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Severe cardiomyopathy associated with the *VCP* p.R155C and c.177_187del *MYBPC3* gene variants

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ABSTRACT

Inclusion Body Myopathy, Paget's Disease of Bone, with Frontotemporal Dementia is a progressive autosomal dominant disease that affects the ubiquitin-proteasome complex, that is caused by variants in the Valosin Containing Protein (*VCP*) gene. We report the first case of concurrent pathogenic variants in both *MYBPC3* and *VCP* that led to earlier onset of congestive heart failure with features of dilated cardiomyopathy. Cardiomyopathy has previously been associated with *VCP* inclusion body myopathy mostly at an advanced stage of the disease. Due to acute onset of cardiomyopathy in a previous asymptomatic individual, a cardiomyopathy gene panel was obtained which revealed an additional c.177_187del variant of the *MYBPC3* gene. We report a first case of concurrent pathogenic variants in both c.177_187del gene of *MYBPC3* and p.R155C *VCP* that led to earlier onset and a more severe form of the cardiomyopathy.

1. Introduction

Hereditary Inclusion Body Myopathy (h-IBM), Paget's Disease of Bone (PDB), and Frontotemporal Dementia (FTD) also known as IBMPFD, or VCP multisystem proteinopathy (MSP) is an autosomal dominant progressive disease caused by variants in the Valosin Containing Protein (*VCP*) gene located on the chromosomal region 9p13.3–12. VCP associated disease is considered a heterogeneous disorder with variable penetrance (Kimonis et al., 2008); approximately 90% develop myopathy in their 30s–40s, clinically manifesting with shoulder and pelvic girdle muscle weakness and atrophy and eventually progressing to involve other organs (Surampalli et al., 2015). A diagnosis of IBMPFD or *VCP* MSP is typically considered when an individual or a family member carries a pathogenic VCP variant and exhibits one or more features, including progressive myopathy, PDB, FTD, or amyotropic lateral sclerosis (ALS) (Kimonis et al., 2008). Affected individuals histologically demonstrate rimmed vacuoles in muscles and ubiquitin and TDP-43 positive inclusions in muscle and the brain (Weihl et al., 2009; Hubbers et al., 2007).

Currently, greater than 200 patients known to have this disease have been reported, and of those, 92% have proximal limb-girdle weakness, 51% with PDB, typically diagnosed in their 30s, and 30% develop FTD at mean age of 55 years (Al-Obeidi et al., 2018). Cardiomyopathy is a less well recognized feature in this disease, Kimonis et al. (2000) described affected individuals within the first family who suffered from heart failure or cardiomyopathy in the later stages of this disease (Kimonis et al., 2000). Several other case studies of patients diagnosed with IMBPFD have similarly reported cardiac involvement in patients affected by a *VCP* variant (Hubbers et al., 2007). There are currently no known cures for the myopathy or the FTD. Those affected with IBMPFD usually die by their 60s due to heart failure, end stage dementia, or respiratory failure (Kimonis et al., 2008).

2. Clinical report

We report a Caucasian woman who is a known carrier of the common

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VCP gene variant (c.463C>T, p.R155C). She had an autosomal dominant family history of *VCP* disease in her father (Surampalli et al., 2015), and several relatives. Though asymptomatic initially, she and her younger brother underwent genetic testing due to her extensive family history of IBMPFD and ALS.

At age 36 years, she reported having minimal muscle weakness, especially right lower extremities. Neurological exam showed an alert and oriented, developmentally normal woman with intact cranial nerve function without muscle weakness or wasting. Laboratory studies showed normal alkaline phosphatase and creatinine phosphokinase. Muscle strength measurement with dynamometry did not reveal any muscle weakness. Echocardiography revealed normal left ventricular function, ejection fraction at 63%, and showed mild left ventricular hypertrophy with interventricular septal (IVS) thickness at end-diastole of 1.2 cm (normal 0.6–1.1 cm), posterior wall (LVPW) thickness at end-diastole of 1.05 cm (normal 0.6–1.1 cm), and internal diameter (LVID) of 4.5 cm (normal 3.9–5.3 cm) at end-diastole. She underwent extensive evaluation with bone scan, DEXA analysis, and pulmonary function tests, all of which were normal for her age group. After extensive workup, no treatments were recommended at the time.

