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Desmoplastic Melanoma: Patterns of Recurrence

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Desmoplastic melanoma is a rare type of malignant melanoma, recognized since 1971. Other variants of desmoplastic melanoma include neural transforming melanoma and neurotropic melanoma.

The pathology and clinical features of 58 patients whose tumor had the features of desmoplastic melanoma, neural transforming melanoma, and neurotropic melanoma, either separately or in combination, were examined to assess patterns of recurrent disease. The tumor was situated on the head and neck in 41% of patients and was amelanotic in 71% of patients. There was an associated superficial melanoma in 48% of patients. There was a combination of the 3 histologic patterns, commonly found in the 1 melanoma. Local recurrence occurred in 29% of patients and malignant cranial neuropathies were documented in 4 patients. Nineteen percent of patients have died from disseminated disease. Neurotropic melanomas had a lower incidence of visceral recurrence. Desmoplastic and neural transforming melanomas had similar rates of local and visceral recurrence.

When this specific variant of melanoma is compared with larger series of malignant melanoma in general, they appear to be more advanced locally, with a higher incidence of local recurrence. When considered in relation to the thicker nondesmoplastic melanomas, the survival is no worse and may be more favorable.

Surgeons should excise the primary tumor and local recurrences with wide margins and adopt close follow-up. On the head and neck, symptoms and signs relating to trigeminal or facial nerve innervation may herald a developing malignant cranial neuropathy.

Since the initial report of desmoplastic melanoma [1] and subsequently its variants, neurotropic and neural transforming (neurosarcomatous) melanoma [2], there have been more than 200 patients with primary or secondary melanomas reported to contain these features alone or in combination [1–9]. Two larger series recently reported from Australia are based on cases referred to pathologists with an interest in melanoma [4, 5]. There were only 45 patients in each study, indicative of the rare nature of these variants, and therefore only clinicians in specialized melanoma units are likely to gain a large experience in managing these tumors. Thus, a collective series may be valuable to general surgeons to indicate the problems in diagnosis and subsequent management.

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There may be a recognizable superficial melanoma associated with this tumor, most commonly a lentigo maligna melanoma or a superficial spreading melanoma [1, 3–5]. Most often the diagnosis is not considered because the majority of desmoplastic melanoma are not pigmented and up to 80% are variously described as nodules, subcutaneous lumps, or plaques [4]. In one study, a diagnosis of melanoma was made in only one third of the patients prior to biopsy, with diagnoses such as "lump", basal cell carcinoma, and sebaceous cyst not unusual [4]. Most of these tumors will arise in sun damaged skin usually with a significant predilection for the head and neck when compared with the more typical melanomas [2, 4–7].

Since the first description, there have been a number of reports aimed at establishing the source of the desmoplastic reaction in this tumor. Although considered to be a reactive fibroblastic response by one group [10], most have suggested an origin from the sarcoma-like malignant cells [5, 11–13]. Within the initial report of the neurotropic variant of desmoplastic melanoma, a further variant with "neuroid appearance or neuro-sarcomatous change" (neural transforming melanoma) was also described [2]. It is confusing to incorporate 3 descriptively different tumors under the single entity of desmoplastic melanoma. Justification for this amalgamation comes from a number of sources where the presumed neural crest origin of the melanocytes allows for the concept of transformation or metaplasia of these cells into those containing fibrogenic or neurosustentacular features [5, 14].

It is not unusual for a pathologist to see a combination of 2 or 3 of these variants within a single primary lesion [4]. Interchange of the various histologic variants occurs with a predominantly neurotropic melanoma having a desmoplastic lymph node metastasis and a neurosarcomatous melanoma in a lymph node metastatic from a predominantly desmoplastic primary lesion [4]. A postulate for the sequence of events which leads to the clinicopathologic features of desmoplastic melanoma is provided by Jain and Allen [5].

Establishing the pathologic diagnosis may be difficult. To assist the pathologist, adjuvant techniques include immunoperoxidase staining for S-100 protein to differentiate melanoma cells from other spindle cell types. Immunostaining with the

mesenchymal marker Vimentin may also be helpful [8]. The pathologist should comment on the presence of perineural or intraneural invasion because of the clinical implications. The pathologic features of each of the variants have been well described in a number of reports [1, 2, 5, 15].

The first challenge for the clinician is the recognition that the lump with which the patient presents is abnormal. Subsequently, the relevance of a pathologist reporting desmoplasia, "neuroid" appearance, or neural transformation or neurotropism within a melanoma that has been excised must be recognized. Clinically, the importance relates to the high incidence of local recurrence [1, 2, 4, 5]. The neurotropic variant of desmoplastic melanoma has further implications relating to its predilection for invasion in and along nerves particularly in the head and neck, causing cranial neuropathies [4, 5, 16, 17].

