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HEART FAILURE AND CARDIOMYOPATHIES

CASE REPORT: CLINICAL CASE

Thromboembolic Risk in Sinus Rhythm

A New Paradigm in Light Chain Cardiac Amyloidosis

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ABSTRACT

Thromboembolic risk is increased in cardiac amyloidosis, and this goes beyond the occurrence of atrial fibrillation in these patients. A 56-year-old man was admitted to our hospital for a presyncopal episode. Clinical and instrumental findings led to a diagnosis of light chain cardiac amyloidosis. Hospitalization was complicated by ischemic stroke resulting from embolization of a left atrial thrombus, that occurred in sinus rhythm. This case highlights the importance of a new diagnostic strategy for thromboembolic risk stratification in patients with cardiac amyloidosis. Left atrial strain assessment should be implemented in patients with cardiac amyloidosis to predict the occurrence of thromboembolic events. (JACC Case Rep. 2024;29:102531) © 2024 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 56-year-old patient presented to our emergency department for a presyncopal episode with traumatic head injury. On admission he was well oriented, asymptomatic, with vital parameters within the normal limits. Physical examination showed the evidence of macroglossia (Figure 1) and a small head laceration. Neurologic examination was normal. The electrocardiogram showed sinus tachycardia with pseudoinfarct pattern in precordial leads and repolarization abnormalities in the inferolateral leads, with peripheral low voltages (Figure 2). High-sensitivity troponin T was elevated (932 pg/mL; normal value below 20 pg/mL), and N-terminal pro-B-type natriuretic peptide was 2,340 pg/mL, with remaining blood tests within normal limits. Brain computed tomography (CT) scan performed early after admission was negative. Transthoracic echocardiography showed concentric left ventricular (LV)

TAKE-HOME MESSAGES

- Patients with cardiac amyloidosis are at risk of thromboembolic events even in sinus rhythm.
- New diagnostic strategies, including assessment of atrial strain parameters, should be implemented to predict thrombotic events in patients with cardiac amyloidosis.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AL-CA = amyloid light chain cardiac amyloidosis

