

## In-utero ultrasonography detection of fetal retinoblastoma and neonatal selective ophthalmic artery chemotherapy

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We report a case of non-familial, sporadic fetal retinoblastoma (RB) that was accidentally detected at 39 weeks of gestation on pre-natal ultrasonography in left eye (OS). Post-natal examination revealed Group A and, Group D RB in right eye (OD) and OS, respectively. At 35 days, selective ophthalmic artery intra-arterial chemotherapy (IAC) was performed in OS and laser for OD. Pre-natal ultrasound and its application in RB are limited to those cases with a strong genetic predisposition. Our case was accidentally detected at late gestation with no familial or genetic predisposition. In addition, this was the youngest reported case that received IAC on literature review.

**Key words:** Fetal retinoblastoma, intra-arterial chemotherapy neonatal retinoblastoma, pre-natal ultrasonography, retinoblastoma

Retinoblastoma (RB) commonly presenting as white reflex and strabismus is often detected in late infancy. Being a hereditary cancer syndrome with associated RB1 gene mutation, prenatal diagnosis of RB is done in the presence of strong familial predisposition. Non-hereditary sporadic RB comprises of 60%. Fetal ultrasound as a routine is an accurate tool in detecting fetal anomalies.<sup>[1]</sup> Indications of ocular screening as a part of fetal ultrasound is yet to be determined, often limited as pre-natal screening in high-risk scenarios.<sup>[2]</sup> We report a case of non-familial, sporadic RB accidentally detected with fetal ultrasonography and successfully received intra-arterial chemotherapy at 35 days of birth.

### Case Report

A 28-year-old G1P1A0, presented at 39 weeks of gestation for routine follow up. Pre-natal ultrasonography showed singleton

fetus with normal growth parameters for the gestational age. It also detected a hyper-echoic intraocular lesion in the left eye (OS) measuring 15 × 15 × 12 mm in size that was suspected to be retinoblastoma (RB). Right eye (OD) was found to be normal [Fig. 1a]. After an uncomplicated caesarean section next day, a healthy male baby weighing 3300 grams was delivered. Immediately after birth an underlying intra-ocular tumor was noticed in OS [Fig. 1b]. Subsequently was referred to us for further evaluation and management at 4 weeks post-natal.

Detailed examination under anesthesia was performed. Intraocular pressure was measured normal. Horizontal corneal diameter was 10 mm both eyes (OU) with normal anterior segment. Fundus evaluation revealed bilateral RB. Right eye had normal optic disc and fovea with multiple small equatorial tumors measuring 1.5 × 1.5 × 1 mm and 1 × 1 × 1 mm [Fig. 2a]. A large exophytic solitary white mass with surface vascularization and feeder vessels occupying the macula and, overhanging the optic disc, measured 15 × 12 × 11.5 mm in OS with exudative retinal detachment and diffuse sub-retinal seeds [Fig. 2b]. Contrast enhanced Magnetic Resonance Imaging (MRI) of orbit and brain confirmed intraocular mass in OS with normal optic nerve and intact ocular coats and, brain was normal. Further it was classified as Group A in OD and Group D in OS; TNMH classification (AJCC 8<sup>th</sup> edition) was cT1a and cT2b in OD and OS respectively with M0, N0, HX status.

After discussion on various management options with the parent, OD received focal laser and IAC was performed in OS at 35 days post-natal with melphalan (3.5 mg) and alternate carboplatin (20 mg) and topotecan (0.5 mg) in the first and second session, respectively. The tumor regressed (Type 1) after 1<sup>st</sup> session with complete resolution of exudative retinal detachment after the 2<sup>nd</sup> session [Fig. 2c]. Following 2 months of focal treatment, OD developed a new tumor that received laser [Fig. 2d]. At 14 months there was no recurrence OU.

