Characterisation of Bardet Biedl Syndrome by post-mortem microfocus computed tomography (micro-CT)

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Letter:

Confirmation of antenatally detected fetal anomalies is vital in informing future management, particularly following termination of pregnancy. Despite significant imaging advances, antenatal ultrasonography only identifies 68% of autopsy confirmed findings[1]. As parental consent for invasive autopsy is declining, important phenotypic information to help guide genetic testing and counselling is being lost.

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Post-mortem imaging using microfocus computed tomography (micro-CT) provides a feasible alternative or complementary tool to autopsy in small early gestation fetuses[2]. It provides high-resolution, three-dimensional digital images which rival light microscopy to enable accurate diagnosis with high sensitivity[3]. In this letter, we describe how micro-CT changed clinical management by confirming an antenatally detected cardiac anomaly and suggestion of a complex multisystem syndrome with subsequent genetic confirmation.

A 33 year old primigravida attended for routine antenatal sonography at 12+5 weeks gestation. The singleton pregnancy had increased nuchal translucency of 8 mm and blood flow only across the right atrioventricular valve, suggestive of tricuspid atresia. The patient underwent chorionic villous sampling (CVS) for fetal array comparative genomic hybridization (CGH) testing, with a resolution of 3MB, returning a normal result [arr(1-22, X)x2]. The parents were counselled that the imaging features could be part of a syndromic genetic condition such as Smith-Lemli-Opitz or other ciliopathies, and opted to terminate the pregnancy by medical induction at 15+6 weeks gestation. The terminated fetus weighed 69g, with crown rump length of 12cm and crown heel length of 17.5cm.

Due to small fetal size and potential difficulty of cardiac dissection, whole-body micro-CT was performed (XTH225 micro-CT scanner; 70µm resolution; Nikon Metrology, Tring, UK) following written parental consent. Images were reconstructed (CTPro3D software; Nikon Metrology, UK) and post-processed (Volume Graphics GmbH, Heidelberg, Germany).

Image analysis revealed an atrioventricular septal defect (AVSD) of 0.2cm diameter, with hypoplastic left heart syndrome (including mitral valve stenosis, left ventricular hypoplasia, aortic atresia and ascending and aortic arch hypoplasia. The ascending aortic arch measured only 0.05cm in diameter. **(Figure 1).** There were bilateral multiple renal cortical cysts **(Figure 2)** and bilateral upper and lower limb post-axial polydactyly **(Figure 3)**, which were not antenatally identified.

Following imaging results, consent was obtained for examination of the heart and kidneys at autopsy with further genetic testing. Autopsy corroborated imaging findings, with renal histology showing extensive cystic dilatation of the renal tubules. Two compound heterozygous mutations in BBS7 gene were found (NM_176824.2:c.187G> A/p.(Gly63Arg)mat and NM_176824.2:c.973G>T/p.(Glu325Ter)pat) by Whole Genome Sequencing, using a trio analysis methodology, consistent with Bardet Biedl Syndrome[4]. Given a recurrence risk for future pregnancies at 25% in this autosomal recessive syndrome[5], the parents received counselling regarding future pre-implantation or antenatal genetic testing.

In conclusion, micro-CT is a non-invasive highly detailed method for assessing early gestation fetal anatomy, and provides an alternative or adjunctive tool to the standard autopsy technique. In this case, micro-CT imaging was able to better characterise the antenatal cardiac anomalies and provide

additional useful information regarding renal and musculoskeletal anomalies, leading to change in future pregnancy management and genetic counselling.

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Conflicts of Interest:

The authors have no conflicts of interest to declare.

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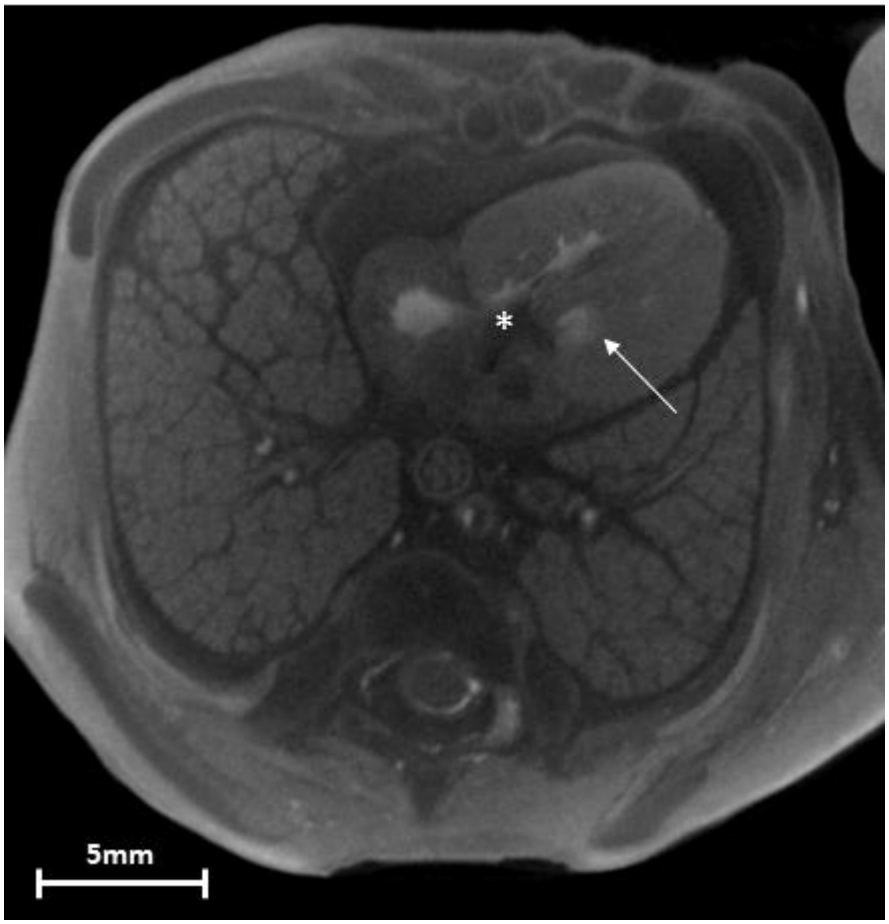
Figure Legends

