Conjunctival Melanoma during Pregnancy

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Keywords

Conjunctival melanoma · Pregnancy

Abstract

Purpose: To describe the clinical and histopathological features of a conjunctival melanoma (CM) during early pregnancy. **Procedures:** A 37-year-old, 20-week pregnant primigravida was referred to the Sheffield Ocular Oncology Service with a rapidly growing lesion arising from the right superior conjunctival fornix, noted from the first trimester of pregnancy. This was associated with pain and bloody discharge. Incisional biopsy confirmed the clinical suspicion of invasive CM. She was treated by primary surgical excision and cryotherapy under local anaesthesia. **Results:** Histology of the excised specimen showed an invasive malignant melanoma with surrounding in situ conjunctival changes arising from a naevus. The melanoma was 10.5 mm thick, focally necrotic, and had a mitotic count of 11/mm² focally. The patient responded well to surgical treatment. She gave birth to a healthy boy, and the placenta showed no evidence of metastatic melanoma. There has been no recurrence or distant metastasis during 5 years of follow-up. **Conclusion:** CM during pregnancy is extremely rare. Because of possible trans-

formation to malignant melanoma, we recommend close monitoring of females known to have pigmented conjunctival lesions of the conjunctiva during pregnancy.

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Introduction

Cancer diagnosis during pregnancy is estimated at 1 out of 1,000 pregnancies [1, 2]. There are conflicting reports of the effects of pregnancy on melanoma. Large studies of pregnancy-associated cutaneous melanoma suggest that pregnancy has no adverse effect on melanoma diagnosed during pregnancy [3], although more recent reports suggest otherwise [4–6]. Conjunctival melanoma (CM) is a rare tumour, with an incidence of less than 1 per million per year [7, 8]. It accounts for about 2–5% of ocular malignant melanomas [9]. CM usually affects patients between the ages of 40 and 70 years. The most common location is the interpalpebral conjunctiva near the limbus, but it may also affect the bulbar and palpebral parts of the conjunctiva [10–12]. Increased tu-

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mour thickness, non-limbal location, high mitotic count, multifocality, and lymphatic or intravascular spread are associated with a worse prognosis [10–12]. We report the unusual case of a 37-year-old primigravida who developed a rapidly growing mass over the right superior tarsal conjunctiva.

Case Report

A 37-year-old Caucasian female, primigravida and 20 weeks pregnant, was referred to the Sheffield Ocular Oncology Service because of a pigmented mass on her right upper lid (Fig. 1a–c). She had no previous ophthalmic or medical history. She reported rapid enlargement of a “cyst-like” lesion on her upper lid during the first 3 months of her pregnancy, which was locally diagnosed as a granuloma due to chalazion. The patient developed pain and bloody discharge from the mass 3 weeks later. The local hospital initially planned excision under local anaesthesia, but the surgeon, seeing pigmentation, postponed the surgery and referred her to the Sheffield Ocular Oncology Service for a specialist ocular oncology opinion.

On examination, an extensive variably brown-pigmented, pedunculated mass arising from the right superior fornix was identified (Fig. 1c). An incisional biopsy of the lesion confirmed the clinical suspicion of invasive malignant melanoma arising from in situ melanoma. Mapping biopsies done at the same time showed no tumour elsewhere on the conjunctiva.

At this stage the prognosis, surgical treatment options, and complications were discussed with the patient. The patient was

informed of the small risk of spread of the melanoma trans-placentally to the unborn child. She preferred to take this risk and continue with her pregnancy, opting for conservative surgical management. A multi-staged procedure, involving primary surgical excision of the lesion with a wide margin of surrounding conjunctiva followed by delayed reconstruction after histopathological confirmation of complete tumour clearance, was planned. She was keen to undergo the multistage procedure under local anaesthesia because of the risks of general anaesthesia to the unborn child.

A primary surgical excision of the tumour was performed under local anaesthesia (topical tetracaine 1% and 2% lignocaine with adrenaline 1:200,000). The lesion was excised with a 3-mm safety margin. During excision, a suspected naevus was noted at the temporal edge of the lesion in the fornix. Once tumour clearance had been histologically confirmed, the second-stage delayed reconstruction was done. Adjuvant triple freeze-thaw cryotherapy to the base and edges of the excised area was performed. Fresh-frozen amniotic membrane graft transplantation to the large defect was done, and the graft was sutured in place with vicryl sutures. Tisseel® glue was used to adhere the graft to the underlying tissue and to reform the superior fornix.

The excised specimen was fixed in standard buffered formalin and sent to the ophthalmic pathology laboratory. The specimen comprised conjunctiva measuring 23 × 9 mm with a thickness of 1.5 mm, giving rise to a variably brown-pigmented, polypoid nodule measuring 17 × 10 mm with a height of 11 mm. Histology revealed a 10.5-mm-thick, non-ulcerated, invasive melanoma composed of highly pleomorphic epithelioid melanoma cells (Fig. 2a, b), with focal necrosis (asterisk in Fig. 2c) and a mitotic count of up to 11/mm². No lymphatic or blood vessel channel invasion was identified. At the edge of the invasive tumour, a cystic intrastromal melanocytic nae-

Fig. 1. a, b External appearance of the right upper lid at presentation to the Sheffield Ocular Oncology Service. c The everted right upper lid showing the invasive melanoma. Note the variable pigmentation, surface vascularity, and fibrosis. d Posttreatment photo.

vus was identified, with in situ melanoma over its surface and colonising some of the epithelial cysts within the naevus (Fig. 2d, e). In situ melanoma was also noted adjacent to the invasive tumour unrelated to the naevus. The invasive melanoma had a Ki-67 proliferation fraction of around 20% (Fig. 2f), whereas the naevus showed no Ki-67 positivity (Fig. 2g). Furthermore, the invasive and the in situ melanoma showed consistent staining with HMB-45 (Fig. 2h, i), whereas the naevus was negative (Fig. 2i). The invasive melanoma was immunohistochemically negative for oestrogen and progesterone receptors (Fig. 2j), as were the in situ melanoma and the naevus. The overall interpretation was of a conjunctival naevus transforming into in situ and extensive invasive melanoma of pathological TNM stage pT2c. The margins of excision were all clear.

