·Opinion·

Intraocular fine needle aspiration cytology as a diagnostic modality for retinoblastoma

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Received: 2015-03-07 Accepted: 2015-07-09

DOI:10.18240/ijo.2016.08.23

Chawla B, Tomar A, Sen S, Bajaj MS, Kashyap S. Intraocular fine needle aspiration cytology as a diagnostic modality for retinoblastoma. *Int J Ophthalmol* 2016;9(8):1233-1235

INTRODUCTION

The diagnosis of retinoblastoma (RB) is usually made by clinical examination and imaging modalities such as B-scan ultrasonography of the eye, CT scan and MRI of the orbits. The role of fine needle aspiration cytology (FNAC) as a diagnostic modality for RB has been controversial, mainly due to concerns of tumor dissemination and extra-ocular spread [1-2]. Although the majority of RB cases can be diagnosed without the need for any invasive procedure, in rare instances, differentiation of RB from benign simulating conditions can be particularly challenging. This study was undertaken to determine the utility and safety of intraocular FNAC as a supportive diagnostic tool in selected cases of RB wherein clinical features and imaging were found to be inconclusive.

CASE SUMMARY

This was a retrospective case series of 4 children who underwent an intraocular FNAC procedure to establish the diagnosis of RB. The study followed the principles outlined in the Declaration of Helsinki and an informed consent was taken. These cases (3 boys, 1 girl) presented to our tertiary referral center between 2010 and 2013 with a history of leucocoria in the affected eye. The mean age at diagnosis was 4.2y (range, 3-6y). On ophthalmological examination, visual acuity was absence of light perception in the affected eye and 20/20 in the fellow eye. Fundus details could not visualized due to advanced disease. The fellow eye was within normal limits. Imaging features on B-scan ultrasonography, CT scan and MRI of the orbits were inconclusive, and RB could not be ruled out (Figure 1). Possible differentials were Coats' disease, persistent hyperplastic primary vitreous (PHPV), endogenous endophthalmitis & RB. To establish the diagnosis, intraocular FNAC was planned after taking an informed consent. The procedure was performed under general anesthesia. Under microscopic view, a site at a distance of 3-3.5 mm from the limbus was marked. A 26-G needle mounted on a 5 mL syringe was introduced through the conjunctiva and the sclera into the intraocular mass. Careful controlled aspiration was done and triple freeze-thaw cryotherapy was applied at the site of entry after the needle was withdrawn. Smears were prepared from the aspirated material. The alcohol fixed smears were stained by Papanicolaou (Pap) stain and air dried smears by May Grunwald Giemsa (MGG) stain. In all cases, smear cytology revealed a malignant round cell tumor with a morphology that was compatible with RB (Figure 2A-2C). Immunohistochemical staining showed cytoplasmic positivity with synaptophysin in the tumor cells (Figure 2D). Once RB was confirmed on cytopathological examination, enucleation surgery was performed. The time interval between FNAC to enucleation was 2-5d. Histopathologic findings in enucleated eyes were consistent with the diagnosis of RB. None of the enucleated eyes had any evidence of high-risk features on histopathology, according to the Children's Oncology Group guidelines. After enucleation, all children were kept under close follow-up for ophthalmic and systemic evaluation. The mean follow up was 38.6mo (range 24-60mo). None of the children had any evidence of local recurrence or systemic metastasis at last follow-up.

