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# Metastases of malignant melanoma simulating soft tissue sarcoma

## A clinico-pathological, light- and electron microscopic and immunohistochemical study of 21 cases*

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**Summary.** Metastases of cutaneous malignant melanoma (MM) of ordinary type can resemble various types of soft tissue sarcoma light microscopically to a degree which has not been previously recognized. Twenty-one cases are described, in which the tumours were originally diagnosed as a soft tissue sarcoma. Seven tumours were predominantly of blue and spindle-cell, fascicular type, resembling malignant peripheral nerve sheath tumour and at times monophasic synovial sarcoma. Ten tumours which were of fascicular and predominantly storiform type, and included uni- and multi-nuleated pleomorphic cells resembled malignant fibrous histiocytoma. Due to the presence of multivacuolated lipoblast-like tumour cells, 2 of these 10 tumours resembled pleomorphic liposarcoma. One had a predominantly myxoid and hypocellular appearance and 5 additional tumours included such areas. The diagnoses were revised after ultrastructural examination with the demonstration of melanosomes in 13 of 16 studied cases and the immunohistochemical demonstration of positivity using anti-S-100 protein antibodies and the anti-melanoma antibody NKI/C3 in all cases. The anti-melanoma antibody HMB 45 gave a positivity in 9 of 21 cases. Light microscopically, sparse amounts of melanin were noted in 7 tumours using the Whartin-Starry technique. Eleven tumours occurred at sites close to major lymph node groups and in 9 of these cases, lymphoid tissue was associated with the tumours, suggesting that they represented lymph node metastases. Following a review of the patients' clinical histories and renewed clinical examination, primary cutaneous MM was demonstrated in 10 of 21 patients and in 1 case an MM in regression was detected. The origin of the 10 tumours without a detected primary is discussed, including the possibility of an overlooked primary, spontaneous regression of a primary and a de novo origin from lymph nodes and soft tissues.

**Key words:** Malignant melanoma – Soft tissue sarcoma

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* Case 2 presented by one of us (L. Angervall) at the Slide Seminar on Soft Tissue Tumors with Special Emphasis on Modern Techniques (Chairman: F.M. Enzinger), Symposium Management of Soft Tissue and Bone Sarcomas, European Organisation for Research on Treatment of Cancer (EORTC), Utrecht, The Netherlands, June 1984
Case 1 presented by one of us (L.-G. Kindblom) at the Soft Tissue Tumors Slide Seminar (Chairmen: L. Angervall and J. Costa), The XII European Congress of Pathology, Porto, Portugal, September 1989

### Introduction

Primary and metastatic malignant melanoma may assume a histological pattern which makes the light-microscopic identification of the tumours difficult, or even impossible, especially when they are amelanotic. An example of the divergent histological appearance of primary cutaneous malignant melanoma is the so-called desmoplastic type of malignant melanoma (Conley et al. 1971; Egbert et al. 1988; Jain and Allen 1989), which is dominated histologically by a normally amelanotic spindle-shaped tumour cell population located deep in the dermis, within a sometimes strongly desmoplastic stroma. At times desmoplastic malignant melanoma has been confused with a fibromatosis or fibrosarcoma (Conley et al. 1971; Jain and Allen 1989). Metastases from a primary cutaneous malignant melanoma of the classical type may also present a divergent histological appearance. In such instances, the identification of the melanocytic nature of the tumour may be difficult, particularly in cases where the primary remains unknown, something which occurs in about 5% of all cases of malignant melanoma (Das Gupta et al. 1963; Milton et al. 1967; Baab and MacBride 1975; Guiliano et al. 1980; Chang and Knapper 1982; Panagopoulos and Murray 1983). Metastases of malignant melanoma with a neurosarcomatous appearance (Nyong'o et al. 1986) and myxoid variants, which may simulate soft tissue sarcoma (Bhuta et al. 1986) have previously been described.

The wide spectrum of histological appearances which metastatic malignant melanoma can assume, including soft tissue sarcoma-like patterns, has not received a great deal of attention in the literature. With the increasing use of immunohistochemistry and electron microscopy as complements to conventional light microscopy in the diagnosis of soft tissue tumours, we have become increasingly aware of the fact that metastases of malignant melanoma have an ability to simulate various types of soft tissue sarcoma to an extent which seems not to be recognized. The present report is an investigation of a series of 21 cases which at initial light microscopy had been diagnosed as various types of tissue sarcoma, but where the complementary electron-microscopic and/or immunohistochemical investigations indicated that they in fact represented a sarcoma-like malignant melanoma, with or without a documented primary in the skin.

## Materials and methods

The series consisted of 21 tumours, which at the initial light microscopic examination had been interpreted as soft tissue sarcoma, but which upon ultrastructural and/or immunohistochemical analysis were re-diagnosed as metastatic malignant melanomas. The patients' previous histories were carefully reviewed. Previously removed cutaneous lesions were re-examined. Renewed clinical examinations were performed in several cases. Six of the tumours were collected from the files of the Department of Pathology, Sahlgren Hospital, Gothenburg, and 15 of the tumours had been referred to us for consultation. In all the cases, up to date clinical and follow-up data were collected and evaluated.

For light microscopy new sections were prepared from the paraffin blocks and were routinely stained with haematoxylin and eosin and the trichrome stain according to van Gieson (the haematoxylin-van Gieson method). The sections were stained according to Masson-Fontana, and with the Wharton-Starry stain at pH 3.2 as described by Warkel et al. (1980) for the demonstration of melanin. In order to characterize the glucosaminoglycans in 6 myxoid tumours, stainings were performed with alcian blue at pH 2.5 and 1.0, and with toluidine blue at pH 4.0 and 1.0.

The antibodies used for immunohistochemistry, their respective working dilutions and control tissues are listed in Table 1. The avidin-biotin complex (ABC) method (Hsu et al. 1981) was employed, using the Vectastain ABC kits (Vector Labs, Burlingame, Calif., USA) according to the instructions except for a prolonged incubation time for the primary antibody (16 h at 4° C). The end products were visualized by treating the sections with a freshly made solution of 0.05% diaminobenzidine tetrahydrochloride with 0.02% hydrogen peroxide. The antibodies and the chromogenic substrate were diluted in TRIS buffer saline (TBS) (0.05 M, pH 7.4). For the study of the cytokeratins CAM 5.2 and AE1/AE3, the ABC-technique was applied with prior digestion with 0.05% trypsin (Sigma, St Louis, Mo., USA) in TBS containing 0.1% $CaCl_2$ at pH 7.8 for 20 min at 37° C. The monoclonal antibody HMB 45 was used with and without prior digestion with 0.01% pronase (Serva, Heidelberg, FRG) in TBS at pH 7.4 for 30 min at 20° C.

Electron microsopy was performed in 16 cases. In 3 cases, small pieces of fresh tumour tissue were put into 3% glutaraldehyde in 0.1 M sodium cacodylate buffer, fixed for 1 h in 1% $OsO_4$ in cacodylate buffer, dehydrated in ethanol, embedded in Epon or Agar resin and cut in an a LKB ultrotome (Bromma, Sweden). In 7 cases, only formaldehyde-fixed tissue was available and, in one case, paraformaldehyde was the primary fixative used. From these 8 specimens, small pieces were fixed for 1 h in 1% $OsO_4$ in cacodylate buffer, and subsequently processed as described above. Small pieces from 5 tumours were selected and cut out from the paraffin blocks, carefully deparaffinized in xylol, rehydrated in decreasing concentrations of alcohol, washed in cacodylate buffer, fixed in 1% $OsO_4$ and dehydrated in ethanol. They were then embedded as described above. One-micrometre-thick sections were stained with toluidine blue, and ultrathin sections were stained with uranyl and lead citrate and examined in a Philips 400 electron microscope. In one case, the Wharton-Starry technique modified for electron microscopy, as described by van Duinen et al. (1983), was applied for the ultrastructural demonstration of melanin.

