Balloon cell malignant melanoma of the choroid: ultrastructural studies

MOURAD K. KHALIL

From the Departments of Ophthalmology and Pathology, Montreal General Hospital, McGill University, Montreal, Quebec, Canada

SUMMARY  I reported the clinical, pathological, and ultrastructural findings in 2 cases of balloon cell malignant melanoma of the choroid. Degradation of the melanosomes of the tumour cells appeared to be the primary biological disturbance in the cell organelles, followed by secondary increase in intracellular lipid secretion and accumulation, leading ultimately to the formation of the balloon cells. Despite the fact that balloon cells are indicative of degeneracy and impending necrosis of the tumour cells, metastases were present in both cases. One of the conclusions this article provides is that the presence of balloon cells does not alter the prognosis of malignant melanomas of the choroid.

Case reports

CASE 1

On 4 January 1980 a 59-year-old white man noticed an increasing shadow in the upper visual field of the right eye, of 2 weeks duration. His vision was 20/25 both eyes. The right fundus showed a large, elevated, nonpigmented tumour occupying the inferonasal quadrant; a serous retinal detachment surrounded the tumour without involving the macula. A dark brown, flat and localised lesion was seen through the greyish detached retina temporal to the tumour. The clinical diagnosis of a malignant melanoma of the choroid was made. Systemic investigation revealed an old calcified granuloma of the right lung and 2 osteoblastic lesions of T5 and T9, which were considered to be bone metastases to the spinal vertebrae. The eye was enucleated on 18 January 1980.

Histopathology. A right globe was received in 10% formaldehyde. It was sectioned along the vertical plane medial to the limbus and transecting the choroidal tumour into 2 halves. The medial calotte was fixed in 3% glutaraldehyde for electron microscopic studies. The tumour occupied the inferonasal and part of the inferotemporal quadrants. The base of the tumour measured 1·6 cm and extended from the edge of the optic disc to the pars plana; it was elevated 1·2 cm. It presented a striking difference in pigmentation. An oblong, deeply pigmented, and well demarcated portion of the tumour extended from the posterior edge to the centre, while the rest of the tumour was amelanotic. Temporal and adjacent to the tumour the choroid showed a localised, flat, and deeply pigmented elevation.

Light microscopy of the posterior basal heavily pigmented portion of the tumour showed the histo-

Fig. 1 Case 1. Histopathology of balloon cells. The cells were large with well defined cellular membranes, the cytoplasm was replaced by multiple vacuoles, the nuclei were scalloped by the vesicles. (Epon section, × 180).
pathology of a benign choroidal naevus. The cells were arranged in nests. They had plump, rounded or oval, uniform nuclei and vacuolated cytoplasm. The adjacent choroid contained multiple foci of similar cytology. The tumour presented a remarkable transition of cell types: from naevus cells at the base to spindle A and small spindle B cells in the heavily pigmented area, to large spindle B and epithelioid cells in a narrow zone bordering the yellowish amelanotic part of the tumour. Dilated blood vessels and blood spaces were seen among the sheets of spindle A and spindle B cells. Those cells close to the blood channels did not show ballooning transformation. The amelanotic part constituted about 2/3 of the tumour and was composed mainly of balloon cells in varying degrees of maturity (Fig. 1). The balloon cell was large, with vascular cytoplasm and well defined borders joined to the nuclear membrane by fine irregular strands which surrounded vacuoles of different sizes. The nuclei were central or eccentric,

Fig. 2 Case 1: Frozen section stained for fat. The cytoplasmic vacuoles of the balloon cells were full of lipids. Lipids were also found extracellularly after rupture of some of the cells. (Sudan stain, ×144).

Fig. 3 Case 1: Melanosomes in different stages of degradation. Upper left: melanosomes with small vesicle (×11,413). Lower left: a swollen poorly melanised melanosome with a larger vesicle (×6,848). Upper middle: a melanosome losing its particulate matrix, allowing visualisation of discrete granules and striated bars (×13,315). Lower middle: incomplete loss of particulate matrix (×25,680). Upper right: atrophic vacuolated melanosome (×25,680). Lower right: lamellar units in totally vacuolated melanosomes (×30,483).
round or oval. In some the nucleus was scalloped by the enlarging vesicles, in others the vacuoles coalesced to form single cavities which pressed the nucleus against the cell membrane. Special stains showed that these cells were devoid of melanin pigment, and fat stain performed on frozen sections showed that the balloon cells both mature and immature forms were loaded with lipids (Fig. 2). The tumour had an intrascleral and orbital extensions. The cells were spindle type and contained vacuoles in their cytoplasm.

