Primary malignant melanoma of the vermilion of the lip

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Summary

Malignant melanoma of the vermilion of the lip is a rare entity, and because of the common occurrence of other benign pigmented lesions, it is easily overlooked. Early diagnosis is of the utmost importance, in the first instance to minimise the risk of haematogenous, lymphatic, perineural and trans- (salivary) ductal spread. The second reason for early diagnosis is that surgery is the only effective form of treatment. A number of important clinical lessons were learned from this cohort study of malignant melanoma of the vermilion of the lip. Two observations are of note – first, the absence of palpable regional lymph nodes does not exclude the presence of a malignant melanoma, yet all patients presenting with palpable nodes were suffering from a pretinal disease. Secondly, apart from 1 case (our case 2), melanoma of the lip seems to occur on the lower lip only. There are no clear guidelines regarding the necessary extent of extirpation for malignant melanoma of the vermilion of the lip, but we propose that clear margins of less than 10 mm are probable inadequate and margins of more than 20 mm are unnecessary. Concern about a resection resulting in a 20 mm clear margin all round is seldom justified as excellent methods of reconstruction achieving acceptable mobile, adequately sensate lips are available.

Almost all cancers of the vermilion of the lip are squamous cell carcinomas (SCCs). SCC of the lip is found on the lower lip in about 95% of cases; only 4% are on the upper lip, while the commissure is involved in less than 1% of cases. Long-term and repeated exposure to sunlight and tobacco use are important risk factors for the development of lip SCC. The remainder of malignant neoplasms of the lips are mainly of salivary gland origin and arise mostly in the upper lip.¹

In general, primary malignant melanoma of the lip is an exceedingly rare condition. Fewer than 55 cases have been reported since the first description in the English literature by Baxter in 1941.² The exact anatomical site on the lip, e.g. the cutis or mucosa, of the malignant melanoma is sporadically specified (Table I); primary malignant melanoma of the vermilion is seldom mentioned.

Pigmented lesions of the lip, specifically of the vermilion, are common and almost always benign, are either naevi or lentigo, and are often regarded as being physiological in dark-skinned people. Occasionally, pigmented lesions of the lip could signal a rare syndrome such as Peutz-Jeghers or Laugier-Hunziker syndromes.³ Armed with the belief that pigmented lesions of the lip are usually benign and suspicion of a malignant melanoma is low, the unwary clinician could fail to establish the early diagnosis of primary malignant melanoma of the lip. This study will attempt to draw attention to a number of seemingly common traits and features of malignant melanoma of the vermilion.

Case 1

A 58-year-old Caucasian man was referred with a pigment macula on the vermilion of the lower lip measuring 10 mm in diameter (Fig. 1). It had allegedly been present for several years and was slow-growing. The lesion was flat and no regional lymph nodes were palpable. It was evident that the head and neck region had been regularly exposed to the sun. Neither general clinical examination nor special investigations revealed any other pathology or abnormalities.

However, a punch biopsy performed by a dermatologist was suggestive of a malignant melanoma. Extirpation of the lesion under 2.5 loupe magnification with a 10 mm macroscopically ‘clear’ border in all dimensions followed, and the resultant defect (approximately 30 mm in width and height, just less than one-half of the lower lip) was primarily reconstructed by means of the (unilateral) ‘step technique’, as originally described by Johanson et al.⁴ Postoperative healing was uneventful.

Features of an early stage of superficial, spreading malignant melanoma were seen on histological examination – nests of atypical melanocytes in the epidermis with infiltration of the latter in a horizontal plane (Fig. 2). Focal areas of the papillary dermis were found to have been infiltrated by atypical melanocytes distinguishable from the pigment-containing macrophages by their strong positive staining for HMB45 and S100 protein (Fig. 3). The atypical melanocytes had infiltrated to a level of 0.3 mm from the granular cell layer (Breslow’s staging). Due to the degree of epidermal atrophy, Clark staging could not be reliably performed; suffice
it to state that infiltration into the superficial reticular dermis was seen. No signs of lymphatic, neural or vascular infiltration were found.

On 5-year follow-up the patient was doing well, with a good functional result (Fig. 4) and no signs of local recurrence or distant metastases.

