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CASE REPORT

Anorectal melanoma metastatic to the breast: a case report and review of the literature

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Abstract: Melanoma develops from melanocytes and typically occurs on the skin and mucosa with a high degree of malignancy. Intensive local invasion and distant metastasis of melanoma result in poor patient prognosis, owing to frequent metastases to the lungs, bones, brains, and other parts of the body. In the present study, we report a case of anorectal melanoma in a 56-year-old woman who was admitted to our hospital because of local recurrence 9 months after local resection. She subsequently underwent radical surgery. Metastasis to the left breast occurred within 4 months after radical surgery. Metastasis of anorectal melanoma to the breast is very rare. In the present case report and literature review, we analyzed the clinical manifestation, diagnosis, and treatment of anorectal melanoma metastatic to the breast.

Keywords: melanoma, breast, metastasis

Introduction

Melanoma is a highly malignant skin tumor caused by the excessive proliferation of atypical melanocytes and frequently occurs on the skin of the trunk and four limbs or in the mucosal layer close to the skin. The incidence of melanoma in the People's Republic of China is low; however, it has been increasing in the recent years. More than 90% of the melanoma cases involve the skin tissues.[1,2] Primary anorectal melanoma is relatively less common compared to the melanoma of other body parts. In addition, metastases of malignant tumors to the breast tissue are uncommon; the patient in the present study represents the fifth case reported in the English literature.

Case report

A 55-year-old woman was initially diagnosed with "mixed hemorrhoids" at the Shenyang Proctology Hospital (Liaoning, People's Republic of China) with complaints of intermittent blood in the stool with tenesmus for 1 month. She underwent surgical resection, and postoperative paraffin pathology confirmed anorectal melanoma. However, the patient refused radical surgery and other treatment options. After 9 months, the patient developed a local recurrence. She was admitted to the Department of Surgical Oncology of The First Affiliated Hospital of China Medical University. Colonoscopy showed a smooth mucosa with a polypoid bulge of ~1.0×0.8 cm in size, located 6 cm close to the anal verge, without any erosion, ulcer, hemorrhage, or necrosis (Figure 1). Microscopic examination showed diffusely distributed, small, and relatively uniform tumor cells with oval-shaped, deviated nuclei and deep staining (Figure 2A). The tumor cells resembled plasma cells, showing evidence of mitosis and less cytoplasm without clear pigmentation (Figure 2B). The results of the immunohistochemistry analyses performed using specific markers to confirm

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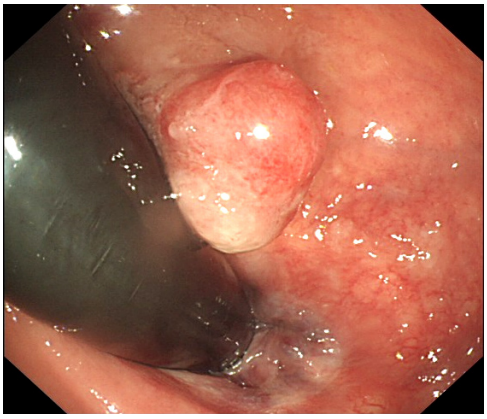

Figure 1 Endoscopic findings: proctoscopy revealed a mass at the anorectal junction.

small-cell melanoma were as follows: cytokeratin (pan, –), synaptophysin (–), chromogranin A (–), CD20 (–), Pax-5 (–), CD3 (–), CDX2 (–), CD15 (–), S-100 (+; Figure 2C); vimentin (+; Figure 2D), HMB-45 (+), Melan-A (+), CD56 (+), CD138 (–), CD38 (–), MUM1 (–), and a Ki67 index of ~60%. Thus, the tumor was confirmed as small-cell melanoma. The patient underwent abdominoperineal resection. There was no metastasis to the regional lymph nodes (zero of eleven nodes); however, a single stage IIIC nodular melanoma with the TNM classification pT4bN1bM0 was found in the drainage region of lymph nodes. The patient still refused chemotherapy and radiotherapy; however, 40 days after surgery, she received biological therapy consisting of dendritic cells combined with cytokine-induced killer cells.

