Clinical Case Report

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Signet-ring cells in the bone marrow as an indication of cryptic metastasis of breast carcinoma

A case report

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Abstract

Rationale: Signet-ring cell is a rare morphological finding in bone marrow, which usually indicates metastatic carcinoma from either the gastrointestinal tract or a primary hematolymphoid neoplasm. Here, we present a very unusual case of lobular breast carcinoma with metastasis to the bone marrow.

Patient concerns: A 67-year-old female with estrogen receptor (ER)-positive lobular breast carcinoma was staged as T3N3M0, and treated with modified radical mastectomy followed by chemotherapy and radiotherapy. One year after treatment, she was noted to have moderate thrombocytopenia on complete blood count with the remainder of the parameters within normal limits. Radiographic examination revealed no evidence of recurrent disease.

Diagnosis: Bone marrow biopsy was performed to exclude therapy-related myelodysplastic syndrome (MDS), which demonstrated hypercellularity with "hyperplastic" hematopoiesis. Upon closer inspection, a few signet-ring cells were identified which morphologically resembled histiocytes. These formed an interstitial infiltrate among the predominantly hematopoietic elements, and could have been easily overlooked. Immunohistochemistry demonstrated that these signet-ring cells were positive for pancytokeratin as well as ER which confirmed metastatic lobular breast carcinoma. On retrospective review of the aspirate smear, rare signet-ring cells were identified.

Interventions: The patient was treated with additional chemotherapy.

Outcomes: The patient eventually succumbed to overt dissemination after 14 months.

Lessons: Due to the relative discohesiveness of lobular breast carcinoma, the cells frequently assume single-cell infiltration in bone marrow. This attribute, along with small cell size, bland cytologic features and paucity of tissue response, contributes to its escaping from identification on hematoxylin-eosin (H&E) sections. In this case, the signet-ring cells were hidden in apparently hyperplastic hematopoiesis. Careful inspection raised the possibility of occult metastasis which was readily detected and confirmed with immunohistochemistry.

Abbreviations: ER = estrogen receptor, H&E = hematoxylin-eosin, LDH = lactate dehydrogenase, MDS = myelodysplastic syndrome, PET/CT = positron emission tomography/computed tomography, PR = progesterone receptor.

Keywords: biopsy, bone marrow, breast carcinoma, histology, signet-ring cell

1. Introduction

Lesions of the bone marrow are best characterized by histopathologic examination on bone marrow biopsy. Whether benign or malignant, primary to the bone marrow or metastasis from another site, signet-ring cell morphology is distinctly uncommon. According to previous reports, when signet-ring cells are identified, metastatic poorly differentiated adenocarcinoma is the most common entity and should be first on the differential

Editor: N/A.

Approval was provided by Medical Research Ethics Committee of China Medical University (2018239). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

This study was supported by National Natural Science Foundation of China (Grant No. 81301930 to L-HY, Grant No. 81372497 to H-TX), General project of Education Department of Liaoning Province (Grant No. L2015595 to L-HY), and Students' Innovation and Entrepreneurship Training Program (Grant No. 201610159000036 to L-HY).

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:11(e14883)

Received: 14 November 2018 / Received in final form: 5 February 2019 / Accepted: 19 February 2019

http://dx.doi.org/10.1097/MD.0000000000014883

diagnosis. Among these cases, gastrointestinal tract sites such as gastric, small bowel, ampulla of vater, and intrahepatic bile duct are the more common sites of origin.[1–24] However, it should be noted that hematolymphoid neoplasms can also present with signet-ring cell morphology which may lead to diagnostic pitfalls.[24–28] Here, we present a very unusual case of a 67-year-old female with invasive lobular breast carcinoma, confirmed by breast biopsy and histopathologic examination. One year after surgery with combined chemotherapy and radiotherapy, the patient was noted to be thrombocytopenic. The patient subsequently underwent a bone marrow biopsy to exclude myelodysplastic syndrome (MDS) related to therapy. Histopathologic examination revealed very rare signet-ring cells scattered within the bone marrow which could easily be overlooked as histiocytes. To the best of our knowledge, this is the first case of metastatic invasive lobular breast carcinoma to the bone marrow with predominant signet-ring cell presentation published in English.

