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CASE REPORT
Cardiovascular imaging

Pitfalls for the non-invasive diagnosis of wild-type transthyretin amyloid cardiomyopathy in a young adult: a case report

Hao-Chih Chang [1,2,3,4], Ling Kuo[2,3,5,6], Fa-Po Chung [2,3,5,7]*, and Wen-Chung Yu [2,3,5]*

[1]Department of Medicine, Taipei Veterans General Hospital Taoyuan Branch, 100, Sec.3, Chenggong Road, Taoyuan District, Taoyuan 330023, Taiwan; [2]Cardiovascular Research Center, National Yang Ming Chiao Tung University, 155, Sec. 2, Linong Street, Beitou District, Taipei 112304, Taiwan; [3]Department of Internal Medicine, College of Medicine, National Yang Ming Chiao Tung University, 201, Sec. 2, Shi-Pai Road, Beitou District, Taipei 112201, Taiwan; [4]Institute of Public Health, National Yang Ming Chiao Tung University, 155, Sec. 2, Linong Street, Beitou District, Taipei 112304, Taiwan; [5]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, 201, Sec. 2, Shi-Pai Road, Beitou District, Taipei 112201, Taiwan; [6]Department of Biomedical Imaging and Radiological Sciences, National Yang Ming Chiao Tung University, 155, Sec. 2, Linong Street, Beitou District, Taipei 112304, Taiwan; and [7] Institute of Clinical Medicine, National Yang Ming Chiao Tung University, 155, Sec. 2, Linong Street, Beitou District, Taipei 112304, Taiwan

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Background Using technetium (Tc)-labelled pyrophosphate (PYP) cardiac scintigraphy, a non-invasive diagnosis of transthyretin amyloid (ATTR) cardiomyopathy can be made without histopathological confirmation. In patients suspected of ATTR cardiomyopathy, however, atypical presentations may necessitate further investigation.

Case summary A 30-year-old man with hypertension and end-stage renal disease on peritoneal dialysis presented with progressive exertional dyspnoea. Left ventricular hypertrophy (LVH) with a maximal end-diastolic wall thickness up to 16 mm was detected on echocardiography. Speckle-tracking analysis revealed a reduced longitudinal strain of left ventricle with a relative apical sparing pattern. Although the absence of monoclonal gammopathy, a grade 3 myocardial uptake in ^{99m}Tc-PYP cardiac scintigraphy, and negative TTR gene mutation inferred the diagnosis of wild-type ATTR, the relative youth of the patient still raised concerns regarding the diagnosis. Under clinical doubt, he underwent further testing. In non-contrast cardiac magnetic resonance (CMR) with native T1 mapping, the native T1 myocardial value was within the normal range. In endomyocardial biopsy (EMB), there was no evidence of amyloid deposition, negative Congo red staining, and no immunohistochemical evidence of transthyretin expression. These results excluded the diagnosis of ATTR cardiomyopathy and prevented subsequent unnecessary treatments.

Discussion When patients with unexplained LVH meet the non-invasive diagnostic criteria for ATTR cardiomyopathy, an EMB should be considered in selected cases. Patients presenting at an atypical age for wild-type ATTR cardiomyopathy, absence of extracardiac symptoms/signs or classic electrocardiogram features for cardiac amyloidosis should be suspected of another diagnosis and require further CMR or EMB to confirm.

Keywords Technetium-labelled cardiac scintigraphy • Transthyretin amyloid cardiomyopathy • Endomyocardial biopsy • Case report

ESC curriculum 2.1 Imaging modalities • 6.5 Cardiomyopathy • 2.2 Echocardiography • 2.3 Cardiac magnetic resonance

* Corresponding authors. Tel: +886 2 2871-2121 ext. 3650, Email: marxtaiji@gmail.com (F.-P.C.); Tel: +886 2 2871 2121 ext. 2997, Fax: +886 2 2877 1746, E-mail: yu.wenchung@gmail.com (W.-C.Y.)

