Bone marrow metastatic neuroendocrine carcinoma with unknown primary site: A case report and review of the literature

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**CASE REPORT**

**Abstract**

**BACKGROUND**

Metastatic neuroendocrine carcinoma (NEC) of bone marrow is uncommon. Here, we report a case of bone marrow metastatic NEC with an unknown primary site.

**CASE SUMMARY**

A 73-year-old Chinese woman was admitted to our hospital because of marked chest distress and asthma lasting 1 d on March 18, 2018. She was initially diagnosed with pulmonary infection, cardiac insufficiency, thrombocytopenia and severe anemia. Following treatment with antibiotic therapy, diuresis and blood transfusion, the patient’s symptoms greatly improved. After bone marrow examinations, the patient was diagnosed with bone marrow metastatic NEC, bone marrow necrosis (BMN) and secondary myelofibrosis (MF). Further imaging workup did not show the primary tumor, we presumed that the primary site might regress spontaneously or merely be unexplored due to lack of positron emission tomography with gallium peptide. Everolimus (10 mg/d) was added to the treatment and the best supportive and symptomatic therapies were also administered. Unfortunately, the patient’s condition continued to deteriorate and she died on May 15, 2018.

**CONCLUSION**

Bone marrow invasion of NEC is rare and our patient who suffered from bone marrow metastatic NEC as well as secondary BMN and MF had an extremely poor prognosis. Bone marrow biopsy plays an important role in the diagnosis of solid tumors invading bone marrow.

**Key Words:** Neuroendocrine neoplasm; Bone marrow metastasis; Bone marrow necrosis; Myelofibrosis; Everolimus; Case report
INTRODUCTION

Neuroendocrine neoplasms (NENs), account for 0.5% of all malignancies, they originate from neuroendocrine cells throughout the body, and are a group of relatively rare and highly heterogeneous neoplasms[1]. Most NENs occur in the gastrointestinal tract (62%-67%) and the lung (22%-27%)[2]. NENs are divided into well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs)[2]. The clinical manifestations of NENs mainly depend on whether they are functional or non-functional and which hormones are secreted[3]. Bone marrow metastasis of NENs is extremely rare. Few studies on this topic have been published since 2000 and most of them are case reports[4-14]. We report a case of bone marrow metastatic NEC accompanied by bone marrow necrosis (BMN) and secondary myelofibrosis (MF). In this patient, no neoplastic lesions were found in the body except the bone marrow.

CASE PRESENTATION

Chief complaints

On March 21, 2018, a 73-year-old woman was admitted to the Department of Hematology and Oncology, Tongling People’s Hospital (Anhui Province, China) due to severe unexplained anemia and thrombocytopenia.

History of present illness

Initially, the patient was hospitalized in the emergency ward of internal medicine because of marked chest distress and asthma lasting 1 day on March 18, 2018. The concentrations of B-type natriuretic peptide, high-sensitivity C-reactive protein and procalcitonin were 853.90 pg/mL, 140.96 mg/L and 1.51 μg/L, respectively. Peripheral blood count showed a leukocyte count of 12.95 × 10^9/L, hemoglobin of 29 g/L, platelet count of 49 × 10^9/L and neutrophil count of 9.84 × 10^9/L. Chest computed tomography (CT) examination indicated bilateral pulmonary inflammation. The patient was preliminarily diagnosed with pulmonary infection, cardiac insufficiency, thrombocytopenia and severe anemia. She was treated with antibiotic therapy, diuresis and red blood cell transfusions. Following the above treatment, the symptoms of chest tightness and asthma were relieved. The etiology of anemia and thrombocytopenia was unknown, and the patient was hospitalized in our department for further hematological examinations.

History of past illness

The patient did not have a previous history of surgery, anemia or malignant neoplasms and was not taking any medication.

Personal and family history

She never smoked and her spouse and daughter were both healthy. Her family history of hematological malignancies and solid tumors was unremarkable.
Physical examination

Physical examination revealed anemia, scattered dry rales in both lungs, a few moist rales in the middle and lower lobe of the right lung and bilateral depressed edema of the lower limbs.