**Table 1.** Antibodies used in the study, their working dilutions and control tissues

| Antibody | Working dilution | Control tissue |
|---|---|---|
| Polyclonal anti-S-100 protein[a] | 1:2000 | Schwann cells of nerves |
| Monoclonal anti-vimentin[b] | 1:100 | Fibroblasts, endothelium |
| Monoclonal anti-chromagranin[c] | 1:2500 | Carcinoids |
| Monoclonal anti-desmin DESM 33[d] | 1:40 | Smooth muscle |
| Monoclonal anti-melanoma HMB 45[c] | 1:20 | Typical cutaneous malignant melanomas |
| Monoclonal anti-melanoma NKI/C3[d] | 1:20 | Typical cutaneous malignant melanomas and pigmented nevi |
| Monoclonal anti-cytokeratin CAM 5.2[e] | 1:4 | Breast carcinoma |
| Monoclonal anti-cytokeratin AE1/AE3[f] | 1:500 | Skin |

[a] Prof K. Haglid, Department of Histology, University of Gothenburg, Sweden
[b] Dakopatts, Copenhagen, Denmark
[c] Enzo, New York, NY, USA
[d] Monosan, Nistelrode, Holland
[e] Bectin-Dickinson, Mountain View, Calif., USA
[f] Hybritech, San Diego, Calif., USA

## Results

The clinical findings are summarized in Tables 2–4. The tumours were divided into two groups: group A, metastases of malignant melanoma for which a primary cutaneous malignant melanoma was established (cases 1–11); group B, metastases of malignant melanoma for which no primary malignant melanoma could be established (cases 12–21).

The majority of the 21 tumours presented clinically as painless lumps. Two of the 6 tumours located in the groin were suspected clinically of being hernias, and another was detected *en passant* at hernia surgery. In only 2 of the cases of group A (cases 3 and 5) was the possibility of a metastatic malignant melanoma raised pre-operatively, since there was a known recent history of malig-

**Table 2.** Clinical findings in 11 patients with sarcoma-like metastases of malignant melanoma, with identified cutaneous primary tumour (group A)

| Case | Sex | Age | Location | Largest ∅ (cm) | Clinical evaluation, course and follow up-duration[a] |
|---|---|---|---|---|---|
| 1 | F | 42 | Right groin | 7 | "Naevus" removed right foot 6 years earlier. Re-evaluated diagnosis: MM Clark III, Breslow 0.7 mm. TTD with metastases to lymph nodes and colon, 3 years |
| 2 | F | 70 | Left groin | 3 | Cutaneous tumour left heel detected and biopsied: MM. Dead from TD with metastases to lungs, liver lymph nodes, 0.5 years |
| 3 | F | 85 | Left groin | 3 | MM Clark III, Breslow 1.2 mm removed left 5th toe 2 years earlier. Dead from TD with metastases to skin and adrenals |
| 4 | M | 58 | Spinal canal | "Large" | Spinal, pulmonary and hepatic metastases detected at pre-operative examination prior to disc surgery. "Atypical naevus" removed temple 4 years earlier. Re-evaluated diagnosis: MM Clark III, Breslow 0.9 mm. Dead from TD, with meatastases to liver, lungs, bone, brain, adrenals, spinal canal, 1 year |
| 5 | F | 56 | Left lower leg | 5 | MM Clark III, Breslow 2.1 mm removed back 2 years earlier. Dead from TD, with metastases to lymph nodes and bone, 1 year |
| 6 | F | 42 | Peri-toneum | 2 | MM Clark III, Breslow 0.9 mm removed back 18 years earlier. Dead from TD with metastases to peri-toneum, liver, lymph nodes, 0.5 year |
| 7 | F | 59 | Left lower arm | 2 | Left 2nd finger amputated 4 years earlier for subungual bleeding "haemangioma", specimen not examined histologically. Dead from TD, 4 years |
| 8 | M | 21 | Occipi-tally | 2 | "Naevus" removed scalp 4 years earlier. Re-evaluated diagnosis; MM. TTD, 2 years |
| 9 | F | 37 | Left lower leg | 1.5 | "Naevus" removed left foot 17 years earlier. Re-evaluated diagnosis: MM Clark III, Breslow 0.9 mm. NETD, 1 year |
| 10 | F | 61 | Left groin | 2.5 | MM in regression detected and removed left lower leg, TTD, 1.5 years |
| 11 | M | 62 | Right thigh | 2.5 | "Atypical naevus" right lower leg removed 23 years earlier. Re-evaluated diagnosis: MM Clark IV, Breslow 3.2 mm. NETD 0.5 year |

[a] Follow-up durations listed indicate the time which has elapsed after the detection of the sarcoma-like metastasis. MM, Malignant melanoma; TTD, terminal tumour disease (wide-spread distant metastasis); TD, tumour disease; NETD, no evidence of tumour disease

nant melanoma. The initial clinical and, in particular, the histological findings of these tumours were such that a diagnosis of metastatic malignant melanoma was, however, considered most unlikely. In 2 cases in group A (cases 2 and 10), a synchronous primary malignant melanoma was detected upon further clinical examination, prompted by the eventual histological diagnosis of metastatic malignant melanoma made by us. In the remaining 7 cases in group A, a history of a primary cutaneous malignant melanoma was confirmed following an extensive review of the clinical records. In 6 of these cases, the re-evaluation of histological slides of the cutaneous lesions provided evidence of malignant melanoma. One patient (case 7) had undergone a left index-finger amputation for a pigmented, bleeding, recurrent, ulcerated, subungual "heamangioma" 4 years earlier. The surgical specimen was never examined histologically. The time elapsing between the removal of the detected primary malignant melanomas and the development of their respective metastases ranged from 0 to 23 years. In 3 cases, the metastases appeared after 17, 18 and 23 years respectively. The follow-up data are summarized in Table 4.

Of the 21 tumours, 6 were located deeply in the groin, 3 deeply in the axilla, 7 in the extremities, 3 in the abdomen, 1 in the neck and 1 in the spinal canal. The cut surfaces of all were uncharacteristic, showing grey-white

**Table 3.** Clinical findings in 10 patients with sarcoma-like malignant melanoma of soft tissues with unknown primary (group B)

| Case | Sex | Age | Location | Largest ∅ (cm) | Clinical course and follow-up duration |
|---|---|---|---|---|---|
| 12 | F | 41 | Pelvis | 7 | Dead from TD with metastases to lymph nodes, breast, lungs, 2 years |
| 13 | M | 50 | Left axilla | 10 | Dead from TD with metastases to lymph nodes, heart, liver, bone, pancreas, lungs, peritoneum, kidney, 2 years |
| 14 | M | 84 | Right thumb | 2 | Dead from cardiac disease, 1 year, NETD |
| 15 | F | 74 | Upper arm | 2 | Dead from TD, with metastases to lung and liver, 1 year |
| 16 | F | 76 | Right groin | 4 | Dead from TD, with metastases to lung, liver, spleen, lymph nodes, pericardium, pleurae, kidney, bone, 1 year |
| 17 | F | 61 | Left groin | 4 | Dead from TD, with metastases to lungs and liver, 1 year |
| 18 | M | 76 | Right axilla | 7 | NETD 10 years |
| 19 | F | 71 | Left upper arm | 6 | Dead from TD, with metastases to lymph nodes, 0.5 year |
| 20 | M | 30 | Left axilla | 2 | Alive with multiple subcutaneous metastases, 1 year |
| 21[a] | F | 51 | Small bowel | 4 | Dead from TD with metastases to liver, lungs, lymph nodes, 1 year |

[a] May possibly be primary in small bowel
TD, Tumour disease; NETD, no evidence of tumour disease

**Table 5.** Predominant histological appearance in 21 cases of sarcoma-like metastases of malignant melanoma

| Predominant appearance | Groups A+B ($n$=21) |
|---|---|
| Fibrosarcomatous, mPNST-like or monophasic synovial sarcoma-like | 7 |
| MFH-like or leiomyosarcoma-like | 8 |
| Liposarcoma-like | 3 |
| Rhabdomyosarcoma-like | 1 |
| Haemangiopericytoma-like | 1 |
| Myxoid | 1 |

mPNST, Malignant peripheral nerve sheath tumour; MFH, malignant fibrous histiocytoma

tumour tissue, sometimes with areas of necrosis. No areas of pigmentation were seen. The largest diameter of the tumours is given in Tables 2 and 3. The median value was 2.5 cm (1.5–7) in group A and 4 cm (2–10) in group B.

