Intra-cardiac tumour and bicuspid aortic valve in a patient with neurofibromatosis type 1—rare associations: a case report

Claire MacLeod [1], Kenneth Mangion [1], Giles Roditi [2], and Faheem Ahmad [1]*

[1]School of Medicine, Dentistry & Nursing, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK; and [2]Department of Radiology, Glasgow Royal Infirmary, 84 Castle St, G4 0SF Glasgow, UK

Background	Neurofibromatosis (NF) is an autosomal dominant neurocutaneous disease with multi-system involvement. Three cardiovascular associations are recognized but infrequently reported: congenital heart disease, vasculopathy, and hypertension. Cardiac outflow tract pathology, pulmonary stenosis, and aortic co-arctation have been described in the literature with varying frequency. The incidence of intra-cardiac tumour is exceeding rare.
Case summary	A 53-year-old man presented to the neurosurgical team with myelopathy secondary to cord compression arising from multiple cervical neurofibromas secondary to NF-1. Further cardiac evaluation with echocardiography and cardiac MRI uncovered the presence of both a bicuspid aortic valve (with mild aortic stenosis and moderate aortic regurgitation) and a concurrent intra-cardiac tumour of the mitral papillary muscle; a combined finding which was not reported previously. Serial evaluation confirmed stable disease with no major progression over time.
Discussion	Our case highlights the importance of recognizing cardiovascular manifestations of NF-1 and instituting appropriate screening and surveillance strategies. Targeted non-invasive imaging strategies may be more suited for this purpose over routine clinical examination alone.
Keywords	Neurofibromatosis • Papillary muscle neurofibroma • Case report
ESC Curriculum	2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 6.8 Cardiac tumours

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Learning points

- NF-1 patients may harbour significant cardiovascular pathologies—these require sophisticated imaging to identify and characterize.
- NF-1 patients require thorough evaluation of hypertension, including screening for vasculopathy.
- Echocardiography is critical to assess for underlying silent structural cardiac disease.
- MRI of the aorta is indicated where vasculopathy is suspected in congenital conditions associated with aortopathy, especially those with bicuspid aortic valve.

Introduction

Neurofibromatosis (NF) is a distinctive autosomal dominant neurocutaneous disease with multi-system involvement.[1] The incidence rate is estimated at 1 in 3000, with neurofibromatosis subtype 1 (NF-1)—also known as von Recklinghausen disease—the most predominant variant comprising over 95% of cases.[2] Clinical features include cutaneous lesions (cafe-au-lait spots), benign dermal and plexiform neurofibromas

and ocular malformations (iris hamartomas).[3] Three cardiovascular associations have been recognized but are infrequently reported: hypertension, vasculopathy (not defined), and congenital heart disease,[4] the clinical expression of which is variable.[4] The incidence of intra-cardiac tumour is exceeding rare.

Timeline

1976 (aged 7)	Initial diagnosis of neurofibromatosis type 1
Jan 2018 (aged 48)	Presented with arm weakness and diagnosis of cervical cord compression Secondary to cervical nerve root neurofibroma. Referred for workup for cervical laminectomy
May 2018 (aged 49)	Ejection systolic murmur was detected on auscultation. Referred for echocardiography which revealed a bicuspid aortic valve with mild aortic stenosis and moderate aortic regurgitation
July 2018 (aged 49)	Cardiac MRI obtained to assess for aortopathy. MR imaging unexpectedly revealed avid late gadolinium enhancement (LGE) of the postero-medial papillary muscle. Patient declined biopsy but NF-1 history strongly points to intra-cardiac neurofibroma
Feb 2022 (aged 53)	Follow-up evaluation revealed stable disease with no major valve or intra-cardiac tumour progression over time

We present a case of a patient with NF-1 who presented to the neurosurgical team with myelopathy secondary to cord compression arising from multiple cervical neurofibromas. Clinical examination elicited the presence of a systolic murmur, and further cardiac evaluation uncovered the presence of both a bicuspid aortic valve and concurrent intracardiac tumour of the mitral papillary muscle; a combined finding which has not been reported previously.

Case presentation

A 53-year-old male with known NF-1 including cervical neurofibromata and essential hypertension was referred to the cardiology service with an audible ejection systolic murmur during pre-operative workup for potential surgical intervention. The murmur was described as an ejection systolic murmur, loudest at the right upper sternal border with radiation to the neck and carotid arteries. Peripheral carotid, brachial, radial, and femoral pulses were all intact. No radio-radial or radio-femoral delay was elicited on palpation. The patient had previously undergone cervical laminectomy for prior spinal cord compression which had resulted in subsequent residual myelomalacia with myelopathy. Exertional capacity was limited secondary to resultant neuromuscular atrophy. However, there were no symptoms suggesting cardiac ischaemia, syncope, or heart failure. Standard 12-lead electrocardiogram demonstrated normal sinus rhythm without any electrographic evidence of conduction system pathology.