At the age of 43 years, she had a sudden onset of chest tightness, shortness of breath, and persistent cough. CT angiogram of her thorax did not show pulmonary embolism, which was anticipated as the explanation for her sudden onset of symptoms. A chest x-ray showed a paralyzed right hemidiaphragm and evidence of pulmonary edema but no effusion. She then underwent an echocardiogram, which showed a left ventricular ejection fraction of 15% with global hypokinesis, noncompressible inferior vena cava, moderately enlarged bilateral atrium, moderate mitral regurgitation and mild tricuspid regurgitation. At end-diastole, left ventricle interventricular septal thickness was 1.1 cm, posterior wall thickness was 1.1 cm, and internal diameter was 5.6 cm, and at end-systole, LVID was 5 cm (normal 2–4 cm). Overall, the second echocardiogram suggested a dilated cardiomyopathy (DCM) rather than hypertrophic cardiomyopathy (HCM). Global right ventricular systolic function was mildly reduced with pulmonary artery systolic pressure severely elevated at 51 mmHg. Additionally, on cardiac MRI, the 4-chamber view of the heart showed dilatation of the left and right ventricles with mitral and tricuspid regurgitation jets (Fig. 1). The left ventricular ejection fraction on cardiac MRI was 20%, and was mildly dilated with left ventricular end-diastolic volume of 300 ml (end diastolic volume index 123 ml/m^2), end systolic volume of 241 ml, and overall stroke volume of 59 ml. The right ventricle was mildly dilated in size (end diastolic volume index 107 ml/m^2) with moderate reduced global systolic function, ejection fraction of 26%). There was no evidence of LV hypertrophy, wall motion abnormalities, or late gadolinium enhancement. She underwent diuresis and was placed on goal directed medical therapy. She was discharged with a wearable defibrillator for episodes of non-sustained ventricular tachycardia.

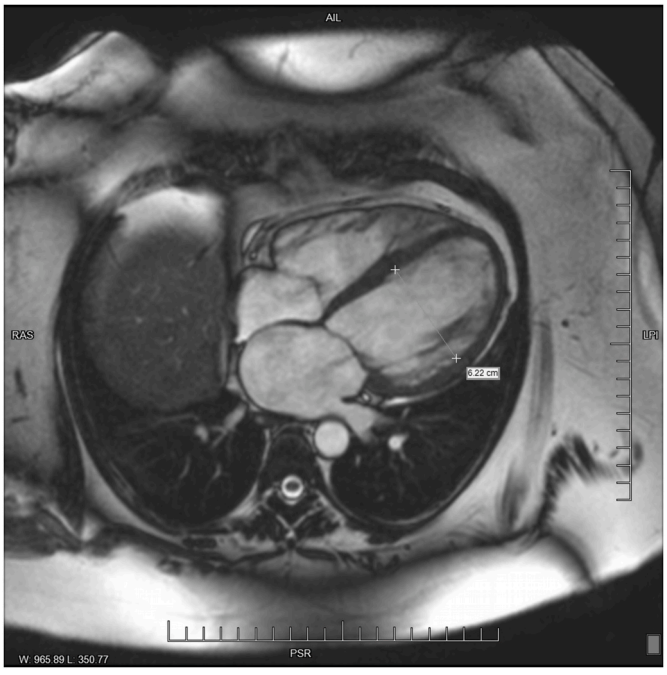

Fig. 1. Cardiac MRI. 4-chamber view of the heart shows dilatation of the left and right ventricles with mitral and tricuspid regurgitation jets.

In view of the early onset of DCM, a NGS panel was obtained revealing a known heterozygous c.177_187del (p.Glu60fs*49) pathogenic variant in the cardiac isoform of the myosin binding protein C gene (*MYBPC3*) (NM_000256.3), which is a major component of the cardiac sarcomere (Carrier et al., 2015). The resulting amino acid change p.Glu60Alafs*49, causes a premature stop codon; this particular variant is classified as pathogenic, and has been previously associated with the diagnoses of HCM and DCM (Carrier et al., 2015). Subsequently with management of her cardiac failure, at follow-up, the patient's cardiac function improved to 63% without any evidence of diastolic impairment.

On review of the family history (Fig. 2), there was a significant variability in the manifestation of the disease with affected individuals manifesting muscle weakness. The family is of German descent. Muscle biopsies performed in affected individuals revealed features of inclusion body myopathy with rimmed vacuoles. Electromyography manifested both myopathic and irritative changes, and two individuals also had myotonic discharges. Paget disease identified in members had a typical distribution in the spine, pelvis and skull. Frontotemporal dementia was evident at a mean age of 55 years, with early demise at an approximate age of 60 years. Her father, paternal uncle and brother were previously evaluated as part of a clinical study at UC Irvine. Her father was first diagnosed with inclusion body myopathy at the age of 46 years. Echocardiogram of her father at age 54 years revealed mild global hypokinesia, moderate concentric left ventricular hypertrophy, ejection fraction of 56% and a normal left ventricular systolic function. A limited autopsy was performed at age 58 years, which did not include the heart and revealed unremarkable findings of the brain. The findings of her father and his unaffected twin brother were previously reported (Surampalli et al., 2015). Her brother, age 46 years, a known VCP carrier, initially did not pursue genetic testing for the *MYBPC3* variant. He was subsequently diagnosed with DCM, with an ejection fraction of 15% with global hypokinesis, normal wall thickness (at end-diastole, LVPW 0.92 cm and IVS 0.97 cm), mild to moderately dilated left ventricle (LVID at end-diastole 6.14 cm), and moderate to severely enlarged right ventricle (diastolic dimension 4.83 cm). The cardiac catheterization demonstrated only mild coronary artery disease. Following his diagnosis of DCM, the proband's brother completed genetic testing, which confirmed that he was positive for the c.177_187del *MYBPC3* variant. Other relatives have subsequently have expressed an interest in pursuing genetic testing.

