CASE REPORT

Bone Marrow Invasion of Small Cell Neuroendocrine Carcinoma of the Endometrium: A Diagnostic Pitfall Mimicking a Haematological Malignancy

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Abstract:
Metastasis of cancer cells to the bone marrow is relatively rare, despite being one of the most important causes of myelosuppression in patients with solid tumours. A bone marrow examination via a biopsy is the standard method of diagnosing cancer cell invasion into the bone marrow. However, it is sometimes challenging to distinguish neuroendocrine carcinoma cells from haematopoietic cells due to their small, round shape and chromosomal abnormalities resembling haematological malignancies. We herein report a case of bone marrow invasion of small cell neuroendocrine carcinoma of the endometrium mimicking therapy-related myeloid malignancy.

Key words: bone marrow metastasis, myelofibrosis, therapy-related myelodysplastic syndrome, small cell neuroendocrine carcinoma

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Introduction
Bone marrow suppression is caused by a variety of mechanisms in patients with solid tumours. Therapy with anticancer drugs or radiotherapy frequently induces transient myelosuppression. Furthermore, some patients treated with chemotherapy or radiotherapy develop myeloid malignancies, known as therapy-related myeloid neoplasms. In addition, although the incidence is relatively low, metastasis of carcinoma cells to the bone marrow can cause severe pancytopenia.

Recent studies have shown that allogenic transplantation can improve the survival of patients with therapy-related myeloid malignancy. In contrast, the treatment of patients with metastasis of carcinoma cells to the bone marrow has not been established, and the prognosis of these patients is extremely poor. Therefore, it is very important to distinguish therapy-related myeloid malignancy from bone marrow metastasis of carcinoma when patients with solid tumours show unexplained or sustained myelosuppression.

A morphological analysis of bone marrow smears is the first step in diagnosing bone marrow invasion of carcinoma cells. Invaded carcinoma cells usually show a sheet-like appearance; however, some types of carcinoma cells have a round appearance, resembling haematopoietic cells. In such cases, an immunohistochemical (IHC) analysis of a trephine biopsy of the bone marrow is helpful for distinguishing carcinoma from haematopoietic cells, as carcinoma are usually positive for cytokeratin, while haematopoietic cells are negative for these markers. Nevertheless, several case reports have demonstrated the presence of bone marrow metastasis of carcinoma without cytokeratin expression. In such cases, the correct diagnosis is sometimes challenging. A chromosomal analysis is also a useful method for diagnosing haematological malignancies. However, several types

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of solid tumours, including endometrial carcinoma (6), also have abnormal karyotypes; therefore, the possibility of invasion of carcinoma cannot be excluded based solely on the results of a chromosomal analysis.

We herein report a case of bone marrow invasion of small cell neuroendocrine carcinoma of the uterine corpus resembling therapy-related myeloid malignancy. Our experience indicates that a careful IHC evaluation with neuroendocrine markers should be performed for the diagnosis of bone marrow invasion of solid cancer.

### Case Report

A 58-year-old Japanese woman was transferred from the gynaecology unit at our institute for the evaluation of sustained anaemia and thrombocytopenia. The patient had been diagnosed with serous adenocarcinoma of the uterine corpus, TNM classification stage IVB, and had received abdominal total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy (pelvic and para-aortic) and omentectomy approximately one year earlier. The pathology diagnosis was serous adenocarcinoma with invasion to the para-aortic lymph node. The clinical stage and diagnosis had not changed after surgery.

After the operation, the patient had been treated with 12 cycles of chemotherapy with paclitaxel and carboplatin. Following the last cycle of chemotherapy, the serous carcinoma of the uterine corpus was not detected on computed tomography (CT) but she presented with persistent anaemia and thrombocytopenia lasting for more than six weeks. At the time of consultation, she had severe anaemia (haemoglobin [Hb] 5.6 g/dL; reference range 11.6 to 14.8 g/dL) and thrombocytopenia (platelet count 52×10^7/L; reference range 158 to 348×10^7/L). In addition, myelocytes and metamyelocytes appeared in her peripheral blood. She also complained of bone pain throughout the body (Table 1).