CA = cardiac amyloidosis

CT = computed tomography

ECG = electrocardiographic

LA = left atrial

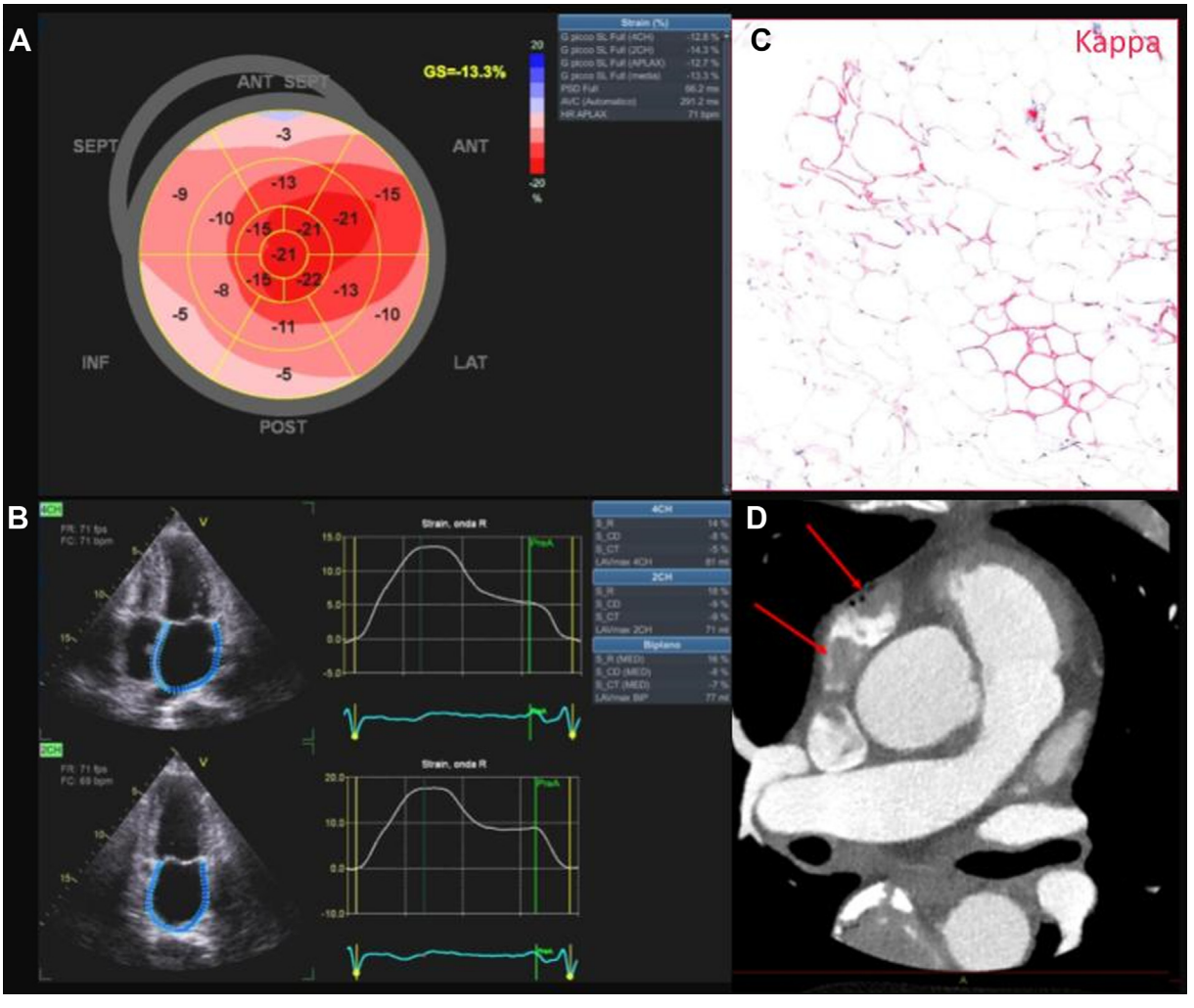
LV = left ventricular

hypertrophy, with preserved ejection fraction and no regional wall motion abnormalities (Video 1). Restrictive diastolic filling (E/e' 21) with no major valvular dysfunctions and a slightly hypertrophic and hypokinetic right ventricle was reported. The inferior vena cava was plethoric. A small pericardial effusion without hemodynamic impact was present. Speckle tracking analysis showed reduced LV global longitudinal strain with evident relative apical sparing (Figure 3A). Importantly, left atrial (LA) strain analysis showed reduction in all components of atrial function (Figure 3B). The patient was admitted for further investigations. On day 4, the patient developed hyposthenia and anesthesia of the left arm for which a new brain CT scan was performed, showing cortico-subcortical ischemia of the right temporo-insular-parietal region with occlusion at the M2 level of the middle cerebral artery (Figure 4).

PAST MEDICAL HISTORY

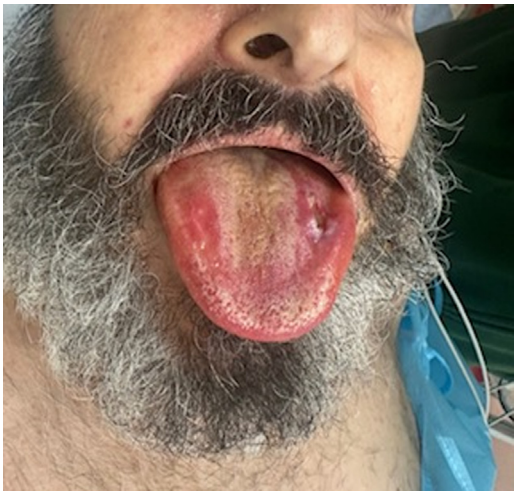
His medical history reported bilateral carpal tunnel syndrome diagnosed 3 years before and recent orthopedic surgery for left coxofemoral prosthesis. He

VISUAL SUMMARY **A 56-Year-Old Patient With Undiagnosed Light Chain Cardiac Amyloidosis, With Reduced Atrial Strain Parameters, Developed a Cardioembolic Ischemic Stroke in Sinus Rhythm**



(A) Reduction in GLS and relative apical sparing at left ventricular strain analysis. (B) Evidence of reduced reservoir, conduit and pump atrial function using atrial strain analysis. (C) Interstitial amyloid deposits with bright positivity for anti-AL-K in an histological sample of subcutaneous periumbilical fat. (D) Right auricle thrombus (red arrows) on chest CT.