The aim of this study is to report the patterns of recurrent disease that occur with this variant of malignant melanoma and assess the relevance to the clinician.

Methods

Until recently, the pathology of patients with a melanoma managed at a single institution was read by one of the authors (J.H.L.). Since 1980, all patients who had histologic evidence of desmoplasia, "unusual fibrosis", perineural/intraneural invasion or neuroid/neurosarcomatous appearance had their pathology reviewed by J.H.L. This has included a number of patients who had their pathology referred for a second opinion by other pathologists. As well, a small subgroup of 8 patients managed by G.R.McL., in whom the diagnosis has been pathologically confirmed, has been included.

The histologic characteristics of desmoplasia, neural transformation, and neurotropism were quantified into marked, moderate, and mild according to details described in a previous study [4]. In the present study, specific attention was paid to tumors that contained moderate to marked changes of these characteristics. For desmoplastic melanoma, this meant more than half of the lesion appeared fibrosed with dense collagen. In the neural transforming melanoma, there was an identifiable neurofibromatous and neurofibrosarcomatous appearance involving >50% of the tumor. With moderate to marked neurotropism, most of the nerves in the biopsy had perineural and intraneural permeation. These changes are distinct from mild changes where one nerve was partially involved or there was suspicion because of perineural lymphocytic infiltration.

The data relating to follow-up and patterns of recurrent disease that have occurred in these patients were retrieved from clinic and hospital records and from questionnaires returned by the treating clinicians. Patients were included in the study if there were suitable clinical and pathological data available for analysis.

Results

There were 58 patients in whom adequate pathologic and clinical details were available to allow inclusion into this study. A further 8 patients who had adequate pathologic data, but no clinical details, were excluded. Twenty-six patients have been managed or seen in consultation by G.R.McL. The median age at diagnosis was 63 years (range 17–89 years) in 33 men and 25 women. The primary lesion was found on the head in neck in 24 (41%) patients, trunk in 20 (35%) patients, and on the limbs in 14 (24%) patients. The lesion was amelanotic in 41 (71%) patients. One patient presented with involved cervical lymph nodes, that is, stage II disease.

Pathology

Twenty-eight tumors had an associated superficial melanoma classified as superficial spreading (n = 21), lentigo maligna (n = 4), and nodular melanoma (n = 3). One patient had regression of the primary melanoma without evidence of desmoplasia but bilateral axillary lymph node recurrences revealed marked desmoplasia. Otherwise, there was desmoplasia alone in 10 patients, and a combination of 2 or 3 of the features of desmoplasia, neural transformation, or neurotropism in 23 patients and 24 patients, respectively. Only 3 tumors were quantified as having minimal evidence of these pathologic features; the other tumors had moderate to marked evidence of desmoplasia (n = 50), neural transformation (n = 20), and neurotropism (n = 23). There was no difference between the 3 histologic variants when related to age, anatomic site, and thickness.

The median thickness of these tumors measured according to Breslow was 4.3 mm (range 0.45–16 mm). The patients who had lymph node, visceral recurrence, and/or cranial nerve neuropathies had a median thickness of 6.5 mm (range 2.15–11 mm) compared with those tumors without systemic recurrence where the median thickness was 3.6 mm (range 0.45–16 mm). There were 29 patients with tumors that had a measured thickness ≥4 mm. Median follow up for this group was 34 months (range 2–120 months) with an actuarial 5 year survival rate of 63% for the 28 patients who were clinically stage I at presentation.

Clinical Progression

Within an overall median follow-up of 30 months (range 1–124 months) there has been no evidence of recurrence in 32 (55%) patients. Local recurrence occurred in 17 patients, lymph node metastases in 8 patients, and visceral metastatic disease in 12 patients. Malignant neuropathies developed in 4 patients, all of whom had head and neck primary lesions. The relationship between the pattern of recurrent disease and the histologic variants present within these tumors is shown in Table 1. Because these variants may be present in combination in a single tumor, it is inappropriate to assess the differences statistically but the trends are interesting. The incidence of visceral recurrence in tumors having moderate to marked neurotropism was less compared with those having moderate to marked neural transformation and desmoplasia. The local recurrence rate appeared higher in the tumors with moderate to marked neural transformation compared with the other variants. Death has occurred in 10 patients due to metastatic melanoma (2 patients with tumor thickness <4 mm) and in 2 patients from prostatic carcinoma and respiratory failure. Three patients are known to be alive with recurrent disease (2 patients with tumor thickness <4 mm).

