Letter to the Editor

Basal septal T1 mapping and extracellular volume as discriminators in cardiac magnetic resonance evaluation of myocardial involvement in advanced Anderson-Fabry disease: a case description

Yaqi Du[1#], Ruoshi Liu[2#], Shuang Ding[3*], Guan Wang[1*]

[1]Department of Radiology, the First Hospital of China Medical University, Shenyang, China; [2]Department of Traditional Chinese Medicine, the First Hospital of China Medical University, Shenyang, China; [3]Department of Rheumatology and Immunology, the First Hospital of China Medical University, Shenyang, China

[#]These authors contributed equally to this work.

[*]These authors contributed equally to this work as corresponding authors.

Correspondence to: Guan Wang, MD, PhD. Department of Radiology, the First Hospital of China Medical University, No. 155, North Nanjing Street, Shenyang 110001, China. Email: cmuwangguan@sina.com; Shuang Ding, MD, PhD. Department of Rheumatology and Immunology, the First Hospital of China Medical University, No. 155, North Nanjing Street, Shenyang 110001, China. Email: fay_ds@163.com.

Submitted May 22, 2023. Accepted for publication Aug 18, 2023. Published online Sep 25, 2023.
doi: 10.21037/qims-23-714
View this article at: https://dx.doi.org/10.21037/qims-23-714

Introduction

Anderson-Fabry disease (AFD) is a rare X-linked inherited lysosomal storage disorder characterized by an accumulation of globotriasylceramide (Gb3) in several affected tissues, which is caused by a deficiency of α-galactosidase A (α-Gal A) activity (1). Cardiomyopathy is the leading cause of death in AFD, accounting for 38% of all-cause mortality (2). Cardiac magnetic resonance (CMR) as a non-invasive imaging method can provide morphological, functional, and histological features of the heart, which has potential in the diagnosis of AFD (3). The typical manifestations of AFD in CMR such as left ventricular hypertrophy (LVH) with lower T1 are easily recognized. However, with the progression of the disease and the occurrence of various patterns of fibrosis, the manifestations exhibit greater variation, and may be more difficult to distinguish from hypertrophic cardiomyopathy (HCM) (4). Therefore, careful observation of the imaging findings was required. Since the degree of cardiovascular involvement of AFD may affect the effectiveness and the choice of treatment, the relatively unique CMR features of advanced AFD were analyzed.

Case presentation

Case 1

A 54-year-old male patient was admitted to hospital with bilateral hand and foot swelling, and fingertip blackening for more than 10 years, a foot ulcer for four months, and a three-year history of chronic nephritis. The patient had taken Corbrin capsules for two years for nephritis and had recently taken amoxicillin and other anti-inflammatory drugs for foot ulcers, but no improvement had been observed. Upon clinical examination, systemic sclerosis was diagnosed. Electrocardiograph (ECG) indicated sinus bradycardia [heart rate (HR): 58 bpm], sinus arrhythmia, left ventricular (LV) high voltage [Sokolow-Lyon index (SLI): 6.5 mV], T-wave inverted and ST-segment depressed, ratio between P-wave and PR-segment durations (P wave/PR

