Lipomatous Change in Uveal Melanoma: Histopathological, Immunohistochemical and Cytogenetic Analysis

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Key Words
Uveal melanoma · Histopathology · Metaplasia

Abstract
Purpose: The aim of this study was to describe a case of lipomatous change in uveal melanoma. Procedures: The patient presented with a 2-year history of blurry vision. A full examination of the right eye revealed a dome-shaped pigmented subretinal mass in the choroid with a thickness of 9 mm and a diameter of 15 mm. The eye was enucleated and prepared for histopathologic, genetic and molecular investigation. Results: Histopathology revealed a small circumscribed area consisting of mature adipocytic appearing cells with abundant clear cytoplasm and small peripheral flattened nuclei within a spindle-cell melanoma of the uvea. The cytoplasm of the adipocytic cells stained negative for periodic acid-Schiff and Alcian blue and positive for Melan-A, HMB-45 and tyrosinase, confirming melanocytic lineage. Fluorescence in situ hybridization analysis confirmed trisomy of chromosome 6p22 and disomy of chromosome 3p13 in the nuclei of both the tumor spindle type B cells and in the nuclei of lipomatous tumor cells. Conclusions: Lipomatous change can be added to the many histopathologic faces of uveal melanoma. To our knowledge, this is the first report of lipomatous change in uveal melanoma performed with cytogenetic investigations.

Introduction
Malignant melanoma is well known for its protean morphologic appearance. Besides the common uveal melanoma types (epithelioid and spindle cell), other histopathologic variants have been reported. Clear cell change of the cytoplasm of uveal melanocytic cells can be observed as balloon cells [1], signet ring cells [2] and clear cells [3]. We describe lipomatous change in uveal melanoma.

Case Description
A 73-year-old male visited the outpatient department of ophthalmology because of a 2-year history of blurry vision, which could not be explained upon two prior visits to an ophthalmologist during these 2 years. At presentation, the best-corrected visual acuity was 20/50 OD and 20/16 OS. On dilated funduscopy (fig. 1a)
and ultrasonographic examination of the right eye, a dome-shaped pigmented subretinal mass was seen with a thickness of 9 mm, a diameter of 15 mm and medium-to-low internal reflectivity. No atypical cutaneous pigmented lesions were observed. Systemic radiologic evaluation revealed no metastatic lesions. The patient opted for enucleation. After a follow-up of 12 months, there were no signs of metastases.

Sections of the eye confirmed a dome-shaped tumor composed almost exclusively of spindle type B melanoma cells. A small circumscribed area consisted of mature adipocytic appearing cells with abundant clear cytoplasm and small flattened nuclei at the periphery (fig. 1b). The cytoplasm stained negative for periodic acid-Schiff and Alcian blue stains, excluding glycogen or mucin. Mitotic figures were present at 4 × 8 mm² (equivalent to 50 high-power fields). Intracytoplasmic brown pigment stained negative for Prussian Blue iron stain. No closed-loop extracellular matrix pattern was present. The tumor did not show extrascleral extension or invasion of the optic nerve. The lipomatous tumor cells stained positive for Melan-A, HMB-45 (fig. 1c) and tyrosinase, confirming melanocytic lineage. All tumor cell nuclei stained positive for BAP1. The lipomatous tumor cells stained negative for CD34.

Single-nucleotide polymorphism array analysis (HumanCytoSNP-12 v2 BeadChip; Illumina, San Diego, Calif., USA) showed gain of chromosome 6p and no loss or gain of chromosomes 3 and 8. Fluorescence in situ hybridization analysis confirmed trisomy of chromosome 6p22 and disomy of chromosome 3p13 in the nuclei of both the tumor spindle type B cells and in the nuclei of lipomatous tumor cells (fig. 1d). Mutation analysis demonstrated a heterozygous GNA11 p.Gln209Leu mutation. GNAQ, SF3B1 and EIF1AX were wild type.

Discussion

Primary uveal melanoma is classified as spindle cell, epithelioid cell or mixed cell type. The epithelioid cell type is associated with a significantly worse prognosis. Unusual cytomorphologic variants of uveal melanoma have been described, such as oncocytic [4], neuroendocrine [5], balloon cell [1], clear cell [3], signet ring cell [2] and, as in our case, lipomatous. Although the prognostic significance of these cytomorphologic variants is unknown, they should be recognized in order to avoid misdiagnosis with metastatic neoplasms. The divergent differentiation patterns of neoplastic uveal melanocytes may recapitulate the plasticity of neural crest stem cells. Individual cells from melanoma spheres (melanoma spheroid cells) derived from metastatic cutaneous melanoma can differentiate under appropriate conditions into multiple cell lineages such as melanocytic, adipocytic, osteocytic and chondrocytic lineages [6]. The current case demonstrates that lipomatous change can also be observed in uveal melanoma. The fluorescence in situ hybridization results showed identical changes in the spindle type B melanoma cells and the lipomatous tumor cells. Immunohistochemistry confirmed the melanocytic lineage of the lipomatous change, whereas CD34 staining, commonly positive in adipocytes, was negative. The process of metaplasia implies full expression of the characteristics
of the ‘new’ cell type. In our case, however, the neoplastic cells resembling mature adipocytes retained the immunohistochemical features of melanocytes and lacked specific immunohistochemical features of true adipocytes. Moreover, definite proof of the lipomatous character of the histomorphologic change would require fresh frozen tissue samples for lipid stainings that were not available in our case. We therefore prefer to refer to this phenomenon as lipomatous change. Other neuroectodermal tumors that may contain adipocytes include cutaneous melanocytic nevi [7], schwannoma [8], neurofibroma [9], perineurioma [10], meningioma [11] and adrenal adenoma [12]. In most cases as well as in the current case, the cells retain at least some of the characteristics of their original lineage, which would argue against true metaplasia. Lipomatous change can also be observed in different cardiac pathologic processes, including ischemia, idopathic dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia [13]. This phenomenon appears to be due to transdifferentiation of multipotential interstitial cells to adipocytes, which would be true metaplasia. Another hypothesis is that lipomatous metaplasia in cardiac muscle may be partially related to progressive myofibril degeneration and lipid accumulation within heart muscle cells, finally leading to phenotypical conversion, or lipomatous change, of cardiac myocytes into adipocyte-like cells [13]. Speculation regarding the cause of lipomatous change in uveal melanoma might include degeneration and lipid accumulation within the melanocytes due to senescence or to chronic injury such as ischemia or inflammation. To our knowledge, this is the first report of lipomatous change in uveal melanoma performed with cytogenetic investigations.

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Statement of Ethics

Informed consent was given by the subject. The study is in compliance with the declaration of Helsinki and was approved by the institutional committee on human research.

Disclosure Statement

The authors have no conflicts of interest to disclose.