Management of conjunctival melanoma

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Introduction to the recommendations:

There is currently no recommendation on the management of conjunctival melanoma probably because of the rarity of this disease. Nevertheless, the recommendations made by the Cancer Plan II and III, the HAS (French Health Authority) and the DGOS (French General Directorate of Care Offer) on the management of rare cancers and cutaneous melanoma may be used as a basis.

Conjunctival melanoma is indeed a malignant tumor closer to cutaneous melanoma than uveal melanoma .

Introduction to conjunctival melanoma:

Conjunctival melanoma is a malignant tumor of the ocular surface which represents about 2% of all malignant intraocular tumors. In the Caucasian population, the incidence is estimated at 0.2-0.8 per million individuals per year. Melanoma is extremely rare in the non-Caucasian population. The mean age of onset is 60 years. In more than 55-60% of cases, the tumor complicates precancerous melanosis with atypia (primary acquired melanosis (PAM) with cytonuclear atypia), in 20% of cases it complicates a preexisting conjunctival nevus and it occurs *de novo* in about 20-25% of cases. The tumor may develop in any location in the bulbar or tarsal conjunctiva. The initial location has a prognostic value (locations at the bulbar conjunctiva are associated with a better prognosis than those developed at the fornix , caruncle or tarsal conjunctiva). Conjunctival melanoma is generally pigmented, but there are achromatic forms whose diagnosis is more difficult that may be mistaken for other achromatic tumors of the ocular surface, in particular conjunctival squamous cell carcinoma.

The therapeutic management of conjunctival melanoma is associated with both local recurrence (in case of incomplete resection or associated PAM), and loco regional or visceral lymph node metastatic spreading issues, knowing that the more a patient relapses locally, the higher the metastatic risk is. Regarding visceral metastases, there is no effective treatment to date.

PAM or Reese's melanosis consists of a more or less dense, more or less extended, flat pigmentation at the conjunctival and/or corneal epithelium. This strictly unilateral pigmentation generally appears in Caucasian adult subjects with clear skin type. Histologically, melanosis is defined as a strictly

intraepithelial melanocytic proliferation and a more or less pronounced cytonuclear atypia may be present. This condition should be monitored on a very regular basis through eye examination and photographs. The monitoring frequency varies (from quarterly to annual) depending on the lesion extent and/or the importance of the cytonuclear atypia on histology, these 2 factors affecting the risk of developing invasive melanoma. This precancerous melanosis should be differentiated from benign racial melanosis which is bilateral and found in the Caucasian population with dark skin type or in the non-Caucasian population. Racial melanosis primarily affects the limbus, decreases as the distance from the limbus increases and is not found in the tarsal conjunctiva.

The TNM (Tumor Node Metastasis) classification of the AJCC (American Joint Committee on Cancer), which is a prognostic classification, takes into account the location for T staging. T1 includes the bulbar conjunctiva, T2 includes the caruncle, fornix and eyelid conjunctiva, T3 includes the lesion invading the adjacent structures, including the eyeball, eyelids, orbit, and T4 includes the intracranial invasion. The classification takes into account the extent of the lesions, the presence of satellite lymphadenopathy (N) and remote metastases (M). Cf. table

Management recommendation (from the HAS)

Diagnosis announcement consultation:

It should include a precise description of the lesion (precise location, size, thickness, presence or absence of an associated melanosis) with drawing up of a diagram and photographs. This description should help to classify the lesion according to the TNM classification. Palpation of the regional lymph nodes and parotid gland should be systematic.

The patient should be informed of the malignant nature of the lesion and receive a **PPHC** (personalized health care plan) which is part of the HAS recommendations and should theoretically be given during this diagnosis announcement consultation. If there is any doubt, the PPHC may be given following a mandatory **MCM** (multidisciplinary consultation meeting) and then a new diagnosis announcement consultation. Patients should be informed of all treatment options available in their situation, with information on the expected benefits and potential adverse events, as well as on the interest to participate in a clinical trial.

Surgical management:

In conjunctival melanoma, the HAS recommendations for cutaneous melanoma should not be completely followed due to the anatomy of the eye. It is not possible to perform a wide resection. Indeed for cutaneous melanoma of 4 mm in thickness, the width and depth of the resection margins should be of 3 cm which cannot be applied to the conjunctiva. Moreover, the HAS authorizes smaller margins in some locations such as the face.

