CASE REPORT

Rare Bone Metastasis of Neuroendocrine Tumors of Unknown Origin: A Case Report and Literature Review

Qing Pan, MD[#], Wenbo Yang, PhD[#], Zhicai Zhang, PhD, Zengwu Shao, PhD

Department of Orthopaedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: The neuroendocrine tumor (NET) is rare, accounting for about 0.5% of all tumors. NETs have the characteristics of metastasis, especially lymph nodes, liver, spleen, and bone.

Case presentation: We report a 30-year-old man diagnosed with a NET with bone metastasis and presented with waist and leg pain. The imaging findings of this case showed multiple osteosclerosis and no apparent bone destruction. We collected the patient's previous examinations, including laboratory, imaging, and pathological examination to get a precise diagnosis. Given this case, we carried out symptomatic support treatment to relieve the patients' pain symptoms.

Conclusion: Bone metastases from NETs of unknown primary site are rare in both clinical and imaging manifestations. The disease is mainly manifested as multiple osteosclerosis, accompanied by muscle soreness and pain. It is recommended to try chemotherapy for this disorder.

Key words: Bone metastasis; Case report; Neuroendocrine tumors; Review

Introduction

Neuroendocrine tumors (NETs) are derived from various cells that form part of the endocrine system, accounting for only 0.5% of all tumors.[1]

According to the histological classification of endocrine cancer determined by the European Society of Neuroendocrine Oncology (NENTS) in 2006 and the update of the World Health Organization Tumor Classification (WHO) in 2019, well-differentiated NETs are classified as low-grade G1 (<2 mitosis per 2 mm^2 and/or Ki-67 index ≤ 3%), medium-level G2 (2–20 mitosis per 2 mm^2 and/or Ki-67 index between 3 and 20%) and high-grade G3 (21 or more mitosis per 2 mm^2 and Ki-67 index > 20%). Poorly differentiated neuroendocrine carcinoma (NEC) is considered to be high grade, which is divided into small-cell type (SCNEC) and large-cell type (LCNEC).[2–4] According to pathological examination, the case we introduced was classified as medium-grade G2.

Because of the distribution of NE cells throughout the body, NETs have been recorded in the central nervous system, respiratory tract, throat, gastrointestinal tract, thyroid, skin, breast, and genitourinary system. The gastrointestinal tract and lungs are the most common primary tumor sites.[5]

The diagnosis of bone metastases from neuroendocrine tumors is relatively complicated and requires a combination of multiple examination methods. The diagnosis is confirmed by X-ray, magnetic resonance imaging (MRI), computed tomography (CT), bone scan, somatostatin receptor imaging (Octreoscan®), DOTATOC-PET-CT, FDG-PET-CT, and other imaging examinations or histopathological biopsy examinations.[6] Pathology is also difficult to point out the primary lesion. Therefore, there is no targeted and effective treatment for neuroendocrine tumor bone metastasis. Here, we describe G2 neuroendocrine tumors of the unknown *in situ*, with extensive bone metastasis and sclerosis and multiple lymph node metastasis as the primary manifestations,

Address for correspondence Zengwu Shao, Department of Orthopaedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. Email: szwpro@163.com
[#]All these authors contribute equally to this research and share the first authors.
Received 12 December 2021; accepted 5 June 2022

and briefly review the manifestations and treatment of neuroendocrine tumors with bone metastasis.

Case Presentation

We describe the case of a 30-year-old man presenting with a skeletal system. The chief complaint was painful swelling of the waist and leg for more than 2 years, aggravating for 2 weeks. Two years ago, the patient had pain in the waist and legs without obvious inducement, which was acid swelling and paroxysmal. The pain of acid swelling increased significantly during the attack, and it was not easy to walk. No obvious abnormality was found in the physical examination.

Imaging examinations revealed considerable uneven increases in bone density throughout the body. The X-ray of the pelvis (Fig. 1) showed patchy and nodular high-density shadows in the ilium, ischia, and pubic bone. Generally speaking, multiple bone diseases are often considered metabolic diseases, metastatic diseases, or blood system diseases. We also read the patient's CT (Fig. 2) and MRI (Fig. 3). Under the CT bone window, a wide range of unevenly elevated bone density lesions are scattered in the axial bone structure, including the thoracic vertebrae below 10, multiple ribs on both sides, shoulder blades, lumbar vertebrae, and sacral vertebrae (Fig. 2). Under MRI, we found that the pelvis, sacrum, L3, 4, and 5 vertebral bodies, and bilateral femurs were diffused with abnormal signal shadows (Fig. 3). In order to comprehensively assess the bones of the whole body, we performed a single photon emission computed tomography examination for the patient, which indicated that: bilateral scapula, sternum, bilateral ribs, vertebral bodies, and appendages are extensively sclerotic, and bone metabolism is diffusely increased, showing a similar "super bone imaging" structural stem, left ninth rib axillary segment, 6th and 10th thoracic vertebrae, local bone density was unevenly reduced, bone metabolism was relatively increased; bilateral upper humerus, bilateral clavicle multiple nodular bone density Increased, uneven bone metabolism increased: the bone metabolism of the lower part of the left femur, the middle part of the right femur, and the upper part of the right tibia were slightly increased. Further confirmed the phenomenon of multiple bone lesions throughout the body.