Figure 1: MicroCT of cardiac anomalies obtained at a resolution of 70μm a) axial image through four chambers of the heart demonstrate a large atrioventricular septal defect (*) measuring 0.2cm, and small volume left ventricle (white arrow) b) Sagittal post-processed maximum intensity projections of 5mm slab thickness through the aortic arch demonstrate a hypoplastic aorta (white arrow) above the level of the patent ductus arteriosus, which later becomes normal in calibre. The ascending aorta was 0.05cm in diameter.



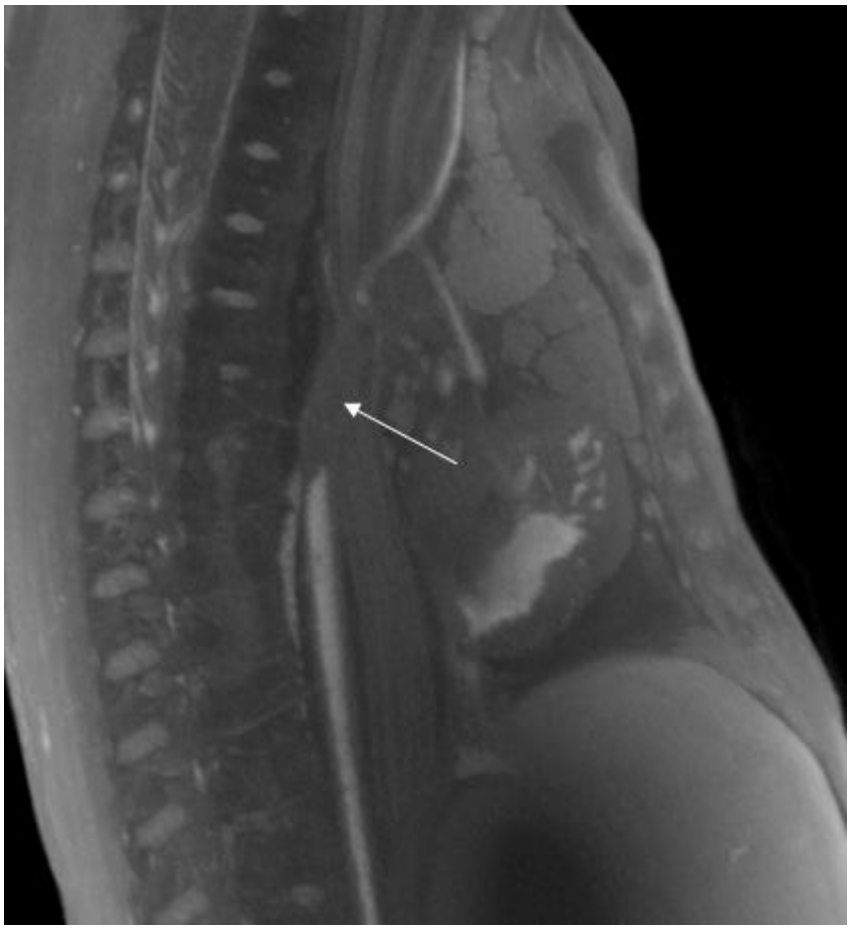
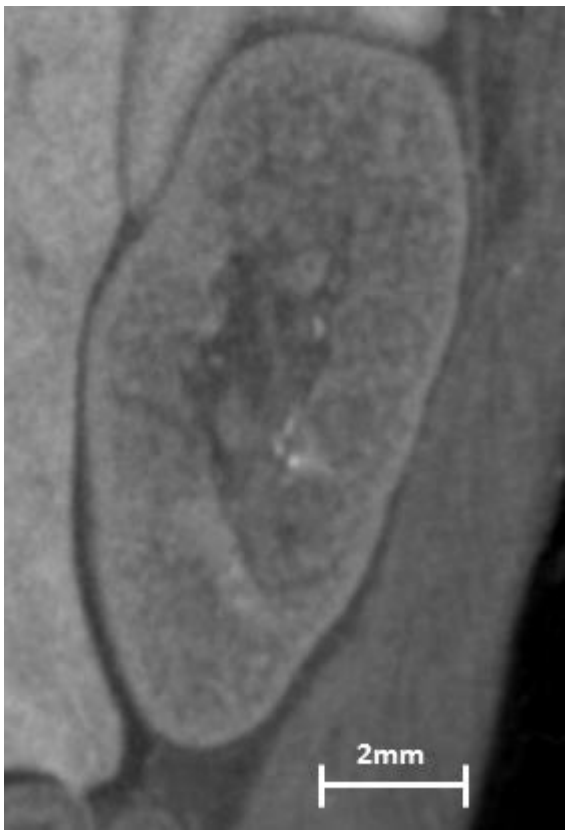
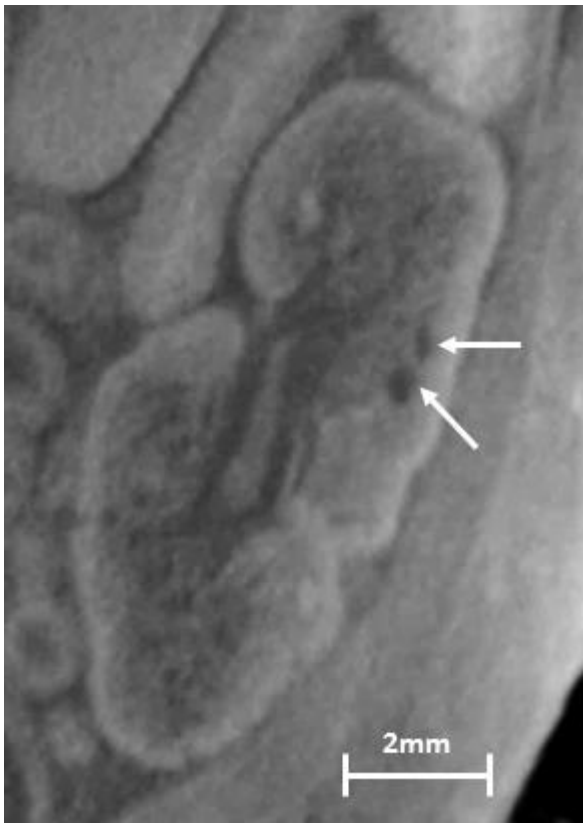


