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Malignant melanomas of the oral cavity: heterogeneity of pathological and clinical features

Kenichi Ohashi[1, 2], Tsutomu Kasuga[1], Nobuyuki Tanaka[3], Syoji Enomoto[4], Junichi Horiuchi[5], and Norihiko Okada[6]

[1] Department of Pathology, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113, Japan
[2] Department of Pathology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105, Japan
[3] 1st Department of Oral Surgery, and [4] 2nd Department of Oral Surgery, Faculty of Dentistry, Tokyo Medical and Dental University
[5] Department of Radiology, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan
[6] Department of Oral Pathology, Faculty of Dentistry, Tokyo Medical and Dental University, Tokyo Japan

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Summary. Data on 35 patients with oral malignant melanomas were pooled and the pathological features and the clinical course were examined in detail. Of these 35 cases, 27 (77.1%) showed a two-phase growth pattern, with both a vertical and a radial growth phase. Moreover, these 27 cases were classified into three subtypes according to gross features of the vertical growth phase; nodular, flat elevated and ulcerated types. Almost two-thirds of the cases were of the melanotic type. Malignant melanomas without a radial growth phase were found in 8 instances, all of which showed a nodular growth pattern, 1 being of melanotic type and 7 amelanotic. Mean latent insidious periods were evaluated for the cases with different growth phases. Cases with a radial growth phase exhibited the longest mean latent period (35.7 months), and a median survival time of 23.5 months. Cases without a radial growth phase showed a short mean latent period (2.1 months), and a median survival time of 7.5 months. The thickness of invasion ranged from 2 to 9 mm. Although 77.1% of the cases depicted similar pathological patterns to acral lentiginous melanomas of the skin, oral malignant melanomas demonstrated heterogeneity in morphological features, developmental process and biological behaviour. The histogenesis of oral melanomas is briefly discussed.

Key words: Melanoma – Oral cavity – Acral lentiginous melanoma

Introduction

Malignant melanoma of the oral cavity is a rare tumour. In Western countries, the incidence of oral melanomas has been reported to vary between 0.2 and 5.6% of all melanomas (Pliskin 1979). It is well known that malignant melanomas in Japan and African countries, such as Uganda, develop at sites other than the skin with a relatively high frequency (Broomhall and Lewis 1967). In Ugandan Africans, Broomhall and Lewis reported that 10 out of 125 melanomas (8%) originated in the oral cavity. In Japan, the reported incidence of mucosal melanoma is 21.7–27.1% of all melanomas (Ohsumi and Seiji 1977; Mori 1979). Of the mucosae, the oral cavity is one of the sites most frequently affected, representing 14.0% of all melanomas reported in Japan (Ohsumi and Seiji 1977).

Clinical and pathological similarities between oral melanoma and acral lentiginous melanoma (ALM) of the skin have been pointed out (Clark et al. 1975, 1979; McDonald et al. 1983; Seiji et al. 1983). However, most of the published papers on oral melanomas are confined to case reports and reviews of previous literature. Therefore, detailed analyses of histological and biological heterogeneity have yet to be made.

We report on 35 patients with oral malignant melanomas and analyse their pathological and clinical features in detail. In addition, the morphological heterogeneity and developmental processes of oral malignant melanomas are discussed.

Materials and methods

This study is based on a review of all patients from the files of the Tokyo Medical and Dental University Hospital from 1962 to 1985 with the diagnosis of malignant melanoma of the oral cavity. Because clinical data and macroscopical photographs of cases before 1961 were not complete these cases were omitted from the present study. There were no patients who had other previous primary lesions such as skin melanomas. Of the 35 patients in this study, 10 were reported by Takagi et al. in 1974. Macroscopic features, primary sites and personal data, such as age, sex and clinical appearance of the lesion have been recorded. In 32 patients, biopsy and surgically resected samples were available for histological analysis. Unfortunately, pre-existing lesions, such as oral pigmentation, had not been examined histologically in the present

Offprint requests to: K. Ohashi

series. Haematoxylin and eosin, Masson-Fontana argentaffin staining, DOPA reaction, S-100 protein immunostaining and electron-microscopic examination were performed for melanoma diagnosis.

The following histological variables were examined: thickness of invasion, tumour cell types, pleomorphism, mitotic activity, desmoplasia, inflammatory cell infiltration, epithelial hyperplasia, and the existence of junctional activity. The thickness of the tumour was measured with a micrometer eye-piece using Breslow's method (Breslow 1975).

Follow-up information was requested on 33 patients. According to the criteria previously described, patients were staged on the clinical finding at the time of their initial examination (Shah et al. 1977). Fourteen patients had tumour at the primary site only (stage I), 16 had clinical evidence of regional node metastases (stage II), and 1 patient had distant organ metastases (stage III). Cumulative survival rates of patients for diagnosis-to-death interval were calculated by Kaplan-Meier's method separately for each tumour stage (Kaplan and Meier 1958). The generalized Wilcoxon's analysis was used to verify the statistical difference in survival rates between subgroups.

