Université de Poitiers
Faculté de Médecine et Pharmacie

ANNEE 2020

THESE
POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(Décret du 16 janvier 2004)

Présentée et soutenue publiquement
le 11 Septembre 2020 à Poitiers
par Arthur Ramonatxo

Randall-type monoclonal immunoglobulin deposition disease: description of cardiac involvement

COMPOSITION DU JURY

Président : Professeur Luc Christiaens

Membres :
- Professeur Claire Bouleti
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- Dr Bruno Degand
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UNIVERSITE DE POITIERS

Faculté de Médecine et de Pharmacie

Le Doyen,

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ABBREVIATIONS

AL amyloidosis: light chain amyloidosis

CNIL: National Commission for Informatics and Liberties

ECG: electrocardiogram

HCDD: heavy chains deposition disease

Holter ECG: holter electrocardiogram (24h hours)

Ig: immunoglobulin

LCDD: light chains deposition disease

LHCDD: light and heavy chains deposition disease

LS: longitudinal strain

LV: left ventricule

LVEF: left ventricular ejection fraction

MGRS: monoclonal gammapathy of renal significance

MIDD: monoclonal immunoglobulin deposition disease

MRI: magnetic resonance imaging

NN50: number of adjacent NN intervals differing by more than 50 ms

NTProBNP: N-terminal pro–B-type natriuretic peptide

NYHA: New York Heart Association (dyspnea classification scale)

PNN 50: NN50 count divided by the total number of all NN intervals

SDNN: standard deviation of all NN intervals

SUMMARY

GENERALITES

La maladie de dépôts d'immunoglobulines monoclonales de type Randall, ou « Monoclonal immunoglobulin deposition disease » (MIDD) pour les anglo-saxons, est une complication rare de prolifération de clones plasmocytaires. Les premières descriptions de cette maladie datent des années 1950 avec la mise en évidence de lésions de glomérulosclérose nodulaire chez des patients non diabétiques et atteints de myélome. En 1976, le Docteur Randall introduit le terme de « maladie de dépôts de chaînes légères monoclonales », définie par la présence de ces dernières, qui se situent le long des membranes basales tubulaires [1,2].

Les complications des différentes proliférations plasmocytaires et lympho-plasmocytaires sont classées en fonction de la topographie des dépôts et des lésions, ainsi que du caractère organisé ou non des dépôts observés en microscopie électronique. Ainsi on distingue:

- Les dépôts d'immunoglobuline monoclonale organisés en fibrilles dans les amyloses immunoglobuliniques à chaines légères et, exceptionnellement, à chaines lourdes ;
- Les dépôts d'immunoglobuline monoclonale non organisés à l'échelle ultra structurale représentés principalement par la maladie de dépôts microgranulaires ou amorphes d'immunoglobulines monoclonale de type Randall (ou MIDD).

Du fait de la rareté de la maladie, les données sur l'incidence, la prévalence et le pronostic ne sont pas connues. Les différentes séries de patients indiquent que la maladie est plus fréquente chez les hommes, avec un âge moyen de découverte à 60 ans mais très variable [2].

La différence entre ces deux types de dépôts est faite par la coloration rouge Congo. Cette dernière s'avère positive en cas d'organisation en fibrille (dans l'amylose), et négative en cas de dépôts d'immunoglobulines non organisés en fibrille [1-4].

La maladie de Randall regroupe trois entités différentes en fonction de la composition des dépôts:

- Maladie de dépôt de chaînes légères (LCDD)
- Maladie de dépôt de chaînes lourdes (HCDD)
- Maladie de dépôt de chaînes lourdes et légères (LHCDD)

Pour comprendre cette distinction en 3 formes, quelques rappels d'immunologie ; les immunoglobulines (Ig) sont composées de 2 chaines lourdes (HC) et de 2 chaines légères (CL), chacune comprenant une région constante et une région variable. La région variable étant impliquée dans la reconnaissance spécifique de l'antigène. Il existe deux isotypes de chaines légères (κ, λ) et 5 isotypes de chaines lourdes (μ, α, δ, ε, γ) définissant respectivement les différentes classes d'immunoglobulines (IgA, IgD, IgE, IgG et IgM).

Les MIDD peuvent survenir dans un contexte de prolifération plasmocytaire ou lymphocytaire B symptomatique (comme un myélome multiple) mais aussi être associées à des formes asymptomatiques tel un myélome indolent ou une gammapathie monoclonale avec un retentissement rénal, appelé aussi MGRS (pour « Monoclonal gammapathy of rénal significance ») [27]. Les MIDD sont la conséquence directe du dépôt de l'immunoglobuline monoclonale, qu'elle soit associée à une prolifération « bénigne » ou « maligne ».

Ce diagnostic doit être évoqué devant un tableau clinique de syndrome glomérulaire avec une insuffisance rénale progressive et une hématurie microscopique et chez un patient suivi pour une gammapathie monoclonale. Néanmoins dans les différentes séries de patients 15 à 30% n'ont pas de gammapathie monoclonale. Le diagnostic de MIDD est histologique, fait sur une biopsie [2,5], le plus souvent rénale. Avec comme aspect :

- En microscopie optique ; d'un épaississement des membranes basales tubulaires avec des dépôts d'éosinophiles, négatifs au rouge Congo

- En microscopie électronique ; des dépôts denses, finement granulaires, non organisés
- Un marquage continu le long des membranes basales tubulaires par la Thioflavine T en immunofluorescence

Le traitement repose sur la suppression de la sécrétion de l'immunoglobuline monoclonale néphrotoxique et donc une chimiothérapie adaptée à la nature du clone sous-jacent [2,5,6]. En raison de l'hétérogénéité des traitements reçus, il est difficile de conclure quant à l'efficacité ou non des stratégies employées, et l'impact de la réponse hématologique sur le pronostic vital et rénal. Néanmoins il a récemment été montré que les schémas thérapeutiques à base de bortézomib (VELCADE) permettent une amélioration franche du pronostic rénal et global [2,25]. Les thérapies ciblées avec l'utilisation du daratumumab (anti CD38) ont montré une bonne efficacité associée à une bonne tolérance dans le traitement du myélome multiple [7] mais leur efficacité dans le traitement de la maladie de Randall est encore à définir.

