Malignant melanoma and the central nervous system
A guide for classification based on the clinical findings

R. D. Hayward

From the Department of Neurosurgery, Atkinson Morley's Hospital, London

SYNOPSIS Twenty-seven cases diagnosed as having malignant melanoma affecting the central nervous system have been studied. In 20 patients the tumours represented secondary spread from elsewhere, but there were six who had a primary melanoma either of the spinal cord, leptomeninges, or brain. Confusion exists in the literature about how to differentiate primary from secondary tumours but this study suggests several clinical factors which may indicate that the lesion is probably a primary one. This method of categorizing the cases is supported by the differences in duration of symptoms and survival times for each group and a simple classification can therefore be proposed.

It is not unusual to find references in the literature to malignant melanoma involving the nervous system (Hirano and Carton, 1960; Pappenheim and Bhattacharji, 1962; Gibson et al., 1967; Salm, 1967), but there is confusion about which are primary and which secondary to malignant melanoma elsewhere in part due to analysis of reported cases along with one or two observed cases.

Analysis of the cases of malignant melanoma involving the central nervous system that have been investigated and treated at this hospital suggests that a simple clinical classification can be recommended and that patients can usually be grouped without difficulty.

METHODS

PATIENTS Twenty-seven cases were collected for study. It was possible to make a positive histological diagnosis based on material obtained either at operation or at necropsy in all cases except one which presented with a previous history of having had a malignant melanoma removed from her thigh at another hospital. This had been followed one year later by a block dissection of the local lymph nodes and one year later still she presented at this hospital with multiple intra-cerebral lesions. Surgery was not recommended and when she died permission for necropsy was not obtained. She has been included in the section headed 'Cerebral secondary tumours'.

RESULTS (Table 1)

CLINICAL FEATURES Cerebral secondary tumours. There were 20 patients in this category and all had at least one intracerebral lesion. In 18 cases (90%) there was a known primary tumour and in those two cases in which there was no known primary, there were multiple discrete intracerebral lesions (see discussion below). Overall, when the patients presented for investigation, nine (45%) had radiological evidence of multiple lesions. The average time between diagnosis of the primary tumour and of the secondary was 38 months with a range from zero (in a patient whose cerebral secondary and the primary tumour were biopsied on the same day) to 120 months (where the primary tumour was in the eye). The average duration of symptoms for the cerebral secondaries was 5.5 months. Many presented with subarachnoid haemorrhage, but even when these cases with an obviously short symptom period were excluded the average time measured only 6.6 months. All secondary
Malignant melanoma and the central nervous system

TABLE 1
CLINICAL DETAILS OF PATIENTS WITH MALIGNANT MELANOMA OF CNS

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>No.</th>
<th>Non-CNS primary malignant melanoma (no.)</th>
<th>Multiple CNS lesions (no.)</th>
<th>Average duration of symptoms before histological diagnosis (m)</th>
<th>Average length of survival after diagnosis (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral tumours</td>
<td>20</td>
<td>18</td>
<td>9</td>
<td>5.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Spinal tumours</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Leptomeningeal tumours</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Other pigmented tumours</td>
<td>1</td>
<td>(Meningioma)</td>
<td>0</td>
<td>12</td>
<td>0.5</td>
</tr>
</tbody>
</table>

tumours were situated in the cerebral hemispheres, but one also had a lesion in the brain stem. These cases are the subject of a more detailed report (Hayward, in preparation).

Spinal cases There were four of these tumours, of which one was situated in the cervical cord, two were dorsal, and one involved the conus. Details of their presentation, operative findings, and subsequent survival are given in Table 2. The duration of symptoms ranged from nine to 24 months with an average of 18 months. In no case was it possible to find evidence of a primary tumour nor was there evidence of metastatic tumour elsewhere. All four cases were explored at operation and on each occasion a black tumour was found to be rising from within the spinal cord and, with one exception, enlarging to form a significant extramedullary component. On two occasions this was large enough to pass out through the adjacent nerve root foramen and present as an extradural mass.

Malignant melanoma of leptomeninges In this condition multiple small deposits of malignant melanoma, often joining to form sheets of tumour, cover the brain surface, particularly in the posterior fossa and basal cisterns. It is often associated with hydrocephalus and with apparent penetration of the tumour process into the brain itself. (See Gibson et al. (1967) for a general discussion of the subject.)

Two cases appeared to come within this category. Both were men, aged 21 and 34 years.