Table 1. Age and sex distribution of oral melanomas

Authors	Age				Sex	
	<20	21–40	41–60	>60	Male	Female
Ohashi et al. (present study)	0	2	15	18	18	17
Chaudhry et al. (1958)	0	21	38	19	53	28
Takagi et al. (1974)	1	21	52	43	61	56
Liversedge (1975)	0	6	28	26	31	33
Rapini et al. (1985)	1	11	31	34	78	46
Overall	2 (0.6%)	59 (18%)	149 (45%)	122 (37%)	223/386 (58%)	163/386 (42%)

Results

Table 1 shows the age and sex distribution based on our present data and on previous communications. Pathological and clinical data in the present study are summarized in Tables 2 and 3. The present 35 patients showed a male to female ratio of 18:17. The peak incidence was recorded in the sixth decade, and the mean age of patients was 62.4 years (age range: 32–92 years). The mean age of our patients was slightly higher than that of cases studied previously (Chaudhry et al. 1958; Liversedge 1975; Rapini et al. 1985) (Table 1).

The anatomical distribution of oral melanoma was localized in the maxillary gingiva and hard palate mucosa in 17 (49%) and 13 patients (37%), respectively. Tumours arising from the mandibular gingiva (4 cases; 11%) and soft palate (1 case; 3%) were scarce. No patients had melanoma of the tongue, floor of mouth or buccal mucosa.

Twenty-seven patients (77%) had an irregularly dark pigmented macule around the tumour. Clark et al. (1969) and Reed (1976) proposed the concept of the radial growth phase (RGP) and all those macular lesions in which histological examination was done showed an RGP consisting of atypical or malignant melanocytes in the epithelium. Therefore, patients who had a macular component around the tumour were grouped as RGP melanomas in the present study. In most cases, the peripheral region of the macule was irregularly depigmented. The macule/normal mucosa border was ill-defined. The invasive lesions of oral malignant melanoma in the pigmented macule showed characteristic gross features. Nodular protruding lesions surrounded by a pigmented macule were seen in 23 patients (66%). Eighteen patients (51%) showed a melanotic type (Fig. 1a) and 5 patients (14%) showed an amelanotic type (Fig. 1b). Three patients (9%) had a flat or slightly elevated lesion in the pigmented macule without an obvious nodular protrusion (Fig. 1c). Only 1 patient (3%) had an ulcerated lesion without a mucosal elevation in the centre of the pigmented macule (Fig. 1d).

Eight patients (23%) showed a nodular lesion without an adjacent macular component. These patients were grouped as non-RGP melanomas in the present study. Of 8 patients, only 1 presented as a melanotic type (Fig. 1e), whereas the remaining 7 cases were amelanotic (Fig. 1f). It appears that a close relationship may exist between melanization of the melanoma cells and RGP.

Histologically, in sites where the vertical growth phase was characterized by nodular, flat elevated or ulcerated lesions, melanoma cells showed obvious cytological and histological heterogeneities. Cytological characteristics of the oral melanomas could be classified into two major types: namely spindle-cell predominant (SP) and round-cell predominant (RO) types (Fig. 2). In most of the cases, both cell types existed in various ratios. In the SP type (46%), pigmented or non-pigmented melanoma cells grew with a bundle-like or whorling pattern. In the RO type, which corresponds to the epithelioid cell type in the previous literature, the size of melanoma cells and the histological appearance were not uniform. Some cases (46%) revealed relatively large round or polygonal melanoma cells with marked pleomorphism. Epithelioid structure and alveolar formation were unclear in most cases (Fig. 2b). The remaining cases (8%) showed small round cells with little pleomorphism. Although this type of cell had a large eosinophilic nucleolus, they were usually amelanotic or only a little pigmented histologically. Therefore DOPA reaction, immunostaining of S-100 protein and electron microscopic studies were helpful in diagnosis (Fig. 2c). In RGP cases, the SP/RO ratio was 14:9, and in non-RGP patients, 4:3.

In 81% of patients, the superficial mucosal epithelium overlying the tumour showed hyperplastic changes such as acanthosis and elongation of the rete ridges. The surface of the tumour showed ulceration in most cases and thus, in non-RGP patients, junctional activity was observed in only 43%. Regressive changes with infiltration of pigment-laden histiocytes and fibrosis in the submucosal stroma were also seen.