En parallèle de ce traitement étiologique, un traitement symptomatique est mis en place visant au contrôle de la pression artérielle et de la protéinurie avec des IEC ou ARA2, à mettre en place précocement. La prophylaxie des complications infectieuses et virales est indispensable chez les patients recevant une chimiothérapie à base de bortézomib.

La maladie de Randall tout comme l'amylose AL, est une maladie systémique pouvant toucher tous les organes (le plus souvent atteinte rénale, cardiaque, hépatique, neurologique) avec une expression rénale prédominante. En revanche à la différence de l'amylose AL, une hématurie microscopique et une HTA sont observées chez environ 75% des patients lors du diagnostic.

À notre connaissance, aucune étude ne s'est concentrée sur la description complète des caractéristiques cardiaques de la maladie de Randall. Dans la littérature, une étude américaine s'est intéressée à des biopsies cardiaques réalisées chez des patients atteints d'une maladie de Randall [4]. Parmi les biopsies, huit étaient en faveur d'une atteinte cardiaque par la MIDD de type Randall. Chez ces huit patients, deux avaient une échographie cardiaque décrite comme normale. Quatre de ces huit patients étaient suivis pour de l'hypertension (sans précision si elle était contrôlée ou non et sa gravité). Cette étude suggère qu'une échographie cardiaque dite normale n'exclut pas la possibilité d'une atteinte cardiaque dans la MIDD. En revanche, l'hypertension pourrait être un facteur de confusion dans le diagnostic de MIDD cardiaque en raison de l'hypertrophie ventriculaire gauche qu'elle peut provoquer.

L'objectif de cette étude était de décrire les caractéristiques cardiaques (cliniques, ECG, Holter ECG, échographie et IRM) des patients atteints de la maladie de Randall.

Ce travail a été rédigé en anglais et sous format article dans l'optique de le soumettre pour une publication dans une revue scientifique. Un résumé de ce travail a d'ailleurs déjà été accepté et présenté sous forme de poster au congrès annuel de la société européenne de cardiologie (European Society of Cardiology) du 29 Aout au 1er Septembre 2020.

INTRODUCTION

Monoclonal immunoglobulin deposition disease (MIDD), also known as Randall's disease, is a rare complication of plasma cell clone proliferation. This disease was first described in the 1950's as nodular glomerulosclerosis lesions in non-diabetic patients with myeloma [1,2,27]. Randall's disease, like AL amyloidosis, is a systemic disease that can affect all organs with predominant renal expression. MIDD differs from AL amyloidosis by the presence of Congo red negative non-organized immunoglobulin (Ig) deposits, most commonly light chains (LCDD), along basement membranes but sometimes heavy chains (HCDD) or light and heavy chains (LHCDD) deposits may also be present. Clinical presentation also differs with AL amyloidosis, because of microscopic hematuria and hypertension, which are present in approximately 75% of patients at diagnosis [2].

Due to the rarity of this disease, data is scarce. The most important cohort of patients with Randall's disease involved 255 patients [5] and demonstrated that extra-renal involvement affected 35% of patients. Nevertheless, cardiac involvement, i.e. electrocardiograms, echocardiographies or cardiac MRIs, have not been described.

To the best of our knowledge, no study has focused on comprehensively describing the cardiac characteristics of Randall's disease. In literature, a small American study analyzed patients with cardiac biopsies [4]. Among them, eight were diagnosed with of Randall type MIDD, although two had a normal cardiac ultrasound. Four of those eight patients were followed for hypertension (unspecified on whether or not it was controlled and its severity). This study suggests that a normal cardiac ultrasound does not rule out the possibility of cardiac involvement in MIDD. On the other hand, hypertension might be a confounding factor in the diagnosis of cardiac MIDD because of the left ventricular hypertrophy which it can cause. The objective of this study was to describe the cardiac characteristics (clinical, ECG, holter ECG, ultrasound and MRI) of patients with Randall's disease.

METHODS

1. Patients

This multicentre retrospective study included all consecutive patients with Randall's disease followed between 2011 to 2020 at the French reference center for AL amyloidosis and other Ig deposition diseases of Poitiers University Hospital. Patients whose ECG and cardiac ultrasounds were not available were excluded. The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and was approved by the French National Commission for Informatics and Liberties (CNIL).

Socio-demographic, clinical characteristics, electrocardiogram (ECG) and trans-thoracic echocardiography, and when available cardiac magnetic resonance imaging and holter-ECG, were collected at the first consultation in the reference center of the Poitiers CHU and during the first para-clinical assessment carried out after this consultation. As hypertension is associated with Randall's disease 75% of the time [2], a patient was considered to have a history of hypertension if they were s treated for hypertension at least one year before the diagnosis of Randall. Dyspnea was assessed according to the NYHA scale (**Annex 1**).

The hospital's archives and the hospital's medical record software were used to. All consultation and hospitalization records were reviewed.

2. Electrocardiogram, echocardiography, MRI and 24-hour holter monitoring

ECGs were recorded during consultation or hospitalization. All the ECGs have been reinterpreted. The corrected QT was calculated by the formula QT measured / $\sqrt{2}$ RR and a corrected elongated QT was defined by a QT> 440 ms in men and 450 ms in women [8]; microvoltage was defined by an amplitude of the QRS of less than 5 mm in the limb leads and

less than 10 mm in the precordial leads [9]; bundle-branch block was defined according to the latest guidelines [10]; signs of left ventricular hypertrophy on ECG were described by the Sokolov index [11]; the definition of Q waves of pseudo-necrosis were based on that used in amyloidosis, that is to say by a Q wave or a or a poor R wave progression [12].