Laboratory examinations

The results of laboratory examinations with the exception of bone marrow tests are listed in Table 1. Both bone marrow aspiration and biopsy were carried out on the right posterior superior iliac spine. Bone marrow cytomorphologic examination revealed that most of the nucleated cells were dissolved and one type of cell characterized by small size, less cytoplasm, no granules in the cytoplasm, a round or irregular nucleus, loose chromatin and distinct nucleoli was discovered. Cytogenetic analysis using both the G-banding and R-banding technique demonstrated a karyotype of 45, XX, del (1) (p13p36.1), I (1) (p10), dup (4) (p15p16), add (6) (p23), der (6) del (6) (p21) del (6) (q23q25), der (7) t (7;11) (p10; q10), add (11) (p11.2), der (12) t (4;12) (q21;p11.2), -13, del (13) (q14), -16, -17, + mar1, + mar2 in 19/20 metaphases examined (Figure 1). Bone marrow biopsy showed that the marrow was characterized by extensive fibrosis and necrosis, moreover, nest-like distributions of small cells with less cytoplasm, round or irregular nuclei and coarse granular and dark stained chromatin were found in the stroma (Figure 2A). Additional immunohistochemistry of this specific category of cells exhibited CD56 (+) (Figure 2C), synaptophysin(+) (Figure 2D), Ki-67 (90% +), CK-pan (scattered and weak +), chromogranin A (-), S-100 (-), TdT (-), CD3 (-), CD5 (-), CD10 (-), CD19 (-), CD34 (-), TTF-1 (-), vimentin (-), and CD117 (-). Reticulin staining was positive (+++) (Figure 2B) and no Janus kinase 2 (JAK2) mutations were detected.

Imaging examinations

Extensive imaging workup including abdominal CT and 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT tumor metabolic imaging did not show the primary lesion (Figure 3).

FINAL DIAGNOSIS

The patient was diagnosed with bone marrow metastatic NEC with unknown primary site, BMN and secondary MF.

TREATMENT

The patient continued treatment with anti-infection medication, blood transfusion, diuresis as well as interleukin-11 after admission to our department. She was subsequently diagnosed with bone marrow metastatic NEC according to bone marrow biopsy and immunohistochemistry. In view of the patient’s poor general physical condition with an Eastern Cooperative Oncology Group performance status of 3-4, chemotherapy was abandoned and everolimus (10 mg/d) was added to the treatment on April 26, 2018.

OUTCOME AND FOLLOW-UP

Following supportive and symptomatic therapies, chest tightness and asthma improved. Hemoglobin was maintained above 60 g/L and platelets were maintained between 20 × 10^9/L and 30 × 10^9/L. The white blood cell count decreased with the lowest leukocyte count of 2.24 × 10^9/L and neutrophil count of 1.15 × 10^9/L following administration of everolimus. Unfortunately, during the treatment process, the patient became more and more emaciated and received repeated albumin infusions due to a significant decline in serum albumin level. Despite being treated with everolimus plus the best supportive treatment, the patient’s condition continued to deteriorate and she died on May 15, 2018.

DISCUSSION

Although NEN is an uncommon malignant tumor, the incidence of NEN has gradually increased over the past decades owing to continuous improvement in diagnostic methods and improved awareness of the disease[2,15]. The most common site of metastasis in NENs is the liver (40%-93%) followed by bone (12%-20%) and lung (10.8%) [16]. Metastatic NEN in bone marrow is extremely rare and most reported cases are NECs[4-8,11,12].

The main treatments in reported cases of bone marrow metastatic NECs consist of chemotherapy, peptide receptor radionuclide therapy (PRRT) and supportive care. Helbig et al[4] and Post et al[5] respectively reported a NEC patient with multiple metastases with bone marrow invasion. Both the
Table 1 Laboratory examinations of our patient

| Testing items                  | Results                                                                 |
|--------------------------------|-------------------------------------------------------------------------|
| Reexamined peripheral blood count | Leukocyte 14.87 × 10^9/L, hemoglobin 65 g/L; platelet 20 × 10^9/L and neutrophil 12.46 × 10^9/L. |
| Peripheral blood smear         | 2% promyelocyte                                                         |
| Coombs test                    | Negative                                                                |
| LDH                            | 1185 U/L                                                                |
| ALP                            | 355 U/L                                                                 |
| Coagulation function           | Fibrinogen 1.09 g/L, D-dimer >20000 μg/L                                |
| Serum tumor markers            | Carbohydrate antigen 125 236.40 U/mL, ferroprotein > 3000 ng/mL         |

LDH: Lactic dehydrogenase; ALP: Alkaline phosphatase.

Figure 1 Chromosomal karyotype analysis of bone marrow. Cytogenetic analysis using both the G-banding and R-banding technique demonstrated a karyotype of 45, XX, del (1) (p13p36.1), i (1) (p10), dup (4) (p15p16), add (6) (p23), del (6) (p21) del (6) (q23q25), der (7) (7;11) (p10; q10), add (11) (p11.2), der (12) (1;4.12) (q21; p11.2), -13, del (13) (q14), -16, -17, + mar1, + mar2 in 19 of 20 metaphases examined.

patients received multiple cycles of chemotherapy; however, no effect was observed[4,5]. Another bone marrow metastatic NEC case was offered best supportive care; however, the patient died 2 wk after diagnosis[8]. PRRT is recommended in advanced NEN patients with positive somatostatin receptors (SSTRs)[7]. After four cycles of PRRT with 177 Lu-DOTA octreotate, a patient suffering from duodenal NEC with extensive metastases including bone marrow achieved a partial response and a progression-free survival (PFS) of 27 mo[6,7].