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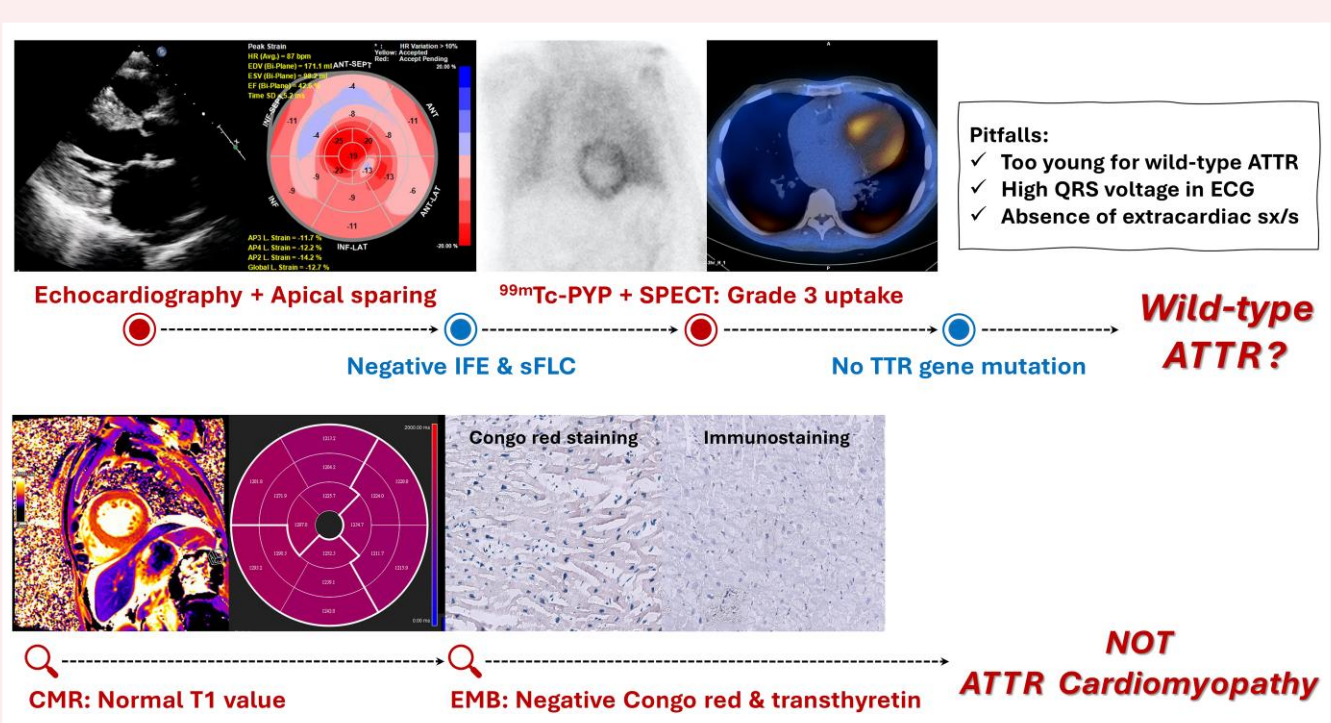
Learning points

- Technetium-labelled cardiac scintigraphy may preclude the necessity of endomyocardial biopsy (EMB); however, false-positive results can lead to unnecessary treatment.
- Despite fulfilling the non-invasive diagnostic criteria for transthyretin amyloid (ATTR) cardiomyopathy, EMB should be considered in selected cases with atypical presentations.
- Atypical age for wild-type ATTR or absence of extracardiac symptoms/signs or classic electrocardiogram (ECG) features should prompt further cardiac magnetic resonance or EMB to obtain a correct diagnosis.

Introduction

For cases with unexplained left ventricular hypertrophy (LVH) and suspected transthyretin amyloid (ATTR) cardiomyopathy, technetium-labelled cardiac scintigraphy is often used to diagnose ATTR cardiomyopathy without the need for endomyocardial biopsy (EMB).[1] While false-positive results may lead to inappropriate therapies and potential harms to patients, histological confirmation should be sought in selected cases even when patients meet the non-invasive diagnostic criteria for ATTR cardiomyopathy.

Summary figure



Case presentation

A 30-year-old man was referred to the cardiologist's clinic with chief complaints of exertional dyspnoea and intermittent palpitations for approximately 2 months. He had underlying diseases of hypertension and end-stage renal disease receiving peritoneal dialysis since December 2013 after taking unauthentic Chinese herbs. The patient was a non-smoker who took 40 mg of olmesartan once daily, 30 mg of nifedipine three times per day, 25 mg of carvedilol twice daily, 60 mg of isosorbide-5-mononitrate once daily, and 75 mg of clonidine twice daily to control his blood pressure.