The 24-hour Holter monitoring was recorded using a Livanova SpiderviewTM holter recorders (Milan, Italy) with 3-channel recording, allowing to search for conduction disturbances, disturbances of the supra ventricular or ventricular rhythm as well as an analysis of the sinus variability when it was possible. An altered SDNN (standard deviation of all NN intervals) was defined by an SDNN less than 100 ms and the PNN50 (NN50 count divided by the total number of all NN intervals) altered by a value less than 5% [13]. A type 2 or 3 atrio-ventricular block and a complete sino atrial block [14] were considered to be a high-grade conduction disorder.

Echocardiographies were performed by senior operators using Vivid 6, 7 or 9 echocardiographs (GE, Medical Systems, Horten, Norway). Echocardiographic standards were taken from European recommendations [15,16]. Left ventricular hypertrophy was defined by a left ventricular mass of more than 95 g / m² in women and more than 115 g / m² in men. This mass was calculated in TM with a parasternal long axis section. This cut also made it possible to calculate the thickness of the interventricular septum and the posterior wall in diastole. The LVEF was measured using the Simpson biplan technique, it was considered normal if more than 50%. The left atrium was measured in ventricular telesystole, also measured in biplane Simpson and its size was indexed to the patient's body surface, considered to be dilated if its size was greater than 34mL / m2; the size of the right atrium was measured in apical section 4 cavities, in ventricular telesystole, considered dilated if its size was greater than 18cm2. The granite or shiny appearance of the interventricular septum, as found in amyloidosis, was left free to the discretion of the senior operator [12]. The definition of diastolic dysfunction used is

that of the last recommendations [15]. Concerning the systolic function of the right ventricle the normal value of the tricuspid annular plane systolic excursion (mm) was greater than 16 and that of the tricuspid annular systolic velocity (cm / s) was greater than 9,5 cm/s. Longitudinal strain analysis was performed with a semi-automated method (Q-analysis). Left ventricular endocardial borders were manually traced in the 3 apical views at end-systole. The area of interest was manually adjusted according to the thickness of the myocardium. The longitudinal peak strain was calculated from the 18 segments (6 basal, 6 mid, and 6 apical) obtained in the 3 apical views. The average of the peak strain in the 18 left ventricular segments ascertained the GLS. Regarding regional LS, the average of the peak strain in the 6 basal, 6 mid and 6 apical segments determined the basal, mid and apical LS respectively. Finally, LS was assessed according to multi-layer analysis in the endocardial, mesomyocardial and epicardial layers. Echocardiographies for which the longitudinal strain analysis was not recorded were retrospectively reviewed using Echo-PAC software (GE, Medical Systems, Horten, Norway) with a semi-automated method. A relative apical longitudinal strain (LS) of 1.0, defined using the equation (average apical LS/ (average basal LS + mid-LS)) [12,17]. The average LS was considered to be altered if strictly less than 18 [16].

Cardiac MRIs were performed on 1.5 or 3 Tesla with gadolinium injection and sequences performed in search of late enhancement.

The ECG, the echocardiography, the magnetic resonance imagingand the 24-hour Holter ECG were analyzed for each patient by a senior cardiologist blinded to clinical data.

3. Statistical analysis

Categorical variables were expressed as number and percentage, continuous variables as median and interquartile range. Comparisons of groups were performed using chi-2 square for categorical variables and student t-test or Mann-Whitney test if appropriate for quantitative variables. Analyses were performed using SPSS 22 (SPSS, Inc., Chicago, IL, USA). Two-sided P values of 0.05 were considered statistically significant.

RESULTS

1. Population characteristics

Among 269 patients with Randall disease, 22 patients were included **(Figure 1)** in this study. Baseline characteristics are summarized in **Table 1**. Among these patients, the average age was 66 ± 10 years old; 12 (55%) were male; 16 (73%) were LCDD and 1 (5%) HCDD and 5 (23%) LHCDD. The hematological disease involved was myeloma for 11 patients (50%) and monoclonal gammapathy of renal significance for 9 (41%) patients and for the majority a production of light chain type kappa 16 (73%).

At baseline, 13 (59%) had a history of hypertension, 1 (3%) had a history of atrial fibrillation. Regarding cardiovascular risk factors, 11 (50%) had dyslipidemia, 9 (41%) had a smoking history and 4 (18%) had diabetes. In terms of clinical characteristics, 4 (18%) patients had NYHA class 3 or 4, 11 (50%) had edematous syndrome and 5 (23%) signs of left heart failure. The mean NT-ProBNP level was 693 ± 15 829 ng/L and mean high sensitivity troponin was 0.03 ± 0.05 ng/mL.

