

Invited Review

Malignant blue nevus. Report of four new cases and review of the literature

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Summary. Malignant blue nevus is a rare melanotic tumor of the skin arising from a pre-existing blue nevus.

To date only few cases have been reported. The diagnosis of malignant blue nevus is frequently difficult. Generally accepted criteria do exist, but their application may be controversial.

The present paper reports four new cases of malignant blue nevus with follow-up of 3-5 years. Our present data, along with those of the literature, suggest that malignant blue nevus may be more aggressive than generally thought.

Key words: Malignant blue nevus, Melanoma, Cellular blue nevus

Introduction

Malignant blue nevus (MBN) is a malignant melanotic neoplasia arising from a blue nevus (Seldman et al., 1974; Ainsworth et al., 1979). The first six cases were described by Allen and Spitz (1953) and 43 more cases have been successively reported by various authors (Jadaassohn et al., 1954; Fisher, 1956; Herber and Klein, 1961; Gunter, 1962; Helwig, 1962; Lund and Kraus, 1962; Kwittken and Negri, 1966; Riley and Pack, 1966; Rodríguez and Ackerman, 1968; Merkow et al., 1969; Hourihane, 1970; Mishima, 1970; Gartmann and Lischka, 1972; Hernández, 1973; Shallman et al., 1974; Gray, 1975; Grouls et al., 1981; Rubinstein et al., 1985; Plantin et al., 1987; Gordeladze and Gaikova, 1988; Hagen et al., 1988; Kuhn et al., 1988) including seven cases arising from a preexisting Ota nevus (Dorsey and Montgomery, 1954; Montgomery, 1967; Zimmermann and Krueger, 1984; Speakman and Phillips, 1973; Lerner et al., 1979; Díaz Pérez et al., 1980; Kopf and Bart, 1982; Noedl and Krueger, 1984) and one in a nevus of Ito

(Van Krieken et al., 1988). Two additional cases of «benign cellular blue nevi» with metastatic spread have been reported, which could be interpreted as MBN (Couperus, 1954; Pond, 1954). Recently, Kao et al. (1981) described 31 similar lesions grouping them under the term «malignant blue melanoma». The diagnosis of MBN is frequently difficult. Generally accepted criteria do exist, but their application may be controversial (Lambert and Brodtkin, 1966; Rodríguez and Ackermann, 1968; Reiss and Gray, 1975; Sterchi et al., 1978; Temple-Camp, 1988). In fact, over or under-estimation of this lesion is not rare. Furthermore, the presence of so-called «benign lymphnode metastases» of benign blue nevus, which may be mistaken for metastatic melanoma, may present a particularly challenging problem to the pathologist (Epstein et al., 1984; Lambert and Brodtkin, 1984; Plantin et al., 1987; Sterchi et al., 1987). The present paper reports four new cases of MBN with follow-up of 3-5 years, along with literature review, emphasizing the difficulties in histological diagnosis and stressing prognostic pitfalls.

Materials and methods

Case I

F.I., a 40-year-old woman, affected since childhood by patchy bluish skin lesion, 24 x 12 cm., on her back, (Fig. 1) came to clinical attention due to the growth of three subcutaneous masses (2-3 cm. in diameter), which appeared 12, 5 and 1 years ago respectively, under the mole. At clinical examination, no palpable lymphnodes were evident. Laboratory tests were in normal range. The lesions were excised and submitted for histology.

Case II

P.L. a 39-year old woman, had been affected since childhood by a grey-bluish-black mole, 2 cm in diameter, on her left arm. Seven years ago she noticed a change in

colour and size of the lesion and eventually she decided to undergo surgery. The lesion was excised and submitted for histology.

Case III

D.U., a 41-year-old man, was referred for treatment because of a growing brown-black mole on his preauricular region, arisen in infancy, which had recently enlarged. The lesion was well circumscribed, symmetrical and measured 1 cm in diameter. Excisional biopsy was performed and the lesion submitted for histological examination.

