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Uveal melanoma – is a biopsy safe and justified?

Czerniak naczyniówki – czy biopsja jest bezpieczna i uzasadniona?

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Summary: Uveal melanoma can be typically diagnosed based on clinical presentation and the A and B mode ultrasound. In some atypical intraocular tumours or for prognostic purposes intraoperative biopsy may be performed. Uveal melanoma biopsy is not safe in 100% and can cause complications (vitreous hemorrhage, retinal detachment and endophthalmitis). Like all biopsies, a biopsy in uveal melanoma biopsy may show limited cellularity and can yield insufficient tissue specimen for histology, cytology and genetic testing. This is most likely in small tumours, below 3 mm in thickness. Another limitation of biopsy-based prognosis is the issue of intratumoural heterogeneity. As a biopsy allows for only a small sample to be removed from the tumour, it is possible to receive false negative results. The most devastating complication of uveal melanoma biopsy is the extraocular spread of the tumour.

The study is a review of the current opinions and findings on the role of biopsy in uveal melanoma.

Key words: uvea melanoma, biopsy, monosomy 3.

Streszczenie: Diagnostyka czerniaka błony naczyniowej może być wykonana za pomocą różnych metod. Najczęściej do postawienia rozpoznania wystarczą standardowe metody diagnostyczne (badania dna oka oraz ultrasonografii w projekcji A i B). W niektórych przypadkach nietypowych guzów lub w celach prognostycznych konieczne staje się wykonanie biopsji guza wewnątrzgałkowego. Przeprowadzając biopsję, należy pamiętać o tym, że nie jest to metoda 100-procentowo bezpieczna i może zagrażać powikłaniami takimi jak krwawienie do ciała szklistego, odwarstwienie siatkówki i zapalenie wnętrza gałki ocznej. Podobnie jak w przypadku biopsji innych narządów, również pobierając materiał z czerniaka błony naczyniowej, należy się liczyć z pobraniem niewystarczającej ilości materiału do badań histopatologicznych, cytologicznych lub genetycznych. Ma to miejsce zwłaszcza w przypadku guzów o grubości mniejszej niż 3,0 mm. Wykonując biopsję, należy również wziąć pod uwagę niejednorodność tkanki guza – jeśli zostanie pobrana niewłaściwa tkanka, wynik będzie fałszywie ujemny. Największym niebezpieczeństwem związanym z wykonywaniem biopsji guzów wewnątrzgałkowych podejrzanych o czerniaka błony naczyniowej jest możliwość rozszewienia komórek nowotworowych.

Celem pracy jest przedstawienie aktualnych poglądów na temat biopsji czerniaka błony naczyniowej.

Słowa kluczowe: czerniak błony naczyniowej, biopsja, monosomia chromosomu 3.

Uveal melanoma is the most common primary ocular malignancy in adults. Typically, uveal melanoma can be diagnosed with non-invasive methods (dilated fundus exam, A- and B-mode ultrasound). In selected cases of atypical presentations, a biopsy becomes necessary (1–5).

Despite effective treatment methods available nowadays, there is always a risk of systemic metastases. The 25-year cumulative mortality associated with uveal melanoma is about 52% for medium-size tumours (1, 6, 7). Most researchers confirm the presence of melanoma micrometastases at the time of diagnosis. Micrometastases can remain as stand-alone sequelae of melanoma or precede systemic, most commonly liver, metastases (1). The following are known as factors predisposing to systemic metastases: larger diameter of a tumour base, tumour location in the ciliary body, epithelioid cell type melanoma, extraocular extension of melanoma, its vascular closed-loop system, chromosomal abnormalities and recurrence (8). Histopathology, cytogenetic, and gene expression patterns can facilitate prediction of systemic metastases (1, 9–13).

Uveal melanoma biopsy is performed for prognostic purposes, in order to detect chromosomal abnormalities associated with the high risk of metastases (most commonly chromosome 3 monosomy), for diagnostic purposes (usually in 1–2% of diagnosed intraocular tumours), and in patients, who refuse therapy for uveal melanoma without prior histopathological verification (1–5, 14). If a biopsy is considered, it is necessary to analyze its likely prognostic and diagnostic outcomes as well as the risk of tumour cell spread, complications, and potential false negative result. In posteriorly located tumours, a biopsy is performed using transvitreal approach through the pars plana, while in patients with ciliary body and anterior choroidal tumours, it is performed by transscleral approach (1, 4, 10). The fine-needle aspiration biopsy (FNAB) is the most frequently used biopsy technique in uveal melanomas (4, 10, 14, 15).

In uveal melanoma, chromosomal abnormalities detected during the prognostic biopsy correlate with the risk of metastases. The alterations most commonly affect chromosome 3, 6q, 8p, 11q, 13, and 1p (11, 16–22). The detection of mo-

nosomy 3 found in almost 50% of uveal melanoma patients is of the highest prognostic value (1, 16–24). It is associated with the high risk of metastases-related death. Survival analyses in the monosomy 3 patients showed 50–70% mortality in this group in the four-year period since the beginning of the therapy (12, 13). Complete monosomy 3 is linked to worse survival prognosis, as compared to the partial monosomy 3 or disomy for chromosome 3 (20). Similarly, gain of chromosomal region 8q, loss of 6q, loss of 1q and lack of BAP1 expression correlate with less favourable prognosis. However, gain of chromosome 6p and EIF1AX expression are associated with better prognosis (11, 17, 18, 25–27).