Microscopically, all the tumours had a wholly or predominantly soft-tissue sarcoma-like appearance. The predominant histological appearances are listed in Table 5. The spectrum of morphological appearance is illustrated by the primary diagnoses, which were as follows: malignant fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, neurofibrosarcoma, synovial sarcoma, liposarcoma, chordoma, malignant haemangiopericytoma, epithelioid sarcoma and unspecified sarcoma.

Eight of the 21 tumours had an appearance resembling that of malignant fibrous histiocytoma of the spindle-cell, fascicular and storiform type, and of the pleomorphic type. These tumours were characterized by polymorphic spindle-shaped, usually large cells, arranged either in more or less distinct bundles forming whorled structures, or forming prominent fascicular or storiform patterns (Fig. 1A, B). In areas there were groups of large, sometimes huge, polymorphic polygonal tumour cells, with one or multiple irregular large nuclei (Fig. 1C,

**Table 4.** Summary of clinical findings in 21 patients with sarcoma-like metastases of malignant melanoma (groups A and B)

| Patients | Age | | Sex | | | | Course | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median | Range | Males | | Females | | NETD | | | | Dead or ATD | | | |
| | | | $n$ | % | $n$ | % | $n$ | % | Follow-up (years) | | $n$ | % | Follow-up (years) | |
| | | | | | | | | | Median | Range | | | Median | Range |
| Group A ($n$=11) | 58 | 21–85 | 3 | 27 | 8 | 73 | 2 | 18 | 0.75[a] | 0.5–1.5[a] | 9 | 82 | 2[a] | 0.5–5[a] |
| Group B ($n$=10) | 66 | 30–84 | 4 | 40 | 6 | 60 | 2 | 20 | 5.5 | 1–10 | 8 | 80 | 1 | 0.5–2 |
| All ($n$=21) | 59 | 21–85 | 7 | 33 | 14 | 67 | 4 | 19 | 1.25 | 0.5–10 | 17 | 81 | 1 | 0.5–5 |

[a] Follow-up durations listed indicate the time which has elapsed after the detection of the sarcoma-like metastasis
NETD; No evidence of tumour disease; ATD, alive with tumour disease

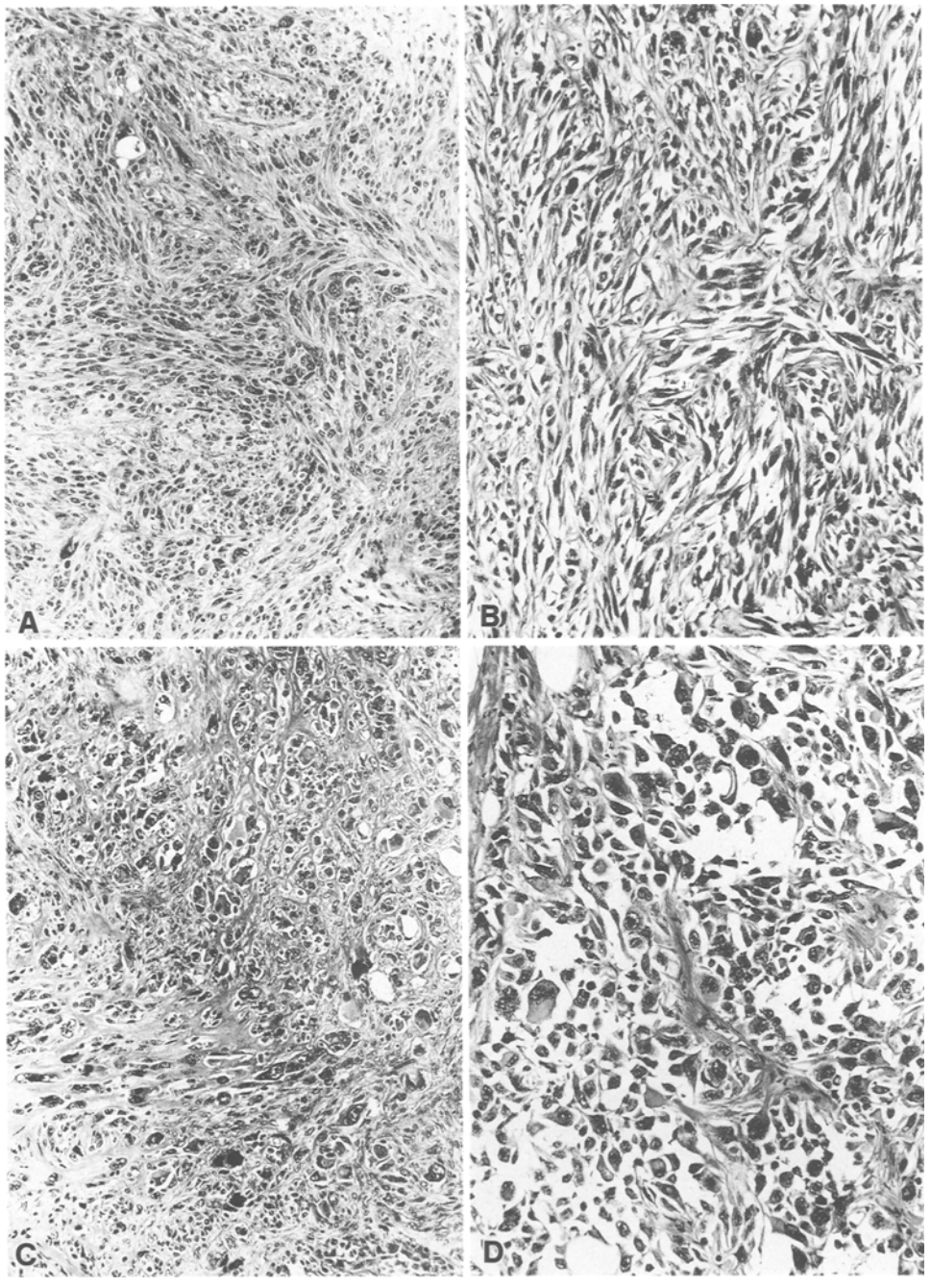


**Fig. 1. A, B.** Fairly large, polymorphic tumour cells tend to form bundles arranged in a whorled or storiform-like pattern. **C, D** Highly polymorphic areas with bizarre, often multinucleated tumour giant cells. H & E; **A–C** ×100; **D** ×240

D). The cytoplasm of some of these large cells was evenly stained and homogeneous, while it was vacuolated in others. In 2 tumours, a distinct eosinophilia and picrinophilia of the cytoplasm, together with a prominent fascicular pattern of the extremely elongated tumour cells sometimes with blunt-ended nuclei, gave rise to a leiomyosarcoma-like appearance. The nuclei of both the spindle-shaped and the large polygonal and polymorphic cells had a prominent and distinct nuclear membrane and often displayed a vesicular appearance, with one or more prominent nucleoli.

Seven of the tumours had a fibrosarcoma-like appearance, being highly cellular and almost entirely composed of often darkly blue-staining spindle-shaped cells of moderate size, arranged in a dense fascicular pattern (Fig. 2). The appearance of these tumours resembled malignant peripheral nerve sheath tumour and monophasic synovial sarcoma.

