Cardiac Amyloidosis Presenting as Congestive Heart Failure: A Case Report and Literature Review.

Abstract:

Amyloidosis is a systemic disease characterized by extracellular infiltration of amyloid fibrils. Cardiac involvement, marked by nonspecific clinical signs, significantly influences prognosis. Initially considered rare, this involvement is increasingly diagnosed through imaging techniques, including magnetic resonance imaging (MRI), which allows for improved characterization of myocardial tissue. We present the case of a 61-year-old patient who exhibited congestive heart failure attributed to cardiac amyloidosis. The diagnosis was suspected due to concentric left ventricular hypertrophy (LVH), myocardial sparkling appearance, and concentric coiled pattern in global longitudinal strain, as revealed in imaging. MRI strengthened the sensitivity of transthoracic echocardiography by identifying myocardial infiltration (T1 mapping > 1100 ms diffusion). Bone scintigraphy showed no signs of increased bone uptake. The biochemical assessment supported the presence of monoclonal gammopathy.

Keywords: Cardiac amyloidosis, Heart failure, Ventricular hypertrophy, Cardiomyopathy.

Introduction:

Amyloidosis encompasses a broad nosological framework, as it represents a systemic disease stemming from extracellular accumulation of misfolded proteins that form insoluble amyloid fibrils, leading to morphological and functional impairments in affected organs [1,2]. Cardiac involvement in amyloidosis is infrequent and has a significant impact on prognosis, characterized by nonspecific clinical manifestations. While cardiac amyloidosis (CA) has been considered rare, recent data suggest its underestimation, with an increasing number of cases being diagnosed through imaging techniques [3].

CA manifests as an infiltrative cardiomyopathy primarily observed in three types of amyloidosis: light chain amyloidosis or AL amyloidosis, transthyretin amyloidosis or ATTR amyloidosis, and senile amyloidosis. Despite its classification as a rare disease, recent findings indicate its potential underestimation as a cause of common cardiac diseases or syndromes [4].

In this context, we present the case of a 61-year-old patient admitted to the department due to rapidly progressing heart failure attributed to cardiac amyloidosis.

Case Presentation:

A 61-year-old adult with no particular cardiovascular risk factors and no notable medical history presented at the emergency department with rapidly progressing heart failure that had been evolving for approximately four months. The patient reported exertional dyspnea that had worsened over the past month, becoming present even at rest. This dyspnea was accompanied by hepatomegaly and an ascitic edematous syndrome.

Upon physical examination, the patient was in relatively good general condition, with a blood pressure of 120/63 mmHg, a heart rate of 105 beats per minute, a respiratory rate of 18 cycles per minute, a weight of 73 kg, and a height of 170 cm, resulting in a BMI of 25 kg/m². Manifestations of right-sided heart failure were evident, characterized by lower limb edema and moderate ascites. Cardiac auscultation revealed regular heart sounds without murmurs or added sounds, and symmetric peripheral pulses. No cutaneous or mucosal lesions were identified during the physical examination,

and there were no signs of peripheral neuropathy. Inquiry did not yield evidence of carpal tunnel syndrome.

Laboratory tests revealed mild anemia (12.5 g/dL), preserved renal function (creatinine 10.6 mg/L, estimated glomerular filtration rate according to MDRD: 97 mL/min), and negative 24-hour proteinuria. Cardiac biomarker measurements showed an elevated troponin level (86 µg/L, reference range: 0.0-0.04) and a B-type natriuretic peptide (BNP) level of 900 pg/mL.

The electrocardiogram displayed a regular sinus rhythm at 70 bpm, peripheral microvoltage, and left anterior hemiblock. [Figure 1]

Transthoracic echocardiography (TTE) revealed significant left ventricular hypertrophy with a sparkling appearance of the myocardium. The hypertrophy was concentric and symmetric (interventricular septum/posterior wall ratio: 1.1), with an interventricular septum thickness of 20 mm and a posterior wall thickness of 18 mm. There was no intra-ventricular obstruction at rest, during exertion, or with the Valsalva maneuver. [Figure 2] Analysis of global longitudinal strain showed basal and mid-segmental impairment while preserving apical segments, resulting in a cocardial appearance (SGL = -13.6%) with an ejection fraction of 46%. [Figure 3,4] Additionally, left ventricular diastolic dysfunction, thickened valves, and a mildly abundant pericardial effusion were noted.