Another means to assess the risk of metastatic disease in patients with uveal melanoma is gene expression profiling (GEP), which simultaneously measures the expression of several (about 12) tumour genes (1, 9–11, 18). The risk of systemic metastases is low in GEP class 1 tumours and high in GEP class 2 tumours (1, 9–11). The five-year risk of developing systemic metastases is only 2% in class 1A tumours, 21% in class 1B tumours, reaching 72% in GEP class 2 tumours (28). However, the detection of monosomy 3, which occurs in about 10% of GEP class 1 tumours is linked to an increased risk of systemic metastases (1).

The results of a prognostic biopsy in patients with uveal melanoma are used for care planning, including diagnostic imaging to detect systemic metastases. In patients with low risk of systemic metastases, abdominal ultrasound and CT should be performed at least once a year, whereas in high risk patients, liver function assays are recommended every 3, 4 up to 6 months, and imaging tests every 3–6 months (9).

According to the literature, 66–97% of biopsies yield positive result, confirming uveal melanoma (2, 3, 5, 7, 15, 29). The numeric discrepancy can be attributed to the insufficient biopsy aspirates as well as cytogenetic and histological heterogeneity of the tumour (1, 4, 10, 15, 29–33). Insufficient biopsy samples for cytological examination were obtained through pars plana vitrectomy in 3–29% of patients and by transscleral approach in 29–44% of cases (3, 7, 10, 30).

Cumulative 5-year probability of death from metastasis was 14.1% for patients whose biopsy aspirates were insufficient for cytology-based classification versus 22.4% for patients whose biopsy aspirates were sufficient for cytology-based classification (10). When assessed in terms of GEP classification, though, it was 8% in cases where biopsy samples were insufficient for GEP classification or in GEP class 1 tumours, as compared to 45% in GEP class 2 tumours (10). It should be noted that for cytology evaluation, bigger tumour tissue samples are required, as compared to GEP classification purposes (2, 10).

Some researchers attempted to relate biopsy feasibility (obtaining positive result) to tumour size. Augsburger et al., Cohen et al., and Chang et al. reported a correlation between a positive result of a biopsy and tumour thickness in 37.5–64.7% of tumours thinner than 3.0 mm, in 75–92% of tumours 3.0–5.0 mm thick, and in 90–100% for tumour thicker than 5.0 mm (2, 3).

Another issue significantly affecting biopsy findings is tumour heterogeneity. Percentage distribution of spindle and epithelioid cells in tumour zones differs. Similarly, the percentage of chromosomal abnormalities, i.e. chromosome 3 monosomy or disomy, may vary (1, 7, 32). Higher rates of monosomy 3

are more likely to occur in large-size tumours (31). The survival prognosis is worse in the patients with detected 33% of monosomy 3 cells (31). Tumour heterogeneity for monosomy of chromosome 3 affects 14–18% of patients with uveal melanoma (1). Thus, it is possible to collect biopsy aspirates from the tumour zone without chromosomal abnormalities, which normally indicate high risk of systemic metastases.

The question should be asked about the most appropriate tumour site for drawing representative biopsy sample. Killgaard J. et al. demonstrated in their research a 58–59% chance for obtaining most representative samples from the central portions of tumours. The chance for obtaining representative samples from the periphery, top or tumour base was only 43–57% (34). It is therefore reasonable to aspirate more than 1 sample (usually 2–12 samples) during a single biopsy (1, 7).

The obtained biopsy result can be false negative. However, even a negative result cannot completely exclude the presence of tumour cells (4, 33). Ideally, an experienced pathologist should be present in the treatment room to immediately assess the quantity and quality of the obtained aspirate, so as to ensure the reliability of a biopsy (4).

When referring the patient for biopsy it is always necessary to consider its potential complications. These may include vitreous hemorrhage which occurs in 21–46% of patients, more commonly when 22G needles are used for aspiration. Usually, vitreous hemorrhage spontaneously resolves after some time (1, 3, 4, 7, 15). Retinal detachment occurring more frequently during pars plana vitrectomy biopsy may lead in some cases to retinal holes just above the lesion. The risk of retinal detachment is lower in small-size posterior tumours with a small amount of subretinal fluid. It increases in large-size tumours, containing more subretinal fluid. Retinal detachment is a rare complication of a biopsy performed through the transscleral approach, and the rates are even lower for the large-size tumours (4). Another very rare complication of a biopsy is uveitis. There are only two reports of uveitis as a complication of biopsy. Cohen et al. reported 2 cases of uveitis in a series of 83 performed biopsies, and Faulkner-Jones et al. reported 1 case in their series of 33 performed biopsies (4, 6).

The most serious biopsy complication in uveal melanoma is intraoperative extraocular tumour spread, which may present either as extraocular extension or as systemic metastasis. The extraocular tumour spread may occur along the aspiration track at the site of sclerectomy (3, 4, 6, 15). The risk of tumour spread is lower when a patient receives brachytherapy. It is also less likely in biopsies performed during the pars plana vitrectomy (3, 4).

In 2013, four cases of extraocular spread of uveal melanoma to the orbit were reported as a complication of a biopsy. In three of these patients, more than one biopsy was performed and 1 patient did not receive brachytherapy (35). The majority of patients undergoing biopsy (83–159) did not develop extraocular recurrence of uveal melanoma (3, 4, 10, 15).

The risk of tumour spread during FNAB is scarce, but cannot be eliminated (4). Until now, there has been no report of systemic metastases as a complication of a biopsy. It is believed that 25–27G may lower the risk of tumour spread in patients with uveal melanoma (4, 6).

FNAB of uveal melanoma is becoming one of the main prognostic examinations. Despite all advantages of a biopsy, its limitations (tumour heterogeneity, obtaining non-representative sample) and complications should be always considered on a case basis.

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