Table 1. Desmoplastic melanoma: Recurrences related to site and histologic patterns.

Recurrence (no. of pts.)	Site of recurrence			Histologic pattern[a]			Follow-up (range) (mos.)
	Head & neck (24)	Trunk (20)	Limbs (14)	Desmoplasia (50)	Neural transformation (20)	Neurotropic (23)	
No recurrence (32)	9	15	8	27	8	13	27 (6–120)
Local (17)	11	1	5	15	9	9	9 (1–38)
Lymph node (8)	3	3	2	8	4	3	42 (18–95)
Visceral (12)	5	4	3	11	5	2	
Neuropathy (4)	4	0	0	4	0	3	

[a]Presence of marked or moderate amounts on microscopy. There may have been a combination of 2 or 3 of these patterns in any 1 primary lesion.

Loco-Regional Recurrence

Local recurrence, where it occurred, was a precursor of wider dissemination in 11 of 17 patients. The median time to local recurrence was 9 months (range 1–38 months). Four patients had more than 1 local recurrence. Local recurrence was more common on the head and neck than on the other sites.

There was no relationship between the site and histologic pattern of the primary lesion in the 8 (14%) patients who had lymph node metastasis. Subsequently, 6 patients had visceral recurrence, with only short follow-up in the remaining 2 patients. In 7 patients, the primary tumor thickness was >4 mm (range 4–11 mm). The other patient had a primary lesion 1.6 mm in thickness associated with marked regression. She subsequently developed bilateral desmoplastic axillary nodal metastases. At the discretion of the treating surgeon, an elective lymph node dissection was performed in 6 patients, all of whom had negative pathology.

Visceral Disease

There were 12 (21%) patients who developed visceral recurrence. Patients with a predominance of desmoplasia and/or neural transformation had twice the incidence of visceral metastasis compared with those patients who had tumors that contained predominantly neurotropic changes. One patient had a pulmonary metastasis treated by lobectomy. This patient is alive with no signs of disease 54 months following surgery. There are 3 patients alive with known metastatic disease. The major sites of metastasis were liver (n = 4), bone (n = 2), cerebral (n = 2), lung (n = 1), spine (n = 1), para-aortic nodes (n = 1), and general dissemination (n = 1).

Malignant Neuropathy

Marked neurotropism was evident in the primary lesions of 12 patients with disease outside of the head and neck. No patient in this group has developed a malignant neuropathy.

The 4 patients who developed a malignant cranial neuropathy had moderate to marked desmoplastic reactions within the primary lesion. Three patients also had associated marked neurotropic changes, but 1 patient had minimal evidence of perineural invasion. Despite this, the recurrent disease developed specifically along cranial nerves. The disease involved divisions of the 5th cranial nerve in 4 patients and the 7th cranial nerve in 2 patients. Three patients had persisting mild parasthesia while the fourth patient developed severe unremitting pain 48 months following excision of the primary lesion. There was definitive magnetic resonance imaging (MRI) of the intracranial disease in 3 patients. The computed tomographic (CT) scans were negative in each of these patients. The fourth patient had negative MRI and CT scan despite clinical evidence and subsequent biopsy proven intracranial disease.

Management of Inoperable Recurrent Disease

Six patients with inoperable recurrent disease received radiotherapy. In 3 patients, the recurrent disease developed after a lymph node dissection (head and neck-2, axilla-1). Four patients had no response and 2 patients had a complete response lasting 14 months and 15 months until they died from metastatic disease elsewhere and respiratory failure, respectively. The dose regimen and methods of radiotherapy were not available for assessment.

There have been 2 patients with disseminated disease who have been treated with decarbazine and recombinant interferon-2α. These patients died 6 months and 7 months following the instigation of the chemotherapy. In each patient, the disease appeared to become static initially, followed by a rapid progression to the terminal phase.