FIGURE 1 Macroglossia



This picture taken during physical examination shows evident macroglossia, pathognomonic for light chain systemic amyloidosis.

reported a relative worsening of this functional capacity in the previous months, for which he decided to limit his daily activities.

DIFFERENTIAL DIAGNOSIS

Possible differential diagnosis includes other conditions presenting with LV hypertrophy, such as Fabry cardiomyopathy, sarcoidosis, or sarcomeric hypertrophic cardiomyopathy. In these cases, although the magnitude and distribution of LV hypertrophy can be similar to that of cardiac amyloidosis (CA), biatrial enlargement and restrictive fillings are less prominent, right ventricular hypertrophy is less common, and cardiac biomarkers are not similarly elevated. More importantly, systemic red flags (eg, bilateral carpal tunnel syndrome, low electrocardiographic [ECG] voltages, previous surgery for coxofemoral prosthesis) should lead our reasoning toward systemic amyloidosis, with macroglossia being pathognomonic for the light chain type.

INVESTIGATIONS

For the clinical suspicion of CA, the patient underwent myocardial scintigraphy with bisphosphonate tracer that showed no uptake at the myocardial level (Perugini score 0). Serum free light chain quantification and serum and urinary immunofixation revealed a type-kappa monoclonal gammopathy. Subcutaneous abdominal fat aspiration revealed light chain deposits, confirming the diagnosis of amyloid light chain cardiac amyloidosis (AL-CA) (**Figure 5**).

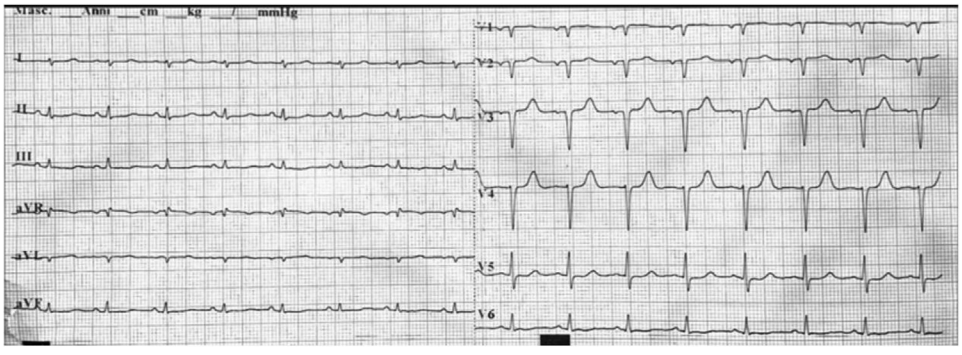
MANAGEMENT

Percutaneous thrombectomy was successfully performed with complete revascularization of the frontoparietal vessel. Aspirin was administered but soon withdrawn for hemorrhagic complications at the ischemic site. During hospitalization, the patient reported worsening of dyspnea and persistent cough for which a chest CT scan was performed, which showed a normal pulmonary parenchyma, but also a thrombus in the right auricle (**Figure 6**). No atrial fibrillation (AF) was detected at continuous ECG monitoring.

