated for surveillance, detection, and management in view of disease rarity. Regular monitoring of serum biomarkers including renal, liver, and endocrine panels is advised. Modalities such as hearing aids or myringotomy may be used for hearing impairment with use of red-orange tinted prescriptions to treat photophobia and improve quality of life.[6] Surveillance TTE is beneficial to exclude cardiac involvement and monitor for disease progression that may warrant intensification of prognostic pharmacotherapy and/or consideration for device therapy. Serial CMR may be more sensitive in the detection of early functional changes, tracking of disease progression, and monitoring the impact of therapeutic interventions.[12]

CONCLUSIONS

This case report highlights an imperative need to have high index of suspicion for thrombus in patients with Alström syndrome, irrespective of anticoagulation status, and to arrange thorough screening in contexts where symptom profile or examination findings are suggestive.

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