Table 2. Oral malignant melanoma with a radial growth phase in 27 patients

Case no.	Age/sex	Site	Depth of invasion (mm)	Cell type	Latent period	Initial sign	Clinical stage	Treatment	Follow-up
(Flat elevated type)									
1.	65 M	Maxil. gin.	4	RO	6Y	Pigmentation	I	R	14 years 3 months
2.	79 F	Hard palate	1	SP	2M	Pigmentation	I	R	Unknown
3.	58 F	Hard palate	?	?	?	?	II	R, C	Alive (5 years)
(Nodular type, melanotic)									
4.	60 F	Maxil. gin.	6	SP	2M	Nodule	I	R, S	9 years
5.	92 F	Soft palate	3	RO	1Y2M	Nodule	?	–	6 months
6.	73 F	Maxil. gin.	3	RO	1Y6M	Nodule	II	R	3 years
7.	57 M	Maxil. gin.	3	RO	1M	Nodule	II	R, C	10 months
8.	76 F	Hard palate	2	SP	6M	Nodule	III	R	6 months
9.	57 F	Hard palate	9	SP	2Y	Pigmentation	I	R	8 years 4 months
10.	59 F	Maxil. gin.	5	RO	7M	Nodule	II	R, S, C	1 years 3 months
11.	72 M	Hard palate	3	SP	5M	Nodule	I	R, S, C, I	3 years 8 months
12.	32 F	Madib. gin.	3	RO	5Y	Pigmentation	I	R, C	2 years 8 months
13.	65 F	Hard palate	2	SP	3M	Nodule	I	R	4 years 5 months
14.	73 F	Hard palate	3	SP	3M	Nodule	I	R	5 years 7 months
15.	61 F	Hard palate	2	RO	1M	Nodule	I	R	1 year 8 months
16.	61 M	Maxil. ging	?	?	2Y	Pigmentation	I	R	1 year 7 months
17.	47 M	Mandib. gin.	2.5	SP	2M	Nodule	II	R	1 year 10 months
18.	58 F	Maxil. gin.	8	SP	1Y6M	Pigmentation	II	R, S	1 year 4 months
19.	48 M	Maxil. gin.	?	?	7Y	Pigmentation	II	R	8 months
20.	60 F	Maxil. gin.	3	RO	2M	Nodule	I	R, I	2 years
21.	44 M	Maxil. gin.	?	?	3Y	Pigmentation	?	R	1 year 11 months
(Nodular type, amelanotic)									
22.	64 M	Maxil. gin.	2.5	SP	1Y5M	Nodule	I	R, S	4 years
23.	71 M	Maxil. gin.	4.5	SP	4M	Nodule	II	R	1 years
24.	36 M	Maxil. gin.	1.5	SP	2Y	Pigmentation	I	R, S	8 years 6 months
25.	57 M	Maxil. gin.	2	SP	2Y	Nodule	I	R	Unknown
26.	46 M	Maxil. gin.	5	RO	2M	Nodule	II	R, C	8 months
(Ulcerated type)									
27.	75 F	Hard palate	2	SP	1M	Pigmentation	II	R, S	7 months

Maxil. gin., Maxillary gingiva; Mandib. gin., mandibular gingiva;
SP, spindle cell predominant type; RO, round cell predominant type;
R, irradiation therapy; S, surgery, resection of the primary lesion and regional lymph nodes;
C, chemotherapy; I, Immunotherapy

Table 3. Oral malignant melanoma without a radial growth phase in 8 patients

Case no.	Age/sex	Site	Depth of invasion (mm)	Cell type	Latent period	Initial sign	Clinical stage	Treatment	Follow-up
(Nodular type, melanotic)									
28	65 M	Maxil. gin.	5	SP	4M	Nodule	II	R, S	3 years 11 months
(Nodular type, amelanotic)									
29	60 F	Hard palate	8.5	SP	2M	Nodule	I	R, C	6 years 3 months
30	86 M	Maxil. gin.	4	SP	1M	Nodule	?	–	1 month
31	82 F	Whole palate	6	RO	3M	Nodule	II	R, I	3 months
32	47 M	Hard palate	4	RO	1M	Nodule	II	R, S, C	7 months
33	67 M	Hard palate	5	SP	1M	Nodule	II	R, S	8 months
34	58 M	Mandib. gin.	3	RO	3M	Nodule	II	R	5 months
35	73 M	Mandib. gin	?	?	?	?	?	R	2 years 7 months

For abbreviations, see Table 2

The macular component of tumour or RGP showed a lentiginous growth pattern with proliferation of large and atypical melanocytes in the epithelio-stromal junction (Fig. 3a, c). No pagetoid growth pattern was observed in the patients examined. Marked acanthosis and elongation of rete ridges were commonly observed. RGP melanoma cells close to the invasive lesion showed remarkable cellular atypia, whereas melanocytes in peripheral regions of the macule revealed hardly any cellular atypia (Fig. 3d). In peripheral regions, it was difficult

