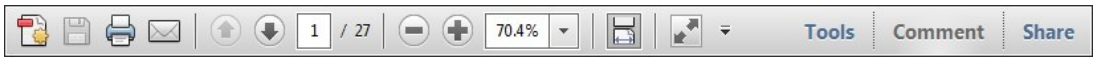
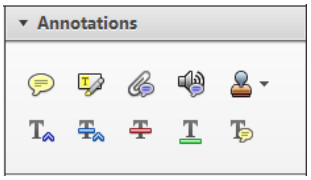
Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

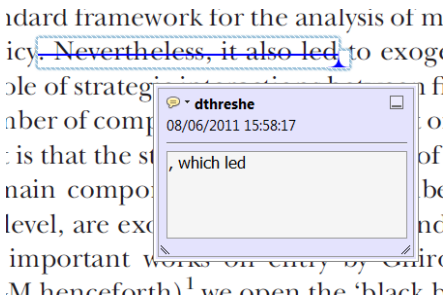


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

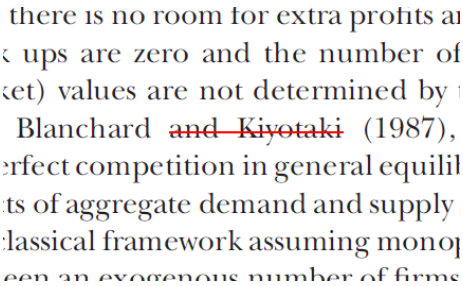


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

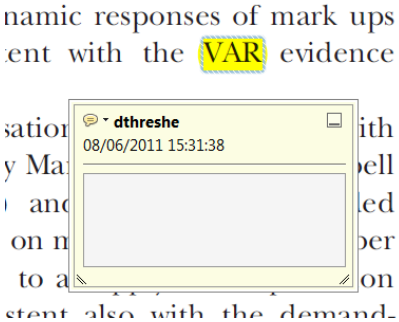


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

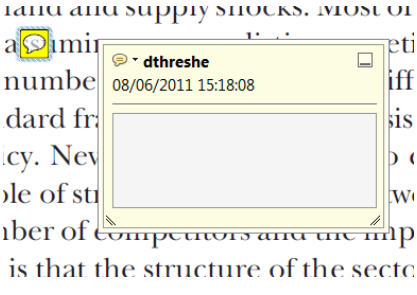


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

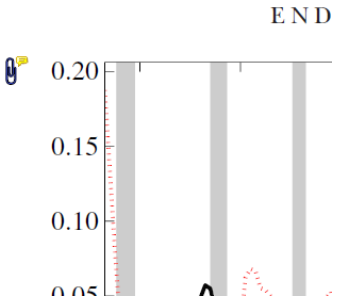


5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

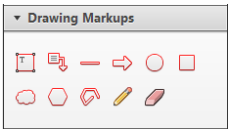
How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



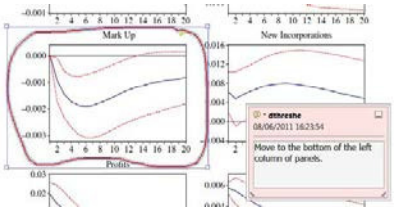
6. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



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CASE REPORT

Apical Left Ventricular Hypertrophy and Mid-Ventricular Obstruction in Fabry Disease

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We report the case of a rare cardiac presentation of Fabry disease. Although concentric left ventricular hypertrophy is a major cardiac finding in Fabry disease, there is no case report of dynamic obstruction at mid-left ventricular level. We describe a 59-year-old- woman suffering from a severe form of Fabry disease, mimicking an apical hypertrophic cardiomyopathy with mid-ventricular obstruction. Differentiation of Fabry disease from hypertrophic cardiomyopathy is crucial given the therapeutic and prognostic differences. Fabry disease should always be suspected in an adult, independently of the pattern of left ventricular hypertrophy. (Echocardiography 2015;00:1–4)

Key words: Fabry disease, transthoracic echocardiography, apical and mid-left ventricular hypertrophic cardiomyopathy, mid-left ventricular obstruction

Case Report:

A 59-year-old woman consulted our hospital because of syncope and dyspnea functional class II–III (NYHA classification). She had suffered an ischemic stroke 1 year before. Brain MRI showed small vessel disease in the periventricular white matter without embolic infarction.

