
CASE REPORT

A Rare Presentation of Low-grade Neuroendocrine Tumour

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ABSTRACT

Neuroendocrine tumours are believed to arise from various cells of the neuroendocrine system. Neuroendocrine cells are present not only in endocrine glands throughout the body that produce various hormones, but also diffusely in body tissues. The majority of neuroendocrine tumours are well differentiated as they usually retain the organ architecture typical of the neuroendocrine organ from where they originate, and they have low proliferative index. Clinical course is highly variable. Small tumours without poor prognostic features are cured by surgical resection. Even if the tumour is advanced and has metastasised where curative surgery is not feasible, surgery often has a role in neuroendocrine cancers for controlling symptoms and, possibly, improves survival. Patients who have metastasis at presentation may live long, thus improving quality of life is important in management. Unfortunately, response to conventional chemotherapy is very low. With the availability of newer agents, disease control rates may increase. Here we report a case with low-grade neuroendocrine tumour with widespread metastases at presentation. The patient was put on everolimus, an oral inhibitor of mammalian target of rapamycin, and has shown good clinical and radiological response.

Key Words: Neoplasms; Neuroendocrine tumors; Sirolimus; Treatment outcome

中文摘要

低度惡性神經內分泌腫瘤的罕見報導

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神經內分泌腫瘤可由神經內分泌系統的多種細胞起源。神經內分泌細胞不僅存在於全身的内分泌腺體，產生多種激素，也瀰漫分佈於全身組織中。大多數神經內分泌腫瘤由於保持了起源神經內分泌器官的典型組織結構，多屬分化良好，並具低增殖指數。該病的臨床表現差異很大。小腫瘤無不良預後因素，手術切除即可治癒。即使腫瘤已屬局部晚期或出現遠處轉移，難以根治性切除，手術仍能有效緩解症狀，並有可能提高生存率。神經內分泌腫瘤患者，即使出現遠處轉移，仍有可能長期生存，因此，改善生存質量是治療的重要考慮因素。可惜，患者對常規化療的反應偏低。隨著新藥物的出現，疾病控制率有可能提升。本文報告了一已出現廣泛轉移的低度惡性神經內分泌腫瘤病例。Everolimus是一種哺乳動物雷帕黴素靶蛋白的口服抑製劑，病人接受everolimus治療後，臨床症狀改善，影像學反應良好。

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INTRODUCTION

Neuroendocrine tumours (NETs) are believed to arise from neuroendocrine cells which function at the interface of the neurological and endocrine systems. Neuroendocrine cells are present in endocrine glands as well as in other glands which produce many hormones in body tissues.¹

CASE REPORT

A 52-year-old female had ongoing, vague, lower abdominal discomfort since mid-2008. In mid-2010, she had a battery of investigations which included ultrasound of abdomen and computed tomography (CT) scan of abdomen. The CT images showed a mass in the liver measuring 2 cm x 2.3 cm x 2.5 cm. The radiologist recommended a follow-up scan after 6 months as the exact nature of the mass was not clear. Patient's symptoms, however, resolved after 4 months without any medical intervention (Figure 1). In late 2010, magnetic resonance imaging (MRI) of the abdomen confirmed a 4.3 cm x 3.6 cm x 3.0 cm mass in the liver that had increased in size from previous imaging. It also showed presence of new multifocal liver lesions and dilatation of the distal pancreatic duct (Figure 2). Endoscopic retrograde cholangiopancreatography (ERCP) was performed in January 2011 but no dilatation was done as it was a difficult procedure. Clinically, the patient had felt better, so she preferred follow-up to any active intervention. She had another ultrasound in August 2011 to assess the progress of the lesion. The main liver mass was static, but there were more new liver lesions with the largest one measuring 7.8

cm x 6.2 cm x 7.8 cm while other lesions measured 2 cm x 3 cm x 2.4 cm in size. Since there was radiological progression, she was evaluated with liver biopsy in September 2011. Histologically, it was shown to be a metastatic NET with low-grade proliferation (World Health Organization [WHO] grade I). The tumour was positive for chromogranin and synaptophysin and negative for breast cancer markers, cytokeratin 7, and cytokeratin 20. There were also changes consistent with steatohepatitis with some hepatocytes swollen with Mallory's hyaline (Figure 3). Serum alpha-fetoprotein, β human chorionic gonadotropin, carbohydrate antigen (CA) 125, CA 19.9 and carcinoembryonic antigen levels were normal. Serum chromogranin level was high at 514 U/l (reference level, <36.4 U/l). Serum somatostatin level was normal at 32 pg/ml, as was glucagon level at 20 pg/ml, measured by radioimmunoassay. Complete staging work up was done. CT chest in November 2011



Figure 1. A computed tomography scan of abdomen showing a mass in the liver (arrow).

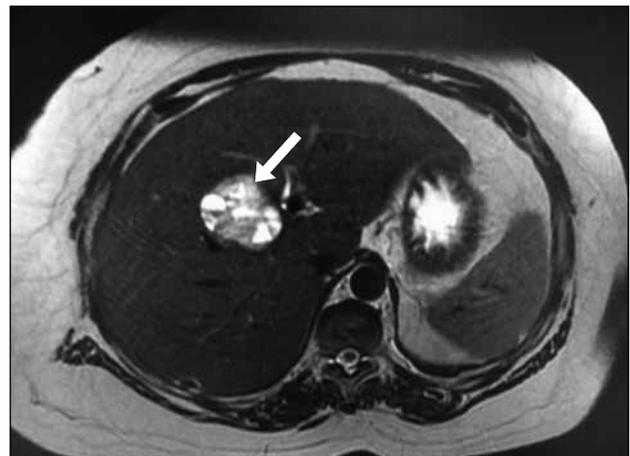


Figure 2. A magnetic resonance image of the abdomen showing a liver lesion that has increased in size on T2 image (arrow).