Nevertheless, a complete resection of the lesion should be performed and not a biopsy which may lead to histological misdiagnosis.

The resection should follow strict rules:

- Intraoperative photograph if not taken in consultation.

- **General anesthesia** (subconjunctival local anesthesia is contraindicated to prevent tumor cell spreading remotely from the initial lesion or in the orbit)
- Measurement of the lesion diameter and thickness with calipers.
- Monoblock resection of the lesion using a no-touch technique with alcoholization of the cornea in case of corneal invasion.
- Formalin fixation of the resection specimen for molecular testing (BRAF, NRAS, KIT mutation)
- Reconstruction should be performed after **changing the instruments,** preferably by direct suturing when possible or amniotic membrane transplantation. Do not collect conjunctival graft in the operated eye nor in the healthy contralateral eye. The implantation of a symblepharon ring should complement wide resection with reconstruction.

Confirmation of the diagnosis:

The diagnosis is confirmed by the histological examination of the resection specimen whose findings should be available within 15 days to 3 weeks maximum.

The histological report should include the following elements:

- Diagnosis of malignant melanoma with or without PAM.
- Size and macroscopic thickness (Breslow index).
- Histological type, mitotic index (number of mitosis/fields), presence of ulceration, epithelioid cells, invasion of lymphatics.
- Presence or absence of PAM.
- Invasion or non-invasion of the lamina propria (invasion = invasive melanoma), no invasion = melanosis with severe atypia or *in situ* melanoma. The proportion of the invaded lamina propria should be specified.
- Careful examination of the lateral resection margins (which should be *in sano*). For conjunctival melanoma, the deep margins have no interest unlike the invasion or non-invasion of the lamina propria.

In case of ambiguous or inaccurate diagnosis, a second reading should be requested from a pathologist belonging to a regional or national referral center.

Presentation of the record at the MCM

The presentation of the record at the regional or national MCM (appeal MCM) should be made by the surgeon himself (HAS). The extent of the examination (Breslow index greater than 2 mm or high mitotic index) will be discussed and should include a scanner of regional lymph nodes and a PET

scanner. Additional treatment will also be discussed in case of incomplete resection, invasive melanoma and/or melanoma complicating PAM.

These additional treatments that are discussed in MCM and relate to invasive melanomas associated or not with PAM include:

- Focal irradiation of the resection bed (by brachytherapy, proton beam therapy or another technique discussed in MCM with the radiotherapist).
- Cryotherapy (less used in France).
- Prophylactic irradiation of the lymph nodes.
- Lymph node dissection in case of metastatic lymphadenopathy.
- Mitomycin eye drops (only to treat PAM with associated atypia since mitomycin eye drops are ineffective on invasive melanoma).

Important: The MCM should be held within 4 weeks after the surgical procedure because the additional treatment should be initiated before any local recurrence. Incomplete records (fragmented clinical data, absence of preoperative photographs or specific diagram, imprecise histology...) cannot be discussed during the MCM.

Appendix

TNM classification (7^{th})

Primary tumor

Tx primary tumor that cannot be classified

T0 no tumor

T(is) *in situ* melanoma

T1 invasive melanoma of the bulbar conjunctiva

T1a <1 quadrant

T1b >1 quadrant and <2 quadrants

T1c >2 quadrants and <3 quadrants

T1d >3 quadrants

T2 melanoma of the caruncle, fornix , tarsal conjunctiva

T2a <1 quadrant without involvement of the caruncle

T2b >1 quadrant without involvement of the caruncle

T2c <1 quadrant with involvement of the caruncle

T2d >1 quadrant with involvement of the caruncle

T3 melanoma with invasion of adjacent structures

T3a invasion of the eyeball

T3b invasion of the eyelids

T3c invasion of the orbit

T3d invasion of the sinus

T4 intracranial invasion

N Involvement of regional lymph nodes

Nx cannot be assessed

N0 no lymph node involvement

N1 lymph node involvement

M Remote metastases

Mx cannot be assessed

M0 no metastasis

M1 remote metastases

References

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