A tumor was detected in the left breast via ultrasonography after 4 months of radical surgery. Breast ultrasonography showed a hypoechoic region in the outer upper quadrant of the left breast sized 1.46×1.26 cm^2 (Figure 3A). The mass had atypical characteristics and strip-shaped blood flow around the edges (Breast Imaging Reporting and Data System 4C; Figure 3B). The pathological examination of the specimen obtained via fine needle aspiration biopsy using a hollow needle showed morphological findings consistent with anorectal melanoma (Figure 4A). The immunohistochemistry results were as follows: cytokeratin (pan, –), vimentin (+; Figure 4B); S-100 (+), Melan-A (+; Figure 4C); HMB-45 (+; Figure 4D); CD3 (T lymphocytes, +), CD20 (B lymphocytes, +), Pax-5 (B lymphocytes, +), chromogranin A (–), synaptophysin (–), CD138 (–), ER (–), Her2 (–), P63 (–), GATA-3 (–), and a Ki67 index of ~70%, which confirmed anorectal melanoma metastatic to the breast.

Discussion

Anorectal melanoma frequently occurs near the dentate line. As the tumor is highly invasive and lymphatic vessels are abundant near the dentate line, local spread and distant metastases may occur in the early phase of the disease, with a 1.2% metastasis rate to the breast, resulting in a 5-year overall survival of <20%.[3–6] In the present study, 30 cases of melanoma metastatic to the breast that were reported from 1995 to 2015, including the present case, were reviewed retrospectively.[7–23] The mean patient age was 54 years, and 87.1% of the patients were women. The most common primary sites of melanoma were the skin tissues of the trunk (28.6%, eight out of 28 patients) and head and face (28.6%, eight out of 28 patients). Including the patient reported in the present study, only five patients were previously reported to have anorectal melanomas metastatic to the breast. Two of the patients died 3 months after metastasis to the breast. The average survival time after metastasis was >12.5 months.

In 1984, Lee[24] showed that melanoma cells expressed estrogen receptors; however, the role of estrogen in the metastases to the breast is presently controversial. An association was previously reported between metastasis of melanoma to the breast and menopausal status. Arora and Robinson[25] reported 15 patients with melanomas that metastasized to the breast, of which 93% were premenopausal. Another retrospective study involving 27 cases also reported that 70% of the patients were at the premenopausal

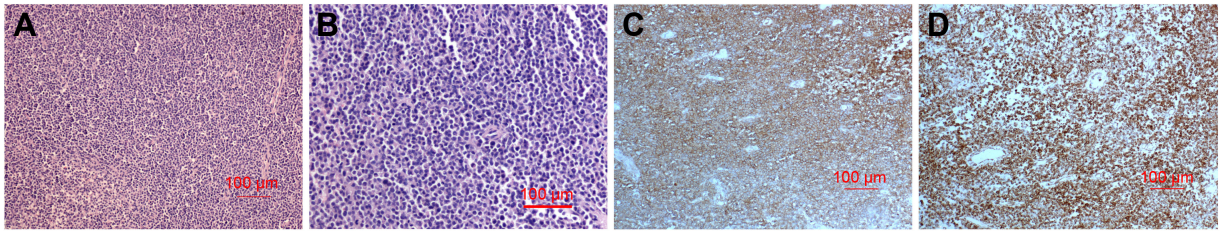

Figure 2 Hematoxylin and eosin immunohistochemical staining findings for the primary tumors are shown.
Notes: (**A**) Smaller tumor cells with a diffuse distribution are observed in the anal tumor; hematoxylin–eosin stain, ×100. (**B**) High magnification microscopy showing a tumor cell morphology similar to that of plasma cells. The nuclei displayed atypia and conspicuous mitotic activity. (**C**) Tumor cells showing positive staining for S-100; immunohistochemistry staining, ×100. (**D**) Tumor cells showing diffuse positive staining for vimentin; immunohistochemistry staining, ×100.