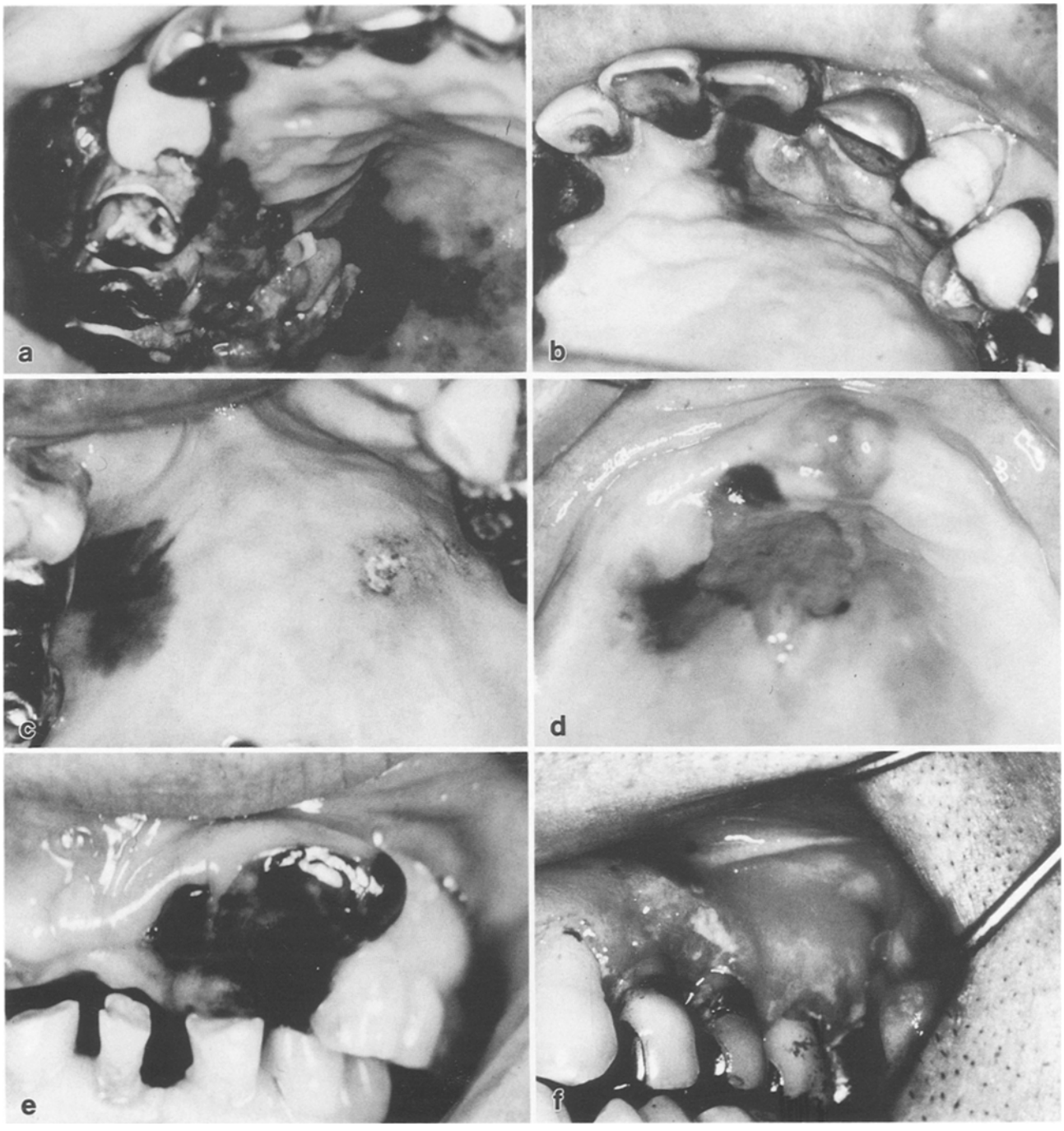

Fig. 1. **a** Malignant melanoma of the oral cavity with a radial growth phase (RGP). A large melanotic nodular lesion located in the maxillary gingiva. Pigmented macular lesion and RGP melanoma proliferating in the palatal mucosa. Note the ill-defined border between macular lesion and normal mucosa. **b** A relatively small amelanotic nodular lesion is located in the maxillary gingiva where the tumour shows a vertical growth phase. Irregularly pigmented macular lesions are of RGP. **c** Flat macular lesion growing in the gingiva-palatal boundary without an evident nodular lesion. In this case the patient survived 171 months. **d** A shallow ulcerated lesion is located in the centre of a pigmented macule without an evident nodular lesion. The thickness of invasion was within 2 mm, but prognosis of the patient (only 7 months) was poor. **e** Non-RGP malignant melanoma. Melanotic type nodular lesion proliferating in the maxillary gingiva without a pigmented macule. The border between the tumour and normal mucosa is distinct. **f** Amelanotic type nodular lesion of the maxillary gingiva. The macular lesion is unclear

to distinguish RGP melanocytes from the benign hyperplastic melanocytes.