OUTCOMES AND FOLLOW-UP

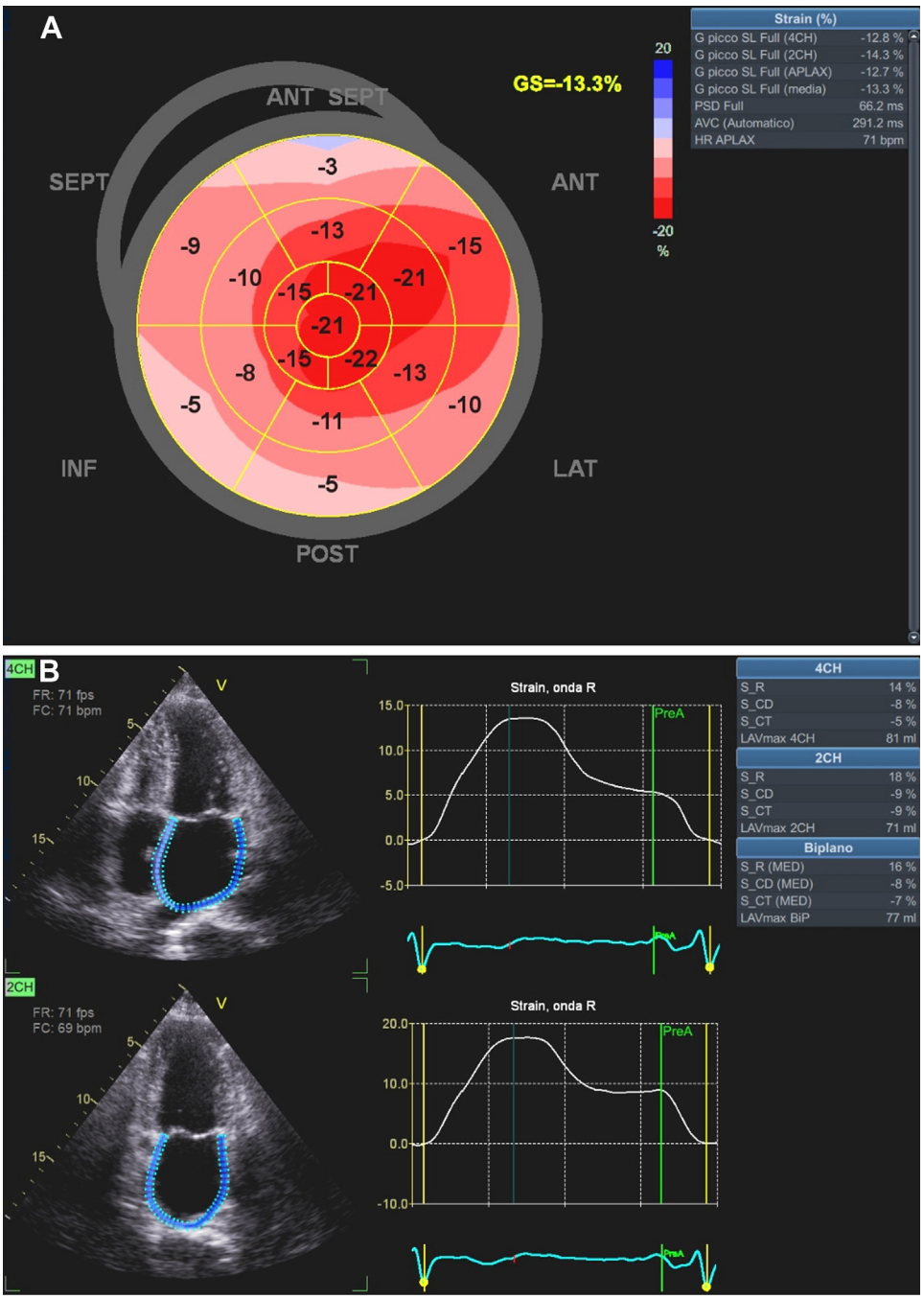
Based on the cerebral infarct site and on the overall clinical picture, the ischemic stroke was considered cardioembolic. The patient was transferred to a

FIGURE 2 Electrocardiogram on Admission



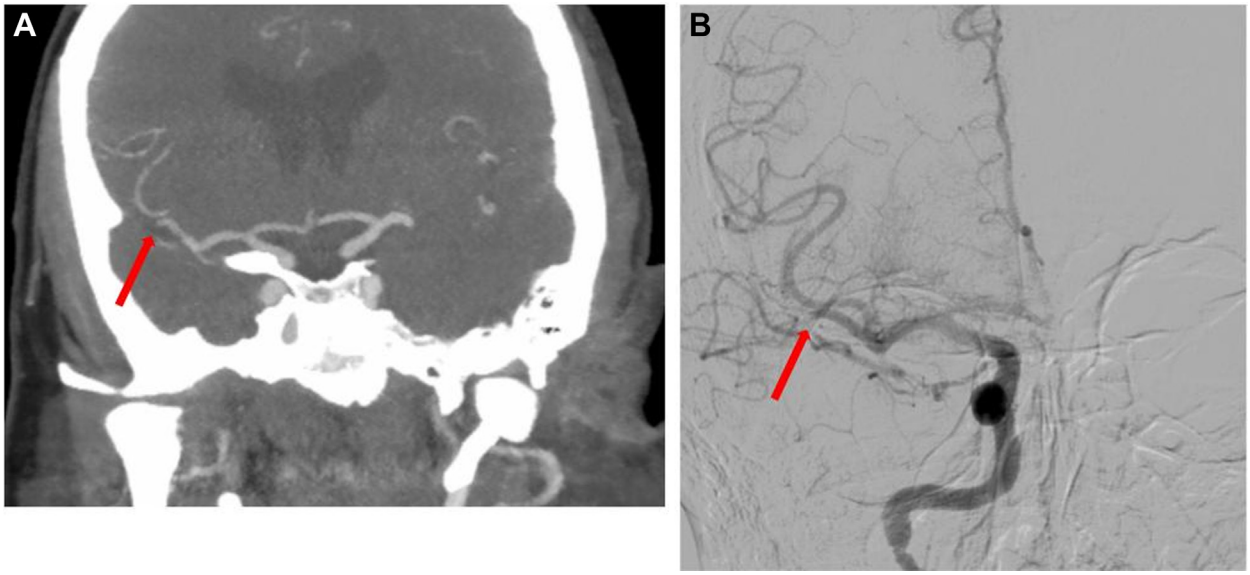
The electrocardiogram shows sinus tachycardia with pseudoinfarct pattern in precordial leads, repolarization abnormalities in inferolateral leads, and low voltages in the peripheral lead.