One tumour, located in the pelvis (case 12), had a largely myxoid appearance, corresponding to that described by Bhuta et al. (1986), and was initially interpreted as a chordoma. Single spindle-shaped, stellate or rounded tumour cells or strands of such cells were enclosed within an abundant weakly basophilic mucous matrix. Three of the 7 fibrosarcoma-like tumours also contained such myxoid areas. In these 3 cases, there were

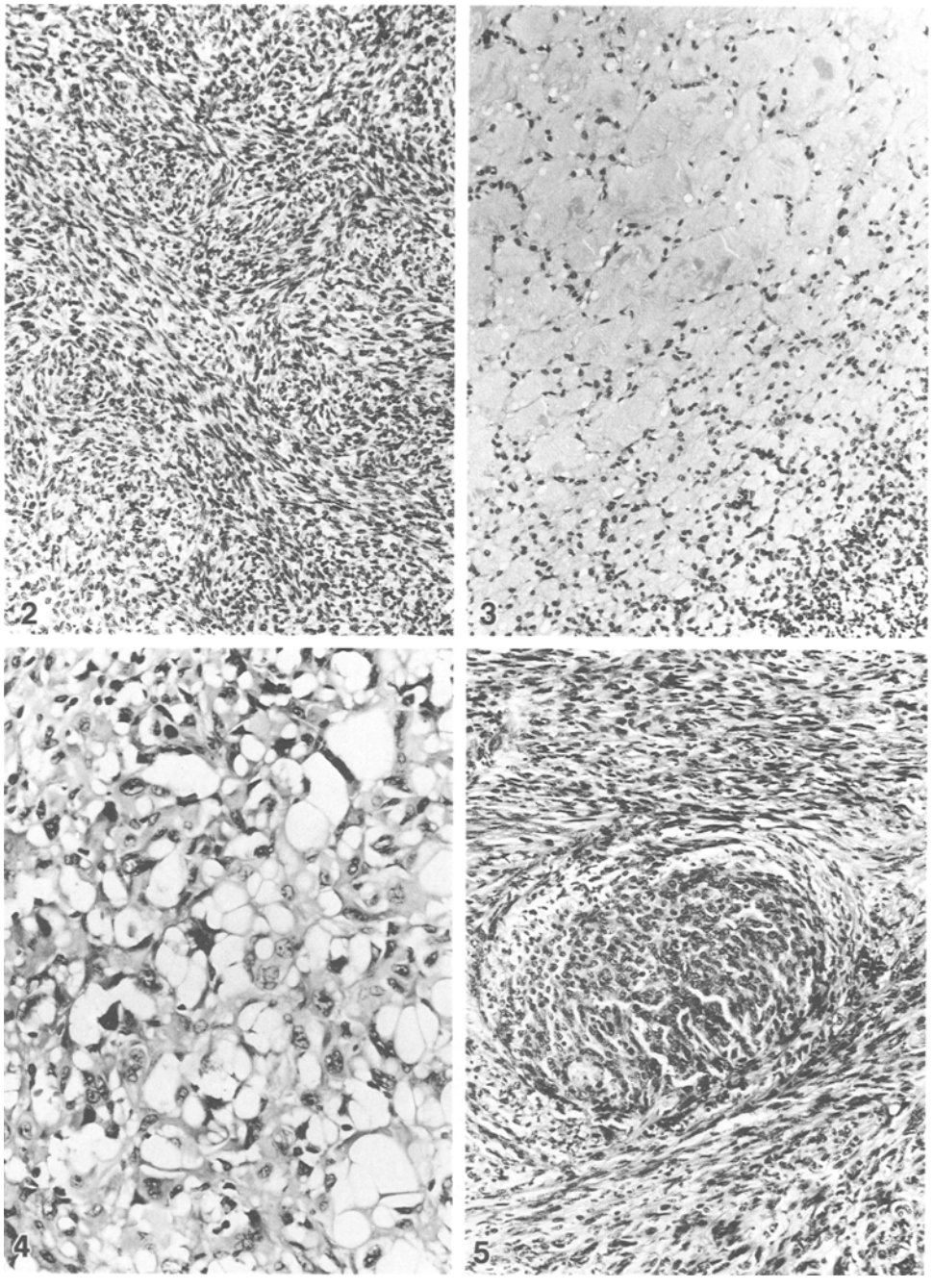

**Fig. 2.** Spindle cells of moderate size forming dense intertwining bundles. H & E, ×100

**Fig. 3.** A poorly cellular myxoid area within an otherwise predominantly spindle cell, fascicular tumour. The abundant mucous matrix tends to form pools surrounded by small, rounded or short spindle cells. H & E, ×100

**Fig. 4.** Large, polymorphic tumour cells with one or more hyperchromatic nuclei, with a partly scalloped shape due to the multiple cytoplasmic vacuoles, resembling atypical multivacuolated lipoblasts of pleomorphic liposarcoma. H & E, ×240

**Fig. 5.** Small nests of epithelioid tumour cells with a "naevoid" appearance within a predominantly spindle cell, fascicular tumour. H & E, ×100

also some large cystic spaces within the myxoid areas resembling those that may be seen in synovial sarcoma (Enzinger and Weiss 1988) and, in 1 tumour, the myxoid matrix appeared in pools, as in myxoid liposarcoma (Fig. 3). Myxoid changes were also present in one moderately cellular tumour, which contained elongated eosinophilic and spindle-shaped cells and thereby resembled embryonal rhabdomyosarcoma.

The 3 tumours which initially had been interpreted as liposarcomas presented features resembling pleomorphic liposarcoma in 2 of the cases and round-cell liposarcoma in 1 case. The 2 tumours which resembled pleomorphic liposarcoma contained areas with a very strong cellular and nuclear polymorphism, including multinucleated bizarre tumour giant cells. In both of these there were numerous uni- and multinucleated tumour cells containing multiple cytoplasmic vacuoles of varying size, occasionally giving a scalloped appearance to the nuclei (Fig. 4). One contained scattered osteoclast-like multinucleated cells. Both the pleomorphic liposarcoma-like tumours also contained spindle-cell areas with a storiform or fascicular pattern. The round-cell liposarcoma-like tumour was mainly characterized by rounded cells of moderate size which contained one or a few cytoplasmic vacuoles in areas, although this did not influence the oval or round shape of the nuclei. The presence in this case of poorly cellular, myxoid areas, with a focal tendency of pooling of mucosubstances, pro-

**Table 6.** Immunohistochemical and histochemical findings, occurrence of identified primary tumour, melanosomes, and naevoid areas in 21 cases of sarcoma-like metastases of malignant melanoma

| Group | Case | Identified primary | S-100 | NKI/C3 | HMB 45 | Vimentin | Desmin | Cytokeratins[a] | Chromogranin | W-S, Masson | Melanosomes | Nevoid areas |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 1 | yes | + | + | + | + | − | − | − | + | + | − |
| | 2 | yes | + | + | − | + | − | − | − | − | ?[b] | + |
| | 3 | yes | + | + | − | + | − | − | − | + | + | − |
| | 4 | yes | + | + | + | + | − | − | − | − | ND | − |
| | 5 | yes | + | + | − | − | − | − | − | − | ND | − |
| | 6 | yes | + | + | + | + | − | − | − | − | ND | + |
| | 7 | yes | + | + | + | + | − | − | − | + | + | − |
| | 8 | yes | + | + | + | + | − | − | − | − | ND | + |
| | 9 | yes | + | + | − | + | − | − | + | + | ND | − |
| | 10 | yes | + | + | − | − | − | − | − | + | + | − |
| | 11 | yes | + | + | − | + | − | − | − | + | + | + |
| B | 12 | no | + | + | − | + | − | − | − | − | + | + |
| | 13 | no | + | + | + | + | − | − | − | − | + | − |
| | 14 | no | + | + | + | + | − | − | − | − | NA | − |
| | 15 | no | + | + | + | + | − | − | − | − | + | − |
| | 16 | no | + | + | − | + | − | − | + | − | + | + |
| | 17 | no | + | + | − | + | − | − | − | − | + | − |
| | 18 | no | + | + | + | + | − | − | − | − | NA | − |
| | 19 | no | + | + | − | + | − | − | − | + | + | + |
| | 20 | no | + | + | − | + | − | − | − | − | + | − |
| | 21 | no | + | + | − | + | − | − | + | − | + | + |

[a] AE1/AE3 and CAM 5.2
[b] Strongly melaninized melanosomes or secondary lysosomes demonstrated
W-S, Whartin-Starry; ND, not done; NA, not possible to assess

duced a further resemblance to liposarcoma. One tumour had the features of a malignant haemangiopericytoma, with small nests of tumour cells protruding into sinusoidal or capillary-like angulated vessels.

Small foci of epithelioid tumour cells, with a tendency of forming nests or whorled structures with a nevoid appearance, resembling classical malignant melanoma, were observed in 8 tumours, 4 in group A and 4 in group B (Fig. 5) (Table 6). Clearly identifiable remnants of lymph nodes were present in 5 of the 21 tumours. In 4 additional, areas of lymphoid tissue were found peripherally and sometimes also more centrally in the tumour tissue. There were thus 9 tumours, 2 of which came from group A and 7 from group B, which probably represented lymph node metastases. All 9 were located adjacent to major lymph node groups; 7 in the groin or axilla and 1 each in the neck and pelvis.