Physical examination revealed a regular pulse; heart rate was 55 beats/min and blood pressure was 130/70 mmHg. A systolic ejection murmur II/VI was heard over the left sternal border. A 12-lead electrocardiogram showed severe left ventricular hypertrophy with associated ST-and T-wave strain abnormalities, sinus bradycardia and a short PR segment. Chest X-ray showed cardiomegaly without pulmonary congestion. Two-dimensional echocardiogram demonstrated apical and mid-ventricular hypertrophy without involvement of the basal segment of the heart (Fig. 1A and Movie clip S1). Global left ventricular (LV) systolic function was normal (ejection fraction: 74%). Regional LV systolic function was markedly reduced with a global longitudinal peak systolic strain of −6.7% (Fig. 1B). When evaluating the influence of all values on global systolic strain, basal-inferior and basal-lateral segments had less influence, suggesting myocardial fibrosis in the remaining segments. The slow tissue Doppler (E') was characteristic of diastolic dysfunction. The apical four-chamber view revealed a narrow outflow of the left ventricular cavity at the apex and mid-ventricle. Color flow Doppler imaging showed a turbulent flow jet in the mid-ventricular cavity ~~from mid- to late systole~~ (Fig. 1C and Movie clip S2). Continuous wave Doppler showed a resting peak gradient of 58 mmHg (Fig. 1D). The anterolateral papillary muscle was hypertrophic and measured 14 × 20 mm (Fig. 2A). Right ventricular inferior wall thickness (10 mm) indicated the presence of right ventricular hypertrophy (Fig. 2B). Normal chamber size and systolic right ventricular function were seen.

The patient had been diagnosed with hypertrophic cardiomyopathy (HCM) in 2002, at age 52. In 2007, the presence of short PR segment, hypohidrosis, cornea verticillata and proteinuria (<500 mg/24 h) with normal kidney function, and an ischemic stroke raised suspicion of an alternative diagnosis.

Leukocyte α galactosidase A activity was low, 37 nmol/mg protein/hour (normal range 395–780 nmol/mg). Genetic testing showed a defect in the GLA gene located in the X chromosomal

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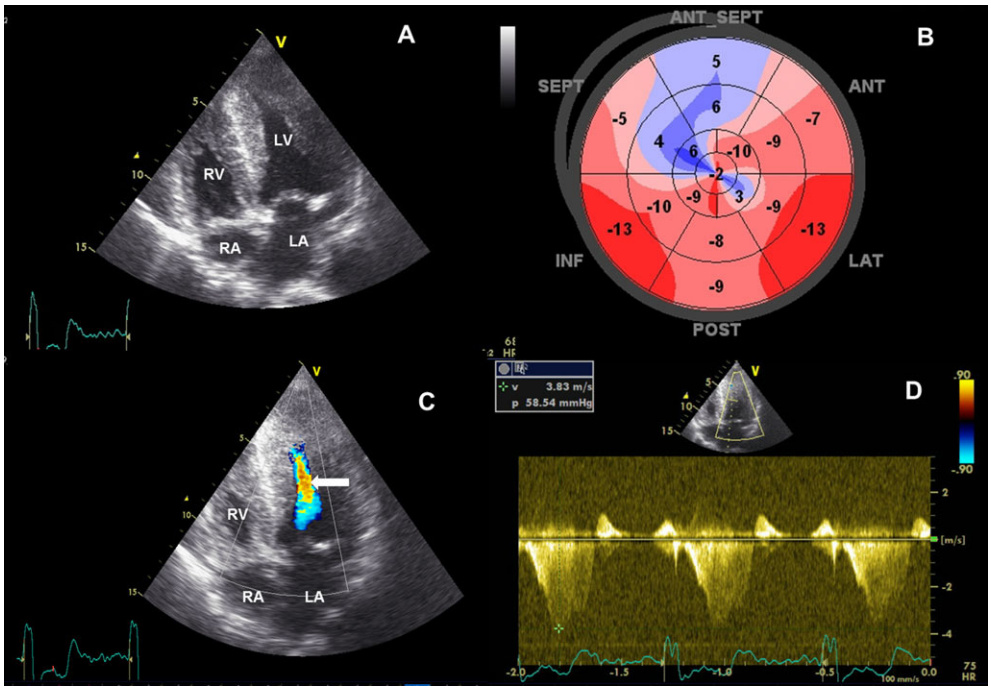

Figure 1. A. Two-dimensional echocardiogram, apical four-chamber view, demonstrated apical and mid-ventricular hypertrophy without involvement of the basal segment of the heart. **B.** Bull's-eye of LV strain obtained using speckle-tracking echocardiography showed markedly reduced global longitudinal peak systolic strain. **C.** Color flow Doppler imaging showed a turbulent flow jet in the mid-ventricular cavity from mid- to late systole (see arrow). **D.** Continuous wave Doppler showed a resting ~~pressure~~ gradient of 58 mmHg. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle.

region Xq22 (c.1122_1125delAGGA exon 7 of GLA gene) confirmed the diagnosis of Fabry disease.