Cardiac magnetic resonance imaging (MRI) enhanced the sensitivity of TTE, revealing amyloid infiltration through myocardial tissue characterization. Delayed enhancement sequences after gadolinium injection indicated myocardial amyloid infiltration, creating a rail-like appearance in the interventricular septum. [Figure 4,5] Moreover, native myocardial T1 mapping exhibited an increased value exceeding 1100 ms. [Figure 6]

Bone scintigraphy demonstrated minimal cardiac uptake classified as stage 1 according to Perugini, with no bone uptake.

Serum protein electrophoresis revealed increased levels of light chains of immunoglobulins, particularly in the gamma globulin fraction.

Taken together, these findings strongly led us to suspect an infiltrative cardiomyopathy suggestive of cardiac amyloidosis, likely of the AL type. The patient was subsequently referred to hematology for a bone marrow biopsy, salivary gland biopsy, and potential initiation of chemotherapy.

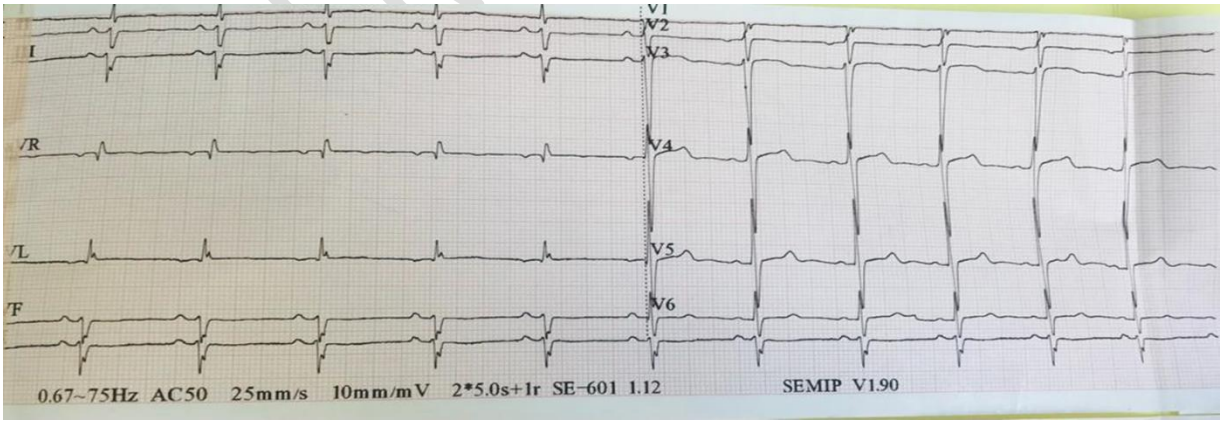


Figure 1: Electrocardiogram showing peripheral microvoltage and left anterior hemiblock