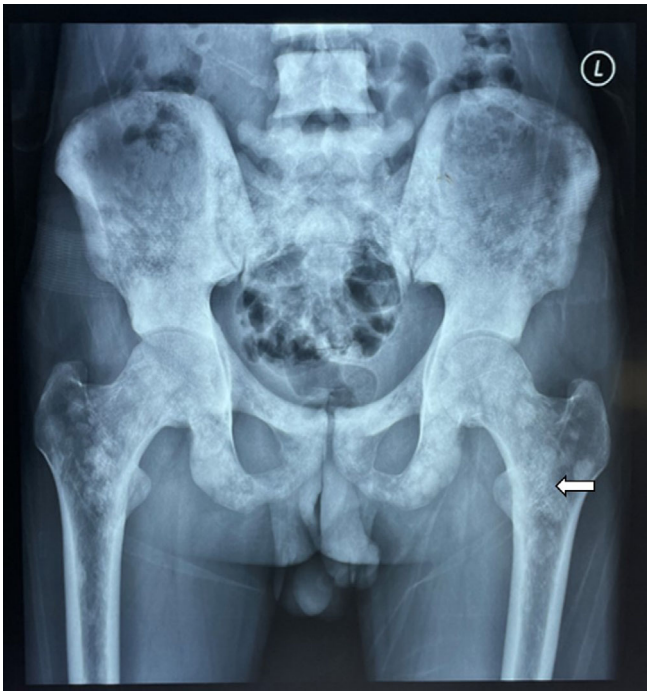

Fig. 1 X-ray showed that there were multiple patchy and nodular high-density shadows scattered in the bilateral ilium, ischium, pubis and bilateral upper femur

Laboratory Inspection

In order to check whether it is related to blood system diseases, the results of bone marrow puncture and urine protein electrophoresis test showed no obvious abnormality, and blood-related diseases were initially excluded. HLA-B27 test was carried out, and the result was negative. Ankylosing spondylitis was not considered for the time being. In order to check whether it is related to metastatic tumors, we examined the tumor markers, except for the slight increase of NSE 19.03 μg / mL. The rest did not show a significant increase and initially excluded the related primary tumors leading to metastasis. There was no obvious abnormality after the improvement of the endocrine examination, except for the slight increase of parathyroid hormone. The levels of various hormones related to bone metabolism were within the normal range. Therefore, we further improved the parathyroid CT and found no obvious abnormality except for the slightly low-density paratracheal nodules behind the inferior pole of the thyroid gland in the right lobe. Primary parathyroid tumors were excluded. When the multiple examinations were not indicated, the patient was given a left iliac puncture biopsy (Fig. 4) and sent to the pathology department for pathological examination. The results suggest that metastatic malignant tumors tend to be neuroendocrine tumors or metastatic tumors with neuroendocrine differentiation. CgA (+) (Fig. 5).

According to the pathological findings, we performed PET-CT for the patient to comprehensively search for the primary lesion. The results suggested multiple lymph nodes in the medial side of the left diaphragm foot, the retroperitoneal abdominal aorta, and the left external iliac, with an abnormal increase in metabolism. Multiple lymph nodes were on both sides of the neck, with an abnormal increase in metabolism, which we considered the possibility of metastasis. No primary tumor was found, and only skeletal and lymph node metastases were found, confirming the diagnosis based on our previous examination of tumor markers. In consideration of multiple enlarged lymph nodes in the patient, we performed cervical lymph node puncture biopsy to confirm the preliminary diagnosis further, and pathological results suggested a metastatic low-grade neuroendocrine tumor (Fig. 6), Ki67 was 10%, classified as G2 according to histology. Based on the above examination, we can now diagnose the patient's disease as a neuroendocrine tumor (NET).