3. Discussion

While cardiac involvement may not a major feature of VCP MSP, it can be seen in advanced stages of disease as previously reviewed (Korb et al., 2022). Kimonis et al. (2000) reported the first family with limb-girdle muscular dystrophy and PDB among whom three individuals were found to have cardiomyopathy (Kimonis et al., 2000). Four members (36%) of a family presented with echocardiographic features of dilated cardiomyopathy (Miller et al., 2009) in the later stages of the disease. All affected members were treated with angiotensin-converting enzyme inhibitors, one of whom had symptomatic improvement. Another individual diagnosed with *VCP* MSP was found to have dilated cardiomyopathy post-mortem, with multiple cardiomyocytes displaying ubiquitin-positive inclusion bodies (Hubbers et al., 2007). Several

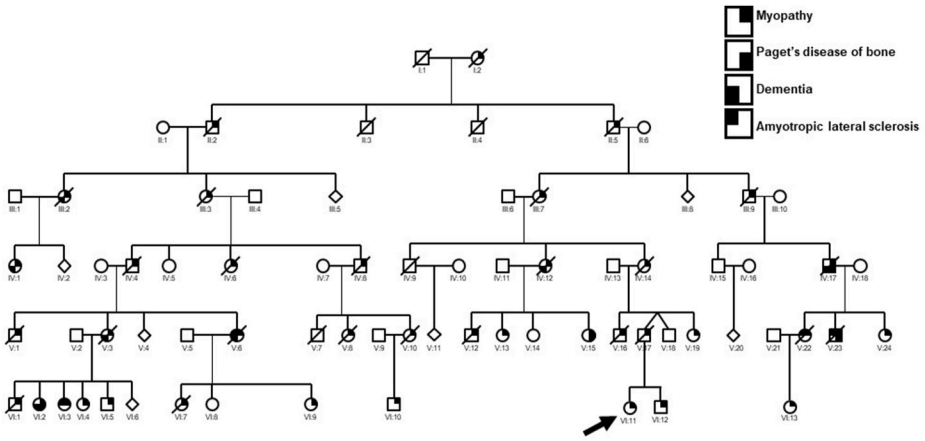

Fig. 2. Pedigree of the 6- generation family. See figure legend for details. The proband for the cardiomyopathy in this family is indicated by an arrow.

members of an affected family were reported to have cardiac failure, and one individual had left ventricular hypertrophy on echocardiography (Watts et al., 2007).

Although initially considered of uncertain significance, our patient's previous echocardiogram obtained 7-years prior to the onset of severe cardiomyopathy showed evidence of mild concentric left ventricular hypertrophy. While cardiomyopathy in patients is not well-understood, there is very little information regarding the symptoms and prognosis of *VCP* MSP patients who begin to show early signs of cardiomyopathy and there is little or no guidance on surveillance strategies for cardiomyopathy. Their significances are often not recognized until advanced stages of cardiomyopathy, marked by reduction in left ventricular systolic function and systemic decompensation. This case study is unique as the patient was found to have a known pathogenic variant in *MYBPC3* associated with cardiomyopathy, in addition to the familial R155C *VCP* variant, this report emphasizes the importance of screening for cardiomyopathy genes, rather than assuming that the *VCP* variant is the sole cause. Though not applicable in every variant, MYBPC3 related disease presents with a variable phenotype, but is relatively later-onset and has more mild disease progression when compared to variants in other genes associated with cardiomyopathy such as, those with MYH7 variants.