Discussion

Desmoplastic melanoma is a variant of malignant melanoma which has a higher incidence in the head and neck, higher rates of local recurrence, and the potential for malignant neuropathies [1–5]. These tumors remain interesting to the pathologist because of the difficulties in diagnosis, the variations that can occur under the single heading of desmoplastic melanoma, and the origins of these variations. The encompassing term "desmoplastic" is realistic because desmoplasia was present histologically in all the tumors in the present series. Tumors with neurotropism and with evidence of neural transformation or neurosarcomatous change, as described by Reed and Leonard [2], have in the past been grouped together as neurotropic melanomas [2, 7]. It seems appropriate to note the presence of 3 different histologic patterns accepting that these variants may co-exist in a single melanoma. In the present study, melanomas which were predominantly neurotropic had a low incidence of visceral metastasis. The melanomas with moderate to marked evidence of neural transformation without neurotropism

seemed to have behavior similar to desmoplastic melanoma with a high incidence of local recurrence and the potential for visceral recurrence rather than perineural and intraneural invasion. With the presence of established neurotropism on the head and neck, the potential for cranial neuropathies exists. Interestingly, there have been no reports in the English literature of a malignant neuropathy associated with a non-head and neck neurotropic melanoma.

Recent series of desmoplastic melanoma have shown a much higher incidence of primary lesions on the head and neck [3, 5, 9] than in the present report. The reasons for the disparity are not clear, but case selection by head and neck surgeons referring to interested pathologists could be an explanation. This suggested potential for bias is not clear from those series.

A previous multifactorial analysis revealed that local recurrence was significantly related to initial incorrect pathologic diagnosis, head and neck primary lesions, Clark level V tumors, primary tumor thickness >4 mm, and excision margins <1 cm [4]. With the trend towards decreasing excision margins when definitively treating malignant melanoma, it would seem appropriate to suggest, when excising a desmoplastic melanoma (including the other variants), the minimum margin of normal skin and subcutaneous tissue should be 2 cm, but the appropriate margin cannot be ascertained from this series nor the literature.

In certain circumstances, such as head and neck lesions, where adequate excision margins can be difficult to assess macroscopically, special histologic techniques have been reported which will assist the clinician. For example, the use of immunoperoxidase stains for the S-100 protein may be useful when the surgeon has re-excised a previously biopsied desmoplastic melanoma [18]. The difficulties in distinguishing histologically between the spindle cells of desmoplastic melanoma and reactive scar tissue can be assisted with such stains. Others have advocated the use of frozen section control for excision on the face, with careful examination for perineural invasion [9].

The actions to be taken with clinically negative regional lymph nodes in patients with a desmoplastic melanoma are not clear. The numbers of patients with lymph node recurrence reported in the literature are small. Most series have not isolated patients who had lymph node metastasis from those that had local or visceral recurrence, or both. In the present series, as with nondesmoplastic melanomas, the tendency was for those patients who developed lymph node recurrence to have tumors >4 mm in thickness. In general, the survival benefits from an elective lymph node dissection in patients with malignant melanomas remains an area of debate. In particular, for thick melanomas (>3 mm) the data using nonrandomized analysis [19] suggest that women may benefit (although not on the head and neck) [20]. Given the present data base, no recommendations can be made related to desmoplastic melanoma and its variants.

Like any other melanoma, desmoplastic melanoma metastasizes to solid viscera. Patients who had metastatic disease tended to have the thicker tumors (>4 mm), but in a multifactorial analysis of metastatic disease, thickness >4 mm was not shown to be a significant factor [4]. Factors which did influence the presence of disseminated disease included: excision margins <1 cm, patents with a head and neck primary lesion, and those patients with Clark level V tumors [4]. The reasons for the exclusion of thickness as a factor given its prognostic importance with nondesmoplastic melanomas is not clear and, once again, may have been related to the small data base.

As a group, the median thickness of 4.3 mm in these melanomas is greater than in the Queensland Melanoma Project series of nondesmoplastic melanomas with a median thickness of 1.2 mm [21]. Despite advanced presentation, it has been suggested that this tumor may have a more favorable pattern of biologic behavior [8]. In the present series, the median follow up of 2.5 years was quite short. The mortality in this time was 19%. To assess the prognosis compared with nondesmoplastic melanomas, it would seem appropriate given the small number of patients, to look at the more advanced tumors, for example, those with a thickness >4 mm. With a median follow up of 2.8 years, patients who had tumors >4 mm thick and who were clinically stage I had an actuarial 5 year survival of 63%, including 3 patients alive with inoperable disease. The actuarial 5 year survival for nondesmoplastic melanomas >4 mm thick has been reported as 48% (Queensland Melanoma Project) [21] and 37% (Sydney Melanoma Unit) [22]. The difference in survival figures does suggest a more favorable disposition for patients with thick desmoplastic melanomas, but given the short follow-up and the small numbers, it is difficult to draw significant conclusions. The numbers of patients with lesions of lesser thickness in this series were too small to make similar comparisons.