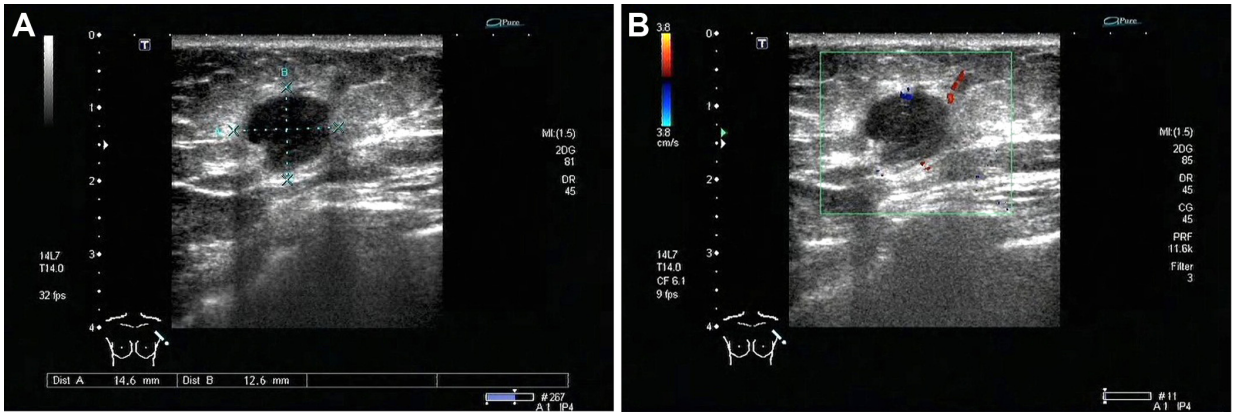

Figure 3 Breast ultrasonography images.
Notes: (**A**) A hypoechoic region sized 1.46×1.26 cm is seen in the outer upper quadrant of the left breast. (**B**) The mass has atypical characteristics and strip-shaped blood flow around the edges (BI-RADS 4C).
Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

stage.[6] The breast tissue of older patients is more fibrous, and the relatively poor blood supply makes the environment unfavorable for metastasis in these patients. Arora and Robinson[25] suggested a direct role for estrogen in facilitating metastatic spread.

The inhibition of antitumor immune responses in human beings is associated with metastatic melanoma.[26,27] Jayaraman et al[28] found, in a mouse model of melanoma, that the number of Treg cells increased in the peripheral blood of mice with metastatic melanoma and that the inhibition of Treg induction could effectively prevent the proliferation of tumor cells. The interactions of tumor cells with the microenvironment and the immune system are significant in the infiltration and metastasis of melanoma. In the clinical setting (Table 1), the average time from the diagnosis of the primary tumor to its metastasis to the breast was 49.9 months. Frequently, the tumors were identified as single lesions sized 0.8–6.0 cm. Primary tumors mostly involve the outer upper quadrant, consistent with the predilection sites for breast cancer.[29] The therapeutic principle used for the treatment of melanoma metastatic to the breast tissue does not differ from that of melanoma metastatic to other sites.[30] The standard therapeutic approach remains surgery supplemented with radiotherapy, chemotherapy, immunotherapy, and other treatments. In the present study, the retrospective analysis showed that almost one-third of the patients received radical mastectomy after the metastasis of melanoma, whereas approximately half of them preferred radiotherapy and chemotherapy as adjuvant therapies for the treatment of metastases to the breast.

Most melanoma patients with metastases to the breast already have local spread and metastases to multiple other organs that commonly include the epithelial tissues, lungs, brain, and liver.[6,31,32] We identified six out of 16 patients (37.5%) with metastases to other tissues and organs in addition to the breast. Metastasis to the breast is an indicator of poor prognosis.[33] Ravdel et al[6] reported that the median survival time of 27 patients who had melanomas metastasized to the breast was 12.9 months. In the present study, we reviewed eight of 15 patients who died within 1 year after metastasis to the breast. The patient in the present study refused chemotherapy after metastasis to the breast. To date,

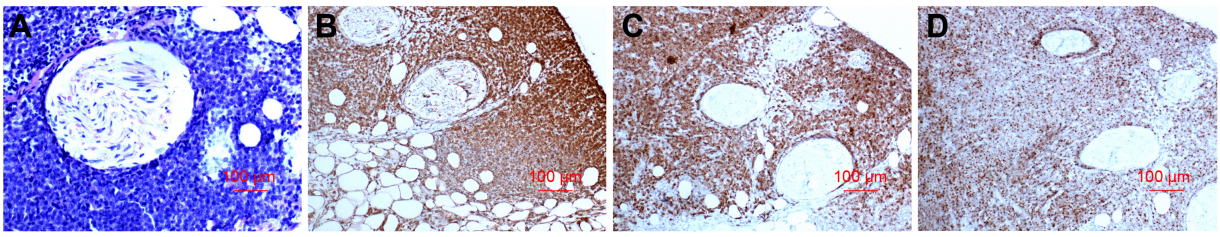

Figure 4 Immunohistochemical staining findings for the metastatic tumors are shown.
Notes: (**A**) Metastatic tumor in the left breast showing morphological findings consistent with those of the anorectal melanoma; immunohistochemistry staining, ×100. (**B**) Metastatic tumor cells showing positive staining for vimentin; immunohistochemistry staining, ×100. (**C**) Metastatic tumor cells showing positive staining for Melan-A; immunohistochemistry staining, ×100. (**D**) Metastatic tumor cells showing positive staining for Hmb45; immunohistochemistry staining, ×100. Scale bar, 100 μm.