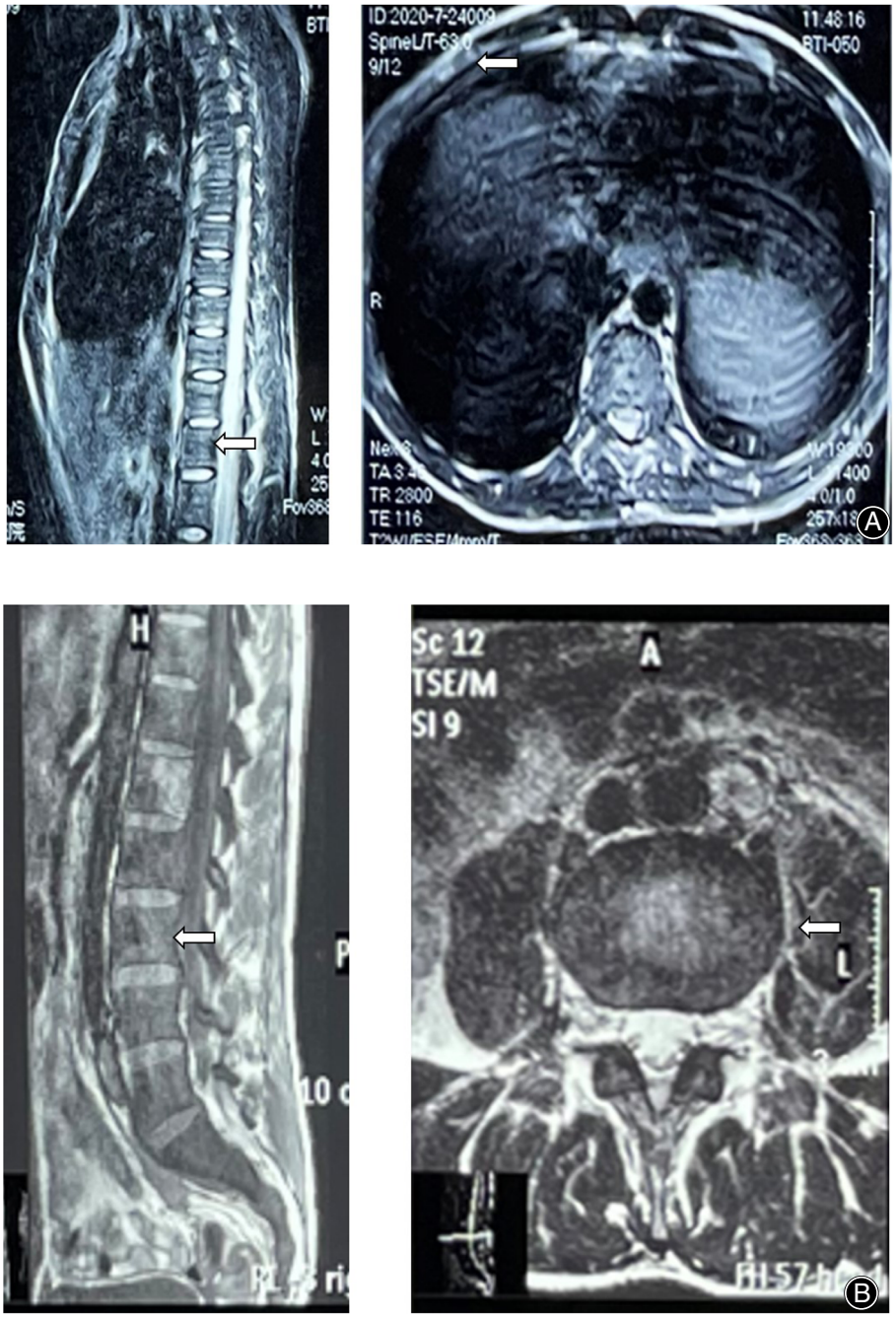

Fig. 2 (A) CT showed an uneven increase in bone mineral density below the ribs, scapula and thoracic 10 vertebrae. (B) CT showed that the lumbar and sacrococcygeal vertebrae showed uneven increase in bone density vertebrae

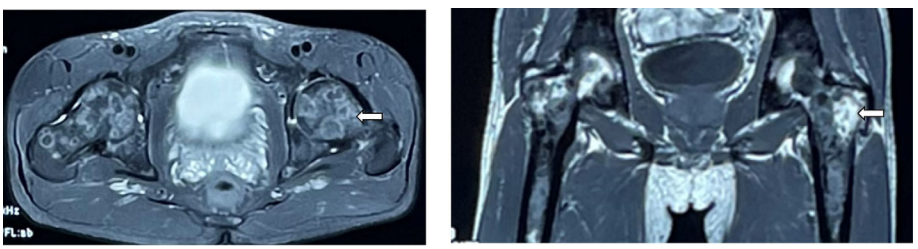

Fig. 3 MRI showed that the iliac and femur bones also had abnormal signal shadows with uneven increase in bone density

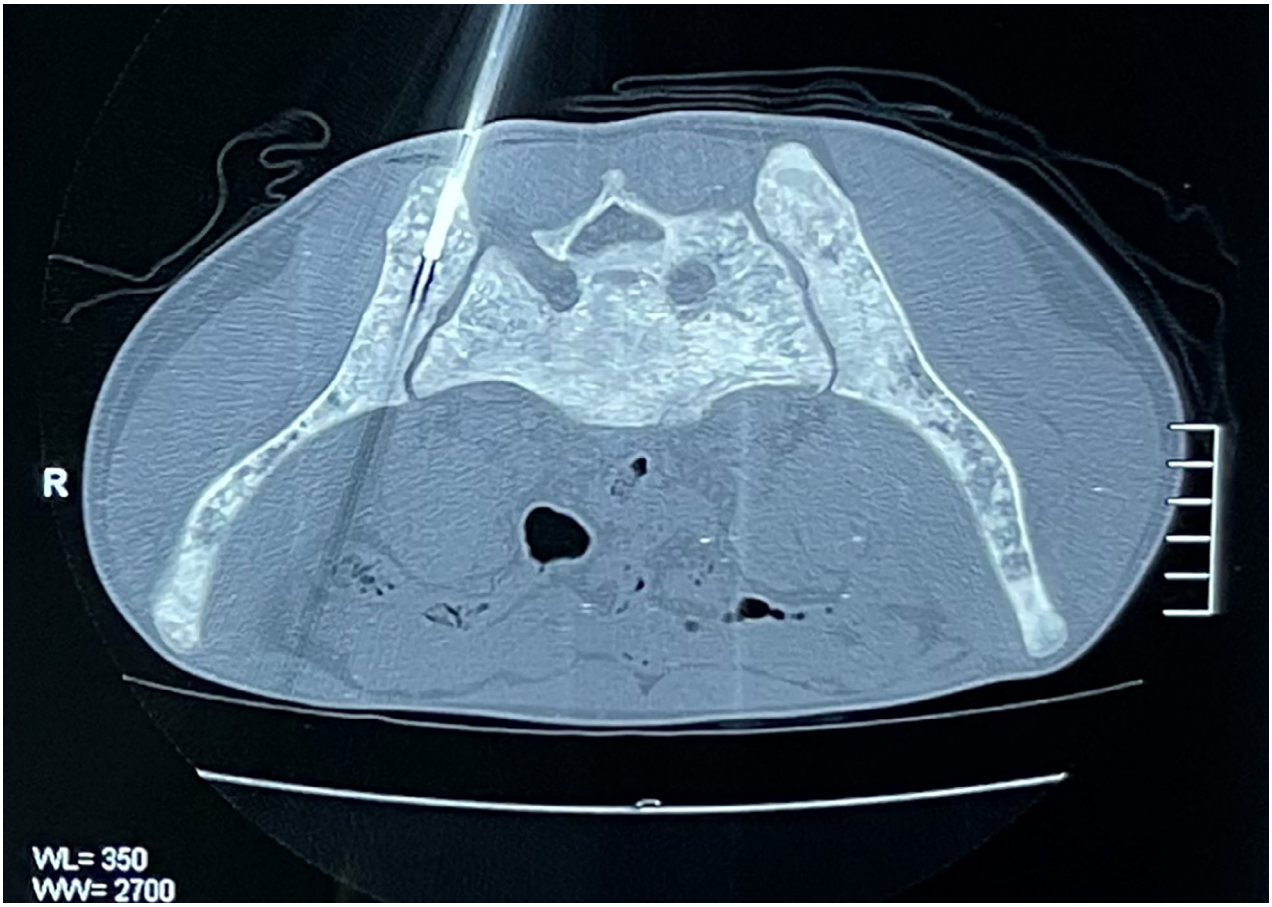

Fig. 4 Under CT guidance, the patient was placed in a prone position for a biopsy of the iliac bone tissue