Case IV

M.I., a 53-year-old woman, was admitted to the Angiological Department because of pain and lymphedema in the right leg, accompanied by fever (38° C). On physical examination, a subcutaneous nodule measuring 1 cm in diameter was discovered on her external thigh. The overlying skin was slightly light-grey. Eighteen months later the lymphedema increased and the skin over the nodule became erythematous and painful. Abdominal C.T. scan showed enlargement of the inguino-crural nodes. The cutaneous and subcutaneous lesions and the inguino-crural nodes were excised.

All specimens were formalin fixed and paraffin embedded. Serial sections were cut and stained with haematoxylin-eosin, Masson-Fontana silver impregnation and PAS. Cases 1 and 3 were additionally immunostained with antiserum against S-100 protein using the ABC technique.

Results

Case n. 1

Microscopically in each lesion the epidermis was normal revealing only flattening of the rete pegs, whereas the dermis and the subcutaneous tissue were occupied by a well delimited multinodular neoplasm, with areas of necrosis and haemorrhage (Fig. 2). The tumor cells were densely packed, large, oval to spindle in shape, with hyperchromatic nuclei, prominent nucleoli and scant or absent pigment. Mitotic figures were rare. Sheets of melanin containing spindle cells delimited the nodule.

Histological diagnosis was malignant melanoma arising in a congenital blue nevus (MBN).

Five years later the patient is alive and well, without progression of disease.

Case n. 2

Microscopically the dermis and subcutaneous tissue was occupied by a multinodular neoplasm showing features of a common blue nevus together with nests of densely-packed cells. One of these nests, in the

deepest portion of the lesion, showed larger heavily pigmented cells, with rare atypical mitotic figures (Fig. 3).

The overlying epidermis was intact.

The histological diagnosis was cellular blue nevus with atypia.

Two years later a bluish nodule, 4 cm in diameter, appeared under the scar. Surgery was performed and histological examination showed a features of malignant melanoma. The slides of the primary lesion were re-evaluated, the neoplasm was reclassified and diagnosis of MBN was made. Five months later two enlarged axillary nodes were found, which proved to be metastases of malignant melanoma.

Five years after the initial diagnosis the patient is disease free.

Case n. 3

Histologically the lesion was located in the dermis, with no activity at the dermoepidermal junction. The neoplasm showed a biphasic pattern, with nodules of oval shaped cells with vesicular nuclei and single nucleoli, surrounded by fascicles of



Fig. 1. Case 1: Patchy bluish skin lesion on the left side of the waist with three subcutaneous nodules, one of them, altering the profile of the waist (arrow).