Table 1 Data summary of the case series

Case number	Sex	Age (years)	History	Primary surgery	Time to metastasis (months)	Other metastasis location	Site	Size (cm)	Management of breast lump	Adjuvant therapy after metastasis	Time interval between breast metastasis and death (months)	References
1	F	55	Anorectal	RR	13	NF	Left upper outer	1.5	NP	Biotherapy	>5	This case
2	F	43	Conjunctiva	LE	24	Nasopharynx, oropharynx	Left	2	LE	Chemotherapy	4	8
3	F	78	Nasal cavity	NP	1	NF	Left upper	4	RR	NP	8	9
4	F	69	Infraorbital area	RR	204	Adrenal gland, anocelia, axilla	Left lower inner and right upper outer	2.3; 1.8	NP	Chemotherapy	NA	10
5	F	58	Chest wall	RR	96	NF	Inferior to the right nipple	2.5	RR	Radiotherapy and chemotherapy	>36	11
6	F	42	Ankle	RR	48	Back, buttock, brain, and right leg	Left upper outer	2	LE	Radiotherapy and chemotherapy	NA	12
7	F	39	Trunk	RR	36	Brain, lung, and abdominal lymph nodes	Left medial quadrant	1.4	LE	Radiotherapy and chemotherapy	NA	13
8	M	62	Auricle	NA	96	Groin, abdominal wall, and arm	Left upper outer	4.5	RR	NP	NA	14
9	M	50	Trunk	RR	2.5	NF	Left lower inner	0.8	RR	NP	>36	15
10	F	53	Foot	NA	24	NF	Left and right	NA	NA	Chemotherapy	8	16
11	F	70	NF	NP	NA	NF	Light upper	8	RR	NP	8	17
12	F	59	Anorectal	RR	4	NF	Left upper outer	4	RR	NP	>42	18
13	F	34	Finger	LE	3	NF	Left and right	1.5	Mastectomy	NA	NA	19
14	F	34	Abdominal wall	NA	18	NA	Right lower inner	1	NA	NA	NA	20
15	F	70	Eye, axilla	NA	12	NA	Right upper outer	2	NA	NA	NA	20
16	F	53	Thigh	NA	72	NA	Right upper outer	0.8	NA	NA	NA	20
17	F	45	Arm	NA	NA	NA	Left upper outer	1	NA	NA	NA	20
18	F	44	NF	NA	108	NA	Right upper outer	3	NA	NA	NA	20
19	M	56	NF	NA	NA	NA	Right lower outer	NA	NA	NA	NA	20
20	M	71	Back	NA	12	NA	Left	3	NA	NA	NA	20
21	F	60	Leg	NA	178	NA	Right upper outer	NA	LE	NA	14	21
22	F	84	Ankle	NA	13	NA	Right upper outer	NA	LE	NA	14	21
23	F	48	Toe	NA	25	NA	Right medial upper	NA	LE	NA	10	21
24	F	68	Calf	NA	101	NA	Right upper outer	NA	LE	NA	NA	21
25	F	47	Abdomen	NA	41	NA	Right upper outer	NA	RR	NA	NA	21
26	F	58	Abdomen	NA	110	NA	Left medial lower	NA	NP	NA	2	21
27	F	28	Temple	NA	72	NA	Left medial lower	NA	LE	NA	NA	21
28	F	43	Scapula	NA	55	NA	Left medial lower	NA	LE	NA	NA	21
29	F	40	Anorectal	RR	6	NF	Left upper inner	6	NP	NP	<1	22
30	F	59	Anorectal	RR	18	NF	Right upper	3	LE	Chemotherapy	>12	23
31	F	55	Anorectal	NP	3	Abdominal lymph nodes	Left	1.5	NP	NP	2.5	24

Abbreviations: F, female; LE, local excision; M, male; NA, not available; NF, not found; NP, not performed; RR, radical resection.

she has been followed-up for 5 months with no considerable changes in her condition.

Conclusion

Metastasis of tumors to the breast is a very rare phenomenon. The possibility of metastasis should be considered in the patients with a history of melanoma or other malignant tumors when masses are detected in the breast tissue. The patients with metastasis to the breast often demonstrate accompanying multiple metastases to other tissues and organs; therefore, a comprehensive examination and assessment of the conditions of the patients are necessary, as it might directly influence the prognostic assessment and the establishment of effective therapeutic approaches.

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Disclosure

The authors report no conflicts of interest in this work.

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