It is the principle of two of the authors (B.M.S. and G.R.McL.) to continue to manage patients with recurrent disease surgically, if feasible, in the absence of disseminated disease. Treatment modalities such as radiotherapy and chemotherapy for desmoplastic melanoma have not been addressed in detail in other studies. The numbers in the present study are too small to influence clinical judgment when considering treatment of a patient in whom either of these options may be worthwhile.

In conclusion, desmoplastic melanoma should be considered in the differential diagnosis of any unusual skin tumor, particularly a nonpigmented lesion on the head and neck. If the pathology report of an excised lesion suggests the presence of an unusual tumor associated with fibrosis, spindle cells, neuroid features and/or neurotropism, one should suspect the diagnosis of a desmoplastic melanoma or one of its variants. Fortunately, the 3 variants have now been well described in the pathology literature and are more readily recognized histologically since the first description in 1971 [1]. Once diagnosed, this lesion demands a wide local excision no matter what the anatomic site. Close follow-up is essential, since the patterns of recurrence in this tumor are similar to a nondesmoplastic melanoma, but there is a higher incidence of local recurrence. Neurotropic melanomas on the head and neck may develop malignant cranial neuropathies which will usually present as parasthesia in the distribution of one of the divisions of the trigeminal nerve or weakness of facial muscles indicative of facial nerve involvement.

Résumé

Le mélanome desmoplastique est une forme rare de mélanome malin, reonnu depuis 1971. D'autres variantes de mélanome malin desmoplastique sont des mélanomes neuraux et neurotropiques. Les caractéristiques anatomopathologiques et clin-

iques de 58 patients ayant un mélanome malin desmoplastique, neural ou neurotropique, observées séparément ou conjointement, ont été analysées pour évaluer les facteurs de récidive. La tumeur était localisée à la tête ou au cou chez 41% des patients et était amélanique chez 71% des patients. Le mélanome était superficiel chez 48% des patients. Les trois types histologiques étaient souvent présents. Une récidive locale a été observée chez 29% des patients. Une neuropathie maligne crânienne a été documentée chez 4 patients. Dix neuf pour cent des patients sont morts de maladie disséminée. L'incidence de récidive viscérale était plus faible chez les patients ayant un mélanome neurotropique. Les taux de récidive, locale et viscérale, des mélanomes neuraux et desmoplastiques étaient similaires. Lorsqu'on compare cette variété de mélanome à de plus grandes séries de mélanomes en général, ils semblent avoir un stade local plus évolué avec un taux de récidive locale plus élevé. La survie des patients atteints de ces tumeurs, comparée à celle des cas de tumeurs non desmoplastiques plus épaisses, est similaire, voire meileure. La tumeur primitive et les récidives doivent être exercisées avec des marges larges. La surveillance doit être rigoureuse. Lorsque le mélanome est situé au niveau de la tête ou du cou, la préscence de signes et symptômes dans les territoires des nerfs trijumeau ou facial, peut annoncer une atteinte nerveuse maligne.

Resumen

El melanoma desmoplásico es un tipo raro de melanoma maligno, reconocido desce 1971; otras variaciones de melanoma desmoplásico incluyen et melanoma de trasnformación neural y el melanoma neurotrópico.

Las características patológicas y clínicas de 58 pacientes cuyos tumores poseían las características de melanoma desmoplásico, de melanoma de trasnformación neural y de melanoma neurotrópico, bien en forma separada o en forma combinada, fueron analizadas para determinar los patrones de enfermedad recurrente. El tumor apareció ubicado en la cabeza y cuello en 41% de los casos y amelanótico en 71%; se observó melanoma superficial asociado en 48% de los pacientes. Existió la combinación de los 3 patrones histológicos comunmente hallados en este tipo de melanoma. La recurrencia local se presentó en 29% de los pacientes y neuropatías craneanas malignas fueron documentados en 4 pacientes; 19% de los pacientes murieron por enfermedad diseminada. Los melanomas neurotrópicos exhibieron una menor incidencia de recurrencia visceral. Los melanomas desmoplásicos y de transformación neural exhibieron tasas similares de recurrencia local y visceral.

Cuando esta variante específica de melanoma es comparada con grandes series de melanomas generales, aparece más avanzado localmente y con mayor incidencia de recurrencia local. Cuando se lo considera en relación con los espesos melanomas no desmoplásicos, la sobrevida no aparece peor, y tal vez más favorable.

Los cirujanos deben resecar el tumpor primario y las recurrencias locales con amplios márgenes y adoptar un estricto regimen de seguimiento. En el caso de los tumores de la cabeza y el cuello, los síntomas y signos relacionados con la inervación del trigémino o del facial pueden anunciar el desarrollo de una neuropatía craneana.

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