Case 2

A 56-year-old man presented with a black lesion of the vermillion of the left side of his upper lip, which was found to be aesthetically displeasing. The lesion had been present for about 1 year and was slow-growing; the patient was asymptomatic. A cleft lip repair had been performed 55 years previously. There was no other medical history of relevance.

Local examination revealed a slightly raised black lesion, measuring 12 x 10 mm, which was soft to palpation. The labial mucosa was normal. There were no palpable parotid and cervical lymph nodes present.

A clinical diagnosis of melanosis was made. Histological examination of a shave biopsy taken by a dermatologist was suggestive of a melanoma (Fig. 5). The tumour stained positive for S100 and Vimentine and to a lesser degree for CD34.

Additional examination, comprising computed tomography (CT) scanning of the head and neck, thorax and abdomen, showed no signs of metastatic disease.

A full-thickness wedge excision of the lesion, with 10 mm clinically uninvolved surrounding tissue of the upper lip, was performed and the defect was closed primarily. Histological examination of the resected specimen showed that the tumour had been completely removed with a margin of at least 8 mm of normal tissue. The tumour was highly pleomorphic and showed features of spindle-shaped cells among the collagen bundles. Immunohistochemistry was not contributory. The final diagnosis was that of a nodular melanoma. Healing was uneventful.

The patient submitted readily to frequent and careful follow-up, and no further treatment was considered necessary.

Three years and 5 months after definite surgery for the melanoma, the patient reported an itching sensation in his left upper lip. On examination, a well-circumscribed, 15 mm subcutaneous swelling was palpable in the cranial aspect of the scar. A biopsy of the swelling and surrounding tissue was taken.

The diagnosis of recurrence of the melanoma was confirmed on histological analysis. No distant metastases or abnormalities were discovered on extensive CT scanning of the head and neck, and the thorax and abdomen.
TABLE I. ADDITIONAL CASES* OF PRIMARY MALIGNANT MELANOMA OF THE LIP

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Lower/Upper lip (L/U)</th>
<th>Origin</th>
<th>MM type</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Clark level</th>
<th>Signs of infiltration/metastasis at first encounter</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conley &amp; Donovan⁷</td>
<td>L</td>
<td>Vermilion</td>
<td>NM</td>
<td>F</td>
<td>52</td>
<td>NS</td>
<td>Negative</td>
<td>36 mo.</td>
</tr>
<tr>
<td>2</td>
<td>Ohtsuka &amp; Nakaoka⁸</td>
<td>L</td>
<td>Vermilion</td>
<td>NM</td>
<td>M</td>
<td>66</td>
<td>NS</td>
<td>Positive</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>Papadopoulos et al.⁹</td>
<td>L</td>
<td>Vermilion</td>
<td>D/N</td>
<td>F</td>
<td>57</td>
<td>II</td>
<td>NS</td>
<td>16 mo.</td>
</tr>
<tr>
<td>4</td>
<td>Tauscher et al.⁷</td>
<td>U</td>
<td>Skin</td>
<td>NM</td>
<td>M</td>
<td>40</td>
<td>III</td>
<td>NS</td>
<td>dead</td>
</tr>
<tr>
<td>5</td>
<td>Tauscher et al.⁷</td>
<td>U</td>
<td>Skin</td>
<td>NM</td>
<td>F</td>
<td>77</td>
<td>IV</td>
<td>NS</td>
<td>dead</td>
</tr>
<tr>
<td>6</td>
<td>Froix &amp; Salti⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>59</td>
<td>II</td>
<td>NS</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>LMM</td>
<td>F</td>
<td>70</td>
<td>II</td>
<td>NS</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>63</td>
<td>V</td>
<td>NS</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>53</td>
<td>V</td>
<td>Positive</td>
<td>NS</td>
</tr>
<tr>
<td>10</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>NM</td>
<td>M</td>
<td>72</td>
<td>V</td>
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<td>Negative</td>
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<tr>
<td>11</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>F</td>
<td>65</td>
<td>I</td>
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<td>NS</td>
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<tr>
<td>12</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>D/N</td>
<td>F</td>
<td>62</td>
<td>V</td>
<td>NS</td>
<td>Negative</td>
</tr>
<tr>
<td>13</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>21</td>
<td>V</td>
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<td>NS</td>
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<tr>
<td>14</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>NM</td>
<td>M</td>
<td>56</td>
<td>V</td>
<td>Positive</td>
<td>NS</td>
</tr>
<tr>
<td>15</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>F</td>
<td>66</td>
<td>I</td>
<td>Negative</td>
<td>NS</td>
</tr>
<tr>
<td>16</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>D/N</td>
<td>F</td>
<td>41</td>
<td>V</td>
<td>NS</td>
<td>Negative</td>
</tr>
<tr>
<td>17</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>21</td>
<td>V</td>
<td>Negative</td>
<td>NS</td>
</tr>
<tr>
<td>18</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>NM</td>
<td>M</td>
<td>56</td>
<td>V</td>
<td>Positive</td>
<td>NS</td>
</tr>
<tr>
<td>19</td>
<td>Tauscher et al.⁷</td>
<td>Ns</td>
<td>Ns</td>
<td>ssM</td>
<td>M</td>
<td>21</td>
<td>V</td>
<td>Negative</td>
<td>NS</td>
</tr>
<tr>
<td>20</td>
<td>Tauscher et al.⁷</td>
<td>U</td>
<td>Ns</td>
<td>Ns</td>
<td>F</td>
<td>66</td>
<td>NS</td>
<td>Negative</td>
<td>53 mo.</td>
</tr>
<tr>
<td>21</td>
<td>Sekido et al.¹⁰</td>
<td>U</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>22</td>
<td>Sekido et al.¹⁰</td>
<td>U</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>23</td>
<td>Sekido et al.¹⁰</td>
<td>L</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
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<tr>
<td>24</td>
<td>Sekido et al.¹⁰</td>
<td>L</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
</tbody>
</table>