In all cases but one the 10 primary cutaneous malignant melanomas available for light-microscopic review were of the classical type, characterized by atypical epithelioid tumour cells with melanocytic features. All 9 of these showed mitotic activity and pagetoid inflitration of the overlying epiderm and, in 4 cases, the tumours were ulcertated. In all cases reducing pigment resembling melanin was demonstrable. Five tumours had been erroneously diagnosed as benign or atypical pigmented nevi. The exceptional 10th primary tumour, located on the left lower leg, was only discovered after the histological diagnosis of a sarcoma-like metastasis of malignant melanoma in the left groin. This primary presented features of malignant melanoma in an advanced stage of regression.

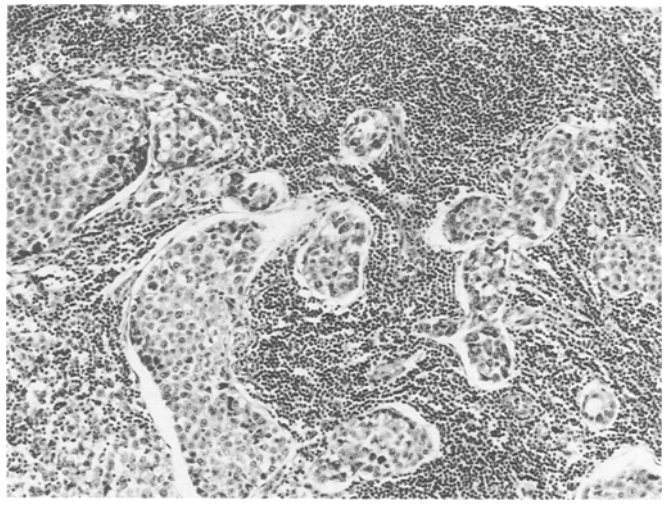

**Fig. 6.** A subsequent lymph node metastasis (case 12) presenting the characteristic appearance of a malignant melanoma. H & E, ×100

None of the primary cutaneous malignant melanomas displayed any sarcoma-like features corresponding to those seen in the metastatic tumours, or any features of desmoplastic malignant melanoma or its variants (Jain and Allen 1989). The thickness of the tumours according to Breslow and the infiltration level according to Clark, when possible to assess, are presented in Table 2.

In 2 cases in group A (cases 1 and 2) and 1 case in group B (case 12), subsequent metastases were available

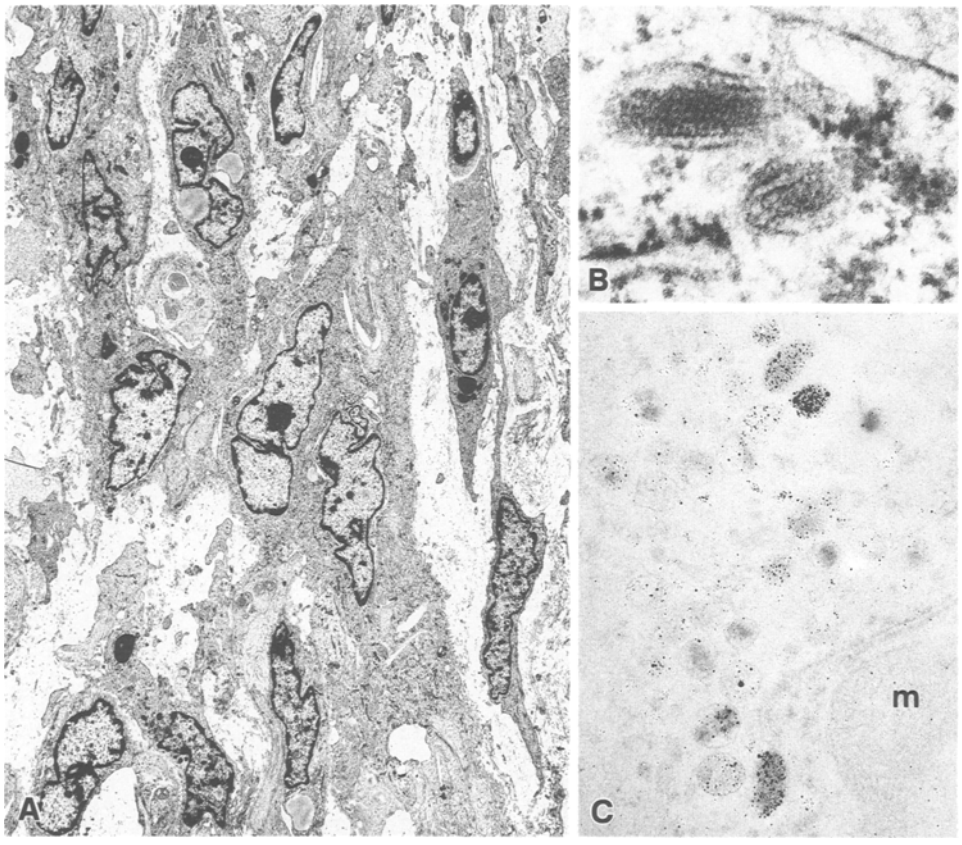


**Fig. 7. A** Spindle cell, fascicular tumour with fusiform tumour cells arranged in parallel. The elongated nuclei have an irregular shape and often contain a prominent nucleolus and a dense rim of heterochromatin condensed along the nuclear membrane. ×3000. **B** Two melanosomes with a characteristic internal structure. ×90000. **C** A section without contrast staining demonstrating deposits of silver granules after performing the Whartin-Starry technique on the grids. The finding indicates the content of melanin and thus the melanosome nature of the membrane bound bodies. *m*, Mitochondrion. ×30000

for analysis. In 2 cases (cases 1 and 12), the metastases, which involved lymph nodes, contained areas with the characteristic appearance of malignant melanoma (Fig. 6) as well as sarcoma-like areas. In case 2, metastases to the lungs, liver, bone and lymph nodes all showed a spindle-cell fascicular sarcoma-like appearance similar to that of the inguinal metastasis with which the patient had initially presented.

In the 4 cases primarily fixed for electron microscopy and the 7 tumours primarily fixed in formaldehyde, the morphology was well preserved, while in 2 of the 5 tumours which were studied after re-processing initially paraffin embedded tissue (cases 14 and 18), the morphology was too poor to make a detailed ultrastructural analysis possible.

The nuclei of the tumour cells were characteristically large, either rounded, oval or elongated and showed convoluted outlines producing deep indentations. The heterochromatin was condensed along the nuclear membrane and formed irregularly distributed clumps. Most nuclei contained one or rarely two large and prominent nucleoli (Fig. 7A). The cytoplasm was richly endowed with organelles: abundant free ribosomes, systems of both smooth and rough endoplasmic reticulum, Golgi zones and mitochondria of varying size and shape. A network of intermediate filaments was observed in many tumour cells and in a few cases there were abundant microtubules. Large glycogen deposits were noted in scattered cells and in a few cells cilia basal bodies and well-developed cilia occurred. The tumour cells often showed cytoplasmic projections, which were sometimes rather long and tended to interdigitate with one another. Cell junctions were a frequent finding, some of which had the appearance of developed desmosomes.

In 13 of the 14 tumours in which a detailed ultrastructural analysis was possible, tumour cells were found to contain melanosomes (Fig. 7B; Table 6). In only 2 did the majority of the tumour cells contain easily identifiable melanosomes, while in the other cases only few melanosomes could be detected after a careful search. The melanosomes presented a wide spectrum in terms of size, shape, internal structure and the degree of melanization. In case 2, there were numerous oval and rounded dense bodies with a rather homogeneous and densely stained internal structure, which could represent secondary lysosomes or strongly melaninized melanosomes. In 1 melanosome-containing tumour, there were also dense-core granules of the neurosecretory type. In the case which had been studied using the Whartin-Starry silver impregnation technique (case 1), distinct deposits of silver granules could be demonstrated within the melanosomes (Fig. 7C). In cases 14 and 18, both of which showed very poor preservation of the morphology due to the re-processing of the initially paraffin-embedded tissue, no convincing melanosomes were identified.