For electron microscopy small pieces from different areas of the tumour were thoroughly washed in cold buffer and postfixed in 1% osmium. The sections were stained with lead citrate and uranyl acetate. Spindle A, spindle B, and epithelioid cells were found. The different cells showed the ultrastructural features previously described. The cells contained a well developed rough endoplasmic reticulum, distinct smooth endoplasmic reticulum, Golgi apparatus, and annulate lamellae, suggesting that these cells were actively producing melanin. Membrane bound melanosomes were abundant; some were poorly melanised.

Degradation of the melanosomes (Fig. 3) appeared to be the primary pathological changes in the tumour cells. These changes included: the formation of microvesicles in the melanosomes; loss of particulate matrix, allowing visualisation of the cross-linked fibres or the individual pigment granules; and coalescence of the cavities, leading to the swelling of the melanosomes and loss of its pigment. Lamellar bodies were seen in some cavities. They were composed of loosely bound concentrically rolled units; the bodies were free of pigment. No lysosomes, phagosomes, tonofibrils, or desmosomes were identified. Sections from the amelanotic portion of the tumour contained balloon cells in different stages of formation. The fully developed balloon cells (Fig. 4) were filled with vacuoles of different sizes. Some

Fig. 4 Case 1: An electron micrograph of a balloon cell, microfilaments surround the lipid vacuoles. (×25 200).
were membrane bound and others had no lining membrane but showed an osmophilic rim. The vacuoles compressed the few remaining cell organelles to a narrow rim close to the cell membrane. Scattered monosomes were detected in the atrophic cytoplasm, and thin microfilaments were also seen between the cavities. Most of the cavities were empty, and few contained fibrillar material and dark dots.

**CASE 2**

In July 1967 a 75-year-old woman presented with the picture of anterior uveitis in her right eye. The vision was 20/50 OD and 20/30 OS. On fundoscopy a partially pigmented, slightly elevated lesion was found in the upper temporal quadrant. It gave a corresponding sector visual field defect. Fluorescein angiography showed an immediate fluorescence associated with the choroidal flush and tiny dark spots through the lesion. The $^{32}$P uptake test was positive. The clinical diagnosis was a suspected malignant melanoma of the choroid.

In October 1967 a macular hole developed in the right eye and the vision dropped to counting fingers. The lesion remained stationary until March 1969, when the tumour showed increased pigmentation and abrupt change in size. The central and largest part of the tumour was yellowish and nonpigmented (Fig. 5). The impression at the time was indeed a progression in a malignant melanoma of the choroid, and the eye was enucleated on 2 April 1969. The diagnosis of malignant melanoma was confirmed pathologically.

The patient did well until November 1972, when she presented with an enlarged, nodular, tender liver. Liver scan revealed the presence of multiple metastases. A liver biopsy performed on 8 January 1973 confirmed the diagnosis of malignant melanoma metastases. The patient was treated with chemotherapy, and she died on 4 April 1973.

**Histopathology.** Grossly the choroidal tumour was tan-grey-cream and marble-like in structure. It measured about 9 mm in diameter and had an estimated thickness of 2 mm. Microscopically over 50% of the tumour was amelanotic. The margins of the pigmented portion of the tumour were composed of nests of naevoid cells which gradually changed to spindle B and epithelioid cells. The amelanotic portion of the tumour was composed of balloon cells. They were large, with well defined cellular membranes, foamy cytoplasm, and multiple vacuoles, and the nuclei were of different sizes (Fig. 6). The balloon cells bordered a large central area of necrosis which contained amorphous eosinophilic material. The liver biopsy revealed sheets of poorly pigmented spindle cells, occasional mitoses, and numerous large foamy vaculated cells similar in morphology to the balloon cells of the primary tumour.

