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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...
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 (−), 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 cm² (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, Lee24 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 Robinson25 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
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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 suggested a direct role for estrogen in facilitating metastatic spread.

The inhibition of antitumor immune responses in human beings is associated with metastatic melanoma. Jayaraman et al. 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. 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. 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. 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. Ravdel et al. 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,
| 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                         | NA                       | Left upper outer          | 1.5 | NP        | Biotherapy                | Chemotherapy                    | >5                                               | This case |
| 2           | F   | 43          | Conunctiva | LE              | 24                         | NA                       | Left                      | 2   | LE        |                           |                               | 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, anocella, axilla | Left lower inner and right upper outer | 2.3; 1.8 | RR | Chemotherapy |                           | 10                  | NA   |
| 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 Brain, lung, and abdominal lymph nodes | Left upper outer | 2 | LE | Radiotherapy and chemotherapy |                           | NA                  | 12         |
| 7           | F   | 39          | Trunk      | RR              | 36                         | 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         | NA              | 8                         | Light upper               | 8 | RR | NP | >42 | 18 |
| 12          | F   | 59          | Anorectal  | RR              | 4                          | Left upper outer          | 4 | RR | NP | Mastectomy | NA                  | 19         |
| 13          | F   | 34          | Finger     | LE              | 3                          | Left and right            | 1.5 | NA | NA | NA | 20         |
| 14          | F   | 34          | Abdominal wall | NA         | 18                         | Right lower inner         | 1 | NA | NA | NA | 20         |
| 15          | F   | 70          | Eye, axilla | NA              | 12                         | Right upper outer         | 2 | NA | NA | NA | 20         |
| 16          | F   | 53          | Thigh      | NA              | 72                         | Right upper outer         | 0.8 | NA | NA | NA | 20         |
| 17          | F   | 45          | Arm        | NA              | 10                         | Left upper outer          | 1 | NA | NA | NA | 20         |
| 18          | F   | 44          | NF         | NA              | 108                        | Right upper outer         | 3 | NA | NA | NA | 20         |
| 19          | M   | 56          | NF         | NA              | 12                         | Right lower outer         | NA | NA | NA | NA | 20         |
| 20          | M   | 71          | Back       | NA              | 12                         | Left                      | 3 | NA | NA | NA | 20         |
| 21          | F   | 60          | Leg        | NA              | 178                        | Right upper outer         | NA | LE | NA | 14 | 21         |
| 22          | F   | 84          | Ankle      | NA              | 13                         | Right upper outer         | NA | LE | NA | 14 | 21         |
| 23          | F   | 48          | Toe        | NA              | 25                         | Right medial upper        | NA | LE | NA | 10 | 21         |
| 24          | F   | 68          | Calf       | NA              | 101                        | Right upper outer         | NA | LE | NA | 14 | 21         |
| 25          | F   | 47          | Abdomen    | NA              | 41                         | Right upper outer         | NA | RR | NA | NA | 21         |
| 26          | F   | 58          | Abdomen    | NA              | 110                        | Left medial lower         | NA | NP | NA | 2 | 21           |
| 27          | F   | 28          | Temple     | NA              | 72                         | Left medial lower         | NA | LE | NA | NA | 21         |
| 28          | F   | 43          | Scapula    | NA              | 55                         | Left medial lower         | NA | LE | NA | NA | 21         |
| 29          | F   | 40          | Anorectal  | RR              | 6                          | Left upper inner          | 1 | NP | NP | <1 | 22 |
| 30          | F   | 59          | Anorectal  | RR              | 18                         | 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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