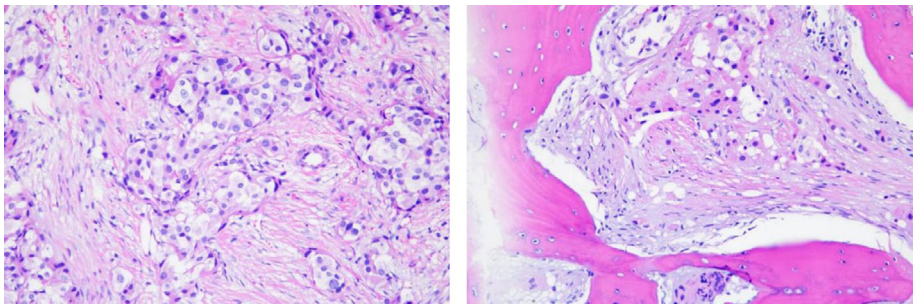

Fig. 5 Iliac crest tissue biopsy and pathological section

Differential Diagnosis

This disease is often differentiated from osteopetrosis, skeletal fluorosis, and bone paget disease.

Osteopetrosis

Osteopetrosis is also known as marbled bone, sclerosing hyperplastic bone disease. It is a rare bone developmental disorder. The disease is characterized by persistent calcified cartilage, causing extensive bone sclerosis. This disease usually has severe progressive anemia, developmental disorders, malnutrition, and often sluggish expression and mental retardation. Basic X-ray manifestations: extensive and uniform, increased bone density and hardening, thickened trabecula, thickened cortex, narrowed or even loss of medullary cavity.

Bone in Bone

Bone in bone is manifested as compact bone islands with obvious boundaries; sandwich vertebrae; iliac wings the annual ring changes.[7] The case we reported showed extensive

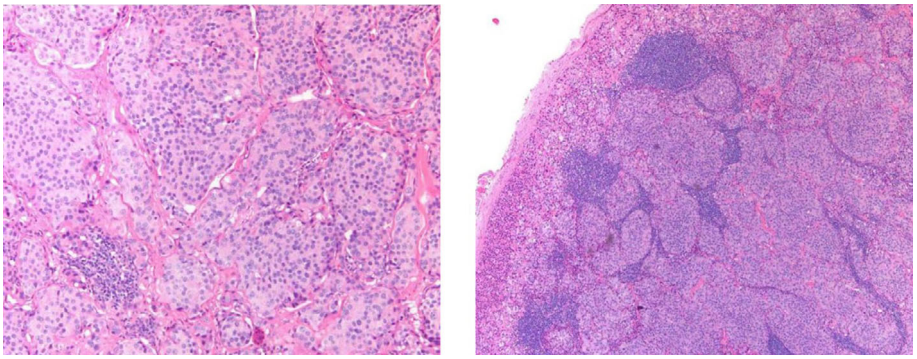

Fig. 6 Biopsy of cervical lymph node tissue. Syn (+), CgA (+), CD56 (+), Villin (+), PSAP (+), Ki67 (LI: 10%)

bone sclerosis similar to osteopetrosis in imaging, but besides that, the patient's mental and physical development was normal, and the trabecular bone and medullary cavity did not change.

Skeletal Fluorosis

Skeletal fluorosisrefers to a chronic invasive systemic bone disease involving bone tissue and fluorosis caused by long-term intake of excessive fluoride. Patients generally have a long history of living in high-fluoride areas or personal exposure to fluoride. Clinical manifestations of skeletal fluorosis have bone joint pain, limb movement disorders or deformity. Blood and urine fluoride exceeded the normal range. X-ray findings: osteosclerosis. Osteosclerosis usually occurs in the spine, pelvis, ribs, and skull. It is usually asymptomatic and is occasionally detected on radiology. It has a wide range of manifestations, including diffuse bone pain, limited movement, bone clotting, or reduced bone mass with ossification of many ligaments and interosseous membranes.[8] The case we reported had osteosclerosis and bone pain similar to skeletal fluorosis, but there was no personal history of long-term fluoride exposure, and the fluorine content in hematuria was normal.

Bone Paget Disease

Thisis a chronic skeletal disease in adults, which is more common in middle-aged and elderly people over 40 years old. It is characterized by increased local bone transformation. Characteristic laboratory tests include elevated serum alkaline phosphatase (increased bone anabolism), but normal GGT and serum PO4. X-rays of the limbs showed deformed bones with thick trabecular bones, "flame-like" osteolytic areas, bone-cotton-like changes in skull CT, vertebral body X-rays showed "square vertebrae," CT showed "ivory vertebrae" and MRI showed signs such as "double concave sign." In addition to increased local bone transformation, this case did not have increased serum alkaline phosphatase and typical imaging findings.

Treatment

During hospitalization, the patient underwent routine examination and nursing treatment, while taking oral analgesic medication. Because the patient's general condition was not very bad, no symptomatic treatment such as fluid replacement was carried out. Chemotherapy was recommended, but he voluntarily chose internal medicine to indicate treatment.

Follow up

Follow-up is usually every 3–6 months, including laboratory tests (CGA, 5-HIAA or other related peptides/hormones). Imaging examinations include CT, MRI, and bone imaging, depending on the clinical situation.

At the last follow-up in April 2022, the patient complained of leg acid weakness and discomfort in both hips, and was given diclofenac sodium dual release enteric-soluble capsule 75 mg qd orally. When the condition worsened, orally diclofenac sodium dual release enteric-soluble capsule 75 mg bid was given. At the same time, the patient was followed up in the outpatient department of oncology, and the doctor suggested the use of chemical therapy, but the patient did not agree (Table 1).