His blood pressure was 150/102 mmHg and his pulse rate was 74 b.p.m. Auscultation of the heart and bilateral lung fields revealed no significant abnormalities. There was no evidence of oedema in the lower limbs. A chest X-ray revealed a marked increase in the cardiac silhouette and lung markings on the bilateral hilum. The electrocardiogram (ECG) revealed sinus rhythm and LVH with left ventricular (LV) strain (*Figure 1*). NT-proBNP levels were up to 399 110 pg/mL (reference range: <125 pg/mL if age <75 years old), while hs-troponin T levels were within normal limits. An echocardiogram revealed severe concentric LVH with a maximum wall thickness of 16 mm at the anteroseptal segment of LV (*Figure 2A*), LV global hypokinesia with a reduced LV ejection fraction (36%), a severely dilated left atrium, and minimal pericardial effusion. The speckle-tracking analysis revealed a reduced longitudinal strain of the LV with a sparing pattern at its apex (*Figure 2B*).

Under the suspicion of cardiac amyloidosis, this patient underwent serial workup. Serum and urine immunofixation electrophoresis (IFE),

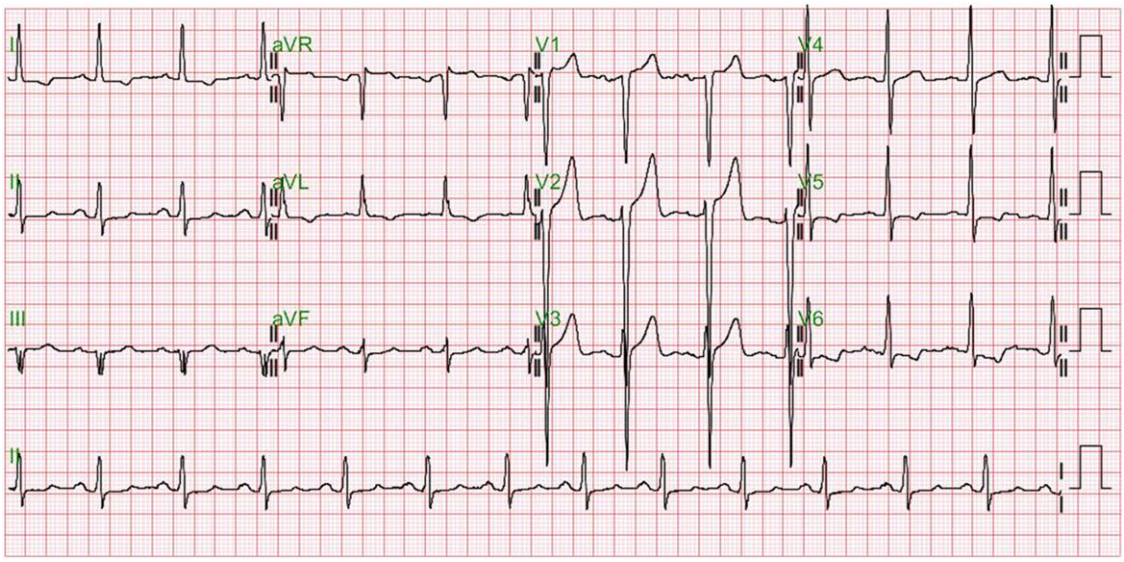


Figure 1 Electrocardiogram showed sinus rhythm and left ventricular hypertrophy with left ventricular strain.