DISCUSSION

Aspiration cytology for orbital and adnexal lesions is a well-established diagnostic modality. On the contrary, intraocular FNAC for RB is controversial and has not gained universal acceptance. A literature search showed that there are very few studies on the safety and efficacy of diagnostic FNAC in RB cases [1-5]. Further, these studies were reported several years ago and there is no recent data to support its use. One reason for this is that in the vast majority of children, RB can be diagnosed on the basis of clinical examination and imaging [3]. In a retrospective study by a

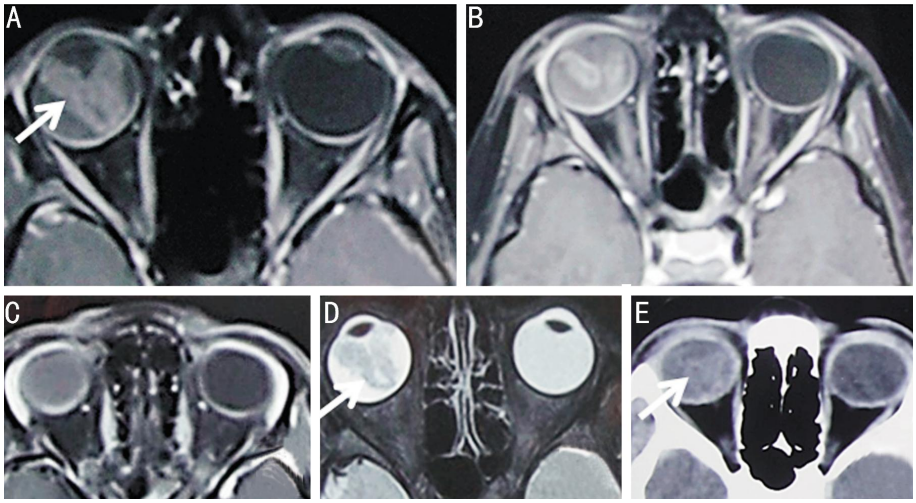

Figure 1 A girl presented with leucocoria in the right eye Intraocular findings on MRI and CT scans of the orbits at the time of presentation. Axial contrast-enhanced T1-weighted (A-C) and T2-weighted (D) MRI showed a bullous retinal detachment and thickened retinal leaves (arrows), with no definite mass. (E) CT scan of orbits (axial cut) to show the absence of intraocular calcification (arrow).

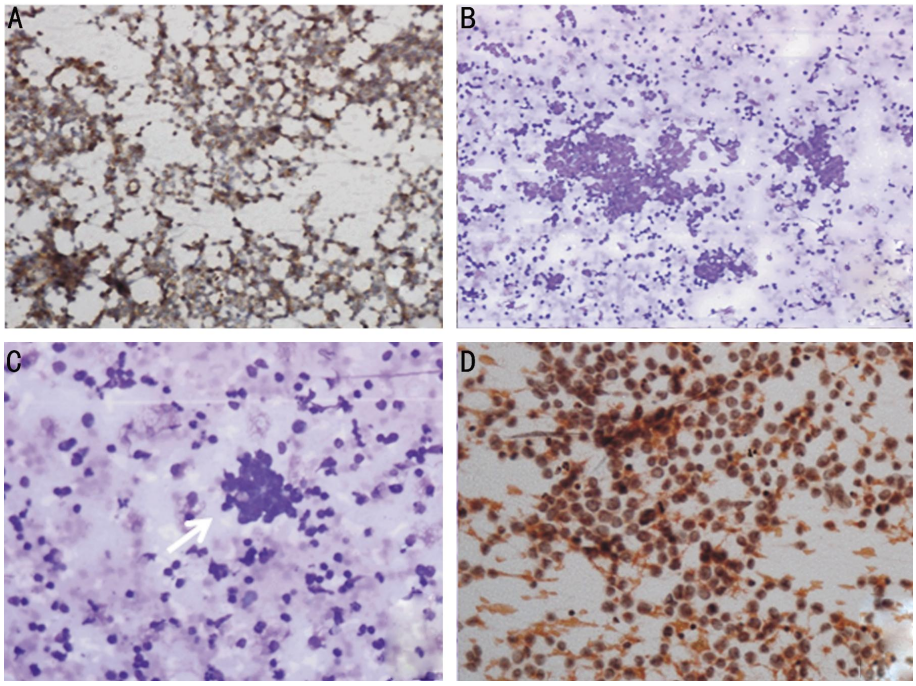

Figure 2 Microphotographs of intraocular aspirate A: Pap stain to show a round cell tumor (×40); B: MGG stain showing tumor cells dispersed singly and in clusters (×40); C: Rosette formation was noted in the tumor cells (arrow) (MGG stain, ×100); D: Immunohistochemical stain showing cytoplasmic positivity for synaptophysin in tumor cells (×100).

survey questionnaire inquiring on the use of FNAC for diagnosis of RB, it was found that out of 3651 cases of RB, only 6 cases had undergone FNAC[4]. The other reason for the hesitation in performing FNAC in RB is the fear of tumor dissemination associated with the procedure.