The immunohistochemical and histochemical findings are summarized in Table 6. All the tumours were positive for S-100 protein (Fig. 8A). There was also positivity in all cases using the NKI/C3 antibody

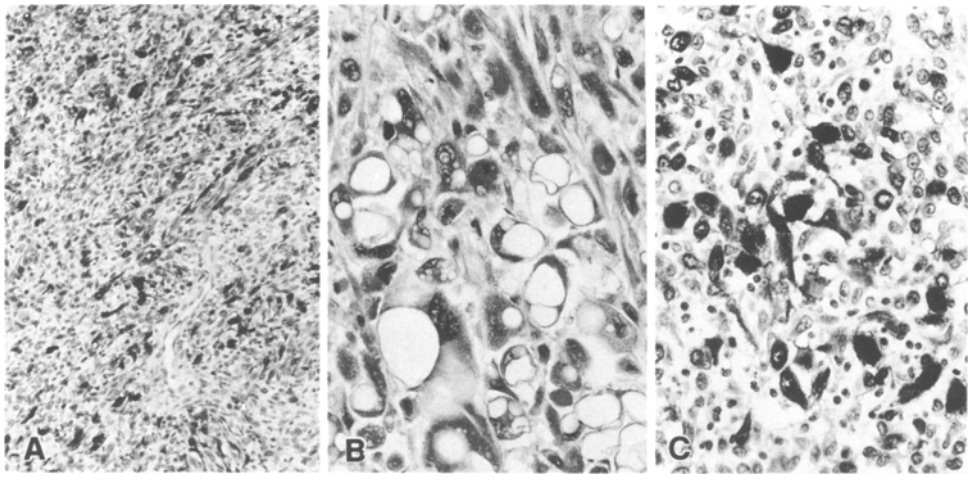


**Fig. 8.** Positive cytoplasmic staining of the tumour cells is observed for S-100 protein (**A**) and when using the anti-melanoma antibodies NKI/C3 (**B**) and HMB 45 (**C**). ABC technique; **A** ×60; **B** ×250; **C** ×100

(Fig. 8B). The staining for S-100 protein was usually strong and evenly distributed among the vast majority of the tumour cells, while the NKI/C3 antibody gave rise to a more irregularly distributed staining. Nine tumours stained positively using the HMB 45 antibody. The staining pattern was usually focal, with groups of strongly positive tumour cells scattered within the sections (Fig. 8C). No significant difference in the staining produced by the HMB 45 antibody was detected between the two tumour groups, and prior pronase digestion did not influence the number of positive cells. All but 2 tumours expressed vimentin and the staining was usually homogeneously distributed and strong. A focal, mostly weak positivity for chromogranin appeared in 3 tumours, while none showed any positivity for cytokeratin using the AE1/AE3 or CAM 5.2 antibodies, or for desmin. The Whartin-Starry technique revealed a positive staining in 7 of the tumours, but, in most of these, the positive cells were extremely few in number. The Masson-Fontana technique produced a positive staining in very few cells in 5 of the tumours, all of which were also positive using the Whartin-Starry technique. The mucous matrix in the myxoid areas seen in 6 of the tumours was metachromatically stained by toluidine blue at pH 4.0 but not at pH 1.0; there was also a weak positive staining with alcian blue at pH 2.5 but not at pH 1.0. These findings thus indicate the presence of non-sulphated glucosaminoglycans.

## Discussion

The present study shows that cutaneous malignant melanoma can give rise to metastases with a strongly deviating light-microscopic appearance, which may simulate various types of soft tissue sarcoma. All the tumours in this series were thus clinically and at the first histological evaluation interpreted as a soft tissue sarcoma. The two most common light-microscopic appearances of the tumours were that of a poorly differentiated, highly cellular, blue-staining spindle-cell malignancy, most closely resembling malignant peripheral nerve sheath tumour or monophasic synovial sarcoma, and that of a polymorphic tumour with a fascicular and storiform-like pattern, resembling the pleomorphic type of malignant fibrous histiocytoma. The occurrence of single or multiple cytoplasmic vacuoles, occasionally giving the nuclei a scalloped appearance, had in 3 cases led to a diagnosis of liposarcoma. It has previously been described that metastases of malignant melanoma may contain tumour cells with a single large vacuole compressing an eccentric nucleus, creating a resemblance to signet-ring cells of adenocarcinoma (Sheibani and Battifora 1988). In the tumour in this series which simulated a round-cell liposarcoma, some of the cells had such signet-ring features. Also liposarcoma of the pleomorphic type can, as in 2 cases of this series, be simulated by metastatic malignant melanoma, due to the presence of large, polymorphic tumour cells containing cytoplasmic vacuoles.

Although the tumours showed a strong resemblance to various soft tissue sarcomas, we also observed features in many which diverged from the well-characterized soft-tissue sarcoma types into which they had originally been classified. For example, the frequent location of the tumours in the groin, in the axilla or close to other major lymph node stations, and the finding of lymphoid tissue adjacent to the tumour tissue in many cases, raised the possibility of a metastasis. The appearance of the large nuclei differed from the simulated soft tissue sarcomas by having a very distinct nuclear membrane, finely dispersed chromatin and one or more very prominent nucleoli. Furthermore, in more than one-third of the tumours, nevoid areas with the appearance of typical malignant melanoma could be found after a careful search. Melanin stainings were found to be of little value in the present study, since only a minority of the tumours contained sparse amounts of reducing pigment in few scattered cells.

The findings providing the strongest support for the diagnosis of a sarcoma-like metastasis of malignant melanoma in this series were the immunohistochemically demonstrable positivity for S-100 protein, the positivity for the melanoma-associated antigens recognized by the two monoclonal antibodies HMB 45 and/or NKI/C3 and the electron-microscopic demonstration of melano-

somes. The finding of a primary cutaneous malignant melanoma at the review of the patients' previous histories or at the renewed clinical examination in 11 of the 21 cases provided further support for the diagnosis, as did the fact that in most of these cases the metastasis had appeared along the vascular and lymphatic pathways of the cutaneous malignant melanoma. The 10 tumours for which no known primary malignant melanoma could be discovered (group B), were, in all but 2 cases, found to contain melanosomes at ultrastructural examination. Furthermore, in 4 cases in group B, the sarcoma-like tumours contained small nevoid areas with an appearance resembling ordinary malignant melanoma and, in 7 of them, remnants of lymphoid tissue or lymph nodes were found, suggesting that they probably represented lymph node metastases. In 1 subsequent lymph node metastasis from a patient in group B, light-microscopic features characteristic of ordinary malignant melanoma were observed. Furthermore, the prognosis was similar in both group A and B, and the clinical course in both groups with wide-spread, sometimes late metastasis showing a predeliction for lymph nodes is typical of malignant melanoma (Cochran 1969). In three cases of group A metastases appeared very late, after 17, 18 and 23 years respectively. In cases where a very long time elapses between the excision of the primary cutaneous malignant melanoma and the development of metastatic disease, it is understandable that the metastases may be interpreted as a primary, unrelated malignancy, even when the patient and the physician are aware of the previous history.