By re-examining the clinical records, the initial signs and latent period between initial symptoms and clinical consultation were investigated. In about 30% of patients, the initial sign comprised oral pigmentation only. In the remaining 70% of patients, a nodule or swelling in the gingiva or palate was noted. Pain, haemorrhage, or ill-fitting denture were other symptoms. The latent period, which ranged from 1 month to 7 years, indicated

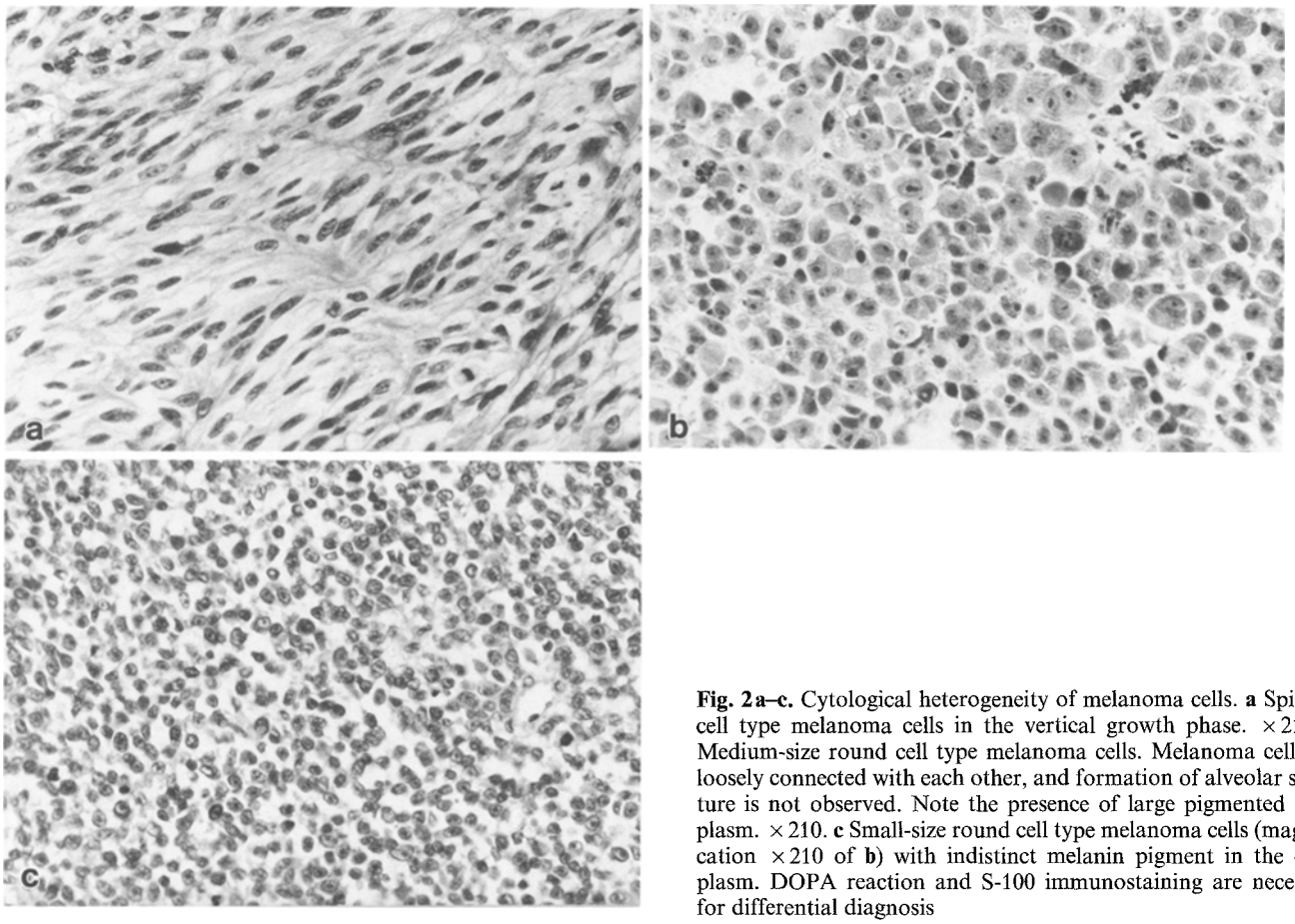

Fig. 2a–c. Cytological heterogeneity of melanoma cells. **a** Spindle-cell type melanoma cells in the vertical growth phase. ×210. **b** Medium-size round cell type melanoma cells. Melanoma cells are loosely connected with each other, and formation of alveolar structure is not observed. Note the presence of large pigmented cytoplasm. ×210. **c** Small-size round cell type melanoma cells (magnification ×210 of **b**) with indistinct melanin pigment in the cytoplasm. DOPA reaction and S-100 immunostaining are necessary for differential diagnosis

a mean interval of 14.9 months. In 27 RGP patients, 11 (31%) noticed oral pigmentation as an initial sign, and the mean latent period extended to as long as 35.7 months. In 3 patients with a flat elevated type of melanoma the initial sign was oral pigmentation. In another 16 patients (46%), a nodule was noticed as the initial sign, with a mean latent period of 6.9 months. However, all 8 non-RGP patients presented with a nodule, the mean latent period of which was only 2.1 months.

Follow-up study was pursued for 33 patients. Only 1 patient is still alive. The survival period or diagnosis-to-death interval ranged from 1 to 171 months, with a median survival time of 22 months. The overall 5-year survival rate was 21%. The median survival times for males and females were 19 and 28 months, respectively. In the female cases, the prognosis was better than observed in males. This is consistent with the tendency in skin melanomas.

