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ORIGINAL ARTICLE

Simultaneous endocrine expression and loss of melanoma markers in malignant melanoma metastases, a retrospective analysis

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Abstract

Malignant melanoma metastases are chameleons of histopathology. In 4 primary malignant melanomas and 20 melanoma metastases expression of S-100, HMB-45 and melan-A as melanoma markers and CD56, synaptophysin and chromogranin-A as neuroendocrine markers was retrospectively analyzed. While all primary tumors expressed all 3 melanoma markers 7/20 of melanoma metastases had lost at least one melanoma marker, one had lost all three markers. Conversely about half of the samples stained for CD56, only 6/20 metastases were negative for all 3 neuroendocrine markers. None expressed chromogranin-A. Partial loss of melanoma markers and expression of neuroendocrine markers seems not to be infrequent. In patients with a history of malignant melanoma and suspected metastases, losing melanoma markers while expressing neuroendocrine markers is a potential diagnostic pitfall. Therefore all 3 melanoma markers should be performed as well as chromogranin-A staining. In doubt, metastases of the melanoma should be assumed.

Keywords Neuroendocrine expression · Melanoma metastases · Loss of melanoma markers

Introduction

It is well known, that melanoma metastases can change their histological appearance and lose expression of typical markers, possibly mimicking other tumors.

Alerted by two cases of mediastinal lymph node metastases of malignant melanoma with loss of typical markers and expression of CD56 that were misclassified as neuroendocrine lung cancer, we performed a retrospective analysis of 14 metastatic melanoma cases with regard to melanoma and neuroendocrine markers.

Methods and patients

in 14 patients, 6 females and 8 males, aged 49 to 90, 70 ± 14, median 70.5 years, 4 primary tumors and 20 metastases were analyzed for melanoma markers (S100, HMB-45, Melan-A) and neuroendocrine markers (CD56, chromogranin-A, synaptophysin).

Results

In Table 1 all relevant data for these patients are available. Table 2 shows a contingency table of the expression of the different markers in the 20 metastases. In samples designated as strongly positive most cells stained for the markers, in weakly positive samples staining was only focal or in isolated cells.

All primary tumors were at least weakly positive for melanoma markers, 2/4 weakly positive for CD56 and 1/4 weakly positive for chromogranin-A.

For the metastases, 20 specimens were evaluable for S-100, 18 for melan-A and HMB-45, 20 for CD-56 and 15 for synaptophysin and chromogranin-A respectively.

Only one patient was negative for all 3 melanoma markers, 5 specimens were at least weakly positive for only one, 1 specimen for 2 and 13 specimens for all 3 melanoma markers.

J. Krugmann, C. Sterlacci and W. Steppert had equal contributions to the design, the analysis and interpretation of the data as well as the manuscript was drafted and revised and approved. All above mentioned authors are responsible for all aspects of the work.

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Table 1 Data for individual specimen

pat id	site	age	sex	S-100	Mel-A	HMB-45	CD56	Chr-A	Synapto
1	Metastasis	67	f	0	0	0	2	nd	nd
1	Metastasis	67	f	0	1	nd	2	nd	nd
1	Metastasis	67	f	0	1	nd	0	nd	nd
2	Metastasis	62	m	0	nd	2	2	nd	nd
2	Metastasis	62	m	0	nd	2	2	nd	nd
3	Primary	62	m	2	2	1	0	0	0
3	Metastasis	62	m	2	2	1	0	0	0
3	Metastasis	64	m	2	2	2	0	0	0
4	Primary	90	f	1	2	2	1	0	0
4	Metastasis	90	f	1	2	2	1	0	0
5	Primary	75	f	2	1	1	0	0	0
5	Metastasis	76	f	2	1	2	0	0	0
6	Primary	86	m	1	1	1	1	0	1
6	Metastasis	86	m	1	2	2	1	0	1
6	Metastasis	86	m	0	0	1	0	0	1
6	Metastasis	86	m	2	1	2	1	0	1
7	Metastasis	87	f	1	2	1	1	0	2
8	Metastasis	80	m	2	2	2	0	0	2
9	Metastasis	67	m	1	1	1	0	0	0
10	Metastasis	74	f	0	2	2	0	0	0
11	Metastasis	49	f	2	2	2	0	0	2
12	Metastasis	55	m	2	2	1	1	0	0
13	Metastasis	85	m	2	2	2	0	0	1
14	Metastasis	50	m	2	2	2	0	0	1