A possible explanation of why no primary malignant melanoma could be detected in 10 of the 21 cases may be the regression and disappearance of the primary. This phenomenon is well-recognized, and may also take place after the onset of metastatic spread (Smith and Stehlin 1965; Guiliano et al. 1980; Panagopoulos and Murray 1983). In fact, one of the primary cutaneous malignant melanomas in group A (case 10) showed a marked degree of regression. Another explanation may be the occurrence of an occult primary, undetected either because of an atypical gross appearance, or because it was located in an unusual site (Das Gupta et al. 1969). Furthermore, the fact that lymph nodes may contain nevus cells has led to the suggestion that some malignant melanomas may arise de novo in lymph nodes (Das Gupta et al. 1963; McCarthy et al. 1974). As there were tumours without any demonstrable primary in this series which were not located adjacent to lymph node groups, the possibility that they had arisen de novo in the soft tissues can also be considered. The very strict criteria for making a diagnosis of unknown primary malignant melanoma defined by Das Gupta et al. (1963) could not be rigorously applied to the patients in group B in this retrospective study. According to these criteria, all the patients who have been subjected to an orbital enucleation or removal of any undefined skin lesion previously, those who have scars from previous injuries or treatments in the draining areas of any affected lymph nodes and those who have not undergone oto-laryngeal, anorectal and genital examinations must be excluded. Even in series of malignant melanoma using the criteria of Das Gupta et al., about 5% of all malignant melanomas have been of the unknown primary type (Das Gupta et al. 1963; Milton et al. 1967; Baab and MacBride 1975; Guiliano et al. 1980; Chang and Knapper 1982; Panagopoulos and Murray 1983). It seems likely, however, that the incidence of unknown primary malignant melanoma is somewhat underestimated in these series, since sarcoma-like metastases, like those in the present study, have probably not been recognized and included. It is possible that cutaneous malignant melanomas which have undergone complete or partial regression are more prone to give rise to sarcoma-like metastases than ordinary cutaneous malignant melanomas. This seems to be implied by the large number of tumours without a demonstrable primary in this series, plus the finding of an almost complete regression in one of the primary cutaneous malignant melanomas in group A.

It is interesting to note that some of the spindle-cell tumours in this series resembled primary cutaneous desmoplastic malignant melanoma, while none of the detected primary cutaneous tumours showed such a resemblance. The possibility of a primary cutaneous desmoplastic malignant melanoma having undergone complete regression cannot be excluded in the patients in group B, but, to the best of our knowlege, this phenomenon has not been described. Desmoplastic malignant melanoma usually presents as an uncharacteristic cutaneous mass (Conley et al. 1971; Reed and Leonard 1979; Egbert et al. 1988; Jain and Allen 1989), and it is therefore possible that some of the tumours in group B were metastases from undetected tumours of this type. Metastases from desmoplastic malignant melanoma, however, generally display features of typical malignant melanoma, although some have been described as exhibiting areas of desmoplastic, sometimes fibro- or neurofibrosarcoma-like tumour tissue (Conley et al. 1971; DiMaio et al. 1982; Nyong'o et al. 1986). Another theoretical possibility is that one or more of the tumours in group B might represent a metastasis from an undetected clear cell sarcoma, a tumour which is immunohistochemically indistinguishable from malignant melanoma, which at electron microscopy often contains melanosomes and is known to frequently give rise to late metastases (Kindblom et al. 1983; Chung and Enzinger 1983; Swanson and Wick 1989). However, as far as we know, clear cell sarcoma has not been described as giving rise to metastases with the appearance of those in the present series.

The ultrastructural demonstration of melanosomes has been considered to be a diagnostic criterion for malignant melanoma, although other tumours, mainly of neuroectodermal differentiation, may also contain melanosomes (cf. Erlandson 1987). As in most of the present cases, the search for melanosomes may be time-consuming and difficult, since they may occur very sparsely, may be atypical (Mazur and Katzenstein 1980; Erlandson 1987) and can sometimes be confused with other intracellular dense bodies (Erlandson 1987). As is illustrated by one of our cases, histochemical techniques applied at the ultrastructural level (van Duinen et al. 1983) can be helpful in the identification of the

melanosome nature of such dense bodies, by demonstrating their content of reducing pigment.

Several studies have shown the demonstration of S-100 protein to be of great value in the diagnosis of malignant melanoma, mainly because of its high sensitivity, also for amelanotic and otherwise divergent types of malignant melanoma (Nakajima et al. 1982; Stefansson and Wollmann 1982; Stefansson et al. 1982; Kindblom et al. 1984; Jain and Allen 1989). S-100 protein is, however, far from specific for malignant melanoma. It is well known that S-100 protein can be demonstrated in a variety of neuroectodermal, mesenchymal and epithelial tumours. Since 3 of the tumours in the present series were primarily diagnosed as liposarcomas, due mainly to the presence of vacuolated tumour cells resembling atypical lipoblasts, it is important to be aware of the fact that liposarcomas may also express S-100 protein (Cocchia et al. 1983). Apart from being positive using the NKI/C3 antibody, all 3 liposarcoma-like tumours also showed melanosomes ultrastructurally, and 1 of them was also positive using the HMB 45 antibody. In our experience, however, a strong diffuse positivity for S-100 protein, in a histologically clearly malignant tumour outside the central or peripheral nervous system, should raise the possibility of a malignant melanoma, and be an incentive to further analyses directed at this diagnosis.

The monoclonal melanoma associated antibody NKI/C3, first produced and described in 1982 (Hageman et al. 1982), has been found to have a sensitivity for melanocytic tumours comparable to that of anti-S-100 protein (van Duinen et al. 1984; Mackie et al. 1984; Gatter et al. 1985; Palmer et al. 1985; Vennegoor et al. 1985; Hagen et al. 1986; Cochran et al. 1988; Henzen-Logmans et al. 1988). Like the anti-S-100 protein antibody, NKI/C3 is not specific for melanocytic tumours, since a positive reaction has been reported in neuroendocrine tumours, clear cell sarcoma, oligodendroglioma, some lymphomas and a few instances of carcinoma (van Duinen et al. 1984; Mackie et al. 1984; Gatter et al. 1985).

Promising results in terms of both specificity and sensitivity for malignant melanoma have been reported for the monoclonal antibody HMB 45, initially produced by Gown et al. in 1985 (Gown et al. 1985, 1986; Esclamado et al. 1986; Columbari et al. 1988; Sheibani and Battifora 1988; Walts et al. 1988; Wick et al. 1988a, b). In addition to malignant melanomas, HMB 45 has been reported to produce in positive staining in single cases of both benign and malignant peripheral nerve sheath tumours (Columbari et al. 1988), and a case of neuroblastoma (Wick et al. 1988a). Furthermore, HMB 45 has recently been reported to produce a positive staining in clear cell sarcoma (Swanson and Wick 1989). In a recent study of HMB 45 in cutaneous malignant melanomas a reduced sensitivity for the spindle cell variant was observed (Wick et al. 1988b). In the present study, however, in which the majority of the tumours were of spindle-cell appearance, almost half of them were positive using the HMB 45 antibody. Our findings thus indicate that the sensitivity using the HMB 45 antibody for metastases of predominant spindle-cell appearance of malignant melanomas is reduced, but to a lesser degree than in the cutaneous spindle-cell malignant melanomas studied by Wick et al. (1988b).

The finding of chromogranin in three of the tumours is of interest, since it reflects the ability of malignant melanomas also of this sarcoma-like type to express signs of neuroendocrine differentiation, a phenomenon previously described for ordinary cutaneous malignant melanomas as well (Gould et al. 1982), reflecting the neural crest derivation common to malignant melanomas and neuroendocrine tumours.

From the present study it can be concluded that whenever a malignant tumour, especially if located close to major lymph node groups, shows features of soft tissue sarcoma and shows a strong positivity for S-100 protein, the possibility of a metastatic malignant melanoma should be considered, and an immunohistochemical and, if possible, electron-microscopic analysis to confirm or rule out this diagnosis should be undertaken.

