

# Malignant melanoma and the central nervous system

## A guide for classification based on the clinical findings

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**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

TABLE 1  
CLINICAL DETAILS OF PATIENTS WITH MALIGNANT MELANOMA OF CNS

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

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

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

DXT: Deep x-ray radiotherapy.

\* Still alive.

respectively. Each presented with communicating hydrocephalus and at the time of their first admission no other definite diagnosis was made. Both were treated initially with ventriculoatrial 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 subarachnoid 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 entire 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 already 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 inconclusive, a posterior fossa exploration was performed. Although the dura mater was normal the underlying arachnoid mater was brownish black in colour, very thick, and apparently infiltrated with tumour. This abnormality extended widely throughout the posterior fossa and no significant removal could be achieved. After surgery the patient's condition deteriorated 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 involvement of the fifth nerve ganglia and cavernous sinuses.

*Pigment containing meningioma* A 58 year old woman presented with a lump on her forehead and complained of deterioration of vision. Clinical examination and plain radiographs 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 melanotic 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 melanomas are not among the commoner malignant tumours in Great Britain they are currently under intensive study because of their immunological 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 evidence of a primary tumour. In a further two cases the primary tumour was discovered only on clinical examination after histological recognition 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 intracranial 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 malignant 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 metastases 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 frequently 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 probable 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 meningioma 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 intracerebral lesion.

Taking into account these criteria, together with any other clinical or pathological information, 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.

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