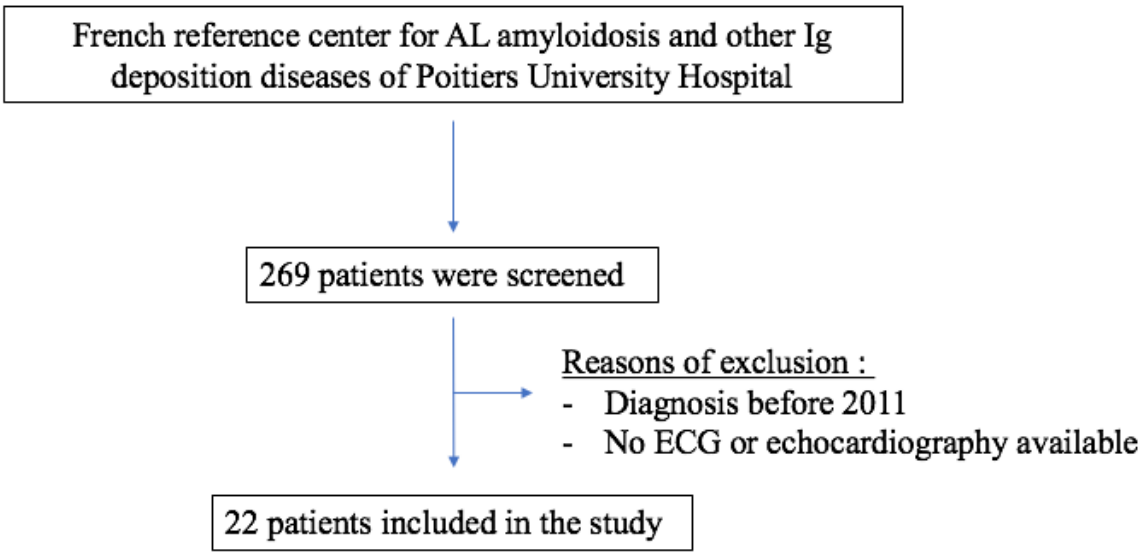

Figure 1 : Screening and enrollment. Abbreviation : ECG = electrocardiogram

Table 1: Baseline characteristics of patients

Clinical characteristics at baseline (n=22)	
Age of diagnosis (years)	66 [58; 72.3]
Male sex, n	12 (55)
Body mass index (kg/m2)	26 [23.3; 27.2]
Heart rate (beats per minute)	60 [52; 68]
Systolic blood pressure (mmHg)	140 [132; 161]
Diastolic blood pressure (mmHg)	80 [70; 89]
Baseline NYHA dyspnea 3 or 4	4 (18)
Edematous syndrome	11 (50)
Signs of left heart failure	5 (23)
Dyslipidemia	11 (50)
History of hypertension	13 (59)
History of smoking	9 (41)
Diabetes	4 (18)
History of atrial fibrillation	1 (5)
NT-ProBNP (ng/L)	693.5 [199; 12 025]
High sensitive troponine* (ng/mL)	0.03 [0.05; 0.2]
Serum creatinine (µmmol/L)	196 [161; 355]
Hematology and renal characteristics	
History of kidney transplant	2 (9)
History of hemodialysis	3 (14)
Light chain deposition disease (LCDD)	16 (73)
Heavy chain deposition disease (HCDD)	1 (5)
Light and heavy chain deposition disease (LHCDD)	5 (23)
Lambda	6 (27)
Kappa	16 (73)
Myeloma	11 (50)
Monoclonal gammopathy of renal significance	9 (41)
Other hemopathy	2 (9)

Data are presented as n (%) or median and interquartile range.
Abbreviations: NYHA = New York Heart Association
*High sensitivity troponin T, data type: alpha numeric. Luminescence electrochemical evaluation method

2. ECG and 24-hour Holter monitoring

Regarding ECG recordings **(Table 2)**, 20 (91%) patients were in sinus rhythm, 1 (5%) had atrial fibrillation and 1 (5%) had a rhythm emerging from the coronary sinus; only 1 (5%) patient had type 1 atrioventricular block. The median PR interval was 155 ± 29 ms; no patient presented a bundle-branch block. The mean QRS duration of 90 ± 16 ms and 2 (9%) patients had an prolonged corrected QT with a median corrected QT within the cohort of 430 ± 16 ms. Some ECG characteristics found in amyloidosis were found in patients followed with Randall's disease. Nine (41%) patients had a Q waves of pseudo-necrosis and 4 (18%) patients presented microvoltage **(Figure 2)**.

Regarding the 24-hour Holter monitoring, a high-grade conduction disorder was recorded in one patient, a type of complete sinoatrial block; regarding ventricular arrhythmia, one patient presented ventricular tachycardia and doublets of extra ventricular systole were recorded in 4 (24%) patients. Atrial fibrillation was recorded in one patient. Heart rate variability was altered in 11 (65%) patients when considering SDNN and/or PNN 50.