* Not included in the study of Raderman et al.⁶

NS = not specified; NM = nodular melanoma; D/N = desmoplastic/neurotrophic; SSM = superficial spreading melanoma; LMM = lentigo maligna melanoma.

The recurrent melanoma was treated by total excision of the left part of the patient’s upper lip. Reconstruction of the defect was delayed until histological examination had confirmed complete extirpation of the tumour. Microscopy of the macroscopically ill-defined, poorly pigmented tumour revealed neurotrophic spindle-shaped cells with multiple mitotic figures. Immunohistochemically, the tumour cells stained strongly positive for S100 and negative for Melan A. The diagnosis of a desmoplastic (neurotrophic) melanoma was made, with wide, clear borders. Reconstruction was then performed by means of a combined Abbe flap and cheek advancement flap.

Five months following reconstruction, the patient is free of local disease.

Discussion

Primary malignant melanoma of the lip is an exceedingly rare condition. In 1986 Raderman et al.⁶ claimed to be reporting the 31st case since the first description of malignant melanoma of the lip in the English literature by Baxter in 1941.

An extensive literature search by the present authors revealed an additional 24 reported cases,⁷-¹³ bringing the total number of reported cases of primary malignant melanoma of the lip in the English literature to 55 (Table I).

The paucity of cases presenting with malignant melanoma of the lip is contrary to what one expects, especially considering that apart from being present in the skin, melanocytes are also commonly found in the normal oral mucosa.⁶,¹⁰ Melanocytes are ectomesenchymally derived dendritic cells present in the germinative layer of the epidermis and mucosal epithelium. Barrett and Beynon⁶ investigated melanin distribution and hence melanocyte activity within the oral epithelium of white-skinned individuals at various sites. Melanin was found in about 50% of the lip samples. From the results of their study, they concluded that there are regional differences in oral epite-
The present study is the first report of a patient with oral malignant melanoma of the upper lip (case 2). The clinicopathological classification of malignant melanoma evolved more than 30 years ago into 6 major groups, of which the superficial spreading type is the most common and accounts for 50–75% of cases. The superficial spreading malignant melanoma is characterised initially by a radial growth phase in which a progressive centrifugal spread of a flat pigmented area is experienced. This growth phase, which is absent in the nodular group of melanomas, was demonstrated in case 1 by the proliferation of atypical melanocytes, singly and in nests, at all levels within the epithelium. The cells may be epitheloid or even spindle-shaped without showing evidence of maturation during the vertical growth phase during which they infiltrate into the dermis. The type of melanoma that develops on sun-exposed skin is the lentigo maligna melanoma and its precursor lesion, the lentigo maligna (or Hutchinson’s melanotic freckle). Lentigo maligna melanoma is characterised by the proliferation of atypical melanocytes in the basal third of the epidermis without pagetoid spread into the other layers of the epidermis. The superficial spreading melanoma is distinguished microscopically from lentigo maligna melanoma by showing pagetoid spread into the other layers of the epidermis. A nodular melanoma generally shows no intra-epidermal component and infiltrates perpendicular to the epidermis, achieving a deeper level more rapidly than the superficial spreading type. The recurrence in case 2 demonstrates the poorer prognosis associated with nodular melanomas.