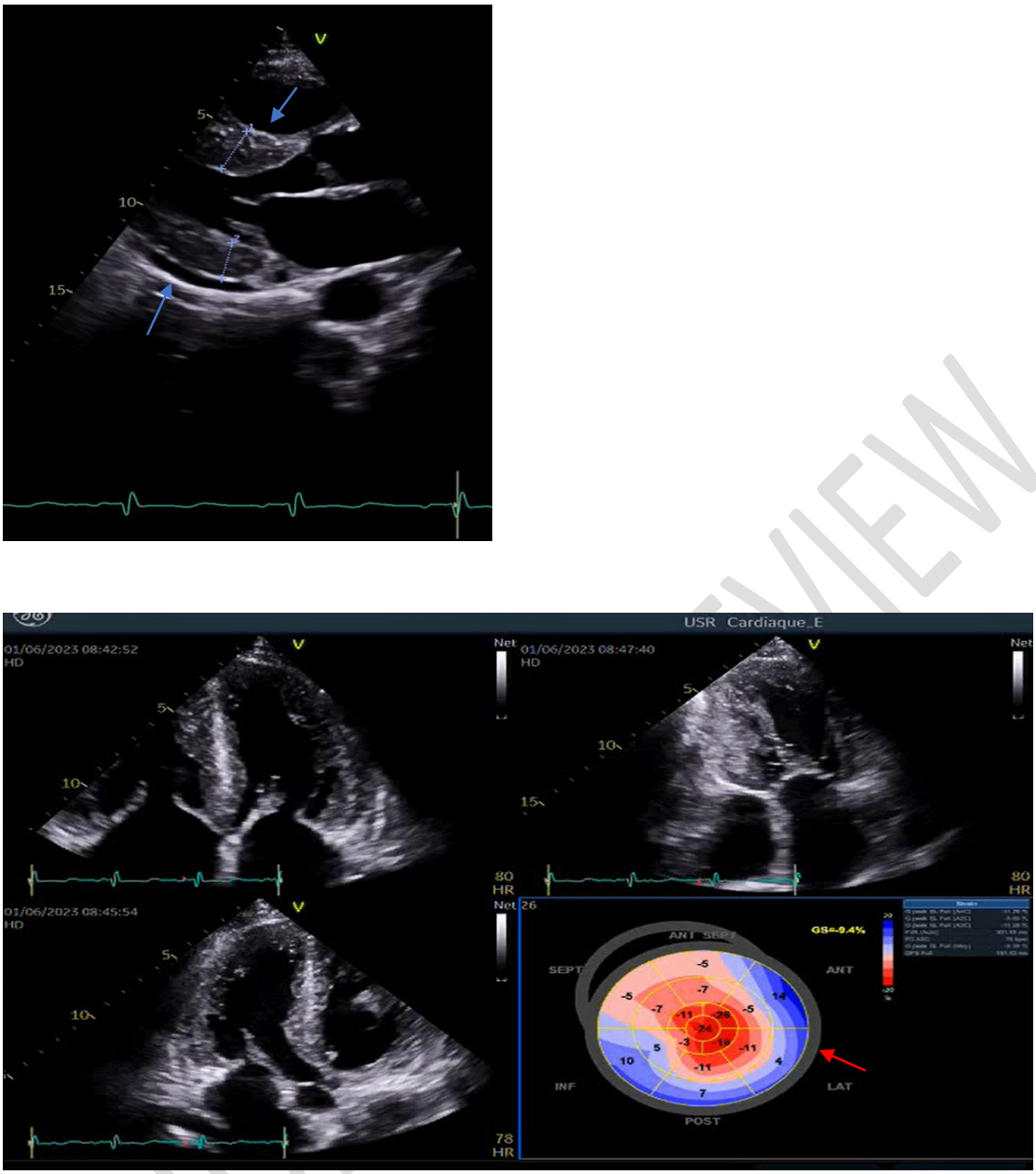
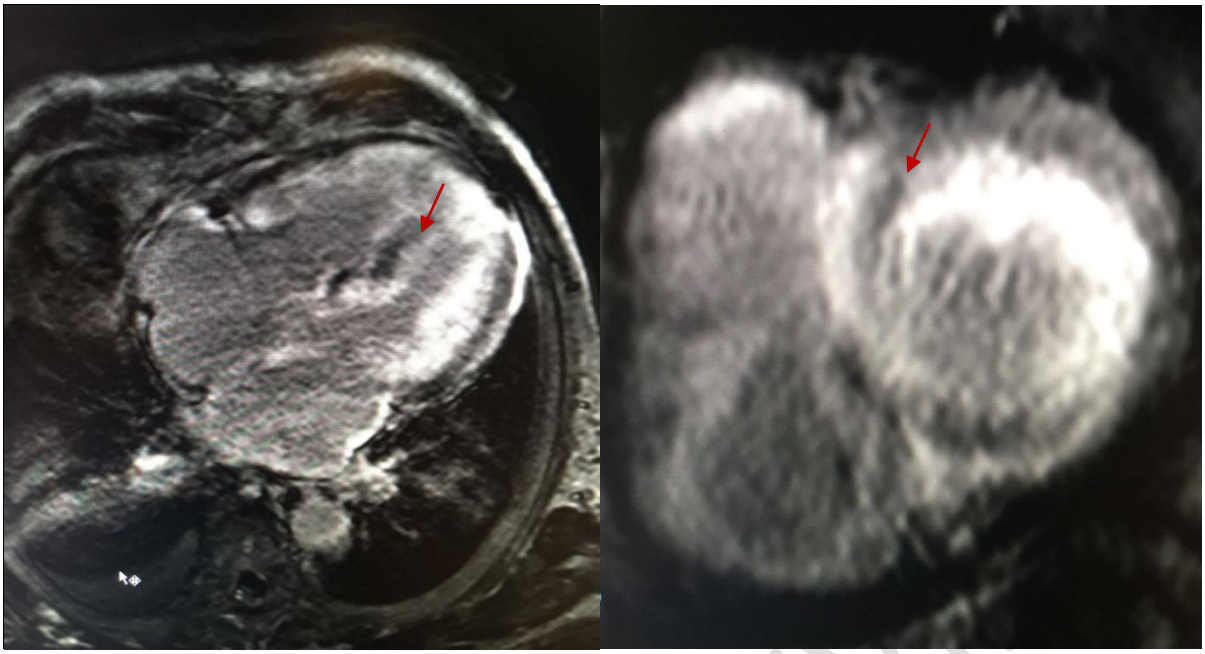