Discussion

Neuroendocrine tumors (NETs) are a relatively rare type of heterogeneous tumors that occur in the secretory cells of the diffuse neuroendocrine system. They are characterized by a relatively slow growth rate and the ability to secrete various peptide hormones and biogenic amines.[9] NETs have been recorded in the central nervous system, respiratory tract, throat, gastrointestinal tract, thyroid, skin, breast, and genitourinary systems, given the distribution of NE cells throughout the body. The gastrointestinal tract and lungs are the most common primary tumor sites.[5] The most common NET sites of NETs are the gastrointestinal tract, pancreas, lung, ovary, uterus, skin, biliary tract, thymus, mediastinum, liver, kidney, pelvis, nasal cavity and so on. The case we introduced was designated as NENs of unknown primary origin (UPO) based on the absence of primary lesion on imaging and pathological examination. According to the SEER database, UPO accounted for 13% of NETs.[10] The primary location of NETs can determine the clinical manifestation of the disease. NETs can be functional or non-functional. Non-functional tumors may be asymptomatic or may have symptoms of local or

TABLE 1 The differential diagnosis

	Disease characteristics	Imaging findings	Identify
Osteopetrosis	The disease is characterized by persistent calcified cartilage, causing extensive bone sclerosis. And severe progressive anemia, developmental disorders, malnutrition, and often sluggish expression and mental retardation	Extensive and uniform, increased bone density and hardening, thickened trabecula, thickened cortex, narrowed or even disappeared medullary cavity; bone in bone: manifested as compact bone islands with obvious boundaries; sandwich vertebrae; iliac wings The annual ring changes	The case we reported showed extensive bone sclerosis similar to osteopetrosis in imaging, but besides that, the patient's mental and physical development was normal, and the trabecular bone and medullary cavity did not change.
Skeletal fluorosis	Patients generally have a long history of living in high-fluoride areas or personal exposure to fluoride. Clinical manifestations of skeletal fluorosis have bone joint pain, limb movement disorders or deformity. Blood and urine fluoride exceeded the normal range.	Osteosclerosis usually occurs in the spine, pelvis, ribs, and skull. It is usually asymptomatic and is occasionally detected on radiology. It has a wide range of manifestations, including diffuse bone pain, limited movement, bone clotting, or reduced bone mass with ossification of many ligaments and interosseous membranes.	The case we reported had osteosclerosis and bone pain similar to skeletal fluorosis, but there was no personal history of long-term exposure to fluoride, and the fluorine content in hematuria was normal.
Paget disease of bone	It is characterized by increased local bone transformation. Characteristic laboratory tests include elevated serum alkaline phosphatase (increased bone anabolism), but normal GGT and serum PO4.	X-rays of the limbs showed deformed bones with thick trabecular bones, "flame-like" osteolytic areas, bone-cotton-like changes in skull CT, vertebral body X-rays showed "square vertebrae," CT showed "ivory vertebrae" and MRI showed signs such as "double concave sign."	In addition to increased local bone transformation, this case did not have increased serum alkaline phosphatase and typical imaging findings.

metastatic diseases, such as right epigastric pain (liver metastasis), back pain (bone metastasis) or abdominal pain (intestinal obstruction), functional tumors secrete polypeptides and neurotransmitters.[11] Gastric neuroendocrine tumors can occur: elevated serum gastrin levels, chronic atrophic gastritis in biopsies, elevated or decreased pH in gastric juice, and symptoms of Zollinger-Ellison syndrome, such as diarrhea, heartburn and peptic ulcers.[11] Small intestinal neuroendocrine tumors usually have carcinoid syndrome: diarrhea, flushing, bronchospasm.[9,11,12] Of pancreatic neuroendocrine tumors, 90% are nonfunctional, while functional tumors are common in insulinoma, glucagon, somatostatin tumor and gastrinoma. The clinical manifestations of insulinoma are characterized by the typical Whipple's triad, including symptomatic hypoglycemia, hypoglycemic levels during episodes and relief of symptoms after glucose administration. Clinical manifestation of glucagonoma: glucagonoma syndrome, characterized by a clinical trial of necrotizing migratory erythema (NME), diabetes and weight loss. Somatostatin tumor usually presents with dysmenorrhea, stomach acid, diabetes and cholelithiasis. Gastrinoma develops Zollinger-Ellison syndrome (ZES): severe and widespread peptic ulcer, dyspepsia, nausea, vomiting, abdominal pain and ulcer complications.[9,11,13] The common symptoms of patients with pulmonary NETs are cough, hemoptysis and blood in the sputum.[14]

Neuroendocrine tumors often metastasize, with the liver being the most common site for both known and unknown even rarer primary tumors, followed by lymph nodes, lungs and bones, and even more rare brain metastases.[14–17] The risk of primary metastases in the small intestine or pancreatic hepatobiliary duct is the highest, while network metastases in the appendix and rectum are low.[16] About 4% to 15% of patients with high to moderately differentiated neuroendocrine tumors will develop bone metastasis, recognized as a late and rare complication caused by neuroendocrine tumors.[18] In a literature review on bone metastasis of carcinoid tumors, 11 (12%) of 90 patients with metastatic carcinoid had symptomatic bone metastasis.[19] In a series of 145 gastroenteropancreatic NETs patients, it is reported that 13% of NETs patients have bone metastases (males are more likely to have bone metastases than females.[16,17] Usually, the bone metastases seen by NETs are osteosclerotic and involve axial bones, including the skull, ribs, vertebrae, and pelvis.[18,20] The main clinical manifestations of bone metastasis include pain, pathological fracture, spinal cord compression and hypercalcemia.[18,21]