Trans-thoracic echocardiography imaging was requested to investigate the ejection systolic murmur. A possible bicuspid aortic valve with mixed aortic valve disease was demonstrated. The peak velocity was 3.2 m/s. The maximal and mean pressure gradients were 41 and 24 mmHg, respectively. The aortic regurgitation pressure half time was 488 m/s. Diastolic inter-ventricular septal thickness was 11 mm,

posterior wall 10 mm. Diastolic left ventricular internal diameter was 44 mm. To evaluate this further, imaging using cardiac magnetic resonance (CMR) was obtained to assess valve disease severity and to exclude associated aortopathy.

CMR imaging confirmed a functionally bicuspid aortic valve with fusion of the left and right leaflets was confirmed on CMR imaging with concurrent mixed valve disease (mild aortic stenosis—peak aortic velocity 2.6 m/s, and moderate aortic regurgitation—regurgitant volume 28 mL, regurgitant fraction 31%). The left ventricle exhibited normal dimensions (left ventricular indexed diastolic volume: 94 mL/m^2), function (left ventricular ejection fraction: 60%), and normal wall thickness (indexed myocardial mass: 73 g/m^2). Avid late gadolinium enhancement (LGE) of the postero-medial papillary muscle was unexpectedly demonstrated (*Figure 1*). No features of functional impact of this papillary muscle problem were evident and there was no other LGE elsewhere to suggest an infiltrative aetiology. Systolic biventricular function was preserved. Magnetic resonance (MR) imaging of the aorta did not identify any distal aortic or great vessel pathology (*Figure 2*). In the absence of major valve stenosis, heart failure or aortopathy, the patient's pre-operative risk for cervical laminectomy was deemed to be low. He proceeded to surgical intervention without requiring any further pharmacological modification of therapy and it was performed without major complication.

Primary differential for the enhancing lesion at that site included fibroelastoma and neurofibroma; however, in the context of the clinical history of type 1 NF-1, the presumed final diagnosis is neurofibroma. Endomyocardial biopsy was not attempted due to patient preference. Given the relative absence of primary features of embolization or haemodynamic consequence from the tumour, the patient was been enrolled for continued surveillance with serial cardiac MRI (CMR) for ongoing quantification of their valvular pathology. Subsequent repeat cMRI imaging demonstrated stable pathology, confirming the appropriateness of this strategy. Screening for valve disease and aortopathy of relatives with NF-1 was offered with echocardiography and MR angiography. None of them had a bicuspid aortic valve or aortopathy.

Discussion

The association with NF-1 and vasculopathy, congenital heart defects and hypertension are all well recognized but exceedingly rare features of this autosomal dominant condition.[4] Significant expressive variability exists within the disease spectrum, and the mechanistic basis for how these phenotypes manifest remain poorly understood.[5] We demonstrate a unique case of NF-1 associated with both a congenital valve lesion and an intra-cardiac tumour, a concurrent manifestation of two cardiac pathologies which has not been reported previously in the literature.