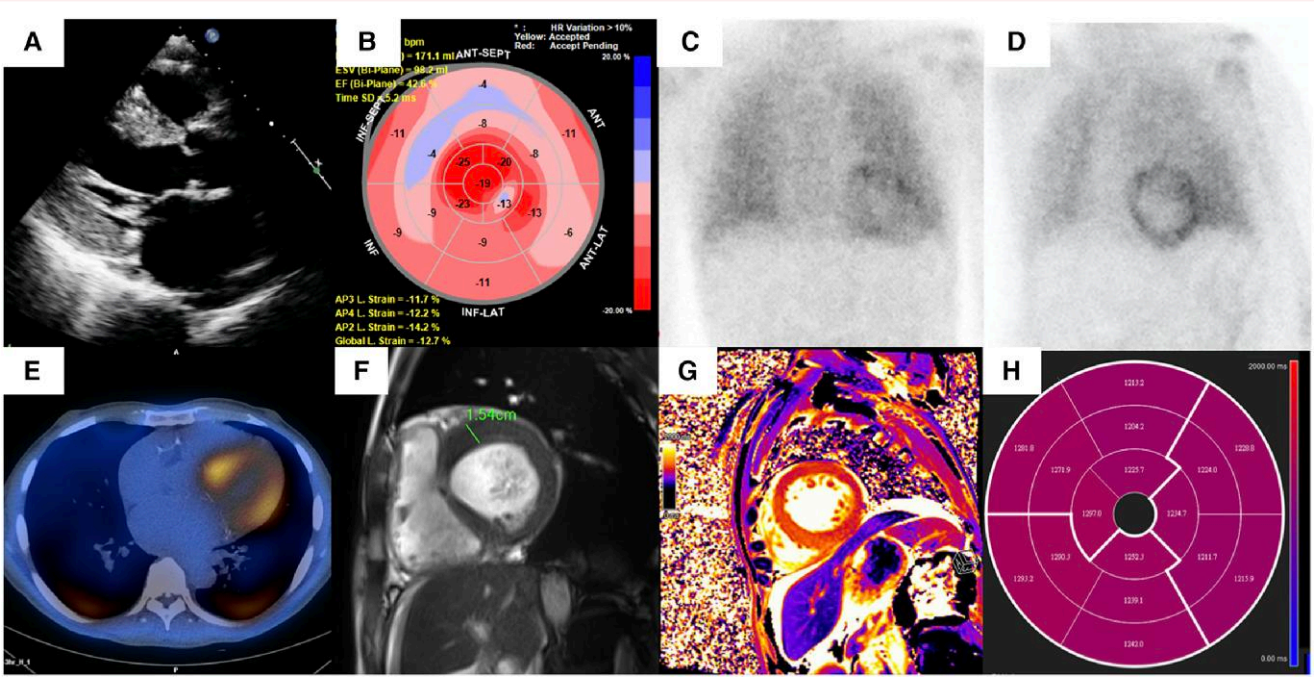


Figure 2 (*A*) Echocardiography revealed severe concentric left ventricular hypertrophy with a maximal end-diastolic wall thickness of up to 16 mm and minimal pericardial effusion. (*B*) A speckle-tracking analysis demonstrated a reduced longitudinal strain in the LV with a relatively sparing pattern at the apex. (*C*, *D*, and *E*) A ^{99m}Technetium-Pyrophosphate Planar and single-photon emission computed tomography (SPECT) scan revealed a grade 3 uptake within the myocardium. (*F*) CMR showed that the maximal end-diastolic wall thickness was 15.4 mm at the anteroseptal segment. (G and *H*) Native T1 mapping revealed that the mean native myocardial T1 value was 1244 ± 74 ms (normal range, 1156–1355 ms; 3-Tesla Vida MR scanner, Siemens Healthcare, Erlangen, Germany). An ATTR cardiomyopathy was less likely.