TABLE 2
CLINICAL DETAILS OF PATIENTS WITH MALIGNANT MELANOMA AFFECTING SPINAL CORD

<table>
<thead>
<tr>
<th>Patient, sex, age (yr)</th>
<th>Presenting symptoms</th>
<th>Situation of tumour at operation</th>
<th>Pial seedlings</th>
<th>Other therapy</th>
<th>Survival time (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M69 W.T.</td>
<td>14 m increasing weakness and numbness of legs with difficulty in passing urine</td>
<td>Intramedullary with extramedullary component</td>
<td>No</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>F47 E.J.</td>
<td>Lump in neck. Brachialgia and increasing spastic paraplegia</td>
<td>Intra- and extramedullary, extradural and extending into neck muscles</td>
<td>Yes</td>
<td>DXT</td>
<td>39</td>
</tr>
<tr>
<td>M57 W.N.</td>
<td>9 m increasing spastic paralysis of legs</td>
<td>Intra- and extramedullary with extradural components</td>
<td>Yes</td>
<td>DXT</td>
<td>66</td>
</tr>
<tr>
<td>F52 E.B.</td>
<td>Cauda equina compression with acute retention of urine</td>
<td>Intramedullary lesion of conus</td>
<td>No</td>
<td>DXT</td>
<td>6*</td>
</tr>
</tbody>
</table>

DXT: Deep x-ray radiotherapy.
* Still alive.
respectively. Each presented with communicat-
ing hydrocephalus and at the time of their first
admission no other definite diagnosis was
made. Both were treated initially with ventri-
culoatrial shunts but they soon returned with
new symptoms despite adequate control of
their intracranial pressure. The first patient
(E.S.) developed epilepsy and then had a sub-
arachnoid haemorrhage. He was now found to
have an avascular right frontal mass and at
operation this was shown to be a haematoma
cavity lying close to the surface, with obvious
melanoma tissue in its wall. At operation it
was also noted that the exposed cortex showed
a grossly abnormal appearance with irregular
black areas apparently extending over the en-
tire hemisphere. Histology confirmed that the
tumour was a malignant melanoma and,
though a subsequent search for a primary
lesion was made, none was found. The patient
was referred for radiotherapy but he was al-
ready in a near terminal condition and died
two months later. The other patient (H.B.)
returned with signs referable to a progressive
lesion of the tectal plate area in addition to his
hydrocephalus. As air studies were inconclu-
sive, a posterior fossa exploration was per-
formed. Although the dura mater was normal
the underlying arachnoid mater was brownish
black in colour, very thick, and apparently in-
filtred with tumour. This abnormality ex-
tended widely throughout the posterior fossa
and no significant removal could be achieved.
After surgery the patient’s condition deterio-
rated and he died a few days later. Necropsy
showed no evidence of other metastases or of
a primary malignant melanoma outside the
CNS but did demonstrate widespread basal
and spinal melanoma deposits with involve-
ment of the fifth nerve ganglia and cavernous
sinuses.

Pigment containing meningioma A 58 year
old woman presented with a lump on her fore-
head and complained of deterioration of
vision. Clinical examination and plain radi-
ographs of the skull suggested that the lump
was a large exostosis typical of a meningioma.
No surgery was performed and when she died
necropsy revealed the presence of a large
endostosis with apparent meningiomatous
tissue displacing the frontal lobes backwards.
There was softening of these frontal lobes, but
no actual infiltration was seen. The histological
report on the tumour showed it to consist of
‘rounded and spindle cells infiltrating a zone
of collagen fibrous tissue. Some cells contained
fine granules of a dark brown pigment and
others were distended forming a large mass of
dense pigment’. It was thought to be a mela-
notic sarcoma.

DISCUSSION
One difficulty when discussing malignant
melanoma of the central nervous system is to
decide which cases represent primary growths
and which are metastases. Although melano-
matas are not among the commoner malignant
tumours in Great Britain they are currently
under intensive study because of their immuno-
logical instability (Lancet, 1974). There has
been increasing interest in the last few years
in the possibilities of both chemotherapy and
immunotherapy and, for this reason, it can be
expected that more patients with advanced
disease will be referred to neurosurgical
centres for consideration of surgical treatment.
The figures collected from this hospital are
small but they show the wide spectrum of ways
in which the disease may present and they
provide a guideline for a simple clinical
classification.

Of those cases with intracerebral lesions
labelled metastatic, only two showed no evi-
dence of a primary tumour. In a further two
cases the primary tumour was discovered only
on clinical examination after histological re-

cognition of the secondary. A 10% failure rate
in the discovery of the primary tumour is low
and compares well with the 17% incidence of
normal chest radiographs noted in patients
later diagnosed at this hospital as having intra-
cranial metastases from carcinoma of the
bronchus (Richards and McKissock, 1963).
None of the spinal tumours had evidence of a
primary lesion or of other metastases. They
also differed in that the duration of symptoms
was longer and the expectation of life greater.
Although there seems to be no pathological
reason why malignant melanomas should not
metastasize to the spinal cord, such cases have
not often been reported in the literature (cf. Pappenheim and Bhattacharji (1962) for references). In one article reviewing the literature on primary malignant melanoma of the spinal cord (Hirano and Carton, 1960) the authors reject five cases because they showed a degree of involvement of the basilar cerebral leptomeninges without actual invasion of the brain parenchyma. As can be seen from the discussion below, these findings should, in fact, encourage diagnosis of a primary malignant melanoma of the CNS.