Elsewhere in the body, depth of infiltration is associated with prognosis. Melanomas less than 0.76 mm in thickness as measured from the outside of the granular cell layer generally fail to show metastases. Several foci in case 1 showed early dermal invasion that did not exceed 0.3 mm and the lesion therefore fell in an excellent prognostic category. The severe degree of solar elastosis bears testimony to the role of sun exposure in the aetiology of melanomas. There is no generally accepted staging system for oral mucosal melanomas as no specific factors are sufficiently prognostic, such as Breslow’s thickness, Clark’s level of invasion and surgical margins, when compared with cutaneous melanomas. In patients with mucosal melanomas, the age and gender of the patient, the anatomical site of origin of the tumour, the clinical stage at initial presentation and ulceration of the primary tumour seem to affect prognosis. Mucosal melanomas less than 1 mm thick without regional lymph node involvement have been reported to have a favourable prognosis.

The prognosis of malignant melanoma of the oral cavity is poor, with a 5-year survival rate ranging from 5% in cases reported earlier to 20% in cases reported later. This has been partly attributed to both the excellent vascularity and good lymphatic drainage of the oral mucosa. Perineural

<table>
<thead>
<tr>
<th>Palate and maxillary gingiva</th>
<th>Mandibular gingiva</th>
<th>Buccal mucosa</th>
<th>Tongue</th>
<th>Lip</th>
<th>Floor of mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>72.7</td>
<td>9.3</td>
<td>7.5</td>
<td>3</td>
<td>7.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>
invasion\textsuperscript{5,9} and infiltration of malignant melanoma of the lip into the minor salivary glands\textsuperscript{3,8} have been described. In a small cohort of patients with malignant melanoma of the lip, with a median follow-up of 40 months, the mortality rate was 36%.\textsuperscript{11} The Sydney Melanoma Unit reported a 40% local recurrence and a 60% mortality rate in their patients with primary malignant melanoma of the lip.\textsuperscript{4} Only 3 of their patients presented with melanoma of the vermilion, of which 2 were desmoplastic. Although dermoscopy offers interesting prospects,\textsuperscript{14} we are of the opinion that clinical suspicion of a malignant melanoma of the lip requires, preferably, an excision biopsy and, on confirmation of the diagnosis, surgical extirpation with adequate surrounding uninvolved lip tissue.

In case 1, the punch biopsy was rapidly followed by full-thickness resection with margins in excess of 10 mm. Exactly what constitutes an adequate resection with ‘clear margins’ in the lip, and specifically the vermilion, has not yet been established with certainty. This may be due to the small number of cases. Some workers argue that the extent of mucosal resection is of little importance, as the prognosis seems to be uniformly poor. We considered a resection with clear margins of 10 mm to be adequate. We do not support the opinion advanced by Sekido et al.\textsuperscript{13} that clear margins of up to 50 mm are still necessary.

Various novel methods of reconstruction of the vermilion and the lip have been proposed. In case 1, reconstruction by means of a full-thickness, unilateral advancement flap (also known as the ‘step-flap technique’), as originally described by Johanson et al.,\textsuperscript{9} was favoured because of the good functional recovery achieved in other patients with similar-sized defects.

Chemotherapy does not contribute to the treatment of non-metastatic melanoma of the lip, and following discussion with the oncologists, it was not considered further. Postoperative, adjuvant radiotherapy to lower the risk of local recurrence has been proposed as being effective in cases presenting with perineural invasion. In a study reported by Owens et al.,\textsuperscript{2} postoperative radiotherapy tended to decrease the risk of local recurrence but did not significantly improve survival in patients with mucosal melanoma of the head and neck.