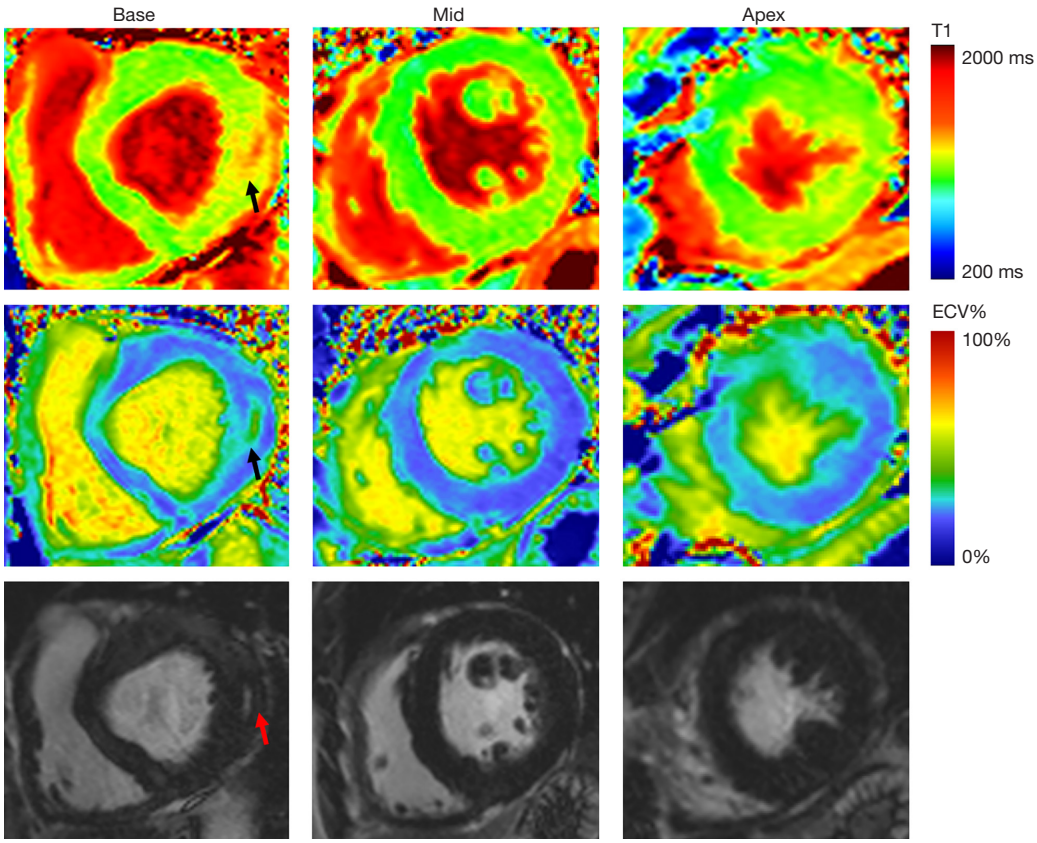

Figure 1 Short-axis T1 maps, ECV% and LGE images of LV in a 54-year-old AFD male patient (Case 1). Concentric hypertrophy of the LV myocardium. The T1 and ECV% decreased globally except for that of basal lateral wall, in which patchy increased T1, ECV% (black arrows) and subepicardial LGE (red arrow) were observed. Global T1: 1,114±85 ms, ECV%: 25±5%; basal interventricular septum T1: 1,061±23 ms, ECV%: 21%±2%. (normal ranges from our center: T1: 1,267±68 ms, ECV%: 30±2%). ECV, extracellular volume; LGE, late gadolinium enhancement; AFD, Anderson-Fabry disease; LV, left ventricular.

segment) of 0.74, QT/QTc durations of 448/439 ms, QRS duration of 106 ms. Echocardiography revealed myocardial thickening with abnormal echogenicity, final renal biopsy indicated AFD. To date, he has exhibited no cardiovascular-related symptoms. CMR presented as enlargement of the LV with left ventricular end-diastolic volume (LVEDV) of 148.05 mL and concentric hypertrophy of the LV myocardium with a thickness up to 21 mm in the basal lateral wall. The LV systolic functions decreased with ejection fraction (EF) of 56.06%. The T1 and extracellular volume (ECV%) decreased globally except for that of the basal lateral wall, in which irregular increases in T1, ECV% and subepicardial late gadolinium enhancement (LGE) were observed (*Figure 1*). The diagnosis of AFD was further confirmed by these CMR findings.

Case 2

A 60-year-old female patient with intermittent chest pain for 16 years and an Electrocardiograph result evincing myocardial ischemia was clinically diagnosed as HCM. Corresponding treatments had been taken (no details). Recent echocardiography results also indicated HCM. ECG indicated sinus bradycardia (HR: 52 bpm), LV high voltage (SLI: 9.8 mV), T-wave inverted and ST-segment depressed, P wave/PR segment of 0.35, QT/QTc durations of 486/451 ms, QRS duration of 112 ms. Further CMR displayed as enlargement of the LV with LVEDV of 143.48 mL and concentric myocardial hypertrophy of LV, mainly located in the septal wall, anterior wall and apex, with the greatest thickness being 30 mm. The LV systolic functions decreased