Initially, we suspected the recurrence of endometrial carcinoma one marrow invasion. However, the levels of carcinoembryonic antigen (CEA), cancer antigen 125 (CA125) and cancer antigen (CA19-9), all of which are markers of endometrial carcinoma, were not elevated. The laboratory test results showed elevated lactate dehydrogenase (LDH) (1,473 U/L; reference range 124 to 222 U/L) in the absence of disseminated intravascular coagulation (Table 1). The clinical course before her consultation with us is shown in Fig. 1. CT at 316 days after surgery showed no findings of recurrence or metastasis of endometrial carcinoma. Gallium (Ga) scintigraphy at 323 days after surgery showed high Ga accumulation in the bone marrow, suggesting the existence of a haematological malignancy rather than the invasion of carcinoma, and a bone marrow smear revealed an increase in round cells with immature nuclei resembling myeloblasts that were negative on myeloperoxidase staining (Fig. 2A-E). The results of a myelogram and analysis of the surface markers by flow cytometry are shown in Table 2 and Fig. 1F. Morphological abnormalities in megakaryocytes were also observed (Fig. 2E).

A bone marrow biopsy showed severe myelofibrosis (MF-2) and an increase in the number of round cells, as shown in the smear (Fig. 3A and B). Some of the cells were positive for P53 (Fig. 3C). For a further study, we performed an IHC analysis with an anti-pan-cytokeratin antibody, AE1/AE3. As shown in Fig. 3D, the cells were negative for cytokeratin. Giemsa banding (G-banding) showed karyotype complex abnormalities (represented by -5, +8, and -9) in 3 of the 20 analysed cells (Fig. 4). Mutations in JAK2, MPL and CALR were not detected. Therefore, we diagnosed the patient with therapy-related myelodysplastic syndrome (t-MDS) with fi-
brosis and began to prepare for allogeneic haematopoietic stem cell transplantation (Allo-HSCT).

Two months later, her anaemia and thrombocytopenia worsened, and she complained of an increase in bone pain. At that time, CT showed multiple hepatic tumours and abdominal lymphadenopathies. A needle biopsy of the hepatic tumour showed invasion of round cells into the liver (Fig. 5A). IHC studies showed that the cells were positive for p16, a marker of endometrial cell carcinoma (Fig. 5B). The cells were also positive for synaptophysin but negative for chromogranin A (Fig. 5C and D). These results indicated that the patient had liver metastasis of small cell neuroendocrine carcinoma.

We attempted to locate the original site of cancer. To this end, we re-evaluated the surgical specimens of the endometrium with an IHC analysis. The endometrial lesion of the patient was composed of two different components: serous endometrial carcinoma and undifferentiated solid-type carcinoma (Fig. 6A). We found that the cells in the undifferentiated component were positive for both synaptophysin
and chromogranin A (Fig. 6B and C). In contrast, some of the cells in that area were negative for AE1/AE3 staining (Fig. 6D). Based on these results, we diagnosed the patient with multiple liver metastases of small cell neuroendocrine carcinoma derived from the endometrium. The bone marrow biopsy specimen was also retrospectively analysed by the same methods. We confirmed that the immature round cells observed in the initial bone marrow biopsy specimens were also positive for synaptophysin but negative for chromogranin A (Fig. 7A and B) and concluded that the cells were metastatic small cell neuroendocrine endometrial carcinoma cells. Based on the diagnosis of multiple metastases of neuroendocrine carcinoma, the therapeutic plan for HSCT was cancelled, and the patient was given best supportive care.