Congenital cardiovascular lesions with NF-1 have a reported incidence ranging from 0.4 to 8.6%.[5] A heterogenous spectrum of anomalies are known to occur comprising both right-sided (pulmonary stenosis, conotruncal lesions) and left-sided obstructive lesions (aortic stenosis, aortic co-arctation). Although most may be mild and not require intervention, appropriate detection is critical to institute timely follow-up. Bicuspid aortic valves do not often exist in isolation, and an assessment must be made for more dangerous—and often clinically silent—downstream aortopathy. Early detection of congenital lesions are necessary to institute early repair (such as in the case of atrial septal defects before the onset of pulmonary hypertension and right ventricular failure). Low-risk stenotic lesions not requiring immediate intervention will require surveillance, as intervention is recommended before critical symptoms develop.[6] These lesions may also be at theoretical risk of bacterial endocarditis, and so specific antibiotic prophylaxis based on nationally accepted clinical practice may be appropriate. As the natural history of these lesions remains poorly understood, these patients should be managed—as in our case—adhering to a monitoring schedule along recognized guidelines for valve surveillance.[6]
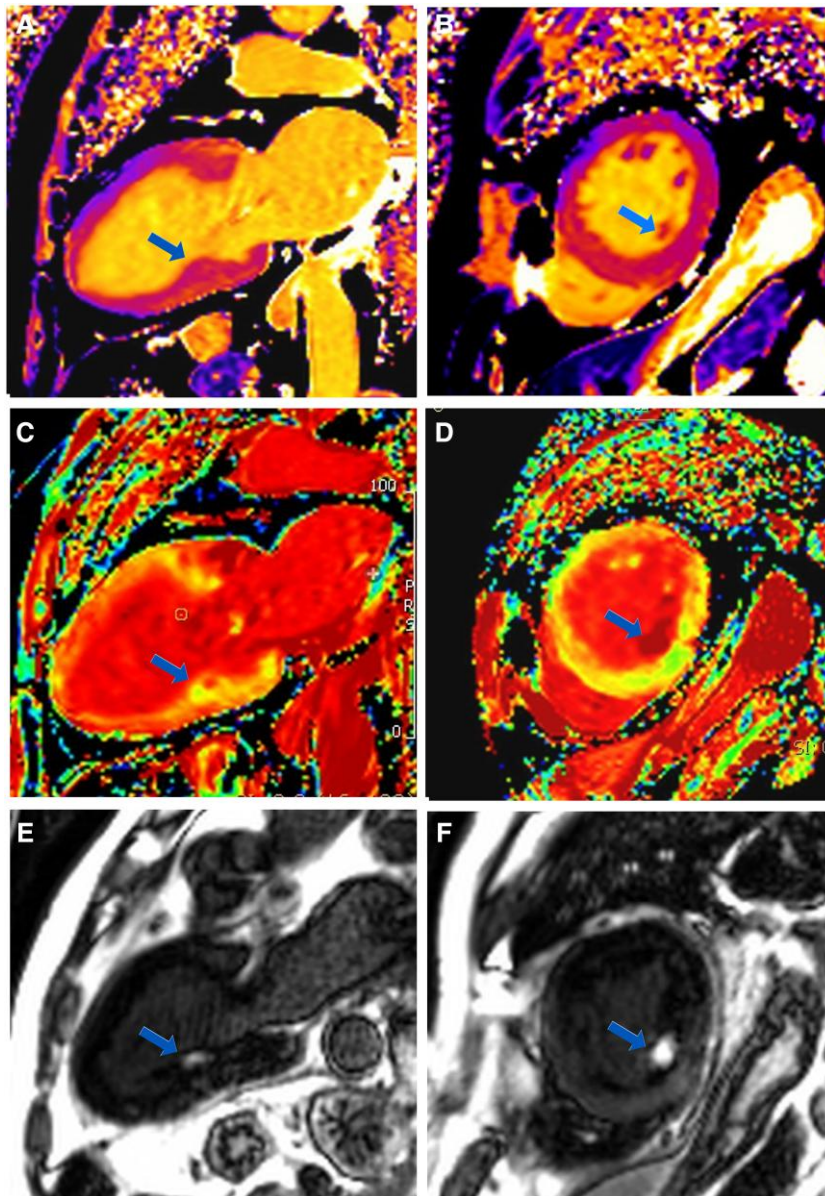
Figure 1 Multi-parametric characterization of a papillary fibroelastoma—identified by the arrow on all six images. (*A*) Native T1 map, vertical long axis view of the left ventricle, with the arrow pointing to the postero-medial papillary muscle. The T1 relaxation time of the papillary muscle was 1295 ms (normal range for our scanner, 1107–1234 ms). (*B*) Native T1 map, short axis slice through the papillary muscles. (*C*) Extracellular volume map vertical long axis view, with the papillary muscle extracellular volume measured at 80% (normal—<28%). (*D*) Corresponding short axis extracellular volume map view. (*E*) Dark blood late gadolinium enhancement sequence depicting hyper-enhancement of the postero-medial papillary muscle. (*F*) Corresponding short axis view.

The cardiovascular pathogenesis of disease in NF-1 is poorly understood. Aberrant neurofibromin-mediated gene control of neural crest migration and endocardial cushion development is believed to play a central role.[7] Experimental studies of homozygous NF-1 knockout mice suggest that the absence of neurofibromin control results in endocardial cushion hyper-proliferation and a failure of regulated apoptosis. This contributes to the observed phenotypes of ventricular malformation, obstruction, and valvular pathology described, though the precise mechanism still remains unclarified.[7]

