Tetrasomy of chromosomes 3 and 8 in a young male with choroidal melanoma

Letter to the Editor

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Conflicts of interest / funding sources: none declared

Key words

Choroidal melanoma

Uveal melanoma

Genetics

Tetrasomy

Text

Choroidal melanoma is a rare, potentially lethal cancer with up to 50% of patients developing fatal metastases.[1] The two most important factors determining the metastatic potential of a tumour are its dimensions and cytogenetics.[1] Copy number aberrations in chromosomes 1, 3, 6 and 8 can be used to predict survival, with the changes that occur in chromosomes 3 and 8 being the best described.[1] The combination of monosomy 3 and multiple 8q gains carries the greatest risk of metastases, whereas disomy 3 and 8 has the lowest.[2,3] We report a case of young patient with choroidal melanoma in whom cytogenetic analysis found tetrasomy 3 and tetrasomy 8, with low risk histopathology and immunohistochemisty. To our knowledge, this is a unique finding.

A 30-year-old Caucasian male was referred for evaluation of a right-sided choroidal lesion in March 2018. Symptoms included a gradual darkening and decline in the right vision over the preceding 3 months. Past medical and family history was unremarkable. There was no history of skin moles or dysplastic naevus syndrome. Examination revealed best-corrected visual acuity of 6/9 in the right eye and 6/5 in the left eye. Intraocular pressure was within normal limits. Examination of the left eye was normal but the right eye had a large superior choroidal lesion with collar-stud shape, pigmented base and amelanotic apex. Vessels were visible within the tumour. An inferior exudative retinal detachment was present. B-scan ultrasonography found a choroidal mass of 9.5 x 10.8 mm basal diameter and 11.4mm elevation, with low to medium internal reflectivity and positive for blood flow. These were typical features of a large choroidal melanoma. After discussion of the treatment options, the patient elected for primary enucleation.

Histopathology confirmed the diagnosis of choroidal melanoma of spindle cell type. There were loops and networks and a mitotic count of 4 mitoses per square millimetre. The vortex veins, ciliary body and optic nerve were uninvolved. There was no extrascleral extension. BAP-1 immunohistochemistry was positive in tumour cell nuclei. A fine needle aspirate biopsy (FNAB) was taken from the freshly enucleated eye for genetic analysis. Interphase fluorescence in situ hybridisation (FISH) analysis showed tetrasomy of chromosomes 3 and 8. Gain of two copies of D3S4559 (3p sub-telomere) and the chromosome 3 centromere were present in 88 out

of 100 cells examined, which was indicative of tetrasomy 3. Similarly, gain of two copies of the chromosome 8 centromere and MYC (8q24) were present in 92 out of 100 cells examined, indicative of tetrasomy 8. Next generation sequencing found a Q209P mutation in the GNAQ gene, which is frequently found in uveal melanoma. There was no abnormality detected in the BAP1 gene, however many BAP1 mutations are intronic and can be missed by NGS alone.[3]

Chromosome instability (CIN), the gain or loss of whole or parts of chromosomes, is a common feature of solid and haematological malignancies.[4] CIN is a well-known feature of choroidal melanoma, with aberrations occurring in chromosomes 1,3, 6 and 8.[3] The first described and most profound predictor of survival is monosomy 3, which can be partial or complete. Others include 1p loss or gain, 6p loss or gain, 6q loss or gain, 8p loss or gain and 8q loss or gain.[2] Whole genome doubling (WGD) can occur in uveal melanoma, which could account for the tetrasomy found in this case.[3] However, previously described uveal melanoma cases that exhibited WGD had loss of heterozygosity of chromosome 3 and were predominantly The Cancer Genome Atlas (TCGA) class 3, which would be expected to have alterations of BAP1 and higher grade histopathology, which was not found in this case.[3]

The clinical implications of the finding of tetrasomy 3 and 8 on FISH analysis are difficult to interpret. Extrapolating from other malignancies, tetrasomy 8 has been found rarely in patients with acute myeloid leukaemia (AML), a condition which, similar to choroidal melanoma, more commonly features trisomy 8.[5] In these patients, tetrasomy 8 may be a poor prognostic indicator, however it is not a risk factor included in the European Leukaemia Net 2017 recommendations.[5] A study of multiple different human cell lines found that trisomy and tetrasomy leads to genomic instability, which causes DNA damage and impaired DNA replication.[4] However, the histopathological findings of a spindle cell melanoma with low mitotic count and retained BAP1 immunohistochemistry are in keeping with a lower risk of metastasis. As we do not know the significance of the tetrasomy 3 and 8, we are monitoring the patient closely for the development of metastatic disease with surveillance liver imaging.

Our case highlights a previously undescribed cytogenetic change in a young patient with choroidal melanoma. The prognostic implications of tetrasomy 3 and 8 are unclear, but in practical terms systemic surveillance is warranted in case of increased metastatic potential.

References

1. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. *Eye Lond Engl*. 2017;31(2):241-257. doi:10.1038/eye.2016.275

2. Damato B, Dopierala JA, Coupland SE. Genotypic profiling of 452 choroidal melanomas with multiplex ligation-dependent probe amplification. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2010;16(24):6083-6092. doi:10.1158/1078-0432.CCR-10-2076

3. Robertson AG, Shih J, Yau C, et al. Integrative Analysis Identifies Four Molecular and Clinical Subsets in Uveal Melanoma. *Cancer Cell*. 2017;32(2):204-220.e15. doi:10.1016/j.ccell.2017.07.003

4. Passerini V, Ozeri-Galai E, de Pagter MS, et al. The presence of extra chromosomes leads to genomic instability. *Nat Commun*. 2016;7:10754. doi:10.1038/ncomms10754

5. Tsirigotis P, Papageorgiou S, Abatzis D, et al. Acute myelogenous leukemia with tetrasomy 8 is a disease with a poor prognosis. *Cancer Genet Cytogenet*. 2005;161(1):78-81. doi:10.1016/j.cancergencyto.2004.12.016