Figure 2, 3. Cardiac echocardiogram displaying myocardial hypertrophy with sparkling appearance of the myocardium, along with pericardial effusion (blue arrow). Impairment of global longitudinal strain with cocardial appearance (red arrow).



Figures 4, 5. Cardiac MRI. Delayed enhancements in all four chambers, biatrial dilation with left ventricular predominance (Figure 3), originating subendocardially with a "rail-like" appearance of the interventricular septum (red arrow).

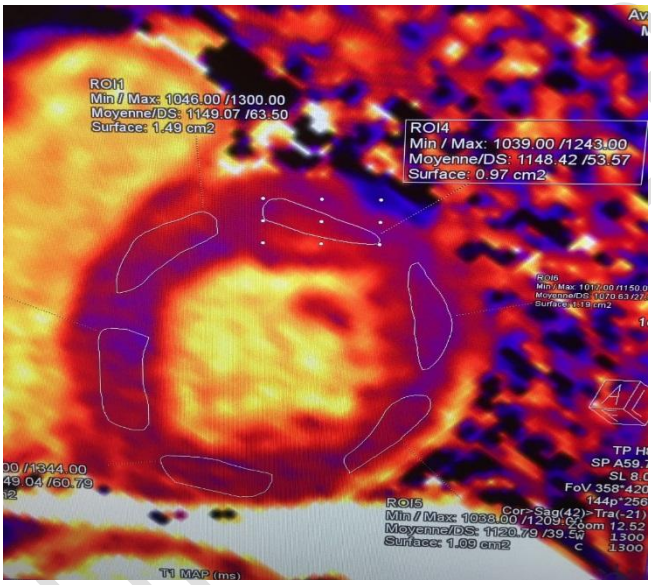


Figure 6. T1 mapping cartography > 1100 ms diffusion: myocardial infiltration.

Discussion:

Cardiac amyloidoses (CA) represent an insignificant proportion of hypertrophic cardiopathies, yet they stand as one of the leading causes of restrictive cardiomyopathy [5]. Cardiac involvement significantly shapes prognosis. It occurs across the three primary types of amyloidosis and is present in approximately 90% of cases [5,6]. Immunoglobulin light chain amyloidosis (AL) is the most common form, stemming from misfolded monoclonal immunoglobulin light chains. The AL subtype is more prevalent in males, presenting at an earlier age than other amyloid subtypes, including hereditary transthyretin (TTR) amyloidosis (ATTRv), caused by deposits of mutated TTR, and wild-type TTR amyloidosis (ATTRwt), also known as senile systemic amyloidosis, which occurs in older patients [6,7].