FIGURE 3 **Speckle Tracking Analysis**



(A) Left ventricular strain analysis showing reduction in GLS and relative apical sparing; (B) atrial strain analysis showing reduction in reservoir, conduit, and pump atrial function.

FIGURE 4 Brain Computed Tomography and Cerebral Angiography



Brain computed tomography scan showing total occlusion of middle cerebral artery at the M2 level (A) and incomplete filling of the cerebral artery after contrast injection at angiography. B shows an incomplete filling of the cerebral artery after contrast injection at angiography (red arrow). The arrow in A shows a total occlusion of the middle cerebral artery at the M2 level; the arrow in B shows an incomplete filling of the cerebral artery after contrast injection at angiography.

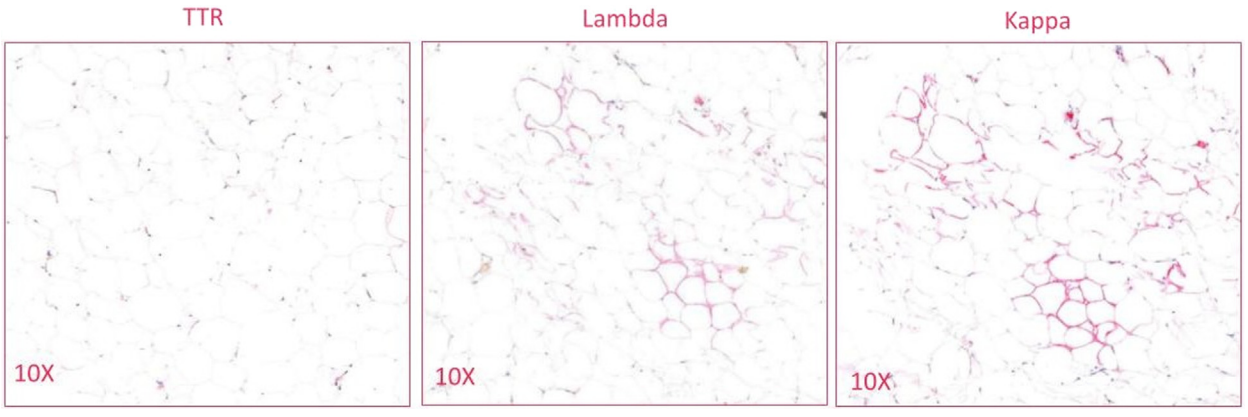
rehabilitation unit with full dose apixaban and a scheduled hematologic treatment plan for his light chain amyloidosis.

DISCUSSION

Current guidelines recommend starting anti-coagulation in all patients with CA and a single documentation of AF, irrespective of the CHADSVASC score.[1]

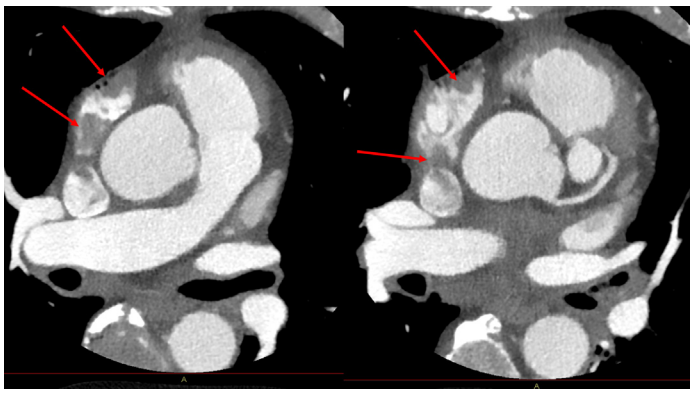
Factors increasing the risk of thromboembolic events in AL-CA are multiple and go beyond the loss of atrial systole in AF: endothelial dysfunction and platelets activation secondary to amyloid deposits, blood viscosity related to circulating monoclonal components, and nephrotic syndrome and the use of