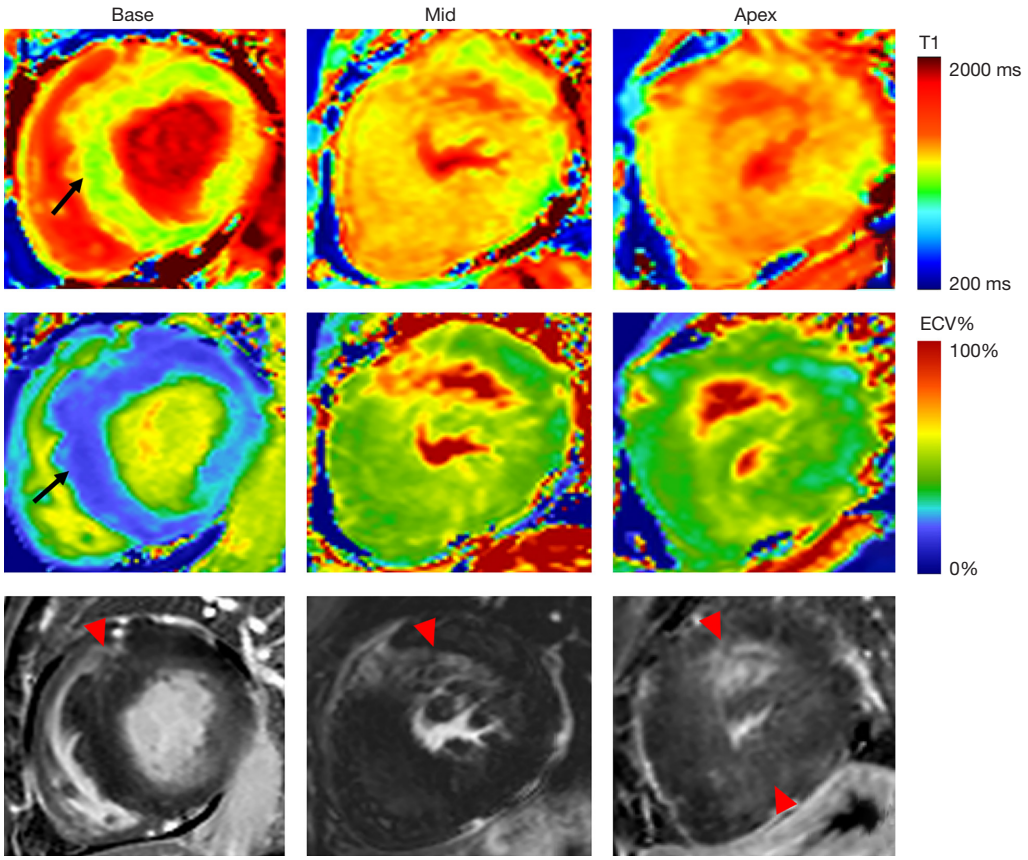

Figure 2 Short-axis T1 maps, ECV% and LGE images of LV in a 60-year-old female patient with advanced AFD (Case 2). Decreased T1 and ECV% only demonstrated in basal LV in advanced AFD, especially in the interventricular septum (black arrows). Patchy LGEs in the mid-anterior and the apex as well as focal LGEs in the anterior-insertion-point were observed (red arrowheads). Global T1: 1,254±77 ms, ECV%: 39%±17%; basal interventricular septum T1: 1,104±12 ms, ECV%: 18%±1%. (Normal ranges from our center: T1: 1,267±68 ms, ECV%: 30%±2%). ECV, extracellular volume; LGE, late gadolinium enhancement; AFD, Anderson-Fabry disease; LV, left ventricular.

with EF of 54.14%. Macroscopically patchy increased T1, ECV%, and LGEs in the mid-anterior and septal wall and the apex were observed. These findings are indicative of HCM, however, genetic testing confirmed AFD. Analysis of CMR found a decreased T1 and ECV% in the basal septal wall (*Figure 2*). After the diagnosis, enzyme replacement therapy (ERT) was performed.

Case 3

A 54-year-old male suspected of AFD eight years ago due to increased creatinine was confirmed by genetic testing showing a homozygote GLA gene mutation three years ago for renal failure. Kidney transplant surgery was performed two years ago and ERT treatment began thereafter. He was suspected of exhibiting cardiac involvement because of shortness of breath after exertion and chest-tightness within the past year. ECG showed sinus rhythm (HR: 63 bpm), LV high voltage (SLI: 4.6 mV), T-wave inverted and ST-segment depressed, P wave/PR segment of 0.64, QT/QTc durations of 448/458 ms, QRS duration of 122 ms. CMR demonstrated enlargement of LV with LVEDV of 201.20 mL and concentric myocardial hypertrophy of LV with the greatest thickness of 22 mm in the septal wall. LV systolic functions decreased with EF of 54.10%. Diffusely increased T1, ECV%, and T2 were determined, while the basal septal wall showed the lowest T1, ECV%, and T2 compared to the other segments. Significant transmural LGE in the basal inferolateral wall with local myocardial thinning as well as focal LGEs in the anterior-insertion-point and posterior-insertion-point were observed (*Figure 3A-3F*). In addition to the LV involvement, patchy increased T1 and LGE of