The first patient (case 1) remained disease-free 60 months after the radical excision of a primary malignant melanoma of the vermilion of the lower lip, with no signs of local recurrence. Good functionality had been obtained with the step-flap technique – at rest, on smiling and when pouting. Case 2 was operated for the recurrent melanoma at an academic institution and seems, 5 months later, to be free of local disease.

We wish to thank Drs Hans Peterse and Christiaan Krabbe for the additional information provided, Dr Ina Franz for assistance with preparation of the manuscript, and Otte Kingma of Medical Photography, Medisch Centrum Leeuwarden, for preparation of the photographs.

REFERENCES


\begin{table}
\centering
\caption{MALIGNANT MELANOMA OF THE VERMILION OF THE LIP}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Author & Case & Lower/upper lip (L/U) & Type & Clark level & Sex & Age (yrs) & Infiltration/meta\sis at first encounter \\
\hline
Raderman et al. & 1 & L & NM & NS & M & 30 & - \\
Ohtsuka & 2 & L & NM & NS & M & 66 & + \\
Nakaoka & & & & & & & \\
Papadopoulos et al. & 3 & L & NM & III & M & 53 & NS \\
& 4 & L & D/N & II & F & 57 & NS \\
& 5 & L & D/N & IV & M & 38 & NS \\
Tauscher et al. & 6 & L & SSM & NS & M & 58 & - \\
Van Wingerden & 7 & L & SSM & M & 58 & - \\
& 8 & U & NM & M & 56 & - \\
\hline
NM = nodular melanoma; D/N = desmoplastic/neurotrophic; SSM = superficial spreading melanoma; NS = not specified.
\end{tabular}
\end{table}
Letter to the Editor

Lentigo maligna successfully treated with imiquimod

To the Editor: Lentigo maligna (malignant melanoma in situ) typically occurs on sun-exposed skin of older patients. Treatment should be excision with at least a 5 mm border of tumour-free skin. However, two therapeutic challenges can arise. Firstly, on some areas of the face appropriate surgery may be technologically challenging. Secondly, in spite of adequate surgical borders, lentigo maligna may recur, and may continue to do so after repeated adequate surgery.

Imiquimod (Aldara; 3M) is a topical cream modifying the local immune response. It is currently registered for treatment of mucosal genital warts and certain basal cell carcinomas. Successful treatment of lentigo maligna using imiquimod has been reported.1 On the basis of this and subsequently published reports, imiquimod was used in the following case.

A 70-year-old man presented with a biopsy-proven lentigo maligna on the forehead. The lesion was treated surgically by a specialist surgeon. Histological examination suggested that it had been completely removed. Ten months later the lesion recurred. Complete surgical removal was performed again, this time by a reconstructive surgeon. Histology confirmed a completely removed multicentric lentigo maligna. Two years later a small, lightly pigmented macule developed in the same area and was treated by a dermatologist with cryotherapy. Treatment was repeated when a new macule appeared a few months later. Two years later the patient presented with two pigmented lesions on the forehead, and two skin biopsies confirmed a multicentric recurrence of lentigo maligna.

Because of failure of surgery and cryotherapy to clear the lesion, imiquimod therapy was initiated. The area was treated once a day, 5 days a week for 6 weeks. The lentigo maligna was clinically completely cleared following this treatment course, and has remained clear for 3 years since then.

What makes this case notable is the fact that the tumour recurred after apparently adequate surgical efforts to eradicate it, while one treatment course of topical imiquimod succeeded in clearing it, with no recurrence 3 years later. Secondly, in most of the published reports treatment was given for 12 weeks or longer. In the case reported here only 6 weeks of treatment, once a day for 5 days a week, was successful, suggesting that very long treatment periods may be unnecessary.

Imiquimod treatment for lentigo maligna should not be seen as a replacement for surgery, but rather as a viable alternative in situations where surgery has failed to eradicate the tumour, or where the potential morbidity of surgery, due to location or size of the tumour, prompts one to consider alternatives.

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REFERENCE