While sharing a common pathophysiological mechanism, the three amyloid types integrated into cardiac involvement differ in their clinical presentation, prognosis, and therapeutic management [8].

The wide spectrum of clinical presentations makes diagnosis challenging. Nevertheless, four major clinical scenarios can raise suspicion: heart failure with preserved ejection fraction, myocardial hypertrophy, rhythm and conduction disorders, and aortic stenosis [7,8]. The diversity of clinical manifestations stems from the localization of amyloid deposits, which can infiltrate all cardiac structures, including ventricles, atria, valves, conductive tissue, pericardium, and vessels [9,10].

Diagnostic suspicion relies on a combination of clinical and morphological evidence. ECG abnormalities occur in 90% of cases, with two very common anomalies, as outlined in the study by Murtagh in 2005 [11]: genuine microvoltage (QRS amplitude < 5 mm in peripheral leads) and a pseudo-infarct pattern in precordial leads. Atrial fibrillation affects around 15% of patients, and conduction disturbances can be observed.

Echocardiography is the main diagnostic tool for evaluating suspected cardiomyopathies. In amyloidosis, it typically reveals ventricular hypertrophy (due to amyloid protein accumulation), often concentric, a granular and bright appearance of the myocardium (attributed to increased echogenicity of deposits), increased thickness of right ventricle walls or valves, left atrial dilation, and pericardial effusion. Reduced global longitudinal strain, predominantly affecting basal segments with a cocardial appearance or apical sparing with base-to-apex gradient, strongly suggests amyloidosis. Several studies have shown the value of myocardial strain analysis in CA for diagnosing subclinical left ventricular dysfunction [12]. Anomalies in diastolic function with a restrictive pattern are seen in late stages, while ejection fraction remains preserved for a long time. Pericardial effusion may be present. The presence of the triad of right (over 7 mm) and septal (over 15 mm) ventricular hypertrophy along with even a mildly abundant pericardial effusion indicates a poor prognosis.

Cardiac MRI provides enhanced myocardial characterization, being indispensable for both diagnosis and prognostic assessment of CA. Amyloid deposits are visualized through characteristic delayed enhancement consistent with CA, displaying a rail-like pattern in the interventricular septum. This enhancement results from gadolinium stagnation and is also observed in cases of myocardial fibrosis. It can be subendocardial or diffuse, present in all myocardial layers, strongly indicating an infiltrative process [13]. However, cardiac MRI cannot definitively differentiate AL and ATTR amyloidosis.

In recent years, bone scintigraphy has demonstrated sensitivity and specificity for detecting cardiac ATTR amyloid deposits, offering many patients a noninvasive option for diagnosis, thus becoming the cornerstone examination for diagnosing ATTR cardiac involvement [14]. Intense myocardial uptake on scintigraphy strongly suggests ATTR (either hereditary or wild-type), especially in the absence of associated gammopathy. Consequently, it differentiates the three main types of amyloidosis.

Endomyocardial biopsy (with Congo red staining), while highly invasive, remains the gold standard for confirming AC subtype diagnoses. Less invasive biopsies, such as periumbilical tissue or oral mucosa biopsies, have variable sensitivities ranging from 14% to 90% [15].

The treatment of cardiac amyloidosis involves two domains: symptomatic management and prevention of complications, as well as halting or delaying amyloid deposition through targeted and specific therapy [16]. The therapeutic management of heart failure in amyloidosis aims to adapt volume, manage conduction disorders, and anticoagulate patients with atrial fibrillation or high embolic risk. Dietary sodium restriction and appropriate diuretics represent the foundation of symptomatic treatment. However, standard heart failure treatments are not recommended due to lack of evidence for their efficacy and the risk of adverse effects [17].

It is important to classify amyloidosis to establish specific treatment. Specific therapy for AL amyloidosis is a therapeutic urgency and involves chemotherapy and immunotherapy. Specific

pharmacological treatments available for ATTR amyloidosis include stabilizing molecules targeting TTR (Tafamidis) and genetic silencers (Patisiran and Inotersen) [18].