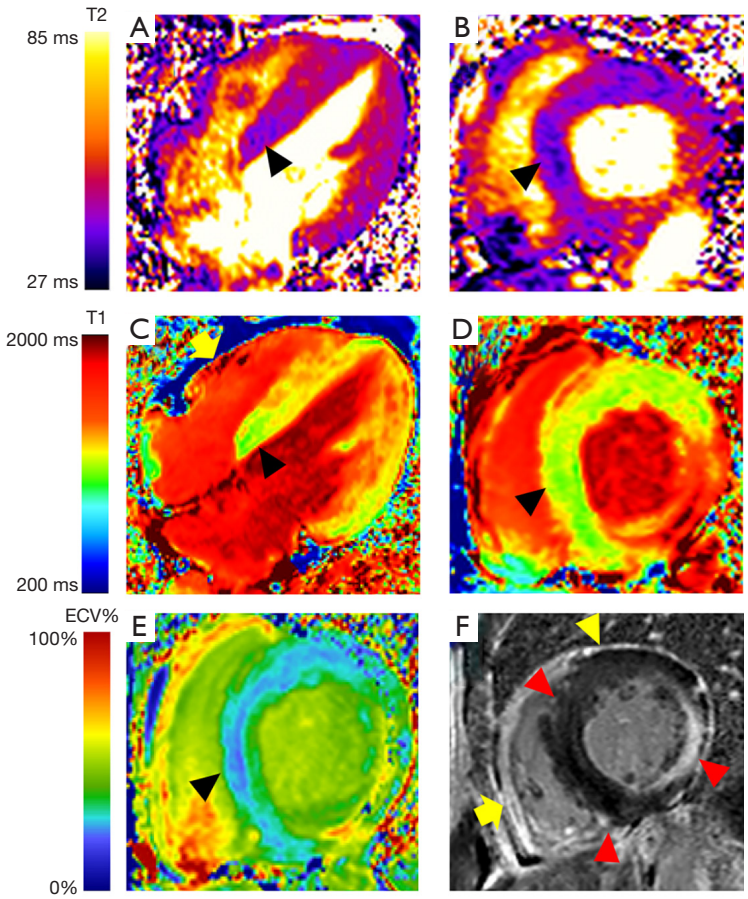

Figure 3 Long-axis and short-axis T2 maps (A,B) and T1 maps (C,D), short-axis ECV% (E) and LGE (F) images in a 54-year-old male patient with advanced AFD (Case 3). The decreased T2, T1 and ECV% were only observed in the basal interventricular septum (black arrowheads). Obvious transmural LGE in the basal inferolateral wall as well as spotty LGEs in the anterior-insertion-point and posterior-insertion-point were observed (red arrowheads). Patchy increased T1 and LGE of the RV free wall were observed (yellow arrows). Pericardium presented as linear LGE (yellow arrowhead). Global T1: 1,268±117 ms, ECV%:34%±7%, T2: 46±5 ms; Basal interventricular septum T1: 1,091±27 ms, ECV%: 23%±1%, T2: 39±3 ms. (normal ranges from our center: T1: 1,267±68 ms, ECV%: 30%±2%, T2: 42±2 ms). ECV, extracellular volume; LGE, late gadolinium enhancement; AFD, Anderson-Fabry disease; RV, right ventricular.

the right ventricular (RV) free wall were also determined. Pericardium presented as linear LGE (*Figure 3C*,*3F*).