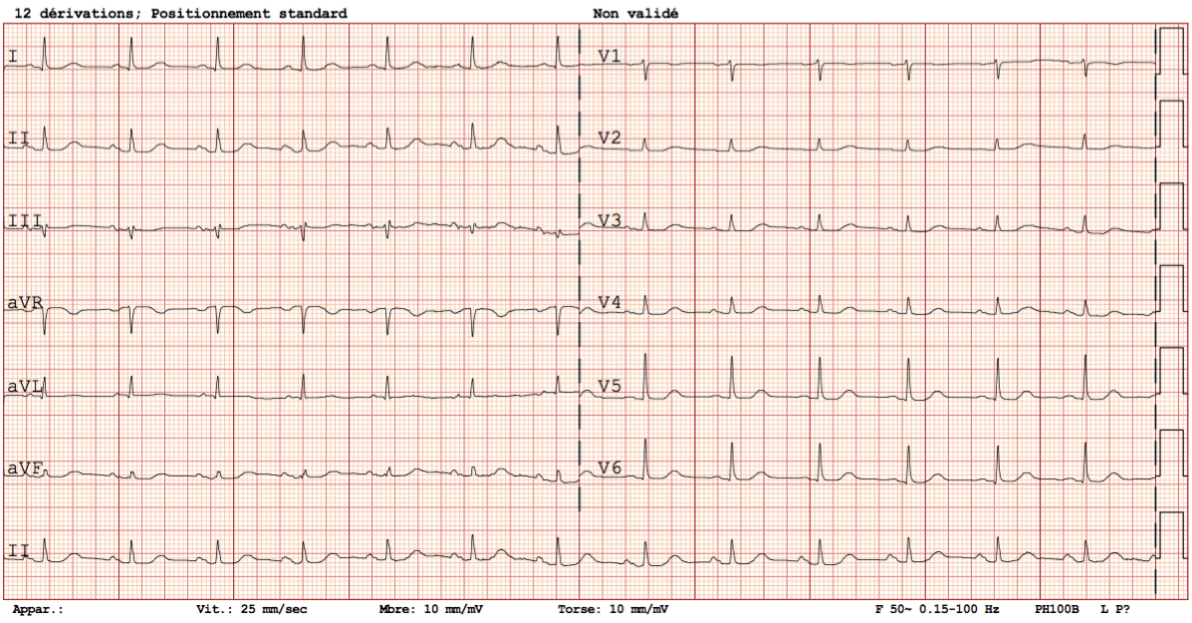

Figure 2: Electrocardiogram of a patient with microvoltage

Table 2: Electrocardiogram and 24-hour Holter monitoring at baseline

Electrocardiogram at baseline (n=22)	
Sinus rhythm	20 (91)
PR interval (ms)	155 [130; 165]
QRS duration (ms)	90 [78.6; 100]
Corrected QT interval (ms)	430 [420; 440]
Sign of left ventricular hypertrophy (Sokolov index > 35mm)	1 (5)
Q waves of pseudonecrosis	9 (41)
Microvoltage	4 (18)
24-hour Holter monitoring (n=17)	
SDNN (ms)	89 [77.3; 105.3]
PNN50 (%)	0.7 [0.3; 3.9]
Doublets of ventricular extrasystole	4 (24)
Ventricular tachycardia	1 (6)
High-grade conduction disorder	1 (6)
Atrial fibrillation	1 (6)

Data are presented as n (%) or median and interquartile range.

Abbreviations: ECG = electrocardiogram; SDNN = Standard deviation of the normal RR interval; pNN50 = NN50 count divided by the total number of all N intervals; NN50 = number of adjacent NN intervals differing by more than 50ms

3. Trans-thoracic echography

Standard echographic parameters at baseline are described in **Table 3**. Mean LVEF was 64 ± 10% and only two patients had a reduced LVEF < 50%. Left ventricular hypertrophy was found in 16 (73%) of the patients. The mean thickness of the interventricular septum was 12.5 ± 2 mm and posterior wall 12 ± 2 mm. Diastolic dysfunction was found in 21 (95%) patients. The granite or shiny appearance of the interventricular septum was noted in only one (5%) patient.

Ventricular hypertrophy affected both ventricles most of the time since hypertrophy of the right ventricular was found in 14 (64%) patients. Right ventricular systolic function was preserved in 19 (86%) of the patients.

The median global longitudinal strain was 19 ± 3 % with impaired strain values in 8 (36%) patients. A relative apical longitudinal strain (LS) of 1.0, defined using the equation (average apical LS/ (average basal LS + mid-LS)) was not found in any patient but an impression of better longitudinal strain from the base to the apex (figure 3) seems to emerge in view of the different average strains.