### Discussion

Retinoblastoma although arising from the embryonal cells, remains undetected until birth to present as white-reflex and strabismus. Prenatal diagnosis of RB is usually done in high-risk scenarios as in the presence of strong familial predisposition, prenatal positive RB1 mutation and, mutation detected in the parent or sibling.<sup>[1]</sup> These comprises of 40% cases reported worldwide and, are often bilateral with multiple tumors. Rest of the 60% is non-familial, nevertheless 20% of this can have germline mutation and present early.<sup>[2]</sup> These often go unnoticed, to present as advanced tumors in neonates that pose risk to life and eye salvage. Neonatal RB was reported as 7–10%.<sup>[3,4]</sup>

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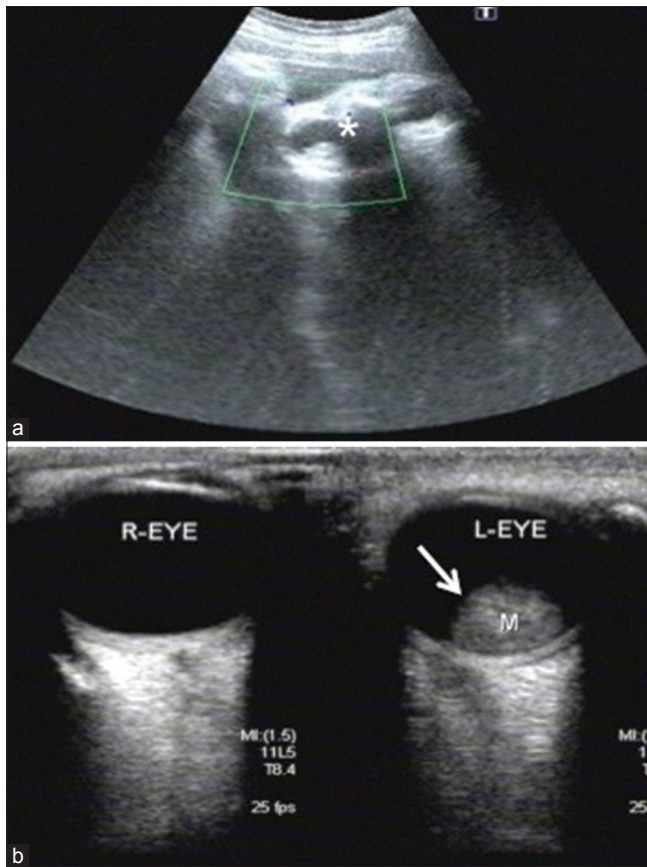
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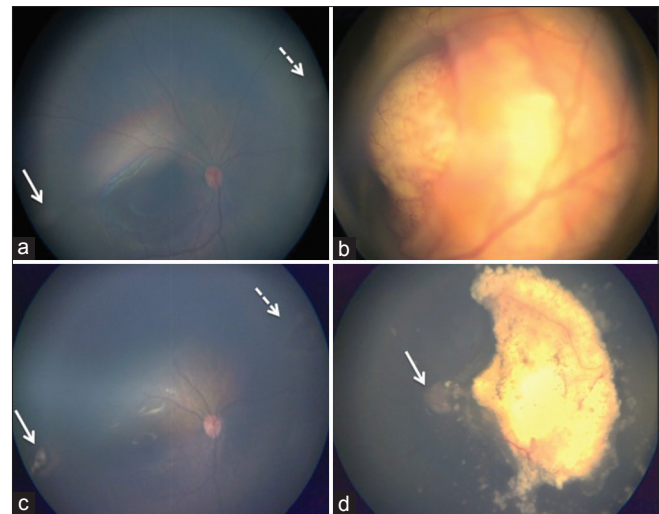
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**Figure 1:** (a) Obstetric ultrasound scan at 39 weeks gestation; coronal image of fetal orbit shows a hyperechoic intraocular lesion on the left side located in the retina measuring 15 × 15 × 12 mm. (white asterisk) No lesions are detected in the right orbit. (b) Ultrasound B-scan of right and left eye at birth. There is a solitary dome-shaped elevated mass in the posterior pole with high internal reflectivity and corresponds to the finding in fetal ultrasound intrauterine. (white arrow) Vitreous cavity is normal with dot like echogenicity adjacent to the intraocular mass