In 2009, enzyme replacement therapy (ERT) was started using agalsidase-β (1.0 mg/kg body weight, intravenous infusion during a period of 4 h every 14 days).

Indeed, adjunctive therapy was started with hypoproteic diet, angiotensin-converting enzyme inhibitors (ACE) to reduce the level of proteinuria. β-Blockers were avoided due to sinus bradycardia.

Because of the shortage of agalsidase-β in 2010, the patient was switched to home therapy with agalsidase-α (0.2 mg/kg body weight, IV infusion, during 40 min every 14 days).

Cardiovascular magnetic resonance imaging showed severe left ventricular hypertrophy (LVH), predominantly involving the mid-LV and apex (Movie clip S3). Pronounced late gadolinium enhancement (LGE) was observed within the mid-myocardial wall in the hypertrophied muscle segments (Fig. 3). The amount of myocardial fibrosis was calculated a~~t~~ 2 ~~.7%~~ of total left ventricular mass.

A 24-h ambulatory Holter electrocardiogram showed several runs of nonsustained ventricular tachycardia. The patient was considered high risk; hence, an implantable cardioverter–defibrillator was recommended for primary prevention of sudden cardiac death.

The patient attended our hospital 2 ~~years~~ after being erroneously diagnosed with HCM, and after a late beginning of treatment with ERT, two-dimensional echocardiography failed to show regression of the LVH.

Discussion:

Linked to the X chromosome, it was considered rare in heterozygous female carriers in the past.[1] This was explained by a skewed inactivated X chromosome (Lyon hypothesis).[2] Nevertheless, it is now widely accepted that heterozygous female carriers could develop severe cardiomyopathy and other organ manifestations.[3] In fact, two-thirds of all patients with Fabry disease are female. Hence, it is important to focus on the cardiac manifestations of Fabry disease in female patients.

Sarcomeric HCM is the most common genetic cause of unexplained left ventricular hypertrophy (LVH) and has no specific treatment. Fabry disease is rare and usually multisystemic, but occasionally is expressed clinically as a predominantly cardiac phenotype mimicking HCM. The LVH in patients with Fabry disease is usually symmetric,

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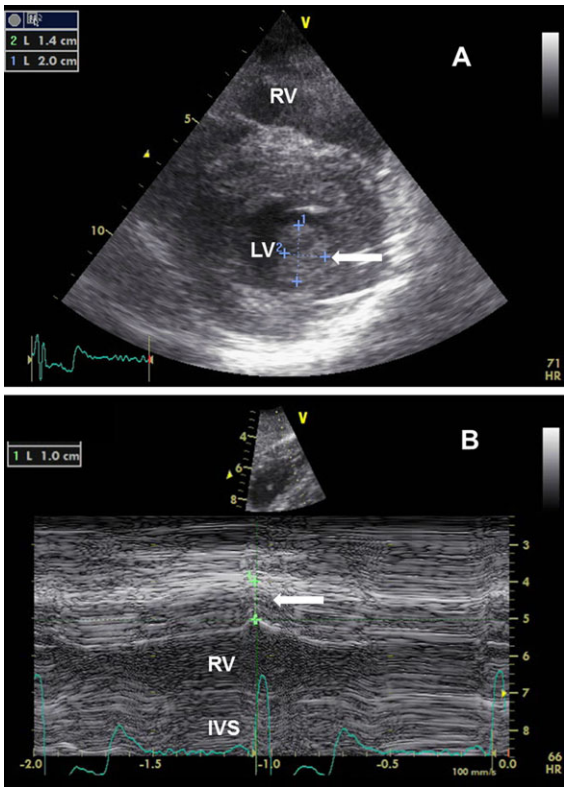

Figure 2. A. Two-dimensional echocardiogram, parasternal short-axis view, at the level of papillary muscle showing hypertrophy of the anterolateral papillary muscle (see arrow, 14 × 20 mm). **B.** M-mode echocardiogram, subcostal view showing right ventricular hypertrophy (see arrow, 10 mm). LV, left ventricle; RV, right ventricle; IVS, interventricular septum.