Following the excision, a head and neck MRI without gadolinium contrast was obtained, which showed no evidence of metastasis; this was a limited investigation because of the pregnancy. Three weeks after surgery, the patient was reviewed and showed no evidence of recurrence, with a good range of eye movement (Fig. 1d).

The patient gave birth to a healthy male child with no evidence of melanoma when examined by the paediatric team. Histology of the placenta showed no evidence of metastatic melanoma. It was noted in the history that the CM had expanded rapidly, and we wished to acquire some insight into this clinical behaviour. Hormonal influences were excluded as alluded to above. There is some evidence suggesting that foetal progenitor cells can engraft into maternal tumours by differentiating into tumour-related endothelial cells [13]. This has the potential of conferring a growth advantage to the tumour by enhancing the vascular supply to it (foetal cell microchimerism). We therefore carried out fluorescence in situ hybridisation to assess for the presence of a Y chromosome, given that the patient gave birth to a male child. This showed no evidence of Y chromosome positivity in the tumour and tumour vessels, excluding this mechanism as the cause for the rapid growth.

Follow-up MRI scans of head and neck region showed no evidence of metastasis. Follow-up of the patient every 6 months for the past 5 years has shown no evidence of local or distant recurrence.

Fig. 2. **a** Haematoxylin and eosin (H&E)-stained section of the pathology at scanning power. **b** H&E-stained section. Highly pleomorphic melanoma cells with atypical nuclei and prominent nucleoli. **c** H&E-stained section. The asterisk marks the zone of necrosis. **d** H&E-stained section. Left: an epithelial retention cyst lined by in situ melanoma (arrow). Right: the benign melanocytic naevus. **e** H&E-stained section showing the benign melanocytic naevus. Note the monotonous cytology with intranuclear inclusions. **f** Ki-67 immunohistochemical staining of the invasive melanoma showing an approximately 20% proliferation fraction. **g** Ki-67 immunohistochemical staining of the melanocytic naevus to compare with the invasive melanoma. Very little staining is identified. **h** HMB-45 immunohistochemical staining of the invasive melanoma. **i** HMB-45 immunohistochemical staining showing positivity in the in situ melanoma colonising the epithelial retention cyst (arrow) and no staining of the naevus (left side of the plate). **j** Progesterone receptor immunohistochemical staining of the invasive melanoma showing no nuclear staining. The oestrogen receptor staining showed the same result for the melanoma and naevus.

Discussion

In the literature 2 cases of CM during pregnancy have been reported, both in the third trimester. The first case was an African-American woman with known neurofibromatosis type I, who had a recurrent, multifocal CM with scleral extension. She underwent early birth induction for treatment and staging and was treated with tumour excision, cryotherapy, and radioactive plaque [14].

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The second patient was 22 years old, known to have a long-standing lesion at the limbus since childhood, which started to grow when she was 7 months pregnant. The lesion underwent local excision [15].

Sex hormones have been shown to play a role in the growth of some tumours such as breast, prostate, endometrial, and ovarian [16]. It has been reported that conjunctival melanocytic lesions express hormone receptors (progesterone and oestrogen), which might explain why these tumours may grow during pregnancy and alter their appearance and behave differently under hormonal changes [17], akin to their cutaneous counterparts [18, 19]. One study found that only progesterone, but not oestrogen, was expressed in melanocytic lesions of the ocular conjunctiva [20], while other authors found no evidence for either oestrogen or progesterone receptor expression in choroidal melanoma or CM [21]. This variability of expressions of hormonal receptors probably reflects lack of standardisation across the studies, with the use of different antibodies on tissue sections from specimens fixed for variable lengths of time, and also the differentiation of the tumour. Our patient's CM was tested, but was found to be hormonal receptor negative, yet this did not explain the rapid increase in size of the CM during early pregnancy. Another mechanism that may account for rapid growth is foetal cell microchimerism [13], as alluded to above. We found no evidence of a Y chromosome in the tumour or endothelial cells. Finally, as pregnancy induces immunosuppression, we speculate that this could have led to the rapid growth of the melanoma. A naevus was seen around the CM at the time of surgery, supporting the interpretation that the invasive melanoma arose from malignant transformation of a long-standing naevus in situ and invasive melanoma.

There is a limited literature base for other ocular melanomas, e.g., choroidal melanoma diagnosed during pregnancy. A few reports have documented rapid growth during pregnancy [22, 23], but a recent case series of 27 pregnant women did not find any difference in survival among these women when compared to controls [24].

In conclusion, CM during pregnancy is extremely rare; this is the first report of CM that grew massively during early pregnancy, although the reasons for this remain unascertained. Despite the large tumour size, non-limbal location, necrosis, and high mitotic rate (all poor prognostic features), no recurrence or distant metastasis has been seen during 5 years of follow-up. Whilst it is difficult to make definitive recommendations based on 1 case, we recommend pregnant females known to have a melanocytic pigmented lesion of the conjunctiva to seek urgent attention if any change is noted in the lesion, in order to detect potential transformation into malignant melanoma.

Statement of Ethics

The subject gave informed consent for publication of this case report. The study was performed in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest and no financial interests to disclose.

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