Fetal ultrasound is an accurate tool for evaluating intra-uterine formative period and, detecting fetal facial anomalies and congenital malformations. Ocular abnormalities detected during pre-natal ultrasound are congenital cataract, teratoma, and RB. Maat-Kievit *et al.* reported the first case of fetal RB presenting as large facial tumor at 21 weeks of gestation with termination of pregnancy.<sup>[5]</sup> Salim *et al.* reported a case presenting as orbital mass at 38 weeks of gestation.<sup>[6]</sup> Indications of ocular screening as a part of fetal ultrasound is yet to be determined. Lehman detected RB in a preterm neonate at 36 weeks that went undetected in pre-natal ultrasonography.<sup>[7]</sup> The ability to detect tumors is dependent on size, smaller tumors may often go undetected as in OD of our patient. However, RB is reported to have a doubling time of 15 days.<sup>[8]</sup> Therefore, in a fetus it grows to attain a large size where eye salvage is hindered by the time it is clinically diagnosed.

Post-natal eye screening of neonates is limited to premature born babies and there are no universal guidelines. In a pilot study from India, 1021 term neonates with birth weight more than 2000 grams (gms) within 3 days from birth were screened and found one RB (0.10%).<sup>[8]</sup> Similarly, Li *et al.* screened 3573



**Figure 2:** Color fundus photograph of both eyes pre-treatment and post-treatment. Pre-treatment a and b, (a) RB Group A - Shows multiple small retinal lesions in the inferotemporal (white arrow) and superonasal equator (white dotted arrow). Optic disc and fovea is within normal limits. (b) RB Group D- Large solitary whitish retinal mass overhanging the optic disc located at the macula. There is total retinal detachment with diffuse subretinal seeds. Post-treatment c and d, (c) shows complete regression of inferotemporal (white arrow) and superonasal (white dotted arrow) tumors with focal laser therapy. (d) following 2 sessions of selective ophthalmic artery intra-arterial chemotherapy, tumor was completely regressed (Type-1). Subretinal fluid has completely resolved and the optic disc is visualized. (white arrow)

healthy full-term Chinese neonates weighing atleast 2500 gms within a week after birth. Of this 2 (0.06%) were suspected to have RB or astrocytic hamartoma.<sup>[9]</sup> Neonatal RB screening is again limited to those that have a family history. But, sporadic variant is not rare, which can present early and often goes undetected unless they enlarge to a size that is visible as white reflex. Kivela *et al.* reported 4 out of 11 (36%) neonates with sporadic RB.<sup>[4]</sup> Since retinal development is known to have a prominent centro-peripheral gradient, it is often foveal in location progressing to involve the entire entire macula. Late detection challenges vision salvage. Although majority is unilateral to begin with, it is not uncommon to find new tumors in contralateral eye subsequently. The disease severity can also be asymmetrical as in our case.

Management of neonatal RB is challenging in terms of treatment and parental psychological stress. They often have tumor relapses, mandating frequent, and long-term follow-up. It is best managed in retinoblastoma centers under a multidisciplinary team considering the complexities. Systemic intravenous chemotherapy (IVC) in bilateral RB is effective and can possibly be protective in the development of pinealoblastoma, although controversial. Intra-arterial chemotherapy is advantageous with negligible systemic side effects, but often preferred in children >6 months of age. The major concerns in neonates include the catheterization of small arterial branches that can cause difficulty in catheterization. Magan *et al.* reported a 2-month-old infant who underwent IAC.<sup>[11]</sup> We successfully performed selective ophthalmic artery chemotherapy at 35 days, the youngest reported, with excellent outcome.

## Conclusion

Pre-natal ultrasound was able to detect a large fetal RB in our case that was non-familial and sporadic. This emphasizes that including facial and ocular examination during fetal ultrasound may help in early detection of fetal RB, a curable eye cancer. A dilated pediatric eye screening during routine neonate and infant examinations may also aid in early detection. We also found that IAC at 4<sup>th</sup> weeks of age was safe and effective with excellent outcome. However, it requires well-trained multidisciplinary team to avoid unforeseen complications.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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