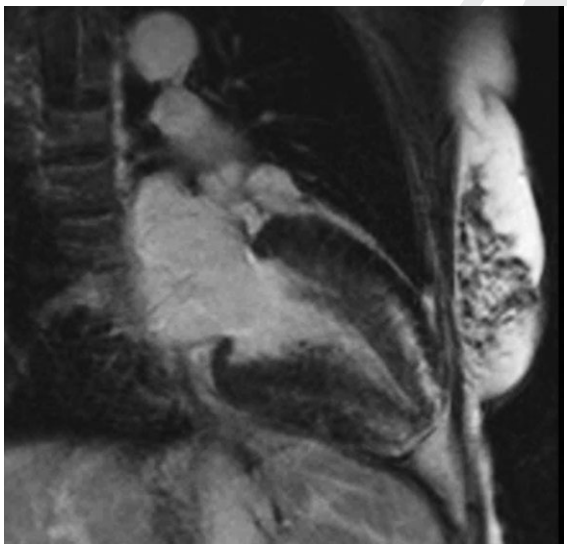

Figure 3. Cardiac MRI: Pronounced late gadolinium enhancement was observed within the mid-myocardial wall in the hypertrophied muscle segments.

not asymmetric as in HCM.[4–6] The asymmetric septal hypertrophy observed in about 5% of the cases is similar to sarcomeric cardiomyopathies. Apical and mid-ventricular hypertrophy without involvement of the basal segment of the heart, as seen in our case, has not been previously reported. While a few cases with pressure gradients at the LV outflow tract have been reported,[7–11] no cases with apical LVH and dynamic obstruction at the mid-left ventricle have been published.

Physicians commonly misdiagnose Fabry disease. If this storage disease were misdiagnosed as HCM, the patient could not be treated with ERT to stop or reduce cardiac involvement related to Fabry disease, with consequent implications for the patient's treatment and prognosis as well as his/her family's screening. Family history is a crucial component of the history both in HCM and Fabry's disease.

The importance of this case is based on the atypical cardiac presentation regarding the location of hypertrophy and left ventricular fibrosis. The LVH in Fabry disease is usually symmetrical and without intraventricular gradient, whereas in our case, it was apical and mid-ventricular with mid-ventricular obstruction. Two-dimensional speckle-tracking imaging in Fabry disease shows a regional deformation pattern with the lowest values in the basal posterior and lateral LV segments. CMR usually shows myocardial fibrosis in the same segments. Contrary, in our case, these abnormalities were localized in the medial and apical segments of the left ventricle.

Myocardial replacement fibrosis is a typical feature of an advanced Fabry cardiomyopathy. Studies using cardiovascular magnetic resonance demonstrated that myocardial fibrosis, detected with late gadolinium enhancement is characteristically confined to the mid-myocardial layers and the basal posterior and lateral segments of the left ventricle, whiles in HCM patients, the pattern of LGE is often described as patchy and most commonly involving hypertrophied segments of the LV wall and the insertion points of the right ventricle into the left ventricle.

Myocardial fibrosis has an impact on subsequent treatment with enzyme replacement. Hence, early diagnosis of cardiac involvement in Fabry disease is very important, as it allows to start ERT as soon as possible to prevent complications such as LVH and irreversible myocardial fibrosis, lethal arrhythmias, and coronary heart disease.

In patients with HCM, CMR with extensive LGE occupying ≥ 15% of the LV myocardium was found to be an independent predictor of sudden death, and therefore potential candidates for implantable cardioverter–defibrillator therapy.

Our patient was considered as high risk due to the presence of ≥1.7% of myocardial fibrosis, runs of nonsustained ventricular tachycardia and syncope; hence, an ICD was inserted as primary prevention of sudden death.

Many patients with cryptogenic stroke (4.9% of males and 2.4% of female) were found to have undiagnosed Fabry disease. Because most Fabry disease patients did not report other major clinical signs before their first stroke (i.e., cardiovascular or renal dysfunction), physicians must be vigilant for cerebrovascular risk factors and complications in all Fabry patients, even those who do not exhibit substantial cardiovascular or renal disease.

In conclusions, the present case demonstrates that Fabry disease can take the form of mid-ventricular obstruction. Fabry disease should always be suspected in an adult who presents unexplained LV hypertrophy, proteinuria, stroke or, particularly when other signs of Fabry disease (e.g., hypohidrosis, cornea verticillata, angiokeratomas, acroparesthesias) are present, independently of the pattern of LV hypertrophy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Movie clip S1. Two-dimensional echocardiogram, apical four-chamber view, demonstrated apical and mid-ventricular hypertrophy without involvement of the basal segment of the heart.

Movie clip S2. Color flow Doppler imaging showed a turbulent flow jet in the mid-ventricular cavity from mid- to late systole.

Movie clip S3. Cardiovascular magnetic resonance. Long-axis view clearly demonstrated apical and mid-ventricular hypertrophy without involvement of the basal segment of the heart.

Mini-Abstract:

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