It seems reasonable that a malignant melanoma could occur in any organ in which melanoblasts can normally be found. This includes the pia mater, which not only covers the brain but also sheathes the blood vessels passing into it and the spinal cord. These pial pigmented cells, although present everywhere, are most numerous around the spinal cord and on the ventral aspect of the brain (Gibson et al., 1967; Russell and Rubinstein, 1971) and it is in these areas that leptomeningeal melanomata are most likely to occur. Melanoblasts can also be seen in the pia mater of the interlobular septa that cross the pineal gland (Gibson et al., 1967) and it is probably the presence of these cells which accounts for the incidence of primary malignant melanoma in this region as demonstrated in case 2 of Gibson et al. (1967). Primary malignant melanoma of the pituitary gland has also been described (Neilson and Moffat, 1963) presenting on that occasion with hormonal insufficiency. It is of interest that the pituitary gland, in addition to the expected presence of pial tissue, also has melanin-containing cells in the pars nervosa.

Finally, one should mention the presence of pigment-containing cells in tumours of other cell types occurring intracranially. In the case described above all the clinical and macroscopic appearances pointed to the lesion being a typical frontal meningioma but, because of the presence of pigment in the tumour cells, the histological diagnosis was changed to one of melanoma. This aspect of the problem is discussed by Russell and Rubinstein (1971). Another tumour that may show pigmentation is the medulloblastoma (Russell and Rubinstein, 1971); however, great care should be taken with the diagnosis as pial involvement can be seen in both this and melanoma.

The following simple classification is therefore proposed:

1. Primary melanoma of the CNS; (2) secondary malignant melanoma of the CNS; (3) melanin-containing variants of other intracranial tumours.

This system avoids the necessity of referring to 'primary melanoma of the spinal cord' or 'primary melanoma of the brain', because some overlap is the rule rather than the exception. Indeed, the presence of other foci of tumour may help to confirm the presence of a primary tumour rather than refute it.

1. PRIMARY TUMOURS

There may be either diffuse leptomeningeal, discrete intracerebral, or intramedullary focal lesions. In the leptomeningeal group, either the brain or the spinal cord or both may be involved. The spectrum of disease stretches from widespread pial involvement of the spinal cord and basal cisterns to discrete lesions occurring partially in the spinal cord, presumably due to tumour arising in the melanoblasts accompanying the pial sheaths of the vascular bundles. Some overlap between the different groups is often seen as if the disease is affecting a 'field of growth'. In the cerebral variety, involvement of the basal cisterns leads typically to hydrocephalus, but once again the tumour may spread a sufficient distance into the brain substance to produce intracerebral as well as subarachnoid haemorrhage (for example, case E.S. above.)

Primary melanoma affecting the spinal cord may show typical pial deposits with an intramedullary tumour that can on occasions spread out along the nerve root sheaths to involve the extradural tissues—for example, cases E.J. and W.J. above the case described by Pappenheim and Bhattacharji (1962). Whether these pial seedlings represent spread via the CSF from the CNS primary tumour or whether there has been a general eruption of malignant change along the meninges cannot be decided from these cases. My own opinion is that the operative and necropsy findings can only be explained if both processes are possible.

In order to make the diagnosis of a primary tumour of the CNS no evidence of a lesion
elsewhere should be evident and it seems wise
to exclude any cases where the primary lesion
itself is thought to have metastasized outside
the CNS (as recommended by Gibson et al.,
1967). It is known that malignant tumours
of the brain can metastasize outside the head, but
this is excessively rare (Russell and Rubinstein,
1971), and there does not seem to be any
reason to make an exception of the occasional
primary melanoma. The presence of metas-
tases strongly suggests that the disease has
originated outside the CNS.

2. SECONDARY TUMOURS
These can occur anywhere in the brain, but have a predilection
for the cerebral hemispheres. Like secondary
tumours from other sites they appear to be
very rare in the spinal cord. They are fre-
quently multiple and in our series the presence
of a known primary tumour is sufficiently
frequent to make it a definite criterion for the
diagnosis. However, I would classify as prob-
able secondary tumours all those cases where,
despite the absence of an extra-CNS primary
tumour, there were multiple intracerebral
deposits without leptomeningeal involvement.

3. PIGMENTATION OCCURRING IN OTHER
TUMOURS OF CNS
This is well recognized in menangioma and medulloblastoma and should
not be allowed to alter a diagnosis made on
clinical and other pathological grounds.

CONCLUSION

In order to diagnose a melanoma as primary
the following factors should be looked for:
(1) No malignant melanoma tumour outside
the CNS; (2) involvement of the leptomeninges
(spinal or cranial); (3) intramedullary spinal
lesions; (4) hydrocephalus; (5) tumour in the
pituitary or pineal gland; (6) a single intra-
cerebral lesion.

Taking into account these criteria, together
with any other clinical or pathological informa-
tion, it should be possible to allocate every
patient to one or other of the following groups
with reasonable certainty:
(1) primary malignant melanoma of the
CNS; (2) secondary malignant melanoma of the
CNS; (3) melanin-containing variants of
other intracranial tumours.

REFERENCES


Malignant melanoma and the central nervous system. A guide for classification based on the clinical findings.

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