## References


Baab GH, McBride CM (1975) Malignant melanoma. The patient with an unknown site of primary origin. Arch Surg 110:896–900

Bhuta S, Mirra JM, Cochran AJ (1986) Myxoid malignant melanoma. A previously undescribed histologic pattern noted in metastatic lesions and a report of four cases. Am J Surg Pathol 10:213–211

Chang P, Knapper WH (1982) Metastatic melanoma of unknown primary. Cancer 49:1106–1111

Chung EB, Enzinger FM (1983) Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. Am J Surg Pathol 7:405–413

Cocchia D, Lauriola L, Stolfi VM, Tallini G, Michetti F (1983) S100 antigen labels neoplastic cells in liposarcoma and cartilaginous tumors. Virchows Arch [Pathol Anat] 402:139–145

Cochran AJ (1969) Malignant melanoma. A review of 10 years' experience in Glasgow, Scotland. Cancer 23:1190–1199

Cochran AJ, Wen D-R, Morton DL (1988) Occult tumor cells in the lymph nodes of patients with pathological stage I malignant melanoma. An immunohistochemical study. Am J Surg Pathol 12:612–618

Columbari R, Bonetti F, Zamboni G, Scarpa A, Marino F, Tomezzoli A, Capelli P, Menestrina F, Chilosi M, Fiore-Donati L (1988) Distribution of melanoma specific antibody (HMB 45) in benign and malignant melanocytic tumors. Virchows Arch [Pathol Anat] 413:17–24

Conley J, Lattes R, Orr W (1971) Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer 28:914–936

Das Gupta TK, Bowden L, Berg JW (1963) Malignant melanoma of unknown primary origin. Surg Gynecol Obstet 117:341–345

Das Gupta TK, Brasfield RD, Paglia MA (1969) Primary melanomas in unusual sites. Surg Gynecol Obstet 128:841–848

DiMaio SM, Mackay B, Smith JL, Dickersin GR (1982) Neurosarcomatous transformation in malignant melanoma. An ultrastructural study. Cancer 50:2345–2354

Duinen SG van, Ruiter DJ, Scheffer E (1983) A staining procedure for melanin in semithin and ultrathin epoxy sections. Histopathol 7:35–48

Duinen SG van, Ruiter DJ, Hageman P, Vennegoor C, Dickersin R, Scheffer E, Rümke P (1984) Immunohistochemical and histochemical tools in the diagnosis of amelanotic melanoma. Cancer 53:1566–1573

Egbert B, Kempson R, Sagebiel R (1988) Desmoplastic malignant melanoma. A clinicohistopathologic study of 25 cases. Cancer 62:2033–2041

Enzinger FM, Weiss SW (1988) Soft tissue tumors. Second Edition. St. Louis, The CV Mosby Co.

Erlandson RA (1987) Ultrastructural diagnosis of amelanotic malignant melanoma: aberrant melanosomes, myelin figures or lysosomes? Ulstrastruct Pathol 11:191–208

Esclamado RM, Grown AM, Vogel AM (1986) Unique proteins defined by monoclonal antibodies specific for human melanoma. Some potential clinical applications. Am J Surg 152:376–385

Gatter KC, Ralfkiaer E, Skinner J, Brown D, Heryet A, Pulford KAF, Hou-Jensen K, Mason D (1985) An immunohistochemical study of malignant melanoma and its differential diagnosis from other malignant tumors. J Clin Pathol 38:1353–1357

Gould VE, Fodstad Ö, Memoli VA, Warren WH, Dardi LE, Johannessen JV (1982) The spectrum of serotonin and peptide immunoreactivity in malignant melanoma. Nordic Congress of Pathology Anatomy and Cytology (Copenhagen)

Gown A, Vogel AM, Hoak D, Gough F, McNutt MA (1985) Monoclonal antibodies to a melanoma-specific cytoplasmic antigen (Abstr). Lab Invest 52:25A–26A

Gown A, Vogel AM, Hoak D, Gough F, McNutt MA (1986) Monoclonal antibodies specific for melanocytic tumors distinguish subpopulations of melanocytes. Am J Pathol 123:195–203

Guiliano AE, Moseley HS, Morton DL (1980) Clinical aspects of unknown primary malignant melanoma. Ann Surg 191:98–104

Hageman P, Vennegoor C, van der Valk M, Landegent J, Jonker A, van der Mispel L (1982) Reactions of monoclonal antibodies against human melanoma with different tissues and cell lines. In: Peeters H (ed). Protides of the biological fluids, Vol 89, Oxford, Pergamon Press, pp. 889–892

Hagen EC, Vennegoor C, Schlingemann RO, van der Velde EA, Ruiter DJ (1986) Correlation of histopathological characteristics with staining patterns in human melanoma assessed by (monoclonal) antibodies reactive on paraffin sections. Histopathol 10:689–700

Henzen-Logmans SC, Meijer CJLM, Ruiter DJ, Mullink H, Balm AJM, Snow GB (1988) Diagnostic application of panels of antibodies in mucosal melanomas of the head and neck. Cancer 61:702–711

Hsu S-M, Raine L, Fanger H (1981) Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:577–580

Jain S, Allen PW (1989) Desmoplastic malignant melanoma and its variants. A study of 45 cases. Am J Surg Pathol 13:358–373

Kindblom L-G, Lodding P, Angervall L (1983) Clear-cell sarcoma of tendons and aponeuroses. An immunohistochemical and electron microscopic analysis indicating neural crest origin. Virchows Arch [Pathol Anat] 401:109–128

Kindblom L-G, Lodding P, Rosengren L, Baudier J, Haglid K (1984) S-100 protein in melanocytic tumors. An immunohistochemical investigation of benign and malignant melanocytic tumors and metastases of malignant melanoma and a characterization of the antigen in comparison to human brain. Acta Path Microbiol Immunol Scand [sect A] 92:219–230

Mackie R, Campbell I, Turbitt ML (1984) Use of NKI/C3 antibody in the assessment of benign and malignant melanocytic lesions. J Clin Pathol 37:367–372

Mazur MT, Katzenstein A-LA (1980) Metastatic melanoma: the spectrum of ultrastructural morphology. Ultrastruct Pathol 1:337–356

McCarthy SW, Palmer AA, Bale PA, Hirst E (1974) Nevus cells in lymph nodes. Pathol 6:351–358

Milton GW, Lane Brown MM, Gilder M (1967) Malignant melanoma with an occult primary lesion. Brit J Surg 54:651–658

Nakajima T, Watanabe S, Sato Y, Kameya T, Shimosato Y, Ishihara K (1982) Immunohistochemical demonstration of S100 protein in malignant melanoma and pigmented nevus, and its diagnostic application. Cancer 50:912–918

Nyong'o AO, Huntrakoon M, Parsa C, Raja A (1986) Superficial spreading malignant melanoma with neurosarcomatous metastasis. Pathol 18:473–477

Palmer AA, Hall BE, Lew M (1985) A comparison of some methods for identifying amelanotic and oligomelanotic melanoma metastases in paraffin sections. Pathol 17:335–339

Panagopoulos E, Murray D (1983) Metastatic malignant melanoma of unknown primary origin: a study of 30 cases. J Surg Oncol 23:8–10

Reed RJ, Leonard DD (1979) Neurotropic melanoma. A variant of desmoplastic melanoma. Am J Surg Pathol 3:301–311

Sheibani K, Battifora H (1988) Signet-ring melanoma. A rare morphologic variant of malignant melanoma. Am J Surg Pathol 12:28–34

Smith JL, Stehlin JS (1965) Spontaneous regression of primary malignant melanomas with regional metastases. Cancer 18:1399–1415

Stefansson K, Wollmann RL (1982) S-100 protein in granular cell tumors (granular cell myoblastomas). Cancer 49:1834–1838

Stefansson K, Wollmann RL, Jercovic M (1982) S-100 protein in soft-tissue tumors derived from Schwann cells and melanocytes. Am J Pathol 106:261–268

Swanson PE, Wick MR (1989) Clear cell sarcoma. An immunohistochemical analysis of six cases and a comparison with other epithelioid neoplasms of soft tissue. Arch Pathol Lab Med 113:55–60

Vennegoor C, Calafat J, Hageman P, van Buitenen F, Janssen H, Kolk A (1985) Biochemical characterization and cellular localization of a formalin-resistant melanoma-associated antigen reacting with monoclonal antibody NKI/C3. Int J Cancer 35:287–295

Walts AE, Said JW, Shintaku IP (1988) Cytodiagnosis of malignant melanoma. Immunoperoxidase staining with HMB 45 antibody as an aid to diagnosis. Am J Clin Pathol 90:77–80

Warkel RL, Lune LG, Helwig EB (1980) A modified Whartin-Starry procedure at low pH for melanin. Am J Clin Pathol 73:812–815

Wick MR, Stanley SJ, Swanson PE (1988a) Immunohistochemical diagnosis of sinonasal melanoma, carcinoma and neuroblastoma with monoclonal antibodies HMB 45 and anti-synaptophysin. Arch Pathol Lab Med 112:616–620

Wick MR, Swanson PE, Rocamora A (1988b) Recognition of malignant melanoma by monoclonal antibody HMB-45. An immunohistochemical study of 200 paraffin-embedded cutaneous tumors. J Cutan Pathol 15:201–207