Figure 2: Sagittal micro-CT images of the right kidney at 70µm resolution, with histopathological correlation. a) Normal expected renal appearances in a 15 week gestation fetus (not reported in this study) b) Multiple cysts within the right renal cortex of this case study (largest two cysts are shown with white arrows) c) Low power photomicrograph of the right kidney stained with haematoxylin and eosin at a magnification of 20 x original size. The nephrogenic zone is intact but the deeper cortical and medullary tissue shows marked cystic dilatation of tubules to many times their normal size (black arrows) and with overall reduction in their number.





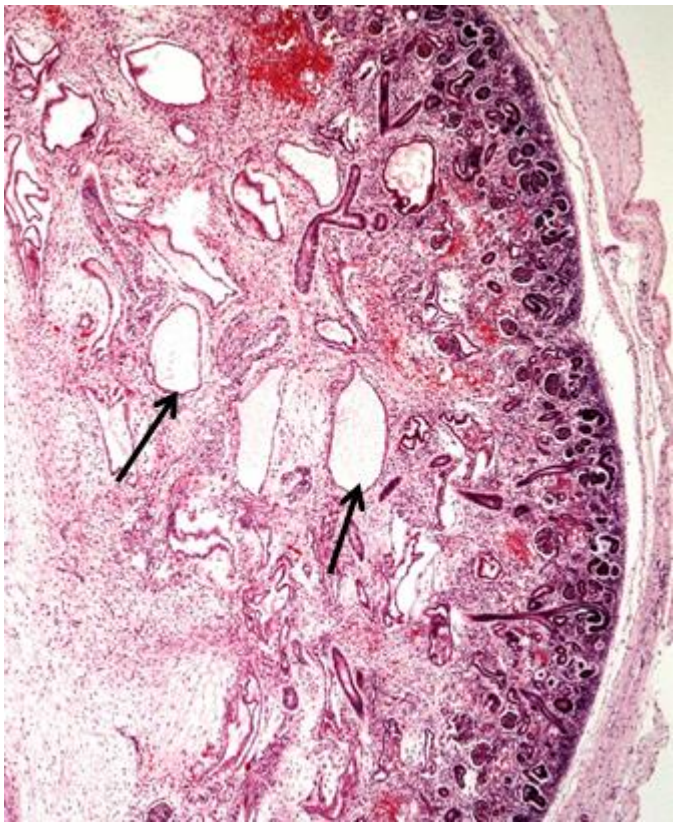


Figure 3: Volume rendered micro-CT examination of both hands with photographic correlation seen at external examination showing bilateral post-axial polydactyly