2. Case presentation

A 67-year-old female was found to have a palpable, mammographically suspicious mass in the right breast. Needle core biopsy revealed moderately-differentiated invasive lobular carcinoma that was positive for estrogen receptor (ER) and progesterone receptor (PR), but was negative for HER2/neu. A modified radical mastectomy with axillary lymph node dissection was then performed. Fifty-two lymph nodes were identified from the main specimen as well as the axillary dissection. All 52 identified lymph nodes were positive for metastatic carcinoma, including 44 ipsilateral axillary lymph nodes. Positron emission tomography/computed tomography (PET/CT) scan demonstrated no bone lesions or other distant metastases. She was staged as T3N3M0 at that time. The patient subsequently received combined chemotherapy and regional radiotherapy, and she responded well. Approximately 1 year after the treatment, she was noted to have moderate thrombocytopenia ($84 \times 10^3/\mu L$) during routine follow-up. Her other blood parameters were within normal limits. At the time, the serum lactate dehydrogenase (LDH) and calcium were unremarkable. Radiographic examination of the chest, abdomen, and pelvis did not reveal evidence of recurrent or metastatic disease. To exclude MDS related to the therapy, a bone marrow biopsy was performed, and demonstrated hypercellularity with apparently increased trilineage hematopoiesis. Close inspection revealed a few scattered signet-ring cells (Fig. 1 A, ×20, inset arrow heads, ×40). These signet-ring cells contained a single cytoplasmic vacuole which compressed the nuclei, resembling activated histiocytes. They formed an interstitial infiltrate of single cells, and rarely 2 to 3 cell clusters, among predominantly hematopoietic elements. Without the pertinent history and careful examination, these few scattered signet-ring cells could have been potentially overlooked. Rare cells with eccentric nuclei and foamy cytoplasm were present on the aspirate smear (Fig. 1B, arrow heads, ×100), but were only noted on retrospective review with an extensive effort to identify. Immunohistochemical analysis of the bone marrow demonstrated that these signet-ring cells were positive for pancytokeratin (Fig. 1C, ×10, inset ×20) and ER (Fig. 1D, ×40). A diagnosis of metastatic lobular breast carcinoma was thus rendered. The patient was treated with additional chemotherapy; however, her disease progressed, and overt metastasis to the colon with peritoneal carcinomatosis was identified 14 months later. At this point she was at the terminal stage of her disease, and remained in hospice where she eventually succumbed to multiorgan failure and passed away.

3. Discussion and conclusion

Signet-ring cells have a characteristic morphological appearance with large clear vacuolated cytoplasmic inclusions displacing the nucleus to the periphery.[1–24] Such morphological appearance is well recognized in lymph nodes from patients with metastatic adenocarcinoma, but rarely seen in bone marrow biopsies. According to previous reports, the most common site of origin of metastatic adenocarcinoma with signet-ring cell morphology involving the bone marrow is the gastrointestinal tract. Among these cases, poorly-differentiated adenocarcinoma (signet-ring cell carcinoma) of the stomach is the most common,[1–24] Paparo et al reported a case of a primary signet-ring cell carcinoma of the small bowel in 59-year-old male with long-standing Crohn disease,[6] Younes et al described a 60-year-old male with signet-ring cell carcinoma originating from the intrahepatic bile ducts,[10] Nabeshima et al presented a 49-year-old man with signet-ring cell carcinoma of the ampulla of Vater with bone marrow metastasis.[13] These reports show that signet-ring cell carcinoma from other gastrointestinal sites are likely sporadic incidents. Although metastasis of gastric adenocarcinoma to the bone marrow is well documented, it is rarely the presenting symptom. If bone marrow involvement is discovered, it is usually during the workup for metastatic disease.[18–20,22,23] When bone marrow metastasis occurs, it is more commonly a signet-ring cell subtype of gastric adenocarcinoma and occurs in younger patients. The prognosis for bone marrow involvement with gastric adenocarcinoma is abysmal, with patient's living an average of 44 days from the time of documented bone marrow involvement.[29–31] Kim et al reported that the median interval from the diagnosis of gastric adenocarcinoma to the detection of bone marrow involvement was 161 days,[29] while the longest interval of gastric signet-ring cell carcinoma was reported by Noda et al, which was 9 years following total gastrectomy in a 57-year-old Japanese male.[4] In the very late stages of malignancy, it may be very difficult to identify the primary site of origin when the bone marrow biopsy shows signet-ring cell carcinoma.

Although it is well known that adenocarcinomas may have signet-ring cell morphology, it should be noted that hematolymphoid neoplasms may also present with signet ring-cell morphology. Since Kim et al described the first case of follicular lymphoma with signet-ring cells presentation in a lymph node in 1978,[24] approximately 40 cases have been reported, but bone marrow is rarely involved in these cases. To the best of our knowledge, this is the first description of invasive lobular breast carcinoma (signet-ring cell variant) with bone marrow metastasis in English. Pathologists can confirm the diagnosis by patients' history, careful inspection, and immunohistochemistry staining. Comparing with the cases mentioned above, our case shows very unusual presentation with only rare single, and 2 to 3 cell clusters, signet-ring cells "hidden" in the hyperplastic bone marrow. Signet-ring cell carcinoma is well known for being missed, even by experienced pathologists, and in the background of hyperplastic marrow it becomes even more difficult.