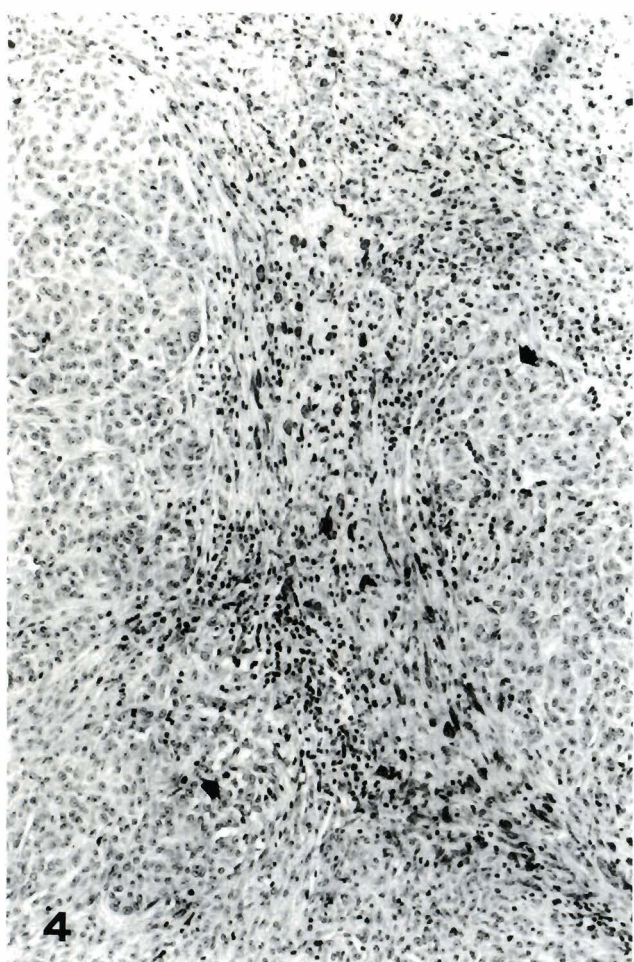
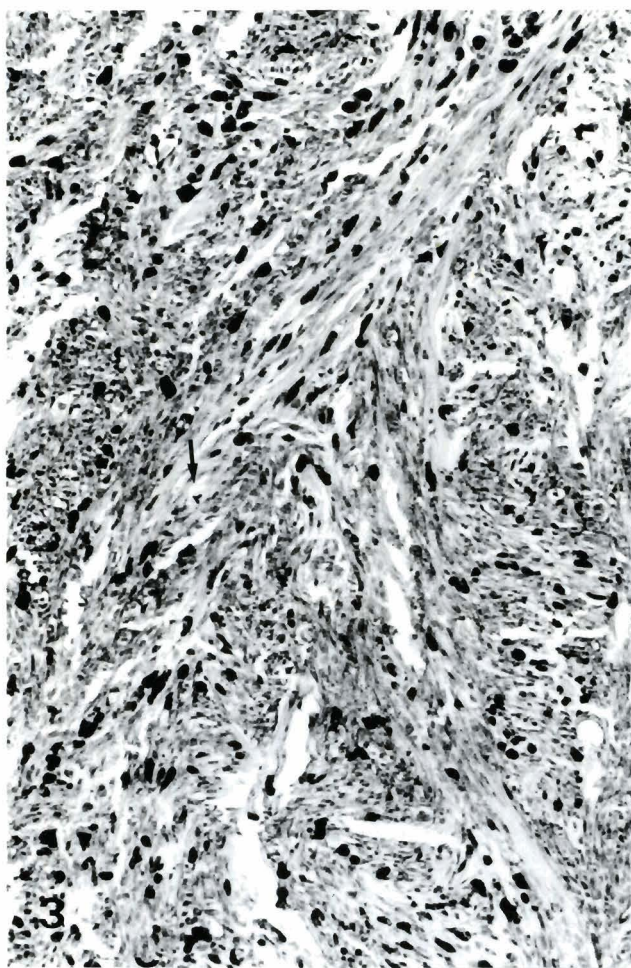


Fig. 2. Case 1: Low power view of the multinodular neoplasm. The nodules are of various dimensions and are separated by strands of slender spindle-shaped cells with abundant melanin. One of the nodules in the upper right corner, shows a necrotic area which causes artifactual fragmentation of the tissue (arrow). H.-E., $\times 63$

Fig. 3. Case 2: Fascicles of heavy pigmented cells with irregular aspects and rare atypical mitoses (arrow). H.-E., $\times 100$

Fig. 4. Case 3: The biphasic nature of the neoplasm, with nodular and fascicular areas, is clearly evident. Two mitoses (arrows) are present in the nodular areas. H.-E., $\times 100$

Fig. 5. Case 4: Two contiguous nodules separated by a fascicle of elongated cells: the oval shaped cells of the nodules show numerous mitoses (arrows). A mitosis is clearly evident also in the area of the spindle cells with «neuroid» features (arrow) H.-E., $\times 100$