Conclusion:

Cardiac amyloidoses encompass a heterogeneous group of diseases unified by the progressive extracellular accumulation of amyloid fibrils. Cardiac involvement constitutes a pivotal turning point in the course of this condition, as it is rapidly progressive and has a decisive impact on prognosis. Once diagnosed, median survival in the absence of treatment ranges up to 6 months after diagnosis for light chain amyloidosis and 3 to 5 years for transthyretin amyloidosis. Utilizing multi-modality imaging judiciously is essential to expedite the diagnosis of cardiac amyloidosis and its subtyping. Hence, early diagnosis and accurate subtyping are imperative for optimal patient management. Such management requires indispensable multidisciplinary collaboration among cardiologists, hematologists, nuclear medicine specialists, internists, and geriatricians.

References :

1. Damy T, Kristen AV, Suhr OB, Maurer MS, Planté-Bordeneuve V, Yu CR, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). European Heart Journal. 1 févr 2022;43(5):391‑400.

2. Grogan M, Dispenzieri A, Gertz MA. Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response. Heart. 1 juill 2017;103(14):1065‑72.

3. Damy T, Maurer MS, Rapezzi C, Planté-Bordeneuve V, Karayal ON, Mundayat R, et al. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. Open Heart. 1 févr 2016;3(1):e000289.

4. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR Stabilizers are Associated with Improved Survival in Patients with Transthyretin Cardiac Amyloidosis. Circulation Heart failure. avr 2018;11(4):e004769.

5. Yadav JD, Othee H, Chan KA, Man DC, Belliveau PP, Towle J. Transthyretin Amyloid Cardiomyopathy-Current and Future Therapies. Ann Pharmacother. déc 2021;55(12):1502‑14.

6. Damy T, Kristen AV, Suhr OB, Maurer MS, Planté-Bordeneuve V, Yu CR, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). European Heart Journal. 1 févr 2022;43(5):391‑400.

7. Escher F, Senoner M, Doerler J, Zaruba MM, Messner M, Mussner-Seeber C, et al. When and how do patients with cardiac amyloidosis die? Clin Res Cardiol. janv 2020;109(1):78‑88.

8. Sperry BW, Vranian MN, Hachamovitch R, Joshi H, Ikram A, Phelan D, et al. Subtype-Specific Interactions and Prognosis in Cardiac Amyloidosis. J Am Heart Assoc. 24 mars 2016;5(3):e002877.

9. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. avr 2021;23(4):512‑26.

10. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and Consequences of Longitudinal LV Dysfunction Assessed by 2D Strain Echocardiography in Cardiac Amyloidosis. JACC Cardiovasc Imaging. févr 2016;9(2):126‑38.

11. Murtagh B et al0 Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol.2005;95:535-7.

12. Buss SJ et al. Longitudinal left ventricular function for prediction of survival in sytemic light-chain amyloidosis:incremental value compared with clinical and biochemical markers. J AM Coll Cardiol.2012;60:1067-76.

13. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation. 20 oct 2015;132(16):1570‑9.

14. Masson E. EM-Consulte. [cité 15 août 2023]. Intérêt de la scintigraphie osseuse dans le diagnostic de l'amylose cardiaque. Disponible sur: https://www.em-consulte.com/article/1506973/interet-de-la-scintigraphie-osseuse-dans-le-diagno

15. Bézard M, Kharoubi M, Galat A, Le Bras F, Poullot E, Molinier-Frenkel V, et al. Real-Life Evaluation of an Algorithm for the Diagnosis of Cardiac Amyloidosis. Mayo Clin Proc. janv 2023;98(1):48‑59.

16. Rapezzi C, Aimo A, Serenelli M, Barison A, Vergaro G, Passino C, et al. Critical Comparison of Documents From Scientific Societies on Cardiac Amyloidosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 5 avr 2022;79(13):1288‑303.

17. Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis. Can J Cardiol. mars 2020;36(3):322‑34.

18. Witteles RM, Liedtke M. AL Amyloidosis for the Cardiologist and Oncologist. JACC: CardioOncology. sept 2019;1(1):117‑30.