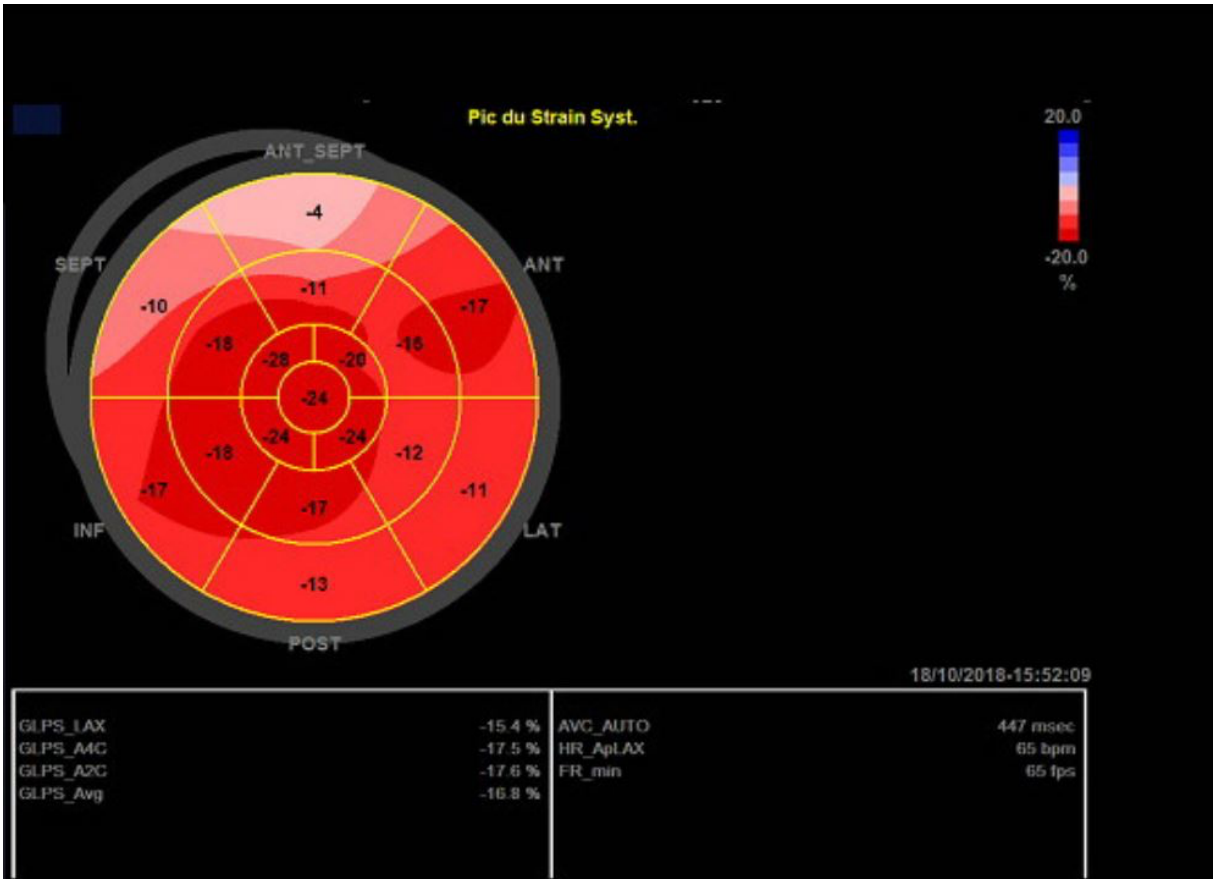

Figure 3: longitudinal strain in patient with Randall's disease

Table 3: Baseline echographic parameters

Standard echographic parameters at baseline (n=22)	
Simpson biplan LVEF (%)	64 [58.8; 72]
Global longitudinal strain %	19 [17; 20]
Basal longitudinal strain	12 [10; 14.8]
Median longitudinal strain	15.3 [11.8; 17.5]
Apical longitudinal strain	19 [15.3; 22.2]
Left ventricle relative apical sparing on global longitudinal strain	0.68 [0.60; 0.75]
Diastolic septum thickness (mm)	12.5 [11.5; 14]
Diastolic posterior wall thickness (mm)	12 [10; 13]
Indexed LV mass (g/m2)	127 [96.5; 137.3]
Diastolic dysfunction	21 (95)
E' lateral (cm/s)	7 [5; 8]
E' septal (cm/s)	5.5 [5; 6]
Mean E/E' ratio	11.5 [10; 16]
Index left ventricular end-diastolic diameter (mm/m2)	26 [24; 28.3]
Indexed left ventricular end-diastolic volume (mL/m2)	43.5 [32; 53]
Indexed left ventricular end-systolic volume (mL/m2)	14 [9.3; 21.3]
Left atrial volume (mL/m2)	38 [22.8; 50]
Tricuspid annular plane systolic excursion (mm)	17 [13.3; 20]
Tricuspid annular systolic velocity (cm/s)	14 [11; 16]
Pericardial effusion	3 (14)

Data are presented as n (%) or median and interquartile range.
Abbreviations: LV = left ventricule ; LVEF = left ventricle ejection fraction

4. Cardiac MRIs

Fifteen (68%) patients had a cardiac MRI. Median LVEF was 61 ± 12%, left ventricular mass was 70 ± 25g / m^2; inter ventricular septum thickness was 12 ± 3 mm and lateral wall thickness was 9 ± 1.5 mm.

There was no late gadolinium enhancement on the 15 cardiac MRIs. Pericardial effusion was found in 5 patients (33%) and areas of myocardial fibrosis only in 1 patient (7%).

Table 4: Baseline cardiac MRI characteristics

Standard cardiac MRI at baseline (n=15)	
LVEF (%)	61 [54; 70]
Diastolic septum thickness (mm)	12 [10.5; 14.5]
Diastolic side wall thickness (mm)	9 [7.25; 10]
Indexed LV mass (g/m2)	70 [58; 90.5]
Index left ventricular end-diastolic diameter (mm/m2)	28 [23; 31]
Indexed left ventricular end-diastolic volume (mL/m2)	74 [61; 102]
Indexed left ventricular end-systolic volume (mL/m2)	25 [21; 42.5]
Thickness of the inter atrial septum (mm)	6 [4.8; 8.3]
Indexed right ventricular end-diastolic diameter (mm/m2)	32 [30; 38.5]
Late gadolinium enhancement, n (%)	0 (0)
Pericardial effusion, n (%)	5 (33)
Myocardial fibrosis, n (%)	1 (7)

Data are presented as n (%) or median and interquartile range.
Abbreviations: LV = left ventricule ; LVEF = left ventricule ejection fraction

5. Comparison of the different characteristics between patients with a history of hypertension and non-hypertensive patients

We compared patients with a history of hypertension (prior to the diagnosis of Randall's disease) and patients without. LVEF and indexed LV mass were not different between the 2 groups whereas diastolic septum wall thickness was lower and GLS was higher in patients with previous hypertension (12 [9.5; 12] mm vs. 14 [13; 15.5] ; P=0.001; 20 [17.5; 20.5] vs.17 [14; 19]%; P=0.047) in patients with history of hypertension and patients without).