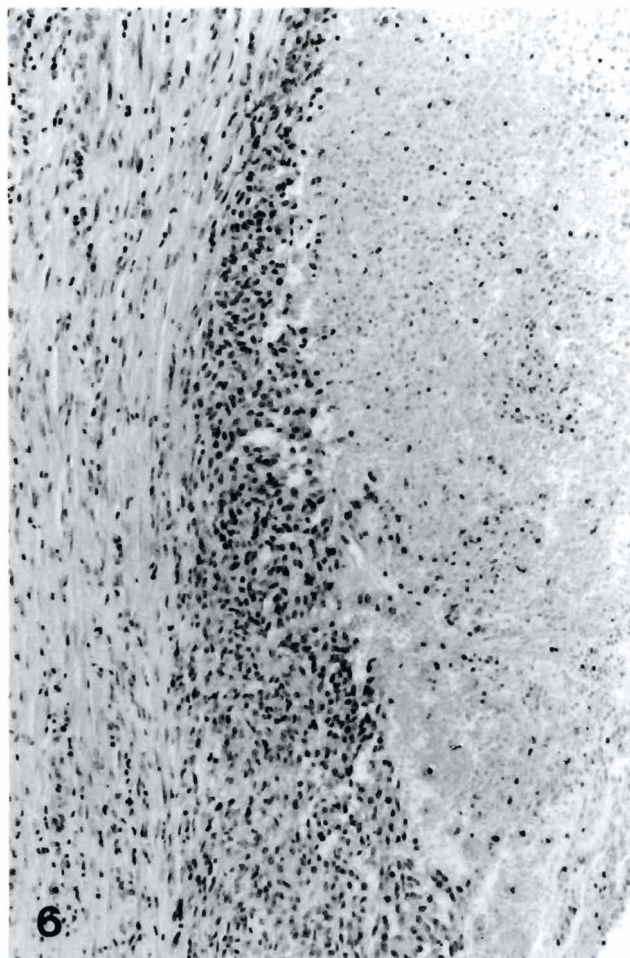


Fig. 6. Case 4: Area of necrosis in the central part of a nodule: the rim of surviving cells surround with nuclear debris and «ghost cells». H.-E., $\times 100$

pigmented spindle cells, with «neuroid features». In some limited areas the cells showed little atypia, with polymorphism, hyperchromasia and prominent nucleoli and rare and typical mitoses (Fig. 4). The diagnosis was cellular blue nevus with areas of atypia. Six months later the patient showed massive

Table I. Rodríguez - Ackermann's criteria for the differentiation between CBN and malignant melanoma.

Microscopic aspects	CBN	Melanoma
Junctional activity	–	+
Epidermal invasion	–	+
Margins	pushing	infiltrating
Peripheral inflammation	–	+
Biphasic pattern	+	–
Fasciculation	+	very rare
Epithelioid cells	never	frequent
Atypia	rare	+
Mitoses	rare typical	abundant atypical
Nucleoli	single small	multiple prominent
Cytoplasm	scant fibrillary	abundant vacuolated
Necrosis	–	+/-
Neuroid structures	+	–

Table II. Ainsworth's criteria for the diagnosis of malignant CBN.

Microscopic aspects of Malignant CBN	
pleomorphic cells	+
mitoses	+
necrosis	+
nests of preexisting CBN	+

metastases of malignant melanoma in two cervical nodes. After a 60-month disease-free period the patient developed multiple cutaneous metastases, histologically confirmed.

Two months later the patient died.

The primary lesion was reviewed, the neoplasm was reclassified and a diagnosis of MBN was made.

Case n. 4

Microscopically the middle and the lower dermis were occupied by a multinodular neoplasm. The cells

Table III. Summary of clinical data regarding 38 cases reported in literature (including the four of the present paper)