In stage I patients, the median survival time was 60 months, and the 5-year survival rate was 50%. In stage II patients, the median survival time was 9 months, and the 5-year survival rate was was 6%. This difference was statistically significant ($P = < 0.01$).

In RGP patients, the median survival time was 23.5 months, and the 5-year survival rate was 24%. In 3 patients with a flat elevated lesion, prognoses were much better than for others. One patient survived for more than 171 months. Another patient has survived for more than 60 months and is still alive at the present time. Follow-up data were not available for the other patients. As for non-RGP patients, the median survival time was 7.5 months and the 5-year survival rate was only 12.5%. In RGP patients, 11 patients were in stage I, 11 patients were in stage II and 1 patient was in stage III. However in non-RGP patients only 1 patient was stage I, and 5 patients were stage II. The difference of clinical stages between RGP and non-RGP patients affected the difference in prognosis.

In 12 stage I patients, the relationship between the survival time and the thickness of invasion was examined. In these patients, the thickness of the tumour ranged from 2 to 9 mm. In 1 patient (case 9), the thickness was 9 mm and reached the level of the maxillary sinus; however, she survived for more than 8 years. Yet another patient (case 27) survived only 6 months although the invasion depth was 2 mm. More stage I cases, especially those in which invasion thickness was less than 2 mm, should be collected to investigate whether there is a correlation between the invasion level and prognosis.

Discussion

By histological findings, original site and clinical course, cutaneous malignant melanomas are morphologically classified into three major types: lentigo maligna mela-