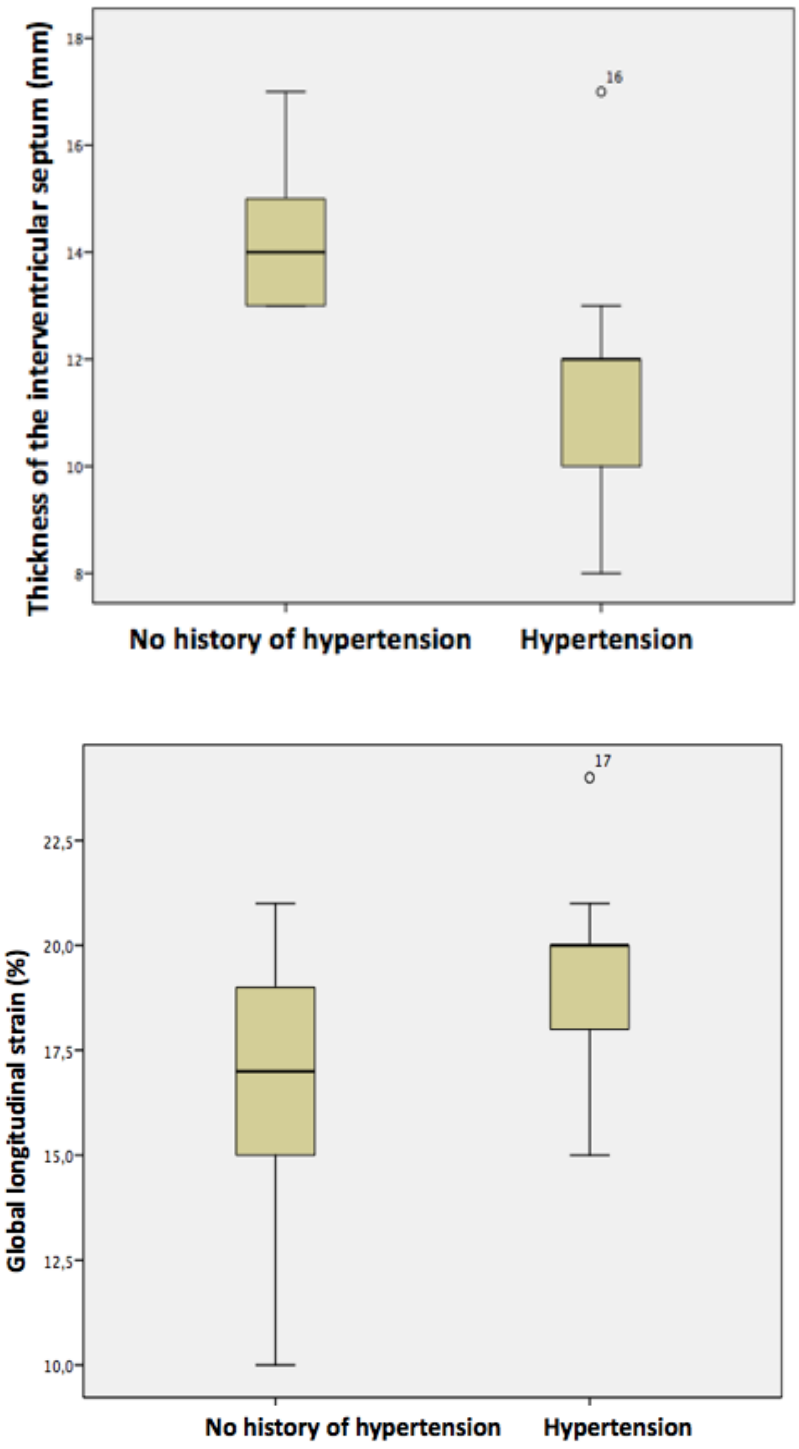

Figure 4: Thickness of the interventricular septum (mm) and global longitudinal strain (%) in patients with and without history of hypertension in echocardiography.

6. Follow-up

Median follow-up was 44 [25; 73] months. Among these 22 patients, 5 (23%) were hospitalized for episodes of heart failure, including one patient for cardiogenic shock. One patient was implanted with a pacemaker for a complete sinoatrial block. No patient has been implanted with a defibrillator; 4 (18%) patients presented with atrial fibrillation after the diagnosis of Randall's disease.

Regarding mortality, 6 (27%) patients died with a median of death at 67 [65; 73] years old. One patient died of heart failure, another died of sudden death, the other causes of death were cancer, infection or hemopathy. A patient was hospitalized for syncope, hospitalized in neurology, no cause found. This patient died of a sudden death at home.

DISCUSSION

This is the first study to describe the cardiac characteristics (clinical, ECG, Holter ECG, ultrasound and MRI) of patients with Randall's disease. The most frequent ECG feature was Q waves of pseudo necrosis in 41% of patients. On the 24-hour Holter monitoring, alteration of sinus variability was found in 65% of patients. Mean LVEF was 64 ± 10% and only two patients had a LVEF < 50%; the global longitudinal strain was 19 ± 3 % with impaired values in 36% of patients. Contrarily to AL amyloidosis, the interventricular septum shiny aspect was noted in only 5% patient and no patient had late gadolinium enhancement.

Episodes of heart failure are mostly with preserved LVEF. The main abnormality found on cardiac ultrasound is diastolic dysfunction and an alteration of longitudinal function explaining the heart failure with preserved LVEF. These abnormalities are similar to the type of heart disease found in amyloidosis.

We present the largest series of patients with cardiac involvement of Randall disease. The various series of cases in the literature [4, 18-22] describe the characteristics of Randall heart disease being comparable to cardiac amyloidosis, that is to say restrictive type. In our echocardiographic data, alteration of LVEF was unfrequent, in only two patients (9%), on the other side, diastolic dysfunction is almost constant in Randall's disease, present in 21 (95%) of the patients in our series. These observations are consistent with the literature [4, 18-22]. Moreover, we found pericardial effusions in 3 (14%) patients, and it has also been already described [18]. While some clinical, echocardiographic, ECG and MRI characteristics appear to be alike those found in amyloidosis, there are also differences. First, concerning echocardiography, regarding the granite or shiny appearance of the interventricular septum found in amyloidosis, it was only found in one patient (5%). This could be explained by the

lack of organization in fibrils in Randall's disease. A relative apical longitudinal strain was not found in any patient, but an impression of better longitudinal strain from the base to the apex (**figure 3**) seems to emerge in view of the different average strains. If hypertension seems to be a confounding factor concerning ventricular hypertrophy and the thickness of the interventricular septum, this is not enough to explain the hypertrophy of the interventricular septum found in the cohort of patients with Randall's disease **(Figure 4).** When we compared patients with a history of hypertension and patients without, diastolic septum wall thickness was lower and GLS was higher in patients with previous hypertension; this result is possibly due to chance and the small size of the population.

Some ECG characteristics found in amyloidosis were found in patients followed up with Randall's disease with Q waves of pseudo-necrosis or a poor R wave progression, what has already been observed in a report case where the cardiac involvement by Randall's disease had been confirmed by myocardial biopsy [20-22].