AUTHORS	N.	AGE	SEX	SITE	FOLLOW UP
Allen & Spitz 1953	5	37-68	M	chest, thigh, hand, neck, scalp	ARM 24m ARM 120 m DOD 12m DOD 24m LOST
	1	61	F	buttock	AWF 72m
Dorsey & Montgomery 1954	1	26	F	malar region	DOD 36m *
	1	16	M	malar region	LOST *
Jadassohn Franceschetti & Golay 1954	1	66	F	sacral reigon	DOD
Fischer 1955	1	27	M	occipital region	ADM 72m #
Helwig 1956	4	7-26			ARM 24m ARM 24m ARM 24m ARM 24m
	1	80	F	cheek	DOD 36m β
	1	59	M	dorsum of feet	ARM 264m
	1	24	F	cheek	DOD
Sweeney 1962	1	24	F	cheek	DOD
Kwittken & Negri 1966	1	33	F	feet	DOD 174m
Merkow et al., 1969	1	34	F	scapular region	ADM 47m
Mishima 1970	1			scalp	ARM 24m
	1			scalp	DOD 60m
Gartman & Lishka 1972	1	43	F	neck	ARM 31m
Hernández 1973	1	34	M	back (T-8 level)	DOD 10m
Reiss & Gray 1975	1	45	M	scalp	DOD 24m
Lerner, Nordklund & Kirkwood 1979	1		F	cheek	DOD
Díaz Pérez, Burgos Bretones & Rivera Pomar 1980	1	24	F	retroauricular	ARM 10m *
Grouls, Helpap & Cornic 1981	1	30	F	cheek	AWF 5m +
Kopf & Bart 1928	1	16	F	cheek	ADM 96m *
Noedl & Krueger 1984	1	21	F	cheek	AWF *
Rubinstein et al., 1985	1	33	M	hand	AWF 24m
Plantin et al., 1987	1	56	M	back	AWF 26m
Kuhn et al., 1988	1	41	F	arm	ADM 48m
Van Krieken, Boom & Scheffer 1988	1	78	M	arm	ARM 48m \$
Temple-Camp, Saxe & King 1988	1	70	M	back	AWF 9m
Present cases	1	40	F	wraistline	AWF 60m ^
	1	39	F	arm	ARM 60m
	1	41	M	preauricular	DOD 68m
	1	53	F	leg	ARM 36m

Legends: AWF = alive and well, free of disease
 ARM = alive with regional metastases
 ADM = alive with distant metastases
 DOD = died of disease
 (*) = arosen in OTA nevus

(\$) = arosen in ITO nevus
 (+) = arosen in giant pigmented nevus.
 (°) = arosen in a giant congenital blue nevus
 (#) = lesion present since the age of 17, which begun to enlarge from the age of 21
 (β) = lesion present since the age of 55, growing slowly until the age of 80

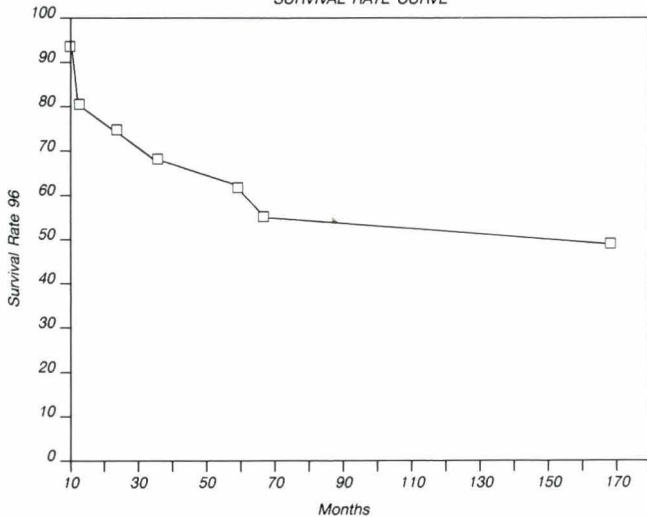
TABLE IV
SURVIVAL RATE CURVE

Table IV. Survival rate curve of MBN (16 cases reported in literature, including the present ones, with 5 year follow-up).

within the nodules were round, polyhedral or spindle in shape with vesicular nuclei and prominent nucleoli. Fascicles of spindle cells with «neuroid features» surrounded the nodules (Fig. 5). Mitoses were present.

One of the nodules showed a central necrotic area (Fig. 6).

The overlying epidermis was normal. The histological diagnosis was MBN. The lymphnodes showed multiple metastasis of malignant melanoma.

Three years later the patient is alive and well.

Discussion

MBN is an extremely rare neoplasia that may present a particularly difficult set of histological and clinical problems. The distinction between MBN and cellular blue nevus may lead to diagnostic errors.