The incidence of vasculopathy in NF-1 patients is somewhat more common (reported at 2.3–3.6%).[8] However, as many lesions are clinically silent, this is likely to be underestimated.[8] A spectrum of pathologies co-exist and can include stenoses, aneurysms, fistulae, and involvement of both the aorta and smaller arterioles.[1] Furthermore, vascular lesions may not necessarily be confluent. Vascular rupture secondary to blood vessel fragility has also been reported, and this significant risk must be appreciated whenever percutaneous or surgical intervention is undertaken. The pathophysiology of aneurysm formation and rupture is postulated to involve either weakening of the tunica media secondary to neurofibromatous encroachment into the vessel wall, or tumour obstruction of the vasa vasorum causing localized vessel wall ischaemia.
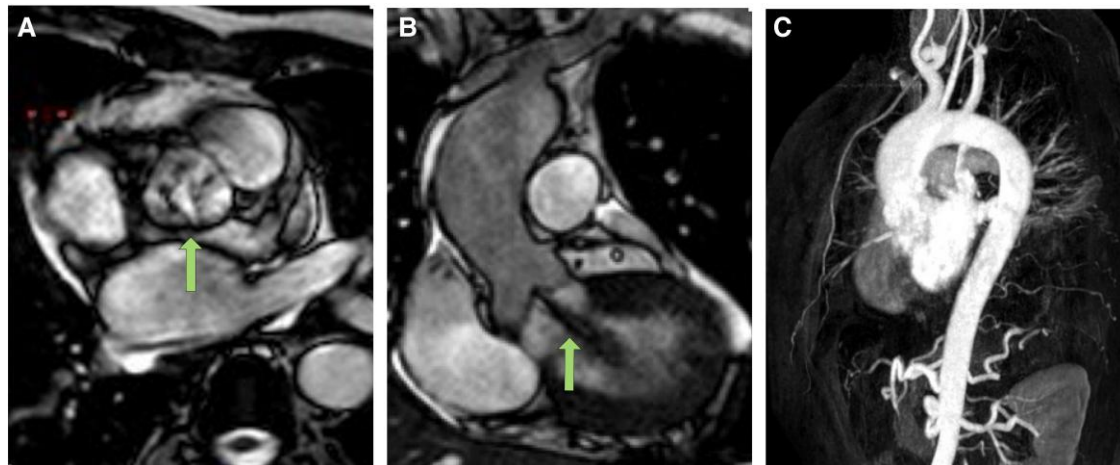
Figure 2 Aortic valve and aorta assessment. (*A*) Short axis view across the aortic valve (green arrow points to valve). Note fusion of right and left coronary cusps. (*B*) Long axis view through the aortic valve, the green arrow demonstrates anteriorly directed aortic regurgitation. Estimated regurgitant fraction was 31% (moderate aortic regurgitation). (*C*) 3D reconstruction of the aorta to rule out associated aortopathy and co-arctation.

Hypertension is a common feature in NF-1 patients, though it remains uncertain whether the association between essential hypertension and NF-1 is due to more rigorous cardiovascular screening or a component of the disease process.[4] Secondary causes such as renal artery stenosis and concurrent pheochromocytoma must be excluded before commencing treatment. Where no secondary cause exists, treatment should continue along guideline-directed strategies.

Our case emphasizes the importance of thorough, multi-modality cardiovascular imaging evaluation in NF-1. With our patient, the congenital bicuspid nature of the aortic valve was only apparent on pre-operative screening once a critical gradient threshold was reached. Many pathological cardiac lesions are often silent and therefore may be missed on routine clinical examination, even when undertaken by a cardiologist.[9] Objective non-invasive imaging with cardiac ultrasound and/or CMR should be considered for complete evaluation of both myocardial structure and cardiac function.

Isolated intra-cardiac lesions as demonstrated in our case may be either fibroelastomas or neurofibromata—here the genetic history of the patient was the key determinant factor for diagnosis. Where multiple tumours exist, rarer pathologies such as tuberous sclerosis must also be considered—though the clinical history will often point to the likely aetiology. The finding of LGE uptake on CMR is consistent with that expected of an intra-cardiac tumour, and has been described previously.[10]

In our case, we adopted an approach of conservative management. High surgical risk precluded both further assessment with endomyocardial biopsy and surgical intervention. As our patient reported no significant sequalae from their intra-cardiac lesion, surveillance was deemed appropriate. No evidence of chamber obstruction or impairment of the mitral valve apparatus was demonstrated on echocardiography or CMR. The tumour is confined to the papillary muscle, and as such, no invasive effect on the cardiac conducting system nor secondary rhythm disturbance was observed.

Conclusion

Our case highlights the importance of recognizing cardiovascular manifestations of NF-1 and instituting appropriate screening and surveillance strategies. Clinical examination alone may not be adequate to detect silent valve disease and vasculopathy, and targeted non-invasive imaging strategies may be more suited for this purpose.

Lead author biography

Claire MacLeod is a senior medical student at the University of Glasgow. During her university career, she has developed a specialist interest in cardiology through focused undergraduate training in the specialty. In particular, she is interested in different modalities of cardiac imaging and is pursuing further research in this field. She is originally from the Western Isles and is proficient in Gaelic and has an active involvement in global health and policy research to reduce health inequalities.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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