Regarding cardiac arrhythmias, only one patient had severe conduction disorder. Moreover, a patient was hospitalized in neurology for syncope, but no etiology was found. A few weeks later, this patient died of a sudden death at home. An implantable Holter may be considered in these patients with unexplained syncope. In the literature, a study looking at 8 patients with cardiac nonamyloidotic immunoglobulin deposition disease proven by myocardial biopsy [4]. In this series of 8 patients, 1 patient was hospitalized for lipothymia with on the monitoring after admission an episode of 15 seconds of spontaneous asymptomatic ventricular tachycardia. Another patient presented with atrial fibrillation during follow-up, which we found in four patients (18%) of our series. The occurrence of atrial fibrillation has also been reported in other case series [22,25]. One patient had a high-grade conduction disorder with complete sinoatrial

block. Conduction disorders have not been described in large cohorts with patients with Randall's disease [5], and we don't know in these cohorts if some patients had pacemakers.

Indeed the 15 cardiac MRIs performed in this series of patients are to our knowledge the first cardiac MRIs described in patients with Randall's disease just like the analysis of the longitudinal strain and sinus variability. The information which seems to us the most relevant is that on none of the cardiac MRIs we found late gadolinium enhancement. This late gadolinium enhancement is found in cardiac amyloidosis [12,23,24]. This difference is explained by the fact that this contrast enhancement is linked to the amyloid fibrils which retain gadolinium explaining why the enhancement of contrast is not found in Randall's disease. Cardiac MRI could therefore help in terms of differential diagnosis between cardiac involvement of amyloidosis or Randall's disease.

The main limitation of the study is the absence of myocardial biopsy with two consequences. It cannot be said that certain ECG or echocardiographic abnormalities are correlated with cardiac involvement by Randall's disease and secondly it cannot be excluded that certain disorders, particularly those close to AL amyloidosis, are in fact linked to amyloid heart disease, concomitant with other organs with Randall's disease. However, no MRI in this series of patients was in favor of cardiac amyloidosis. Another limitation of this study is the size of the population making it difficult to analyze the prognosis, especially in the case of cardiac involvement in Randall's disease but also to explain a low number of events such as ventricular arrhythmias or disorders of the heart. high grade conduction.

CONCLUSION

We presented the first series of cases dedicated to the description of cardiac parameters in patients with Randall's disease. The type of heart disease seems like that in AL amyloidosis with episodes of heart failure, in patients with preserved LVEF and diastolic dysfunction. We found similarities with amyloidosis also in terms of ECG signs and cardiovascular event (ventricular tachycardia, complete sino atrial block, atrial fibrillation, sudden death or syncope). This study is the first description of the longitudinal strain in Randall's disease. The main difference with cardiac involvement in amyloidosis is at the level of cardiac MRI with no late gadolinium enhancement in Randall's disease.

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ANNEXE

Annex 1 : The New York Heart Association (NYHA) Functional Classification

- Class I : No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).

- Class II : Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).

- Class III : Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.

- Class IV : Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

ABSTRACT

Randall-type monoclonal immunoglobulin deposition disease: description of cardiac involvement

Background: Randall-type monoclonal immunoglobulin disease (MIDD) is a rare complication of a monoclonal plasma cell clone. MIDD differs from AL amyloidosis by the presence of Congo red negative non-organized immunoglobulin (Ig) deposits, most commonly light chains (LCDD) along basement membranes and sometimes heavy chains (HCDD) or light and heavy chains (LHCDD). As AL amyloidosis MIDD is a multi-systemic disease, and affect the heart. To date no study has focused on the clinical characteristics of heart disease in MIDD.

Purpose: The aim of this study was to describe the cardiac characteristics (clinical, ECG, holter ECG, ultrasound and MRI) of patients with Randall's disease

Methods: This multi-center, nation-wide retrospective study extracted from the database of the French reference center for AL amyloidosis and other Ig deposition diseases between 2011 to 2019. Histological evidence was obtained on biopsies, most often renal with typical linear non-organized Ig deposits along basement membranes. Patients whose ECG and cardiac ultrasounds were not available were excluded

Results: Among 22 patients included (mean age was 66 ± 10 years), 12 (55%) were male; 16 (73%) were LCDD, 1 (5%) HCDD and 5 (23%) LHCDD. At baseline, 13 (59%) had a history of hypertension, 1 (3%) had a history of atrial fibrillation and in terms of clinical characteristics, 4 (18%) patients had NYHA class 3 or 4, 11 (50%) had edematous syndrome and 5 (23%) signs of left heart failure. The mean NT-ProBNP level was 693 ± 15 829 ng/L and mean high sensitivity troponin was 0.03 ± 0.05 ng/mL. The most frequent ECG feature was Q waves of pseudo necrosis in 41% of patients and microvoltage in 18%. On the 24-hour Holter monitoring, alteration of sinus variability was found in 65% of patients; one patient had a high-grade conduction disorder and another had ventricular tachycardia. On echocardiography, mean LVEF was 64 ± 10% and only two patients had a LVEF < 50% but diastolic dysfunction was present in 95% of patients; the global longitudinal strain was 19 ± 3 % with impaired values in 36% of patients. Contrarily to AL amyloidosis, the interventricular septum shiny aspect was noted in only one patient and no patient had late gadolinium enhancement on cardiac MRI.

After median follow-up of 44 [25; 73] months, 5 (23%) were hospitalized for episodes of heart failure, including one patient for cardiogenic shock; 4 (18%) patients presented with atrial fibrillation after the diagnosis of Randall's disease. Regarding mortality, 6 (27%) patients died with a median of death at 67 [65; 73] years old.

Conclusions: To our knowledge, we present the first case series dedicated to the description of cardiac parameters in MIDD patients with cardiac involvement. Except for MRI appearance of cardiac infiltration and interventricular septum shiny aspect in echocardiography, these patients showed features close to that of AL amyloid heart disease.

Keywords: *Randall-type monoclonal immunoglobulin deposition disease, monoclonal immunoglobulin deposition disease, Randall disease, AL amyloidosis, restrictive cardiomyopathy, heart failure*

SERMENT

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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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