The diagnosis of NETs is based on clinical manifestation, pathology, laboratory examination or imaging examination. Laboratory inspection: Most neuroendocrine tumors produce and secrete peptide hormones, and NETs patients with the suspected hormonal syndrome should be tested for corresponding hormone levels.[9] Some nonfunctional neuroendocrine tumors have no obvious hormone-related symptoms. Therefore, it is usually based on the presence or absence of specific markers in the blood. Through the introduction of plasma or serum CGA detection as tumor markers. CGA is a glycoprotein of the chromaffin granule protein family, which exists in the secretory granules that store peptide hormones and catecholamines in the neuroendocrine system,[22] CGA is the most sensitive and reliable

TABLE 2 A review of diagnosis, treatment and prognosis of organ metastasis of neuroendocrine tumors

Author	Pathological type	Disease site	Treatment measures	The way of diagnose	Prognosis
Bongiovanni *et al.*[30]	Osteoblast bone metastasis from NET	Unexplained metastatic tumors of the liver and bone	Octreotide,177LuDOTATE-PRRT,Capecitabine, Temozolomide	18F-CH and 68Ga PET/CT, Tissue puncture	Stable condition
Hori *et al.*[31]	Lung carcinoid	Liver and spinal metastasis	Surgery and chemotherapy	Not referred	Still alive 1 year after surgery
	Lung carcinoid	Left femur and multiple bone destruction	Surgery	Not referred	Can walk 3 months after surgery
Poiană *et al.*[32]	Lung carcinoid; after surgery:G1 NET	Systemic osteoporosis	Alendronate, Supplementation of vitamin D and calcium at the same time	Not referred	No obvious symptoms
Nassiri *et al.*[33]	NET	Lumbar spine, pituitary gland	Surgery and chemotherapy	Not referred	When he died of pulmonary embolism unexpectedly in the 21st month of the course of the disease, his condition was improving.
Cojocari *et al.*[34]	Highly to moderately differentiated NET	Subcutaneous abdominal fat	Surgery, extensive local lymph node dissection	Not referred	No other tumors were found in the body. After 1 year of follow-up, all biochemical indicators were within the normal range
Yoshida *et al.*[35]	Small cell neuroendocrine carcinoma	Glossopharyngeal part	Radiotherapy	All examinations, CT scan, radionuclide scan, urinary amine secretion and sputum cytology	The patient had no tumor recurrence or metastasis, but died of weakness 2 months after completing the treatment. No autopsy was performed.
Soeiro *et al.*[36]	Non-functioning neuroendocrine tumors	pancreas	Surgery, radiotherapy	pet-ct	No symptoms or evidence of active disease found
Makis *et al.*[37]	Small bowel G1 NET	Small intestine, liver and bone metastases	177Lu-DOTATE,Peptide receptor radionuclide therapy(PRRT)	Not referred	Significant improvement in metastatic liver and bone disease
Yasuda *et al.*[38]	PNEN G1 and multiple G2 liver metastases	Metastases of pancreas, liver and bone.	Surgery, everolimus 10 mg daily and lanreotide 120 mg once every 28 days	Not referred	10-month progression-free survival
Saranga-Perry *et al.*[39]	"Moderately differentiated" carcinoid	Thymus	Surgery, Carboplatin and paclitaxel, Capecitabine and temozolomide	Not referred	The disease continues.
	Intermediate neuroendocrine tumors	Thymus	Radiotherapy, Cisplatin and etoposide. Octreotide and IN-α,Capecitabine combined with temozolomide	Not referred	21% reduction in tumor burden
	Intermediate neuroendocrine tumors	Thymus, cervical lymph nodes, bone metastasis	Somatostatin analogues; Capecitabine combined with temozolomide	Not referred	Stable condition

TABLE 2 Continued

Author	Pathological type	Disease site	Treatment measures	The way of diagnose	Prognosis
Guo *et al.*[40]	Poorly differentiated gastrointestinal neuroendocrine carcinoma	Gastrointestinal, liver and bone metastasis	Trial of chemotherapy regimen (etoposide 180mg, carboplatin 160mg)	Not referred	His clinical condition deteriorated and he could not tolerate therapy again. Unfortunately, the patient had progressive intrahepatic cholestasis and died of subacute hepatic failure.
Radu *et al.*[41]	NET	Pancreatic reticulum, liver, spleen and bone metastases	Chemotherapy, somatostatin analogs and radiation therapy, oxaliplatin and capecitabine chemotherapy	Not referred	His condition worsened and died in July 2017.

marker of circulation in patients with immunohistochemical and neuroendocrine tumors.[23] According to the combined evaluation of CGA and pancreatic polypeptide (PP), these two substances are usually immunohistochemical positive in tumors with a sensitivity of up to 90%.[22] However, the elevated level of CGA is not unique to neuroendocrine tumors,[23] and the extent of elevated level is not related to the location of the primary tumor. Bone-specific alkaline phosphatase (BSAP) is a non-specific marker of bone metastasis, which can be used to detect the activity of osteoblasts or bone formation.[19]

As for imaging examination, the sensitivity of dynamic CT to the diagnostic value of PanNets is 64%–81%, and CT can also distinguish between liver metastases caused by PanNets/Gi-Nets and liver metastases caused by gastrointestinal adenocarcinoma.[24] MRI has a similar function to CT and can play an essential role in treating small sporadic PanNets and inherited PanNet syndrome.[24] Cross-sectional images scanned by CT or MRI can be used for the location and range of Gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Positron emission tomography (PET)/CT imaging has been widely used due to its increased sensitivity. PET/CT imaging can be used to detect gastrointestinal and pancreatic neuroendocrine tumors and detect neuroendocrine tumors at unknown primary sites. It can also be used to assess systemic staging and detect lymph nodes or bone metastases. In a study of 131 patients with known or suspected NETs, 95% of the total lesions were detected by 68Ga-DOTATATE PET/CT, while only 45.3% of the lesions were detected by anatomical imaging, and the primary lesions were unknown in 14 cases, of which four cases were found by 68Ga-DOTATATE PET/CT imaging, no primary lesions were found by 111in-pentylenetetrapeptide SPECT/CT, and no primary lesions were found in two cases of CT/MRI. Of the 113 lesions, 72 (63.7%) correctly detected primary lesions, lymph nodes and distant metastases, of which 22.1% and 38.9% were detected by 111In-Pentetretic SPECT/CT and anatomical imaging respectively).[25] In a study of 59 patients with neuroendocrine tumors with unknown primary sites, 35 (59%) could locate the primary sites by 68Ga-DOTA-NOC PET/ CT.[26] In a study of 68Ga-DOTANOC and 68Ga-DOTATE in 18 patients with GEP-Nets confirmed by biopsy, there were 248 lesions, and the sensitivity of 68Ga-DOTANOC PET to lesions was 93.5%. 68GamurDOTATE PET was 85.5%. 68Ga-DOTANOC PET showed significantly more lesions in this group of GEP-Net patients.[27]