Rodríguez and Ackerman (1968) summarized the differential criteria for the differentiation between cellular blue nevus (CBN) and malignant melanoma (Table I) and more recently Ainsworth et al. (1979) summarized the criteria for the diagnosis of MBN (Table II). Despite the apparent clearcut limits between these two entities, in individual cases the diagnosis remains difficult, and McGovern (1978) emphasized that even mitotic index is not always an absolute criterium of malignancy.

Dermatologists and pathologists should also be aware of the tendency of CBN to colonize local lymphnodes. Rodríguez and Ackerman (1968) reported an incidence of this kind of so-called «benign metastasis» in 5.2% of lymphnodes draining a CBN. The problem of the so-called «locally aggressive» CBN is also noteworthy. One case was described by Leopold and Richard (1966), who reported a locally aggressive CBN in a 25-year-old woman. The lesion was on her chin and infiltrated the striated muscle

of the lower lip. Marked mitotic activity was noted. There was no recurrence of the tumor 42 months later. A second case is reported by Silverber et al. (1971) who described a lesion of the scalp which infiltrated through the occipital bone into the occipital pole of the brain, involving the major dural sinuses. Wetherington et al. (1987) reported a third case of locally aggressive CBN of the scalp in a 14-year-old boy, extending beyond the posterior spinal processes of C4 and eroding the occipital bone. The lesion showed aggressive behaviour without cytological signs of malignancy. However, three years later the patient complained of a pelvic mass, 7 cm in diameter, involving the ileum, mesentery and peritoneum. Histological diagnosis of the mass was «metastatic malignant melanoma».

It is our opinion that so-called «locally aggressive» CBN should be regarded very cautiously. In fact one of the three above reported cases showed evidence of metastatic spread and perhaps the follow-up period of the cases of Leopold and Richards (1966) and of Silverberg et al. (1971) is not long enough to exclude the possibility of a metastatic spread of the neoplasms.

The clinical outcome of MBN is generally considered like that of a low grade malignancy (Rubinstein et al., 1985) but this view is perhaps too optimistic (Ginzburg et al., 1986).

Frequently the disease has a biphasic course. The patient may have a long symptom-free period, followed by a rapid lethal metastatic outbreak of the disease (Kwitken and Negri, 1966). In the series of Rodríguez and Ackerman (1968) five patients died from metastatic disease, four were alive with evidence of disease and only two patients were considered cured. Kao et al. (1981) reported metastatic spread in 55% and recurrence in 25% of their 31 patients affected by MBN. This aggressive clinical course prompted these authors to call the lesion «malignant blue melanoma» to point out the malignant potential of the disease.

The results of our study are in keeping with this latter view. Out of our 4 cases, only one (case I) showed limited disease without signs of recurrence or metastases. The others, either showed lymphode metastases from the beginning or recurred and/or metastatized within 6 to 60 months. Moreover, one of these patients died with generalized metastases.

The data we were able to collect from literature are presented in Table III. Follow-up and clinical data are not always comparable, but one of the most interesting features is the high frequency of disseminated metastases, which generally developed within 2-6 years. Considering the cases with a follow-up period of at least 5 years, we can draw a survival rate curve which shows that there is a quite high degree of mortality within the first 5 years (Table IV).

After 5 years only 9 out of 16 patients are alive and among them one died 68 months and another 174 months after the excision of the primary neoplasm. Moreover, of the remaining 7 patients, two showed evidence of distant metastases and their

prognosis may be very guarded. It is our opinion that these data should induce the clinicians to regard patients affected by MBN as suffering from a severe disease with a high risk of fatal outcome.

Our study offers an interesting view on histopathological diagnostic problems. In fact only two cases were initially diagnosed as MBN. The other two were classified as CBN bearing areas of atypia. These difficulties should alert pathologists to the fact that CBN may be less innocuous than suspected. It is mandatory to investigate very carefully any similar lesion, especially if areas of atypia are detectable. In fact, in our series two cases, although not completely fulfilling Rodríguez and Ackerman's (1968) and Ainsworth's (1979) criteria of malignancy, behaved aggressively.

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