Multiple studies have indicated that the mammalian target of rapamycin (mTOR) pathway participates in the development of NENs and mTOR is expected to become a promising therapeutic target for NENs[17]. The clinical trials RADIANT-2 and RADIANT-4 revealed that advanced NEN patients might benefit from the mTOR inhibitor everolimus and achieve a longer median PFS[18,19].
Spontaneous regression (SR), an extremely rare phenomenon, is defined as the partial or complete disappearance of a tumor without any treatment[20]. The burned-out tumors represent tumors presenting SR followed by metastases[21,22]. With regard to NENs, SR of the tumor has been reported in Merkel cell carcinoma (MCC), bile duct NET, and both lung and gastric large-cell NECs[23-26]. Longo et al[27] reported a case of inguinal lymphadenopathy histologically corresponding to MCC. The lesion later spontaneously regressed and histopathological examination showed negative results. However, five months later, a nearby lymphadenopathy appeared which was diagnosed as MCC metastasis. Our patient was diagnosed with bone marrow metastatic NEC and further imaging examinations showed no other neoplastic lesions in the body. Similarly, Helbig et al[4] and Schlette et al[13] also reported 2 cases of bone marrow metastatic NENs without primary sites. We hypothesize that the primary tumors of such NENs which can be called burned-out tumors may be located in the gastrointestinal system, pancreas, lung or bile duct and develop SR in order to originate metastases. Furthermore, we did not perform PET with gallium peptide, which may have resulted in potential bias in our diagnosis. Therefore it should be taken into account that the unknown primary lesion was unexplored.

BMN is a relatively rare clinicopathological entity and most common in malignant tumors (80%-90%) [28-30]. Anemia (91%) and thrombocytopenia (78%) are the most frequent hematologic abnormalities in BMN and almost 50% of BMN patients have elevated lactate dehydrogenase and alkaline phosphatase levels[28]. It is reported that 30% of BMN cases are found in solid tumors[28]. As previously mentioned, a patient with BMN caused by a thymic NET died 2 wk after diagnosis[8], and another case of BMN secondary to gastric cancer passed away shortly after hospitalization[31]. Thus, the prognosis of patients suffering from solid tumors with BMN is significantly worse than that of patients with malignancies alone.

MF represents increased fibers in the bone marrow stroma and is usually caused by numerous reactive and neoplastic disorders. There are two types of MF: Primary and secondary. The former is often characterized by splenomegaly and mutations of JAK2, MPL or CALR. Our patient had no splenomegaly or mutations of the above genes, thereby excluding primary MF and the patient's MF was due to bone marrow metastatic NEC. Secondary MF is very common in patients with bone marrow metastatic tumors. Xiao et al[32] reported that all 101 patients with bone marrow metastatic malignancies showed various degrees of MF and 17% of patients also had both anemia and thrombocyto-
openia. Patients with secondary MF, especially accompanied by anemia and decreased platelets, have very poor survival[33].

We report a case of bone marrow metastatic NEC with an unknown primary lesion accompanied by secondary BMN and MF. To our knowledge, few such cases have been reported in China to date. As the patient’s condition was very poor, chemotherapy was ultimately discontinued. According to published reports, NEC patients with multiple metastases including bone marrow infiltration may benefit from treatment with PRRT[6,7]. However, very few hospitals in China can carry out PRRT at present and our hospital is unable to implement SSTR detection and PRRT treatment; thus, we unfortunately failed to attempt PRRT in this patient. On the basis of relevant reports[18,19], the patient received everolimus treatment; however, the patient’s condition did not improve and she died 2 mo after admission.

CONCLUSION

Bone marrow metastasis of NENs is rare and patients suffering from bone marrow metastatic NEC as well as secondary BMN and MF may have an extremely poor prognosis. Bone marrow biopsy plays an important role not only in the diagnosis of hematological diseases, but also in the diagnosis of solid tumors invading bone marrow.

FOOTNOTES

Author contributions: Shi XB participated in the treatment of the patient, collecting and analyzing the clinical data, and writing the manuscript; Deng WX contributed to the treatment of the patient, data analysis, and revision of the manuscript; Jin FX was involved in guiding the treatment of the patient and designing the research; all authors read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient’s offspring for publication of this case report.

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