Current treatments are also designed to relieve symptoms, prolong survival and improve quality of life. Currently, there is no effective treatment for poorly differentiated and moderately differentiated NETs, but new drugs are being actively studied recently, some of which have been proven to be effective, such as symptomatic supportive treatment, pain relief, such as non-steroidal anti-inflammatory drugs, bisphosphonates; chemical therapy, including octreotide, cisplatin and etoposide, everolimus, streptozotocin, sunitinib, bevacizumab, capecitabine and oxaliplatin, interferon-alpha (IFN-α), 131i-metaiodobenzylguanidine (MIBG); Radiation therapy: peptide receptor radionuclide therapy (PPRT). Surgical treatment is only appropriate for locally isolated metastatic tumors.[1,5,9,18,21,28,29] For example, in Table 2, a case of osteoblast bone metastasis from NET reported by Bongiovanni *et al.* the condition remained stable after treatment with octreotide, capecitabine, temozolomide and PRRT. A case of Lumbar spine, pituitary gland metastasis from NET reported by Nassiri *et al.* was improved after surgery and chemotherapy treatment. Makis *et al.* reported a case of liver and bone metastases from small bowel G1 NET with significant improvement after Peptide receptor radionuclide therapy (PRRT) treatment. A case of pancreas, liver and

bone metastasis from NET reported by Yasuda *et al.* obtained 10-month progression-free survival after treatment with surgery and everolimus and lanreotide. A case of pancreatic reticulum, liver, spleen and bone metastasis from NET reported by RaduEC was treated with oxaliplatin and capecitabine chemotherapy, but his condition worsened.

More tests should be developed to identify the primary tumor in patients with unknown primary tumors. The tumor will be treated according to the primary site if the primary site is determined by inspection. For example, the pancreatic islet cell network can be treated with sunitinib as a second-line treatment, while the cancer-like network can be managed by adding interferon.[10] The European Neuroendocrine Tumor Society (ENETS) describes that if the primary tumor is not found despite a comprehensive examination, treatment decisions are mainly based on grade, function, SSTR status, tumor size, and liver tumor burden.[42] Net treats according to the grade in these cases where no primary tumor is found. Highly differentiated and moderately differentiated tumors are considered carcinoids, while poorly differentiated tumors are similar to small cell lung cancer as aggressive and responsive to platinum-based chemotherapy.[43] In the future, new technologies may detect the primary sites of more specific neuroendocrine tumors of unknown origin and are expected to provide personalized treatment to these patients.

Authors' Contribution

Dr. Pan Q and Dr. Yang WB are responsible for manuscript idea selection, clinical data finishing, manuscript writing and manuscript proofreading. Professor Shao ZW and Professor Zhang ZC are responsible for the idea selection and manuscript proofreading.