It is well known that several benign lesions such as PHPV and Coats' disease can simulate RB. In the majority of cases, it is not difficult to differentiate these lesions from RB. Very rarely, in end stage disease, it may be particularly challenging to differentiate RB from a benign simulating lesion on clinical examination and imaging, resulting in a misdiagnosis[6]. All the cases in our series had end stage disease and the fundus details could not be visualized. On imaging studies, there was presence of exudative retinal detachment, diffuse thickening of retina and vitreous haemorrhage, and absence of intra-ocular calcification. This resulted in a diagnostic dilemma and an FNAC procedure was performed in these cases to arrive at a definite diagnosis.

In cases of diagnostic dilemma where RB cannot be excluded, the clinician has the option of performing an enucleation, or of keeping the child on close follow-up if the parents are unwilling for enucleation in the absence of diagnostic certainty. A wait-and-watch attitude in a child with suspected RB is not the safest approach, especially when parents are not willing for regular follow-up. On the other hand, in some instances, parents refuse to give consent for an

enucleation unless the diagnosis is confirmed. The loss of an eye for a benign condition can be particularly traumatic. In such a situation, FNAC can prove to be a useful tool in guiding further course of action, provided it is performed with utmost caution. The main concerns are tumor dissemination and extra-ocular spread, which were not observed in any of our cases. Among other complications associated with the procedure, Shields *et al*[1] have reported sub-retinal haemorrhage (13%), vitreous haemorrhage (8%), and retinal hole (60%). No such complications were observed in our series.

The cytological diagnosis of RB was fairly straightforward. On cytology, small, round, uniform tumor cells were seen in loose clusters, tightly packed clusters, or singly. The nuclear features included uniformly distributed nuclear chromatin, paucity of nucleoli and nuclear moulding. The cytoplasm was scanty and ill-defined. Immunohistochemical staining with synaptophysin showed positivity in the cytoplasm of tumor cells. Histopathological correlation was confirmatory of RB in all our cases. A high specificity of intraocular FNAC procedure has been previously reported by Shields *et al*[1] (98% in diagnostic FNAC) and Augsberger *et al*[2] (94.3% in combined post-surgical and diagnostic intraocular FNAC). Both series included a variety of intraocular neoplasms, in addition to RB.

It is important to emphasize here that FNAC should only be used as a last resort in selected cases. In our series, 4 out of 600 children (0.6%) who were diagnosed with RB during the study period required an intraocular FNAC. Nevertheless, FNAC can have a supportive role in the pre-operative diagnosis of RB cases that pose a dilemma to the clinician. Our experience showed it to be a safe diagnostic modality, provided it is performed with adequate precautions to minimize the chances of tumor seeding and extra-ocular spread. Recently published reports on intra-vitreal chemotherapy suggest this route to be potentially safe for the local delivery of anti-cancer drugs [7-8]. It may be time to revisit and redefine the role of intraocular FNAC as a diagnostic tool for RB and lay down further guidelines for its application. Careful case selection, good co-ordination between the ophthalmologist and pathologist and a cautious approach is recommended for optimum results.

ACKNOWLEDGEMENTS

Presented in part as a paper at World Ophthalmology Congress, 2014, Tokyo, Japan.

Conflicts of Interest: Chawla B, None; **Tomar A,** None; **Sen S,** None; **Bajaj MS,** None; **Kashyap S,** None.

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