In our case, metastasis of the signet-ring cell carcinoma to the bone marrow was the first presentation of the recurrence of the patient's primary lobular breast carcinoma. After the detection of the bone marrow metastasis, the disease progressed rapidly and

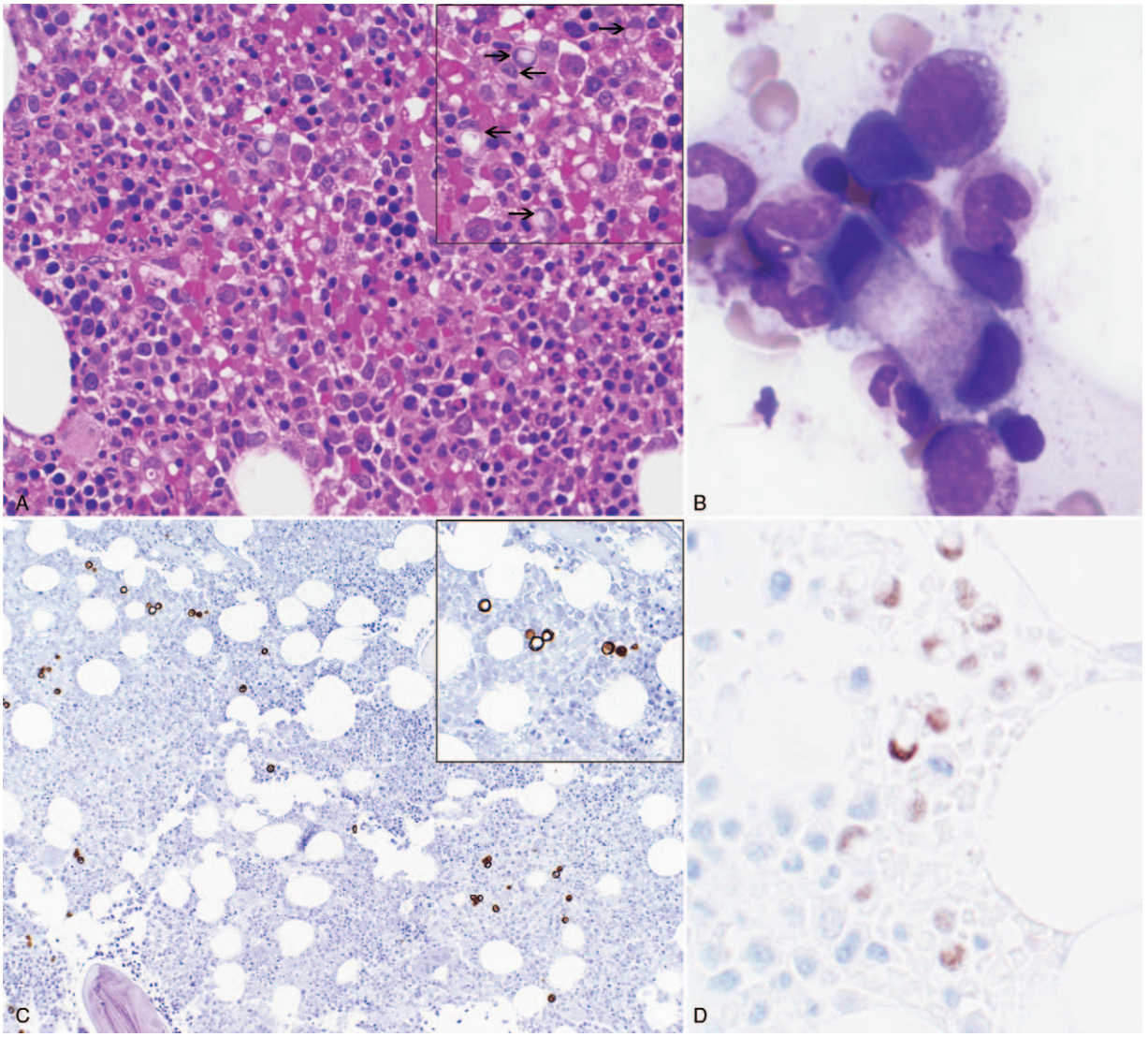

Figure 1. Histological and immunostains of cryptic metastasis of breast carcinoma in bone marrow. A, Atypical tumor cells show large clear vacuolated cytoplasmic inclusions displacing the nucleus to the periphery, "hidden" in hypercellular bone marrow (×200, inset ×400). B, Rare tumor cells present with atypical eccentric nuclei and foamy cytoplasm on aspirate smear (arrow heads, ×1000). C, Scattered tumor cells are positive for pancytokeratin (×100, inset ×200). D, Tumor cells show nuclear positive for ER (×400). ER = estrogen receptor.

the patient passed away 14 months later. It is unclear whether or not the limited bone marrow metastasis in this case corresponded to the rapid progression of her disease. This case emphasizes the importance of patient history, careful examination, and immunohistochemical analysis in the evaluation of bone marrow biopsy in a patient with a history of invasive lobular breast carcinoma.

Metastatic adenocarcinoma is sometimes seen in bone marrow biopsies, where it usually shows segmental involvement with tumor nests or glands and associated desmoplastic tissue reaction. Due to relative discohesiveness, lobular breast carcinoma frequently assumes a pattern of single-cell infiltration in bone marrow, which, along with its small cell size, bland cytologic features and paucity of tissue response, contributes to its escaping from identification on hematoxylin-eosin (H&E) section. In this bone marrow biopsy, the "signet-ring" cells were hidden in apparently hyperplastic hematopoietic elements. The occult metastasis was readily detected with immunohistochemical analysis.

Author contributions

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