References

1. Zamborsky R, Svec A, Kokavec M, Galbavy S. Bone metastases in neuroendocrine tumors. Bratisl Lek Listy. 2017;118:529–34.
2. Couvelard A. Ki67 and neuroendocrine tumors. Ann Pathol. 2011;31:S55–6.
3. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Archiv. 2006;449:395–401.
4. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182–8.
5. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia. 2017;19:991–1002.
6. Scharf M, Petry V, Daniel H, Rinke A, Gress TM. Bone metastases in patients with neuroendocrine neoplasm: frequency and clinical, therapeutic, and prognostic relevance. Neuroendocrinology. 2018;106:30–7.
7. Bénichou OD, Laredo JD, de Vernejoul MC. Type II autosomal dominant osteopetrosis (Albers-Schönberg disease): clinical and radiological manifestations in 42 patients. Bone. 2000;26:87–93.
8. Sellami M, Riahi H, Maatallah K, Ferjani H, Bouaziz MC, Ladeb MF. Skeletal fluorosis: don't miss the diagnosis! Skeletal Radiol. 2020;49:345–57.
9. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68:471–87.
10. Polish A, Vergo MT, Agulnik M. Management of neuroendocrine tumors of unknown origin. J Natl Compr Cancer Network. 2011;9:1397–402. quiz 403.
11. Pasricha G, Padhi P, Daboul N, Monga DK. Management of well-differentiated gastroenteropancreatic neuroendocrine tumors (GEPNETs): a review. Clin Ther. 2017;39:2146–57.
12. Zuetenhorst JM, Taal BG. Metastatic carcinoid tumors: a clinical review. Oncologist. 2005;10:123–31.
13. Guilmette JM, Nosé V. Neoplasms of the neuroendocrine pancreas: an update in the classification, definition, and molecular genetic advances. Adv Anat Pathol. 2019;26:13–30.
14. Song L, Zhai X, Yu S, Ma Y, Wang F, Yu X, et al. Clinical analysis of 547 patients with neuroendocrine tumors in a Chinese population: a single-center study. Cancer Med. 2019;8:3729–37.
15. Kim SJ, Kim JW, Oh DY, Han SW, Lee SH, Kim DW, et al. Clinical course of neuroendocrine tumors with different origins (the pancreas, gastrointestinal tract, and lung). Am J Clin Oncol. 2012;35:549–56.
16. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer. 2016;139:2679–86.
17. Zheng Z, Chen C, Jiang L, Zhou X, Dai X, Song Y, et al. Incidence and risk factors of gastrointestinal neuroendocrine neoplasm metastasis in liver, lung, bone, and brain: a population-based study. Cancer Med. 2019;8:7288–98.
18. Kavecansky J, Wei L, Caronia L, Ramirez MT, Bloomston M, Shah MH. Bone metastases in well-to-moderately differentiated neuroendocrine tumors: a single institutional review from the Ohio State University medical center. Pancreas. 2015;44:198–203.
19. Meijer WG, van der Veer E, Jager PL, van der Jagt EJ, Piers BA, Kema IP, et al. Bone metastases in carcinoid tumors: clinical features, imaging characteristics, and markers of bone metabolism. J Nucl Med. 2003;44:184–91.
20. Zuetenhorst JM, Hoefnageli CA, Boot H, Valdés Olmos RA, Taal BG. Evaluation of (111)in-pentetreotide, (131)I-MIBG and bone scintigraphy in the detection and clinical management of bone metastases in carcinoid disease. Nucl Med Commun. 2002;23:735–41.
21. Van Loon K, Zhang L, Keiser J, Carrasco C, Glass K, Ramirez MT, et al. Bone metastases and skeletal-related events from neuroendocrine tumors. Endocr Connect. 2015;4:9–17.
22. Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology. 2012;95:120–34.
23. Eriksson B, Oberg K, Stridsberg M. Tumor markers in neuroendocrine tumors. Digestion. 2000;62(Suppl 1):33–8.
24. Lee L, Ito T, Jensen RT. Imaging of pancreatic neuroendocrine tumors: recent advances, current status, and controversies. Expert Rev Anticancer Ther. 2018;18:837–60.
25. Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-Entero-pancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol. 2016;34:588–96.
26. Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. Eur J Nucl Med Mol Imaging. 2010;37:67–77.
27. Wild D, Bomanji JB, Benkert P, Maecke H, Ell PJ, Reubi JC, et al. Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. J Nucl Med. 2013;54:364–72.
28. Bajetta E, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? Cancer Chemother Pharmacol. 2007;59:637–42.
29. Ayala-Ramirez M, Palmer JL, Hofmann MC, de la Cruz M, Moon BS, Waguespack SG, et al. Bone metastases and skeletal-related events in patients with malignant pheochromocytoma and sympathetic paraganglioma. J Clin Endocrinol Metab. 2013;98:1492–7.
30. Bongiovanni A, Recine F, Celli M, Marcantognini G, Foca F, Liverani C, et al. Osteoblastic bone metastases from neuroendocrine tumor (NET) of unknown origin detected by 18fluorocholine PET/CT and its comparison with 68gallium-DOTATOC PET/CT: case report and review of the literature. Medicine. 2017;96:e8567.
31. Hori T, Yasuda T, Suzuki K, Kanamori M, Kimura T. Skeletal metastasis of carcinoid tumors: two case reports and review of the literature. Oncol Lett. 2012;3:1105–8.
32. Poiană C, Carşote M, Neamţu MC, Avramescu ET, Vasilescu F, Terzea D, et al. Well-differentiated neuroendocrine tumor and osteoporosis: incidental findings? Rom J Morphol Embryol. 2013;54:1169–71.
33. Nassiri F, Cusimano M, Rotondo F, Horvath E, Kovacs K. Neuroendocrine tumor of unknown origin metastasizing to a growth hormone-secreting pituitary adenoma. World Neurosurg. 2012;77:201.e9–e12.
34. Cojocari N, David L. Soft tissue primary neuroendocrine tumor: a case report. Am J Case Rep. 2018;19:778–82.
35. Yoshida H, Onizawa K, Hirohata H. Neuroendocrine carcinoma of the tongue: report of a case. J Oral Maxillofac Surg. 1995;53:823–7.
36. Soeiro P, Martins H, Silva R, Moreira AP. Complete remission of inoperable hepatic and bone metastases due to neuroendocrine pancreatic tumour 3 years after peptide receptor radionucleotide therapy. BMJ Case Rep. 2020;13:e233263.

37. Makis W, McCann K, Buteau FA, McEwan AJ. Liver and bone metastases from small bowel neuroendocrine tumor respond to 177Lu-DOTATATE induction and maintenance therapies. Clin Nucl Med. 2015;40:162–5.
38. Yasuda M, Takeda S, Lee M, Hoshi S, Hoshi T, Tanaka Y, et al. Small cystic pancreatic neuroendocrine neoplasm with huge liver and bone metastases. Intern Med. 2020;59:3027–32.
39. Saranga-Perry V, Morse B, Centeno B, Kvols L, Strosberg J. Treatment of metastatic neuroendocrine tumors of the thymus with capecitabine and temozolomide: a case series. Neuroendocrinology. 2013;97:318–21.
40. Guo T, Ng KK, Chiang HW, Ma MF, Lin Y, Qian JM. Duodenal neuroendocrine carcinoma presenting with disseminated liver and bone metastases as the primary manifestation: case report and literature review. Cell Biochem Biophys. 2015;72:305–9.
41. Radu EC, Saizu AI, Grigorescu RR, Croitoru AE, Gheorghe C. Metastatic neuroendocrine pancreatic tumor—case report. J Med Life. 2018;11:57–61.
42. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology. 2016;103:172–85.
43. Stoyianni A, Pentheroudakis G, Pavlidis N. Neuroendocrine carcinoma of unknown primary: a systematic review of the literature and a comparative study with other neuroendocrine tumors. Cancer Treat Rev. 2011;37:358–65.