Medulloepithelioma

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Medulloepithelioma (MEP) is a rare tumor derived from the primitive neuroepithelium that forms the ciliary body of the eye, iris, retina, or optic nerve head. It usually arises from the non-pigmented ciliary body of the eye; however, tumors arising from the optic nerve, retina, or central nervous system have also been described (Vajaranant et al. 2005; Molloy et al. 1996).

It represents the second most common intraocular tumor in childhood after retinoblastoma, with 75–90% of cases occurring in children aged less than 10 years (Tadepalli et al. 2019). Very rarely, these tumors can affect adults, in some cases as a late malignant transformation of a benign asymptomatic MEP arisen in childhood (Husain et al. 1998).

MEP is a locally aggressive tumor that may extend anteriorly into the iris or posteriorly into the vitreous cavity, involving the retina, with the entire globe filled with tumor similar to retinoblastoma. In advanced cases, it may present with extraocular extension and involve the regional lymph nodes. Distant metastasis to the lungs and parotid gland has been rarely described (Broughton and Zimmerman 1978; Viswanathan et al. 2008). There is no racial or gender predilection, and both eyes are equally affected, but it is commonly unilateral (Tadepalli et al. 2019).

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MEP can be associated with central nervous system malignancies (i.e., pinealoblastoma) or malformations (i.e., corpus callosum agenesis, schizencephaly) (Vajaranant et al. 2005). In addition, MEP has been found associated with pleuropulmonary blastoma (Priest et al. 2011) as part of the DICER1 familiar tumor predisposition syndrome. It has been reported that 5% of patients with MEP have a history of pleuropulmonary blastoma but the risk for MEP in pleuropulmonary blastoma patients is low (<1%) (Kaliki et al. 2013). Recently, somatic mutations of the KMT2D gene have been found, but their role in MEP needs to be further elucidated (Sahm et al. 2016).

37.1 Clinical Presentation

MEP is characterized by a slow growth, and it is often asymptomatic until it is large enough to be seen through the pupil. The most common presenting symptoms are pain and poor vision, related to secondary lens subluxation, glaucoma, or cataract formation. Leukocoria, strabismus, and the evidence of a mass in the iris or ciliary body are also part of the initial signs (Chung et al. 2007; Tadepalli et al. 2019).

On fundoscopic examination, the tumor presents an irregular surface with characteristic cystic lesions (Fig. 32.3 1a). In up to 60% of patients, cysts break off the surface and float freely in

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aqueous or vitreous humor. Retinal detachment is seen in many cases (Chung et al. 2007). On ultrasound, MEP appears as an echogenic irregular mass with a cystic structure and calcifications in some cases. Ultrasound biomicroscopy is more precise to define tumor dimensions and internal characteristics (Bianciotto et al. 2011). CT scan shows a dense irregular mass in the region of the ciliary body with marked to moderate enhancement after contrast, but MRI is preferred to investigate MEP. On MRI, the mass shows both solid and cystic components and appears moderately hyperintense compared to vitreous on T1-weighted images and hypointense on T2-weighted images with marked enhancement after gadolinium administration (Fig. 42.3.1b). Invasion of the sclera or optic nerve can also be identifiable (Sansgiri et al. 2013).

37.2 Diagnosis

The diagnosis requires a histopathologic examination. MEP is characterized by proliferating folded and multilayered sheets and cords of poorly differentiated neuroepithelium, resembling the primitive medullary plate and neural tube. Cystic spaces full of hyaluronic acid are present. MEP has been classified as nonteratoid (approximately two-thirds of cases) and teratoid type, and both types can be benign or malignant. The nonteratoid MEP is a pure proliferation of cells of the medullary epithelium, and it is typically positive for vimentin and neuron-specific enolase. The teratoid subtype includes also heteroplastic elements, such as cartilage, skeletal muscle, and brain-like tissue, and accounts for 30–50% of cases.

The histopathological criteria for malignancy are the presence of frequent mitotic figures or nuclear pleomorphism, poor cellular differentiation with or without rosettes, sarcomatous changes, and invasion of surrounding ocular tissues with or without extrascleral extension (Broughton and Zimmerman 1978).

When MEP is very extended and includes calcification, it may be difficult to distinguish it from an anteriorly located retinoblastoma. Differential diagnosis should also include benign conditions such xanthogranuloma, a cyst of the ciliary body, or the persistence and hyperplasia of the primary vitreous (Vajaranant et al. 2005; Chung et al. 2007).

A recent study investigating for MEP biomarkers found that EZH2, an epigenetic enzyme that regulates tumor suppressor genes or oncogene expression, is strongly positive in moderate to poorly differentiated primitive/neuroblastic MEP cells and negative in the surrounding non-neoplastic tissues. EZH2 positivity has been observed in other forms of cancer including retinoblastoma, and this limits its diagnostic utility (Avedschmidt et al. 2016). More interesting may be the role of LIN28A, a miRNA binding protein, able to downregulate tumor suppressing microRNAs of the let-7 family. LIN28A is positive in all tumors showing the tendency to form rosettes and tubules, but it is negative in retinoblastoma, showing a potential role to differentiate MEP from retinoblastoma and representing a possible therapeutic target (Stagner and Jakobiec 2016).

37.3 Treatment and Prognosis

MEP treatment is usually based on the surgical removal of the tumor. Enucleation may be necessary in larger lesions and exenteration when there is evidence of extraocular extension. Limited local resection has been used in small tumors, but the risk of recurrence is high. The successful use of brachytherapy after conservative surgery has also been reported, and cryotherapy has been used in recurrent tumors (Tadepalli et al. 2019; Cassoux et al. 2010). The prognosis is less favorable for tumor with extraocular extension. In these cases, chemotherapy and radiotherapy have been adopted. Recent reports have showed tumor response after chemotherapy including vincristine, carboplatin, cyclophosphamide, and etoposide underlining the possible use of preoperative chemotherapy to limit the aggressiveness of surgery (Meel et al. 2010) or for metastatic tumors (Hellman et al. 2018).

Prognosis is excellent (5-year survival of 90–95%) for patients with MEP without extraocular

extension treated with enucleation (Vajaranant et al. 2005). When extraocular extension is evident, the prognosis is poor (Broughton and Zimmerman 1978) although a report exists of a metastatic MEP long-term survivor after multimodality treatment (Hellman et al. 2018).

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