Mel-A melan- A; *Chr-A* chromogranine- A, *Synapto* synaptophysin; *0* negative; *1* weakly positive, *2* strongly positive; *nd* not done

On the other hand only 6/20 specimen were negative for all neuroendocrine markers, 11 at least weakly positive for one and 3 specimen for two neuroendocrine markers.

No specimen stained for chromogranin A.

Discussion

Malignant melanoma is known for the ability of various histopathological presentations mimicking other tumors.

Table 2 Contigency table for metastases regarding expression of melanoma and neuroendocrine markers

	S-100	HMB-45	Mel-A	CD56	Chr-A	Synapto
Negative	7	1	2	11	15	7
Weakly positive	4	5	5	5	0	5
Strongly positive	9	12	11	4	0	3

Mel-A melan- A, *Chr-A* chromogranine- A, *Synapto* synaptophysin

Additionally especially metastases can lose immunohistochemical expression of S100, HMB-45 and melan-A [1, 2]. There are also reports about carcinoid- like appearance and neuroendocrine differentiation in metastases [3–5]. But in all reported cases melanoma markers were preserved.

To our best knowledge our patient is the first case of neuroendocrine expression and complete loss of S-100, HMB-45 and melan-A. Interestingly as reported before the expression of the melanoma markers and the neuroendocrine markers can vary between the different sites of metastatic disease [5].

In contrast to the 96% - 99% positivity for S-100 in the literature in about one third of the evaluated samples, staining for S-100 turned out negative. Melan-A staining was lost in only 2 and HMB-45 in 1 case. HMB-45 also was strongly positive in most samples.

On the other hand HMB-45 seems not to be as specific as melan-A. Especially single cell positivity seems not always to be melanoma associated [6].

Despite the rare published cases of positive neuroendocrine markers in malignant melanoma, CD56 was positive in about half of our samples. In contrast, chromogranin A was not positive in a single patient.

Single cell positivity of CD56 can also be found in CD56-positive tumor infiltrating lymphocytes [7], but the strong positivity should rely on the CD56 expression of the tumor cells themselves. Synaptophysin was expressed in 8/15 samples with a strong expression in 3/15. In contrary no expression of chromogranine A could be found in our series.

This is in line with a recently published paper where synaptophysin expression could be detected in about 30% of the cases while chromogranin-A expression was negative in all cases as well [8]. This could be a good distinction from neuroendocrine cancer, whereas chromogranin-A expression is normally in the range of one third [9].

We therefore encourage the additional staining for chromogranin- A for the classification of neuroendocrine tumors. In case of a history of malignant melanoma in doubt metastases of melanoma should be assumed and the tumor treated as melanoma.

Conclusions

The combination of partial loss of melanoma markers and expression of neuroendocrine markers seems not to be too infrequent in metastatic melanoma. In patients with mediastinal lymphomas and a history of malignant melanoma even in the absence of S100 and presence of neuroendocrine markers, metastases have to be taken into consideration. CD56 expression should be double checked with chromogranin-A staining as well as staining for the other markers. Chromogranin-A expression and absence of melanoma markers seems to rule out a tumor as melanoma metastasis.

Compliance with ethical standards

As the work is retrospective in nature compliance with ethical standards is guaranteed.

Conflict of interests The authors state that there is no conflict of interests concerning this paper.

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