All procedures performed in this study were in accordance with the ethical standards of the institution and the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In the early progression of AFD, the intracellular accumulation of glycosphingolipid will lower T1 without increasing the myocardial ECV% (1); cell hypertrophy even decreased the myocardial ECV%, allowing CMR to be used as a non-invasive discriminatory tool for diagnosing early myocardial involvement in AFD. However, the mean time from onset of the symptoms to diagnosis of AFD is about 15 years, the disease then enters its advanced phase with extensive interstitial fibrosis and myocardial scarring which will elevate the T1, inflate the ECV%, and make the LGE extensive and diffuse (1). Case 1 showed low T1 and ECV% for early myocardial involvement in AFD, while the distinctive low T1 and ECV% were only observed at the basal septum in advanced AFD (Cases 2 and 3). This

finding indicated the basal septum is the most preserved region during progressive fibrosis, which is distinctly different from other pathogenic LV hypertrophies. Previous necropsic work found the presence of limited microscopic septal fibrosis (1% septal *vs.* 17% lateral wall) (5); other previous studies using CMR also indicated that the basal septum would appear to be a better region of choice for measurement of decreased T1 for cardiac involvement in AFD compared to other segments (6,7), in keeping with our results and reaffirming the heterogeneity of fibrosis pattern in AFD. Myocardial ischemia and focal inflammatory processes triggered by globotriasylceramide storage in the coronary arterial wall and cardiomyocyte were two possible explanations of the pathophysiological mechanism of myocardial fibrosis. Narrowing of the coronary arterial lumen leads to hypoperfusion in the downstream myocardium, and a regional heterogeneity of hypoperfusion prevailing in the more apical regions. However, blood supply to the interventricular septum arose predominantly from penetrating arteries, sufficient anastomoses between the anterior and inferior septal perforating arteries can provide collateral arterial supply in case of ischemia (8). In Case 3, the T2 value in the basal septal wall is the lowest in all segments, indicating the lightest inflammatory response. Inflammation also has recently shown a predilection for the lateral and inferolateral regions as evinced by CMR imaging (9). Thus, the basal septum was deemed to be the last preserved region against pseudo-normalization or elevated T1 and ECV%. Notably, the anterior-insertion-point and posterior-insertion-point LGE were observed in Case 3 and were described in a previous study (10). The myocardia at hinge points were disarrayed and likely to be subject to encounter increased tension and junctional stresses, the fibrosis and widened interstitial matrix herein would affect quantitative measurement.

The disease-specific treatment ERT, which has no significant effect on CMR mapping, LGE, and cardiac pathologic findings (11), has been applied in long-term follow-up studies and registry data show that it can delay cardiac disease progression and reduce the cardiovascular event rate (12), but in advanced cardiac AFD, response to ERT is poor, with no data suggesting any effect on myocardial fibrosis and LVH progression (1). Even so, updated expert recommendations provided in a recent consensus document implied that patients with extensive fibrosis may become the candidates for ICD implantation to prevent sudden cardiac death (12), indicating that the identification of AFD with fibrosis is of great significance.

A previous study has demonstrated the potential of ECG-based scores in detecting low myocardial T1 values by CMR in patients with AFD. Specifically, LVH-positive patients with low T1 values exhibited higher SLI and P wave/PR segment, widened QRS and QT intervals compared to healthy controls (13). In our cohort, except for the presence of inverted T-waves and depressed ST-segments, the value of the scores proposed by the authors is confirmed in our cases, intercepting patients at very high likelihood of low T1 values in the basal interventricular septum. Other signs of cardiac involvement including biomarkers and CMR markers have been reported in the literature (14-16) but not involved in our study due to lack of availability of these markers in daily practice. Future studies with sufficient sample sizes are needed to corroborate the clinical value of these novel markers.

Conclusions

In conclusion, although our observations were derived from only three AFD patients, combined with previous reports and studies and relevant literature review, we consider the basal septum excluding insertion points as an appropriate region for CMR quantification of myocardial involvement in patients with advanced AFD. When preserved/low T1 without increased ECV% of this region presented in elderly patients with LVH, the suspicion of AFD should be raised.

Acknowledgments

The authors would like to acknowledge all who contributed to this case diagnosis, therapy, and decision-making.
Funding: This work was supported by the Natural Science Foundation (Nos. 2022-BS-143 and 22-321-33-31).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-714/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institution and the Helsinki Declaration (as