**Conclusion**

Neuroendocrine carcinomas arise from various organs, including the lung and gastrointestinal tract; however, neuroendocrine carcinoma originating from the female genital tract, especially the endometrium, is relatively rare (7). To date, fewer than 100 cases of neuroendocrine carcinoma of the endometrium have been reported (7). These case reports indicate that neuroendocrine carcinoma from the endometrium usually displays an aggressive phenotype and tends to spread to many organs, including the bone marrow, and the prognosis of these patients is extremely poor. Koo et al. reported six cases of small cell neuroendocrine carc-

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**Table 2. Myelogram Findings at the First Bone Marrow Examination Performed 310 Days after Surgery.**

<table>
<thead>
<tr>
<th>NCC, x10⁶/L</th>
<th>2.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal round cells, %</td>
<td>1.8</td>
</tr>
<tr>
<td>Myeloid series, %</td>
<td>65.4</td>
</tr>
<tr>
<td>Promyelocyte, %</td>
<td>1.2</td>
</tr>
<tr>
<td>Myelocyte, %</td>
<td>14.6</td>
</tr>
<tr>
<td>Metamyelocyte, %</td>
<td>6.6</td>
</tr>
<tr>
<td>Band form, %</td>
<td>17</td>
</tr>
<tr>
<td>Segment, %</td>
<td>24.2</td>
</tr>
<tr>
<td>Immature eosinophil, %</td>
<td>0.4</td>
</tr>
<tr>
<td>Mature eosinophil, %</td>
<td>1.4</td>
</tr>
<tr>
<td>Erythroid series, %</td>
<td>27.8</td>
</tr>
<tr>
<td>M/E ratio</td>
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</tr>
<tr>
<td>Monocyte, %</td>
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</tr>
<tr>
<td>Lymphocyte, %</td>
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</tr>
<tr>
<td>Plasma cell, %</td>
<td>0.6</td>
</tr>
<tr>
<td>Megakaryocyte, %</td>
<td>0.2</td>
</tr>
</tbody>
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NCC: nucleated cell count, M/E ratio: Myeloid/Erythroid ratio

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**Figure 3.** The results of the pathological analysis of the bone marrow trephine biopsy sample. (A) Increased numbers of small round cells are shown (Hematoxylin and Eosin staining). (B) A marked increase in reticulin fibre is shown (silver staining). (C) Some cells were positive for TP53, (D) but there were no AE1/AE3-positive cells.
The results of the chromosomal analysis of the bone marrow aspiration sample. The chromosomal analysis showed hyperploid abnormalities. 63, -X, del (1), +der (1), -5, +add (6)(q13), del (6) (q?), +7, +8, -9, +add (11)(q23), +13, +14, +17, +20, +21, +22, +22, +30mar.

Histopathological and immunohistochemical analyses of the liver biopsy specimen. Invasion of carcinoma cells is shown (Hematoxylin and Eosin staining) (A). Immunostaining for p16 (B), Chromogranin A (C), synaptophysin (D) is shown.

Among them, four cases showed early recurrence with systemic dissemination (8). More recently, Pocrmich et al. reported 25 cases of neuroendocrine carcinoma of the endometrium (9). Most of the cases were stage III/IV, and the survival of these patients was poor (9). From a pathological aspect, more than half of
the cases of neuroendocrine cell carcinoma in the uterine corpus are mixed with other types of endometrial carcinoma, including conventional endometrioid carcinoma, carcinosarcoma or serous carcinoma. (9) Notably, the prognosis of patients with a mixed type of endometrial carcinoma is often determined by the neuroendocrine carcinoma components (10). In these cases, compared to other histopathological components, the neuroendocrine carcinoma component tends to spread to other organs (10, 5). In accordance with this notion, in the present case, the metastatic cells in both the liver and bone marrow displayed characteristics of neuroendocrine carcinoma. These results suggested that the presence of a mixture of neuroendocrine components with other types of carcinoma might be a poor prognostic factor for endometrial carcinoma.