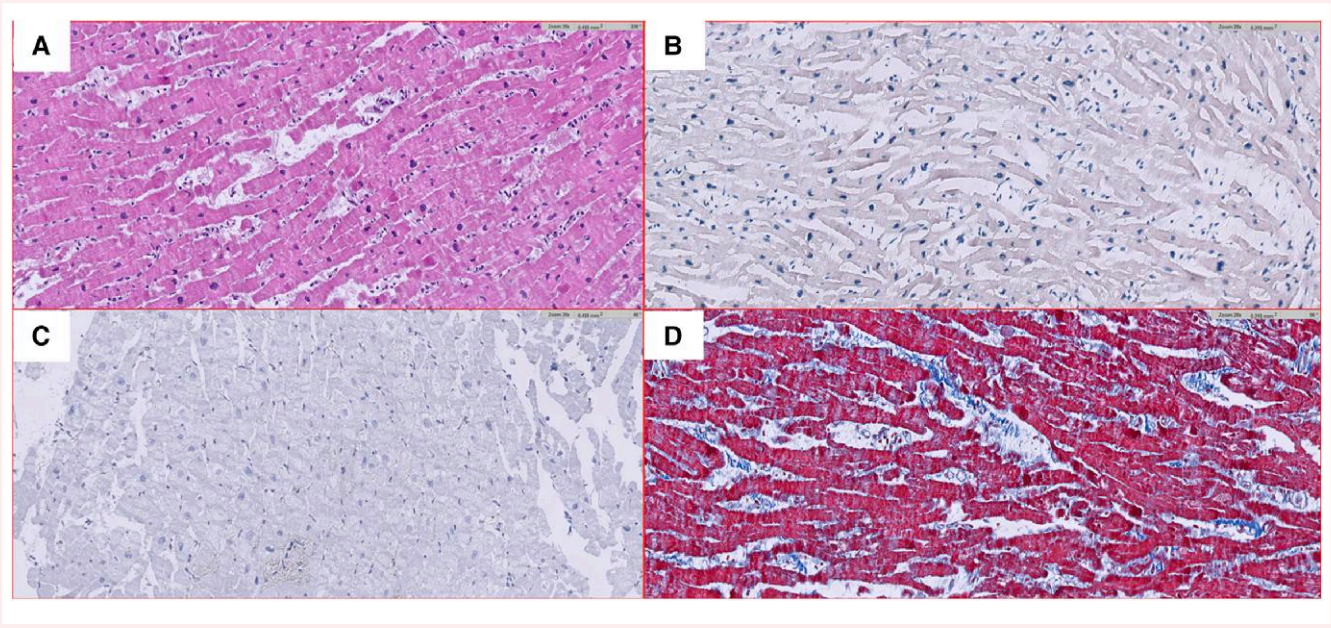


Figure 3 (*A*) The H&E staining showed no amyloid deposits, but only hypertrophied cardiomyocytes. (*B*) A Congo red staining at polarized light indicated that apple green fluorescence was not present. (*C*) Immunostaining for transthyretin was also negative. (*D*) Masson's trichrome stain showed that there was no significant collagen deposition within the myocardium.

as well as a serum-free light-chain (sFLC) assay, all showed negative results, and light-chain amyloidosis (AL) was excluded. For ATTR cardiomyopathy, the patient underwent a ^{99m}Tc-pyrophosphate (PYP) scan with single-photon emission computed tomography (SPECT), which revealed a grade 3 uptake of the radiotracer within the myocardium (*Figure 2C, D, and E*). We conducted a TTR gene analysis due to the clinical suspicion of ATTR cardiomyopathy; however, no pathologic mutation was detected. In view of the fact that this patient is relatively too young for a tentative diagnosis of wild-type ATTR, a cardiac magnetic resonance (CMR) was performed. Since he had end-stage renal disease, he underwent a non-contrast CMR. An analysis of the native T1 mapping revealed a mean T1 value of 1244 ± 74 ms, which fell within the normal range (1156–1355 ms; 3-Tesla Vida MR scanner, Siemens Healthcare, Erlangen, Germany) and did not support the diagnosis of ATTR cardiomyopathy (*Figure 2F, G, and H*). We further performed an EMB for histopathological confirmation. Four specimens of EMB were collected from different sites of the right ventricular septum for pathological evaluation. The histology, however, revealed no amyloid deposition, but only a hypertrophied myocardium (*Figure 3A*). In polarized light, Congo red staining did not reveal apple green fluorescence (*Figure 3B*), and immunohistochemistry analysis did not reveal the presence of transthyretin (*Figure 3C*). Electron microscopy failed to identify amyloid fibril aggregates. Masson's trichrome stain showed that there was no significant collagen deposition within the myocardium (*Figure 3D*). The diagnosis of ATTR cardiomyopathy was finally excluded. For possible hypertensive cardiomyopathy, this patient was on more rigorous control of blood pressure during follow-up.