There are over 350 identified pathogenic variants in *MYBPC3* among patients with autosomal-dominant inherited HCM and DCM. The gene spans 34 coding exons, and codes for cMyBP-C, a multi-modular structural protein component of the sarcomere (Carrier et al., 2015). Studies on MyBPC-3 suggests that it is involved in the stabilization of thick filaments in the sarcomere, but not essential for its formation (Schlossarek SM and Carrier, 2011). *MYBPC3* knock-out mice remain viable, suggesting that MyBPC-3 may not be required for sarcomere formation (Winegrad, 2004). The majority of known *MYBPC3* variants result in a truncated protein. Studies performed on human myocardial samples show that truncated forms of cMyBP-C, resulting from truncating variants in *MYBPC3*, result in reduced expression on Western-blot analysis, but detectable as mutant RNA transcripts (Schlossarek SM and Carrier, 2011) suggesting that the mechanism is due to haplo-insufficiency (Carrier et al., 2015). Indeed, studies have identified nonsense-mediated mRNA decay, the ubiquitin-proteasome system (UPS), and the autophagy-lysosomal pathway as mechanisms by which myocytes regulate the protein expression of truncated cMyBP-C (Schlossarek SM and Carrier, 2011; Sarikas AC et al., 2005). Depending on the type and location of the variants in *MYBPC3*, some resulting protein structures have been shown to impair the UPS system, and lead to aggregates of ubiquinated protein accumulating in the associated cells. In fact, the UPS system preferentially degrades truncated cMyBP-C proteins, impairing the degradation of other ubiquinated substrates; leading to aggregates of ubiquinated-substrates accumulating in nearby cells (Sarikas AC et al., 2005). However, their studies showed that mutant protein structures of cMyBP-C can impair the function of the UPS system (Schlossarek SM and Carrier, 2011). Deposition of ubiquitylated proteins is a characteristic of many other disorders including Alzheimer's disease, Parkinson's disease, and amyotropic lateral sclerosis (Kimonis et al., 2008).

It is possible that the patient's DCM was aggravated by her *VCP* variant. The *VCP* gene encodes for an essential component of the ubiquitin proteasome pathway, and variants lead to impairment of the CD48/p97 chaperone, which is necessary for the degradation of ubiquinated substrates (Kimonis et al., 2008). Individuals diagnosed with *VCP* MSP have ubiquitin-positive protein aggregates that can be found accumulating primarily in skeletal muscle, and in some cases affecting cardiomyocytes (Hubbers et al., 2007). Mutated *MYBPC3* gene product also results in ubiquinated substrates accumulating in cells; either through competitive inhibition, in which mutated cMyBP-c is preferentially degraded, resulting in accumulations of other ubiquinated substrates, or by impairment of the UPS system itself by blocking proteasomal degradation (Sarikas AC et al., 2005). In fact, impairment of the UPS system may be caused by the accumulation of protein aggregates, as was previously shown. If this is the case with mutated *MYBPC3* gene products, this could lead to a vicious cycle in which aggregates of either mutated cMyBP-C or competitively inhibited protein substrates lead to the inhibition of the UPS system—which may have already been impaired due to the mutated *VCP*.

As there are many pathogenic variants identified in *MYBPC3*, the phenotypes of each may vary. *MYBPC3* variants are found in various forms of cardiomyopathies including DCM, HCM and noncompaction cardiomyopathy. A study including 680 subjects examined clinical phenotype and cardiovascular outcomes in patients with HCM, and in 141 founder mutation probands, 95% had HCM; 3% had noncompaction; and 2% had dilated cardiomyopathy (Van Velzen et al., 2017). While more significantly associated with HCM, *MYBPC3* variants have been reported in associated with DCM are associated with higher cardiovascular mortality, heart failure related deaths, and sudden cardiac death than genotype negative HCM (Hershberger et al., 2010; Van Velzen et al., 2017). Based on previous studies performed on truncating variants in *MYBPC3*, evidence suggests this is typically late onset with a mild disease progression (Carrier et al., 2015). Certain variants in *MYBPC3* can present with more aggressive phenotypic expression, resulting in heart failure or advanced cardiomyopathy. Patients who are heterozygotes in relevant cardiomyopathy genes in addition to *MYBPC3*, can be predicted to develop more severe cardiomyopathy (Carrier et al., 2015). The patient's specific *MYBPC3* pathogenic variant is rare, additionally this is the first report of the phenotypic expression for the c.177_187del pathogenic variant in *MYBPC3* in conjunction with a *VCP* variant. Prior knowledge of the second variant in *MYBPC3* would have been critical in early intervention, management and potentially

prevention of associated cardiomyopathy. Future research focusing on genetic testing and integrating this data for diagnosis, treatment, risk-stratification and prognosis may offer improved long-term morbidity and mortality in patients.

Authors statement

Nicole Choy: Writing - Original draft preparation, Reviewing and Editing, Stephani Wang: Methodology, Writing - Reviewing and Editing, Pablo Abbona: Methodology, Reviewing and Editing, Dale Leffler: Reviewing and Editing, Virginia Kimonis: Conceptualization, Methodology, Data curation, Resources, Writing - Review & Editing, Validation, and Supervision.

Declaration of competing interest

Authors declare that there is no conflict of interest.

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