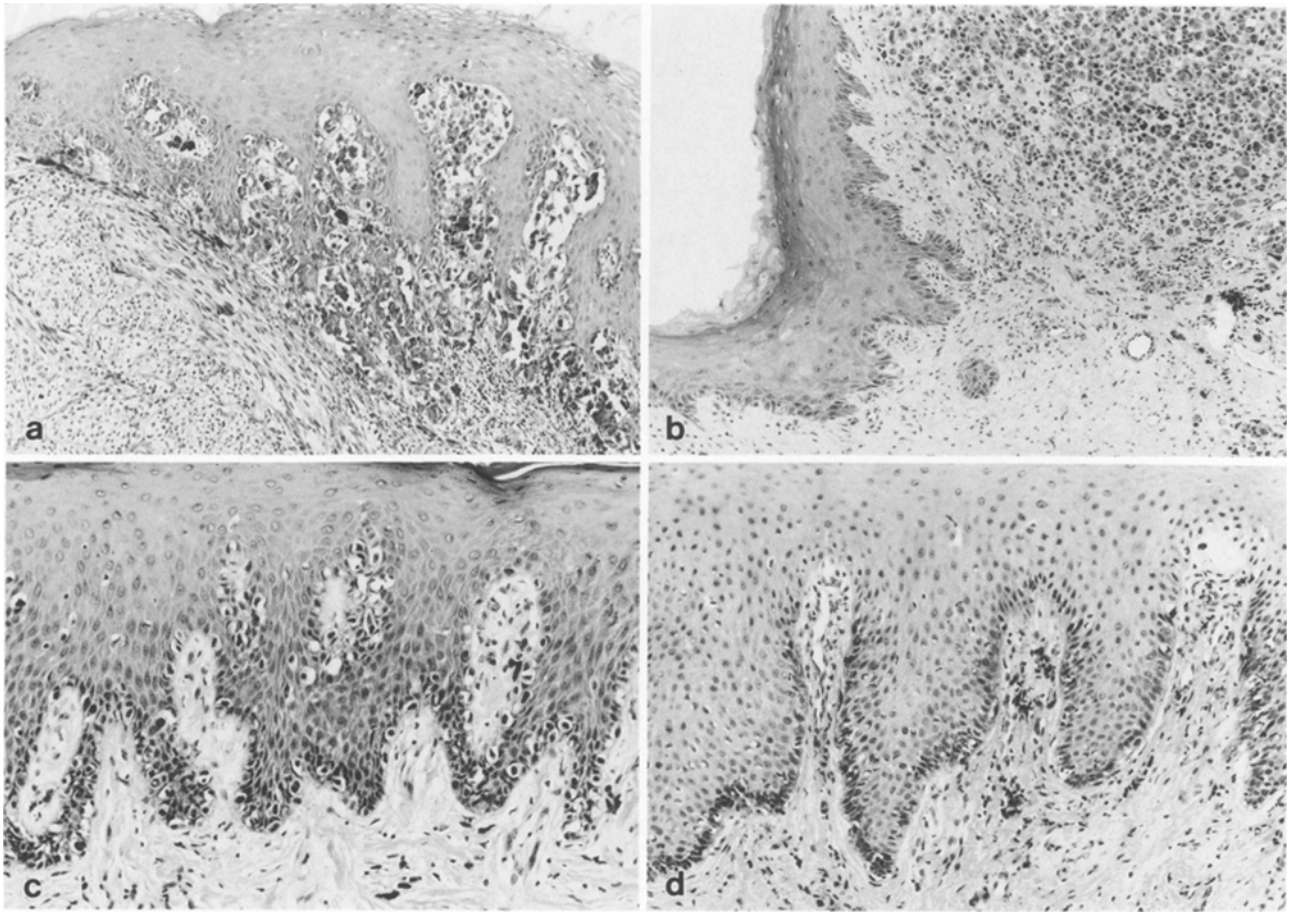

Fig. 3a–d. Border area between the vertical growth phase and the radial growth phase (RGP). **a** RGP malignant melanomas. Spindle-cell type melanoma cells grow in the submucosal stroma (*left half*). Right half shows intraepithelial proliferation of melanoma cells with a lentiginous pattern. Note the marked elongation of rete-ridges. ×82. **b** Non-RGP malignant melanoma. Melanoma shows massive submucosal growth. No intraepithelial proliferation and extension are observed. Hyperplastic changes in the epithelium are not observed. ×110. **c** RGP malignant melanomas. In the macular component close to the invasive lesion, atypical melanocytes proliferate mainly in the epithelio-stromal junction. Hyperplastic changes in the epithelium are evident. ×120. **d** In the peripheral area of the macule, hyperplastic changes of epithelium and pigmentation are remarkable, but melanocytes show no cellular atypia. It is histologically difficult to distinguish the benign melanocytic hyperplasia. ×120

noma (LMM), superficial spreading melanoma (SSM) and nodular melanoma (NM) (Clark et al. 1975). In recent years, a fourth type, ALM, which represents a distinct entity, was proposed by Clark et al. (1975) and Reed (1976). They applied the RGP concept to malignant melanomas involving the palms, soles and subungual regions. RGP lesions of ALM illustrate a similar histology to that of LMM, and it is difficult to distinguish ALM from LMM histologically. However, as ALM represents the characteristic distribution of primary sites combined with the aggressive biological activities of NM, ALM is thus categorized as a new entity.

Including 18 cases with malignant melanomas of the oral cavity, Takagi et al. (1974) reviewed the Japanese literature. They pointed out that oral pigmentation existed prior to the development of these melanomas. Moreover, the pigmented macule around the tumour resembled that of LMM histologically. As such, malignant melanomas of the oral cavity are considered to correspond to LMM pathologically (Takagi et al. 1974). After the proposal of the new ALM entity, Clark et al. (1979) stated that most lesions in the oral cavity with an RGP closely resemble ALM of the skin. They did not consider the term LMM to be appropriate for oral melanomas, since the aggressive biological behaviour of oral melanomas resembles that of ALM more closely than LMM of the skin derivative. Seiji et al. (1979) reported on patients having plantar, subungual and mucosal (P-S-M) melanomas, and they concluded that these melanomas form a clinicopathological entity different from the classification of the other three major types. They designated these as P-S-M melanomas. McGovern et al. (1986) used the term "mucosal lentiginous melanoma" and grouped oral malignant melanomas with other mucosal melanomas. Rapini et al. (1985) stated that it may be preferable to designate such mucosal lesions with a RGP simply as "oral malignant melanoma with an RGP" because the distinction between LMM, ALM and SSM has yet to be evaluated prognostically in a prospective study.

As mentioned above, mucosal and oral melanomas have usually been categorized as one entity, and are considered to correspond to cutaneous ALM. The patholog-

ical heterogeneity of mucosal melanomas has not been fully discussed previously. In Japan, the incidence of mucosal melanomas in non-cutaneous regions is about 20–30% (Ohsumi and Seiji 1977; Mori 1979). Investigations on pathological or biological characteristics of mucosal melanomas are thus warranted in Japan.

Re-examination of the present 35 patients revealed various types of macroscopical and histological features of oral melanomas. In 77.1% of all patients, the tumour showed a two-phase growth pattern with radial and vertical growth phases. The RGP of these cases depicted a lentiginous instead of a pagetoid growth pattern. As Clark et al. described (1975, 1979), these characteristic features of oral melanomas are similar to ALM of the skin. However, 23% of patients had a vertical growth phase only, and RGP was not observed around the tumour. These features correspond to NM of the skin. Further, the size and shape of melanoma cells are not uniform and the degree of melanization is inconsistent. Some round-cell-type melanoma cases showed a small cell size, uniform nucleus and meagre cytoplasm. This type of cell was amelanotic in most cases and was rarely seen in skin ALM. In non-RGP cases without an RGP, most cases were of the amelanotic type.