Discussion

In this report, we presented a case of unexplained LVH with typical findings for ATTR cardiomyopathy based on the echocardiography, speckle-tracking analysis, and ^{99m}Tc-PYP-SPECT scan. Despite fulfilling the non-invasive diagnostic criteria for ATTR cardiomyopathy, this patient had an ECG absent for the classic features of cardiac amyloidosis and was too young for the diagnosis of wild-type ATTR. Under the clinically doubtful diagnosis of ATTR cardiomyopathy, further confirmation by CMR and EMB excluded the diagnosis and prevented the patient from unnecessary treatment. It is important to emphasize the role of EMB in determining a diagnosis of wild-type ATTR cardiomyopathy in patients with atypical clinical presentations.

As bone scintigraphy has been validated for the diagnosis of cardiac amyloidosis without the histological information,[1] EMB is no longer an indispensable requirement for the diagnosis of ATTR cardiomyopathy if non-biopsy criteria are met.[2,3] Grade 2 or 3 radionuclide uptake with an absence of monoclonal gammopathy had a specificity and positive predictive value of 100% for ATTR cardiomyopathy.[1] It should be noted, however, in less-selected populations, diagnostic yield and specificity may be reduced.[4] It is important to consider this caveat before concluding that the diagnosis is attributable to ATTR cardiomyopathy.[2,5]

The significant uptake of bisphosphonate within myocardium can also be caused by a variety of other conditions apart from ATTR cardiomyopathy, including hydroxychloroquine cardiotoxicity, other subtypes of cardiac amyloidosis, metastatic myocardial calcification, or hypertrophic cardiomyopathy.[2,6–8] In this regard, the clinical presentation, including previous medications used, family history, or the presence of extracardiac red-flag symptoms or signs, may be essential to differentiate the diagnoses. The TTR genetic test may be helpful in confirming the diagnosis of hereditary ATTR; however, a negative TTR genetic test still cannot exclude the possibility of wild-type ATTR. Therefore, the diagnosis of wild-type ATTR is largely based on the degree of clinical suspicion. Discordant clinical findings will require further EMB in order to ensure the correct diagnosis of wild-type ATTR cardiomyopathy and avoid unnecessary treatment, such as tafamidis, patisiran, diflunisal, or any other emerging therapies.[9]

As indicated by previous cohort studies, wild-type ATTR, also known as senile systemic amyloidosis, is most commonly seen in men over the age of 60.[10,11] Aside from the fact that it was less clear why normal transthyretin would develop amyloid deposition, the aging process

has been considered to be a driving cause of protein instability and misfolding.[12] With increasing awareness of ATTR, a wider range of ages has been reported to be affected.[13,14] The heterogeneity of the clinical spectrum of wild-type ATTR makes the diagnosis of ATTR without biopsy uncertain. Despite the presence of a relative apical sparing pattern, it is important to note that it was not specific for ATTR cardiomyopathy and could also be observed in other false-positive cases of ^{99m}Tc-PYP scans, such as metastatic myocardial calcification in dialysis patients, which could be the possible cause of positive ^{99m}Tc-PYP scan in our case.[5,8] The present case demonstrated that before concluding the diagnosis to ATTR cardiomyopathy using the non-invasive criteria, the absence of constellation of extracardiac symptoms/signs or the classic ECG features for cardiac amyloidosis, as well as the atypical age for wild-type ATTR, should raise a high index of suspicion that should prompt further CMR or EMB testing.[15]

Conclusion

It is imperative to carry out EMB even when considering the diagnosis of wild-type ATTR in a relatively young patient who meets the non-invasive diagnostic criteria for ATTR according to current guidelines. The clinical presentation of cardiac scintigraphy should not preclude an EMB in selected cases, even if they meet the non-invasive diagnostic criteria for ATTR cardiomyopathy.

Lead author biography

Dr Wen-Chung Yu graduated from National Yang Ming University and completed the training at Taipei Veterans General Hospital. He is currently a professor in the College of Medicine, National Yang Ming Chiao Tung University, and also the director of the echocardiography lab at Taipei Veterans General Hospital. Dr Yu is an experienced cardiologist in diagnosing and treating patients with ATTR-CM and as well as other cardiomyopathies, such as Fabry disease or hypertrophic cardiomyopathy. He participated in the international clinical trials ATTR-CM including ATTR-ACT extension study and APOLLO-B study.

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Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with the Committee on Publication Ethics (COPE) guidance.

Conflict of interest: None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

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