Metastasis of carcinoma cells to the bone marrow is a
relatively rare event; however, it causes severe pancytopenia and results in a very poor prognosis (1). In contrast, haematological malignancies can be cured with adequate chemotherapy or allo-HSCT. Thus, it is very important to distinguish carcinoma cell invasion into the bone marrow from haematological malignancies.

A bone marrow smear analysis is key for the diagnosis of metastasis of solid cancers. Solid tumour cells can usually be easily distinguished from haematopoietic cells by their sheet-like appearance. However, due to their round shape, neuroendocrine carcinoma cells invading the bone marrow frequently mimic haematological malignancies, such as lymphoma or acute leukaemia. Ali et al. reported a patient with metastatic small cell lung cancer with anaemia who was initially diagnosed with acute leukaemia (11). Iguchi et al. reported a case of bone marrow metastasis of lung small cell carcinoma showing Burkitt lymphoma-like morphology (12). A case of mediastinal neuroendocrine carcinoma, initially thought to be mediastinal lymphoma, has also been reported (13). Furthermore, Harrison et al. reported a case of neuroendocrine carcinoma with bone marrow metastasis mimicking myeloid malignancy (14). The carcinoma cells invading the bone marrow resembled immature myeloid cells and expressed several myeloid cell markers, including CD13 and CD117 (14).

A bone marrow biopsy is also an indispensable diagnostic method for distinguishing carcinoma metastasis to the bone marrow from haematological malignancies (3). The expression of cytokeratin is a hallmark of solid tumours, and the evaluation of the cytokeratin expression is strongly recommended when bone marrow metastasis of carcinoma is suspected (3). Small cell neuroendocrine carcinoma cells are also usually positive for cytokeratin. Pocrnich et al. reported that 17 of 18 cases of neuroendocrine carcinoma in the endometrium were positive for cytokeratin (9). However, despite its low incidence, several groups have reported cases of cytokeratin-negative neuroendocrine carcinoma of the endometrium (15, 5). In addition, in cases with a mixture of neuroendocrine carcinoma and other pathological types of cancer, the two components often show different immunoreactivity (5). The cytokeratin expression has been reported to be positive in areas of typical adenocarcinoma but negative in neuroendocrine carcinoma (5). In accordance with these case reports, in the present case, the neuroendocrine carcinoma cells were negative for cytokeratin. These differences in cytokeratin expression might be one of the reasons for the misleading diagnosis.

Abnormal karyotypes are a hallmark of haematological malignancies; a chromosomal analysis is therefore useful for the diagnosis of haematological cancer. However, endometrial carcinoma frequently displays various types of chromosomal abnormalities. Pere et al. reported chromosomal abnormalities in 17 of 24 uterine serous carcinoma patients (6). Recent studies have shown that small cell neuroendocrine carcinoma of the uterus frequently has many different chromosomal abnormalities (10). Indeed, bone marrow-invaded neuroendocrine carcinoma cells have complex chromosomal abnormalities resembling those in MDS (14). Our present case also showed complex chromosomal abnormalities involving chromosomes 5, 8 and 9. Therefore, the possibility of carcinoma cell invasion into the bone marrow could not be excluded based solely on the presence of chromosomal abnormalities.

The rarity of small cell neuroendocrine carcinoma mixed with endometrial carcinoma also made a diagnosis difficult. In gynaecologic malignancies, neuroendocrine carcinoma typically occurs in the uterine cervix (10). To our knowledge, only one case with a mixture of small cell neuroendocrine carcinoma and serous endometrial carcinoma has previously been reported (16).

In conclusion, we encountered a case with bone marrow invasion of small cell neuroendocrine carcinoma of the endometrium. The round shape of the tumour cells on smear, negative staining for pan-cytokeratins on a bone marrow biopsy and complex chromosomal abnormalities led to a misdiagnosis of t-MDS. Our experience emphasized the need for a careful examination of bone marrow specimens with an IHC analysis using neuroendocrine markers when bone marrow invasion of carcinoma is suspected.

The authors state that they have no Conflict of Interest (COI).

References

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