In order to investigate the developmental process of oral melanomas, the initial symptoms or signs and the latent period before melanoma diagnosis were investigated. In 30% of patients, pre-existing moles had been recognized. Unfortunately these pre-existing moles were not observed histologically; these lesions might be melanocytic hyperplasia or malignant melanoma in situ. Atypical melanocytes or in situ melanoma cells proliferated during RGP to show subsequent submucosal invasion, resulting in the formation of nodular, flat elevated, or ulcerated lesions. In the remaining 70% of patients, malignant melanoma cells invaded the submucosal tissue during the early development stage and a nodule was recognized by patients. Moreover, in some patients (46%), the RGP was extended as the vertical growth phase developed. As regards whether the oral pigmentation is an initial sign, Takagi et al. (1974) considered it to be a pre-malignant melanosis. However, Rapini et al. (1985) pointed out that it is difficult to distinguish this stage from the intra-epithelial malignancy of malignant melanomas. In recent years, many studies on skin malignant melanoma in situ have been reported. Saida and Ohshima (1989) reported on ALM in situ cases in Japan where the symptom-diagnosis latent period ranged from 3 to 10 years. This suggests that some oral melanomas and ALM of the skin show a similar developmental process but other oral melanomas might propagate more rapidly and aggressively than skin ALM.

In general, oral malignant melanomas show a poor prognosis. In our data, most of the cases showed a more aggressive clinical course than skin melanomas, inclusive of NM and ALM. Several hypotheses which explain the poor prognosis of oral melanomas have been discussed. Firstly, the development of oral melanomas is more difficult to discern in the early stage than that of skin melanomas. Most patients only become aware of the tumour in the advanced stage, because of the indistinct onset and asymptomatic nature during the early stage. In the present 29 patients in whom the clinical stage was evaluated, 12 patients were in stage I and the remaining 17 patients had metastases in regional nodes and distant organs. Secondly, it is difficult to perform a radical resection for oral melanoma, especially in advanced cases, because of anatomical considerations and poor accessibility. In the present series, resection of the tumour was performed in only 10 patients and radiation and chemotherapy was given to the remaining patients.

In cutaneous melanomas, the single most important prognostic factor is related to thickness of the invasion (Breslow 1975; Clark et al. 1975; Day et al. 1981; Worth et al. 1989), and in oral melanomas the thickness of invasion is expected to be similarly important. Our present investigation examined if whether the clinical stage and various histological features in the vertical growth phase, such as thickness of invasion, cytological type, cellular pleomorphism, mitosis index, desmoplasia and inflammation, were valuable factors affecting the prognosis. There is a correlation between the clinical stage and the survival time but the other histological variables could not be evaluated because there were not enough patients in stage I. In RGP cases, a small population with relatively good prognosis was recognized. In these 3 cases nodular protrusion due to vertical growth was not obvious; however, flat and elevated pigmented macules did exist, and the invasion in these 3 cases did not extend as deep as in others. Comparing the survival time between RGP and non-RGP malignant melanoma cases showed that the latter presented a more aggressive course than the former because most non-RGP patients already had lymph node metastases (stage II) when the diagnosis was established.

The histogenesis of malignant melanomas in mucosal tissues has not been extensively investigated. Trodahl and Sprague (1970) reported that the incidence of naevocellular naevi in the oral cavity is low compared to that of malignant melanomas. Therefore, naevus cells are considered to be precursor cells in a minority of cases. In our 35 patients, no naevocellular naevi co-existed with malignant melanomas. Buchner and Hansen (1980) reported that naevus cells in the oral cavity are most commonly distributed in the palatal mucosa, which is also the commonest site for oral malignant melanomas.

In cutaneous malignant melanoma, most cases begin de novo from normal melanocytes at the dermoepidermal junction (Ackerman 1980; Ackerman and Mihara 1985). However, in the mucosal tissue, mechanisms related to the melanocytic increase have not been clarified. In human oesophageal mucosa, melanocytes in the mucosal epithelium increase in proportion to the degree of hyperplastic change, and the existence of a growth factor as a mediator has been speculated (Ohashi et al. 1990). Another possibility considers the submucosal melanocyte or other neural crest cells as a precursor. Uehara et al. (1987) reported that melanocytes are mainly distributed in the stroma but not in the epithelial cells of nasal mucosa. They further emphasized the stromal melanocyte as a precursor cell for malignant melanomas. Kanno et al. (1987) demonstrated that perifollicular

Schwann cells in mice are able to produce melanosomes after exposure to chemical carcinogens, and suggested that melanocytes and Schwann cells may be precursor cells of malignant melanomas. As regards non-RGP cases, especially the cases in which junctional activity was not clear, stromal melanocytes and Schwann cells cannot be excluded as possible precursors.

Our 35 oral malignant melanoma cases showed heterogeneity in morphological features, developmental process and biological behaviour. A majority of the cases showed similar pathological features and developmental processes to skin ALM, but other cases manifested no RGP (like NM) and a more aggressive clinical course than ALM. We conclude that, for the time being, skin ALM and oral melanomas should be treated as separate entities. More information on oral and other mucosal melanomas must be gathered to establish the distinct characteristics of mucosal melanomas. Patients with oral melanoma at an early stage, malignant melanoma in situ, or melanocytic hyperplasia must be collected for further studies on the histogenesis of these lesions. If accurate diagnosis and adequate treatment were performed during RGP, in early invasive cases, the prognosis of oral melanomas might be improved remarkably.

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