CASE REPORT

Heritable retinoblastoma and accelerated aortic valve disease

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SUMMARY

Heritable retinoblastoma is associated with a germline mutation in the tumour suppressor gene *RBI*. The Rb protein (pRb) arises from the *RB1* gene, which was the first demonstrated cancer susceptibility gene in humans.[1] Second primary malignancies are recognised complications of retinoblastoma. Furthermore, pRb is implicated in valve remodelling in calcific aortic valve disease.[2 3] We report a family with hereditary retinoblastoma and associated secondary primary malignancies. There are two interesting aspects to this family. The first is the concept of 'cancer susceptibility genes'; the RBI gene being the first reported in humans. A further feature of note is that two family members also have bicuspid aortic valves. We discuss a potential association between the gene defect responsible for retinoblastoma (with its associated propensity for further malignancies) and accelerated deterioration of the bicuspid aortic valve in the proband carrying this gene defect.

BACKGROUND

Heritable retinoblastomas are, in themselves, unusual clinical entities and the association with subsequent primary malignancies is of note. The potential association of an inherited gene defect contributing to a failure of a cardiac valve is a more novel concept that we felt worthy of discussion.

CASE PRESENTATION

A 32-year-old man underwent curative radiotherapy for familial bilateral retinoblastoma within the first year of life. His mother, two sisters and niece were also diagnosed with bilateral retinoblastoma (figure 1).

At age 16 he developed acinic cell carcinoma of the left parotid gland, treated by surgical excision and radiotherapy. At age 29, a chest radiograph revealed an increased cardiothoracic ratio.

On examination he was tachycardic, with an elevated jugular venous pressure, laterally displaced apex, a systolic and diastolic murmur in the aortic area and gallop rhythm.

The impression was one of left ventricular failure secondary to mixed aortic valve disease.

INVESTIGATIONS

Echocardiography demonstrated a bicuspid aortic valve (figure 2) with severe regurgitation. The left ventricle was markedly dilated.

Molecular genetic studies and DNA sequencing have revealed that our patient and all the affected members of his family have an oncogenic point mutation involving exon 8 (*RB1*g.59,683C>T c.751C>T (p.R251*)) giving rise to a nonsense mutation.[4]

TREATMENT

The patient underwent a successful bioprosthetic (porcine) aortic valve replacement, without intervention to a mildly dilated aortic root. The patient had a stormy postoperative course, requiring the use of a Levitronix left ventricular assist device for 8 weeks following surgery. After a period of rehabilitation following multiorgan dysfunction, caecal perforation and ventricular rhythm disturbances he underwent implantation of a biventricular automatic implantable cardioverter defibrillator. Criteria for implantation were satisfied by a still significantly impaired ventricle, prolonged QRS duration of 144 ms and florid ventricular arrhythmia.

OUTCOME AND FOLLOW-UP

The patient is now fully ambulatory and undergoes regular annual surveillance echocardiograms to assess his prosthetic aortic valve and left ventricular dimensions. In addition, potential progression of his mild aortic root dilation needs to be considered at these annual reviews.

DISCUSSION

The novel form of the protein pRb has a fundamental role in cell cycle control. Deregulation of

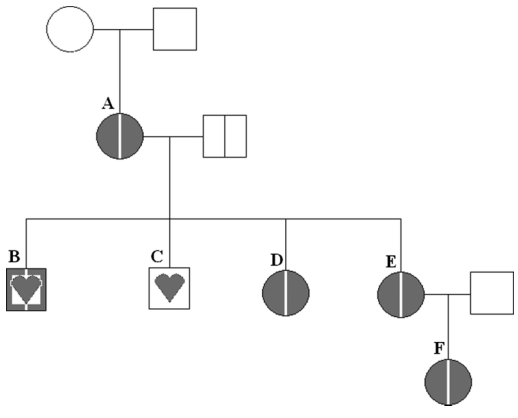

Figure 1 All affected members of this family have bilateral ophthalmic involvement. Subject 'A' underwent enucleation of one eye. Subject 'B', the proband, underwent radiotherapy and has a bicuspid aortic valve. Subject 'C' has a bicuspid aortic valve and no eye involvement by retinoblastoma. Subject 'D' received radiotherapy and cobalt plaque therapy. Subject 'E' received chemotherapy and cryotherapy. Subject 'F' has undergone cryotherapy.

To cite: Abeyratne LR, Kingston JE, Onadim Z, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-009233

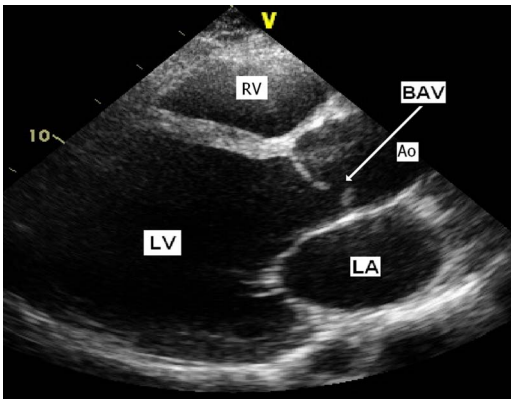

Figure 2 Transthoracic echocardiogram of the proband (subject 'B') showing a severely dilated left ventricle (dimensions of 9.9 cm in diastole and 8.9 cm in systole, normal range 4.2–5.9 cm) and BAV (white arrow) with a typical off-midline closure of leaflets. Left ventricular ejection fraction 14% (normal >55%). Ao, aorta; BAV, bicuspid aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle.

this protein and the pathways it interacts with is documented in multiple human cancers. This mutation is one of the 11 recurrent CGA>TGA nonsense *RB1* mutations and comprises ~2.4% of mutations in the LOVD RB1 locus. An increased risk of secondary primary tumours is observed among carriers of nonsense *RB1* mutations, with risk higher in patients with bilateral retinoblastoma and an inherited germline mutation compared to a de novo germline mutation.

The mechanism lies in the fundamental role of pRb in cell cycle arrest in the presence of DNA damage. Aberrant pRb allows cells to commit to further replication, despite damage caused by radiation exposure, thereby promoting oncogenesis.

Two subjects in this family (figure 1B,C) have bicuspid aortic valves (BAVs). A 2002 study reported that >33% of patients with a BAV will develop serious complications.[5] Such patients can present in early adulthood with accelerated calcific aortic valve disease (CAVD), as we describe. Cell proliferation is critical in valve remodelling, contributing to CAVD and pRb is known to inhibit this process.[3] Furthermore, mutations in the NOTCH1 pathway influence development of BAVs and CAVD,[6] and pRb is fundamental to this antiproliferative pathway.[2]

It seems likely that abnormal pRb may play a role in the pathogenesis of CAVD in the context of familial BAVs.

The presence of a mutation in the *RB1* gene within families predisposes to heritable retinoblastoma and to further secondary primary malignancies. Moreover, the fundamental role of pRb in the control of the cell cycle means that other cell processes, including 'a response to tissue injury', may also be aberrant, as demonstrated by our patient with accelerated BAV disease.

Learning points

- Patients with inherited retinoblastoma are susceptible to further primary malignancies.
- The *RB1* gene was the first demonstrated cancer susceptibility gene in humans.
- Mutations of tumour suppressor genes may play a role in tissue repair mechanics.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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