**Discussion**

Balloon cells have been observed in naevi and malignant melanomas of the skin, conjunctiva,
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and ciliary body and choroid.6,7 They also occur in the depigmented zone of halo naevi,8 in the halos around malignant melanomas of the skin,9 and in melanocytes during their scheduled disappearance from human embryonic hair follicles. The tumour is classified as balloon cell variant when balloon cells constitute more than 50% of the cellular components of the particular neoplasm.3 Their incidence among malignant melanomas of the choroid is about 2%.

Clinically the ballooning of the tumour cells appears as a yellowish halo in the form of a complete circle, forming an arc-shaped rim round the tumour, or as yellowish hypopigmented central patches.10 11 These patches fluoresce with the choroidal flush, and this distinguishes them from the orange pigment contained in the retinal pigment epithelium.12 13

Balloon cells are present considered to be altered melanocytes; at one time they were regarded as histocytes that ingested degenerating tumour cells. Balloon cells develop as a result of increased intracytoplasmic accumulation of lipids, hence changing the melanocyte to a large, foamy, vesicular or clear cell. Failure to detect lipids in balloon cells in many previous reports was due to the lack of using frozen fresh tissue sections, as placing or processing any specimen in alcohol will immediately dissolve the lipids. Residual fat could also be identified in methylene blue stained plastic sections prepared for electron microscopy as green rims in the vacuoles.14 The light and electron microscopic pictures of a mature balloon cell presented a striking resemblance to the xanthoma cell. The ultrastructural features of cellular metabolism of lipid remains unknown. However, it was suggested that smooth endoplasmic reticulum is important in this regard and that cytoplasmic lipid vacuoles represent grossly dilated cytoplasmic reticulum.15

Whether the fat accumulation in balloon cells occurs from passive imbibition of lipids from plasmatic material or is due to increased active intracellular secretion is not clear. I found that the tumour cells adjacent to the large blood spaces showed minimal or no ballooning transformation. In addition, segmental dilatation of the smooth endoplasmic reticulum was evident in the tumour cells undergoing degradation of their melanosomes. These findings favour the active intracellular secretion rather than the passive imbibition as the mechanism of fat accumulation in balloon cells of malignant melanomas.

The pathogenesis and biological mechanisms involved in the development of balloon cells remain controversial. Schrader and Helwig4 suggested that balloon cells result from an arrest in the biosynthesis of melanin. Hashimoto and Bale4 16 and Okun and Donnelan17 in 2 separate studies attributed the ballooning changes to coalescence of degenerating abnormal melanosomes producing the intracytoplasmic cavities. Jacobiec et al.14 studied 2 cases of balloon cell malignant melanomas of the ciliary body and concluded that balloon cells represent spindle melanoma cells that had undergone extensive metamorphosis. The light and electron microscopic findings in our 2 cases illustrated that ballooning transformation can occur in atypical melanocytes regardless of their cell type. The degradation of the melanosomes as seen by electron microscopy appeared to be the primary biological disturbance in the process of balloon cell formation. These early changes in the melanosomes were detected in areas of the tumour where the cells appeared viable with light microscopy. Subsequent to such organelle and secretory disorganisation, secondary accumulation and increase in the cytoplasmic lipids occurs and leads to the formation of the balloon cells.

Balloon cells were seen in malignant melanomas of the choroid undergoing necrosis16 or spontaneous regression,19 and they preceded the individual cell lysis or the massive cellular necrosis in our 2 cases. Balloon cell degeneration in pigmented tumours represents a stage in the process of necrosis or spontaneous regression of these tumours. Despite the fact that ballooning degeneration in malignant melanomas of the choroid is indicative of degeneracy and impending necrosis, metastases were detected in our 2 cases and were also reported in balloon cell malignant melanomas of the skin.20-22 Metastases could have spread before the process of ballooning degeneration occurred in the tumours, or the autoimmune mechanism was not sufficient to suppress the tumour cell replication, activity, and spread. Balloon cell degeneration in malignant melanomas of the choroid does not change the prognosis and outcome of the tumour unless the whole tumour is transformed to balloon cells before the onset of metastases.

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References
Mourad K. Khalil