revised in 2013). Written informed consent was provided by the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovac AC, Elliott PM, Hagege A, Kuusisto J, Linhart A, Nordbeck P, Olivotto I, Pietilä-Effati P, Namdar M. Cardiac Involvement in Fabry Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2021;77:922-36.
2. Mehta A, Clarke JT, Giugliani R, Elliott P, Linhart A, Beck M, Sunder-Plassmann G; FOS Investigators. Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. J Med Genet 2009;46:548-52.
3. Perry R, Shah R, Saiedi M, Patil S, Ganesan A, Linhart A, Selvanayagam JB. The Role of Cardiac Imaging in the Diagnosis and Management of Anderson-Fabry Disease. JACC Cardiovasc Imaging 2019;12:1230-42.
4. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudová J, Karetová D, Zeman J, Ledvinová J, Poupetová H, Elleder M, Aschermann M. New insights in cardiac structural changes in patients with Fabry's disease. Am Heart J 2000;139:1101-8.
5. Sheppard MN, Cane P, Florio R, Kavantzas N, Close L, Shah J, Lee P, Elliott P. A detailed pathologic examination of heart tissue from three older patients with Anderson-Fabry disease on enzyme replacement therapy. Cardiovasc Pathol 2010;19:293-301.
6. Sado DM, White SK, Piechnik SK, Banypersad SM, Treibel T, Captur G, Fontana M, Maestrini V, Flett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neubauer S, Elliott PM, Moon JC. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6:392-8.
7. Wilson HC, Ambach S, Madueme PC, Khoury PR, Hopkin RJ, Jefferies JL. Comparison of Native T1, Strain, and Traditional Measures of Cardiovascular Structure and Function by Cardiac Magnetic Resonance Imaging in Patients With Anderson-Fabry Disease. Am J Cardiol 2018;122:1074-8.
8. Kaul S, Hopkins JM, Shah PM. Chronic effects of myocardial infarction on right ventricular function: a noninvasive assessment. J Am Coll Cardiol 1983;2:607-15.
9. Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250-8.
10. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, Iwanochko RM, Thavendiranathan P, Crean AM. Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson-Fabry disease. J Cardiovasc Magn Reson 2016;18:14.
11. Thurberg BL, Fallon JT, Mitchell R, Aretz T, Gordon RE, O'Callaghan MW. Cardiac microvascular pathology in Fabry disease: evaluation of endomyocardial biopsies before and after enzyme replacement therapy. Circulation 2009;119:2561-7.
12. Linhart A, Germain DP, Olivotto I, Akhtar MM, Anastasakis A, Hughes D, Namdar M, Pieroni M, Hagège A, Cecchi F, Gimeno JR, Limongelli G, Elliott P. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail 2020;22:1076-96.
13. Figliozzi S, Camporeale A, Boveri S, Pieruzzi F, Pieroni M, Lusardi P, Spada M, Mignani R, Burlina A, Graziani F, Pica S, Tondi L, Bernardini A, Chow K, Namdar M, Lombardi M. ECG-based score estimates the probability to detect Fabry Disease cardiac involvement. Int J Cardiol 2021;339:110-7.
14. Bernardini A, Camporeale A, Pieroni M, Pieruzzi F, Figliozzi S, Lusardi P, Spada M, Mignani R, Burlina A, Carubbi F, Battaglia Y, Graziani F, Pica S, Tondi L, Chow K, Boveri S, Olivotto I, Lombardi M. Atrial Dysfunction Assessed by Cardiac Magnetic Resonance as an Early Marker of Fabry Cardiomyopathy. JACC Cardiovasc Imaging 2020;13:2262-4.
15. Augusto JB, Nordin S, Vijapurapu R, Baig S, Bulluck H, Castelletti S, Alfarih M, Knott K, Captur G, Kotecha

T, Ramaswami U, Tchan M, Geberhiwot T, Fontana M, Steeds RP, Hughes D, Kozor R, Moon JC. Myocardial Edema, Myocyte Injury, and Disease Severity in Fabry Disease. Circ Cardiovasc Imaging 2020;13:e010171.
16. Camporeale A, Moroni F, Lazzeroni D, Garibaldi S, Pieroni M, Pieruzzi F, Lusardi P, Spada M, Mignani R, Burlina A, Carubbi F, Econimo L, Battaglia Y, Graziani F, Pica S, Chow K, Camici PG, Lombardi M. Trabecular complexity as an early marker of cardiac involvement in Fabry disease. Eur Heart J Cardiovasc Imaging 2022;23:200-8.

Cite this article as: Du Y, Liu R, Ding S, Wang G. Basal septal T1 mapping and extracellular volume as discriminators in cardiac magnetic resonance evaluation of myocardial involvement in advanced Anderson-Fabry disease: a case description. Quant Imaging Med Surg 2023;13(12):8817-8823. doi: 10.21037/qims-23-714