FIGURE 5 Subcutaneous Abdominal Fat Aspiration



Histologic evidence of interstitial amyloid deposition with bright positivity for anti-AL-K in subcutaneous periumbilical fat. TTR = transthyretin.

FIGURE 6 Atrial Thrombus on Chest Computed Tomography



Chest computed tomography scan showing an intracavitary thrombus at the level of the right auricle. The arrows indicate the thrombus inside the right auricle.

immunomodulatory drugs create a prothrombotic state that increases the likelihood of thrombus formation irrespective of the loss of atrial contraction.[2,3]

Moreover, recent studies conducted with advanced imaging techniques are proving that the atrial paralysis favoring LA thrombosis in CA precedes the occurrence of AF and together with the restrictive hemodynamic profile and the other disease-specific factors can result in cardioembolic events also in sinus rhythm.[4-7] Notably, LA strain parameters, expression of the 3 phases of atrial function, are markedly compromised in individuals with CA; this correlates with LV dysfunction, symptoms, and the occurrence of thromboembolic events also in sinus rhythm.[8,9] Atrial amyloid infiltration, expressed by reduction in LA reservoir, conduit, and contractile functions, can lead to loss of mechanical atrial contraction even in patients with electrocardiographic evidence of P waves: this state of electromechanical dissociation defines a long-term prognosis similar to patients in AF.[10]

Altogether this evidence supports the need for a new perspective for thromboembolic risk evaluation in patients with AL-CA: indication to anticoagulation therapy in these patients should be based on multiparametric factors able to estimate the thromboembolic risk also in patients in sinus rhythm, including concomitant systemic conditions and therapies, disease-specific factors, and the assessment of atrial myopathy through atrial strain parameters and atrial stiffness evaluation.

None of these factors alone should be considered enough to estimate the thromboembolic risk in these patients, but together they might help the clinician in identifying those at the highest risk. In these patients, implementation of continuous ECG monitoring through implantable loop recorder is a reasonable strategy to detect potential episodes of asymptomatic paroxysmal AF or an elevated burden of supraventricular ectopies, which most of the times precedes the occurrence of AF in these patients. Moreover, the value of implantable loop recorders extends also to the detection of clinically relevant bradyarrhythmias, incredibly prevalent in this population.

Finally, it should be considered that thromboembolic risk in these patients is influenced by systemic and hemodynamic factors that vary over time. For this reason, thromboembolic risk stratification should not be limited to the first evaluation, but should be reassessed at every visit, especially for patients with AL-CA, in which elimination of circulating monoclonal components with disease-specific therapies translates to the removal of one of the mechanisms responsible for atrial myopathy and atrial arrhythmias. A study investigating variations in atrial strain parameters and atrial arrythmias during hematologic treatment is currently ongoing and will give additional answers to this question (Left Atrial Strain and Supraventricular Arrhythmia Burden in Cardiac Light Chain Amyloidosis Following Chemotherapy; NCT05448716).

FOLLOW-UP

Six months after hospital discharge, the patient showed no neurologic sequelae, had no bleeding event on full dose apixaban, and reported improvement of his functional capacity and symptoms after starting hematologic therapy.

CONCLUSIONS

This clinical case reports an important limitation of current guidelines on thromboembolic prophylaxis in patients with AL-CA.

The prothrombotic status and the atrial myopathy typical of AL-CA can favor atrial thrombosis even in patients in sinus rhythm.

A new strategy to predict thromboembolic risk in patients with AL-CA should be implemented to reduce the occurrence of those events in this

population, and in this setting a multiparametric approach seems to be more appropriate.

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KEY WORDS anticoagulation, atrial fibrillation, atrial strain, cardiac amyloidosis, stroke, thromboembolic risk

APPENDIX For supplemental videos, please see the online version of this paper.