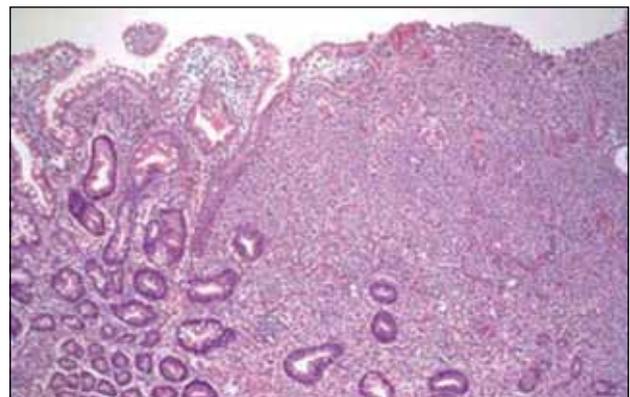


Figure 3. A micrograph of low-grade neuroendocrine neoplasm (H&E; original magnification, x 400).

showed a 6-mm nodule in the right middle lobe and a new mass in the right paravertebral region adjacent to T8 measuring 1.9 cm x 1.4 cm x 1 cm. By this time, there were numerous deposits in the liver, with the largest measuring 7.5 cm x 7.1 cm x 7 cm (previously 4.3 cm x 3.6 cm x 3.0 cm); a left adrenal mass measuring 2.0 x 1.2 cm (probably adenoma); and minimal free fluid adjacent to the uterus (Figure 4). She had a positive octreotide scan in November 2011 which was avid in the liver and showed small uptake in the paratracheal area and left mandibular area. The patient had definite radiological progression of disease. Clinically, she had fatigue, nausea, and some weight loss. She was treated with 12 cycles of injectable octreotide LAR 30 mg every 4 weeks, which she tolerated very well. Clinically, the left mandibular soft tissue mass started growing during 12 weeks of sandostatin but the growth was asymptomatic (Figure 5). CT scan of the face and head confirmed a 2-cm brain lesion in the left frontal lobe. Since no prior neuroimaging for correlation was available, the differential diagnosis included brain metastasis and meningioma. MRI brain confirmed an extra-axial growth in the frontal area which looked like a meningioma (Figure 6). The patient had a craniotomy in mid-2012 with excision of an extra-axial dural-based mass. The pathology of brain sections revealed a well-differentiated neuroendocrine carcinoma as identified in the preceding liver biopsy, growing as ribbons, trabeculae and glands, and composed of low columnar cells with uniform, slightly oval nuclei with finely granular chromatin, small nucleoli, and moderate

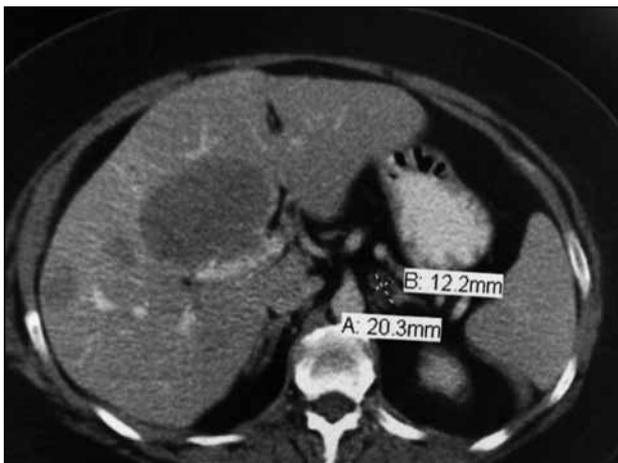


Figure 4. A computed tomography scan of abdomen showing numerous deposits in the liver with the largest measuring 7.5 cm x 7.1 cm x 7 cm (previously 4.3 cm x 3.6 cm x 3.0 cm). A left adrenal mass measuring 2.0 x 1.2 cm (probably adenoma) is also seen.

amounts of eosinophilic cytoplasm. The mitotic rate was reported to be very low (1 per 10 high power fields) with no necrosis. On immunohistochemistry, tumour cells were synaptophysin/chromogranin/CD56/CAM 5.2 positive. Biopsy of the left mandibular lesion also confirmed a metastatic NET showing the same features as in the brain and liver biopsies. The patient was started on everolimus while continuing octreotide. She declined

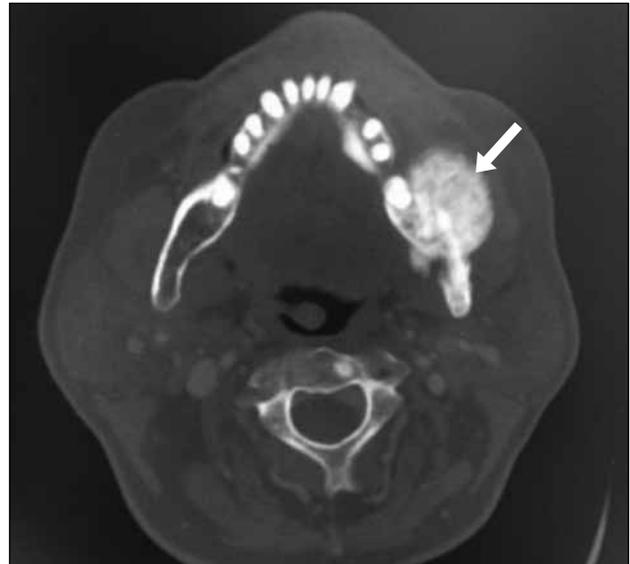


Figure 5. A computed tomography scan of the face and neck confirming a left mandibular soft tissue mass (arrow).

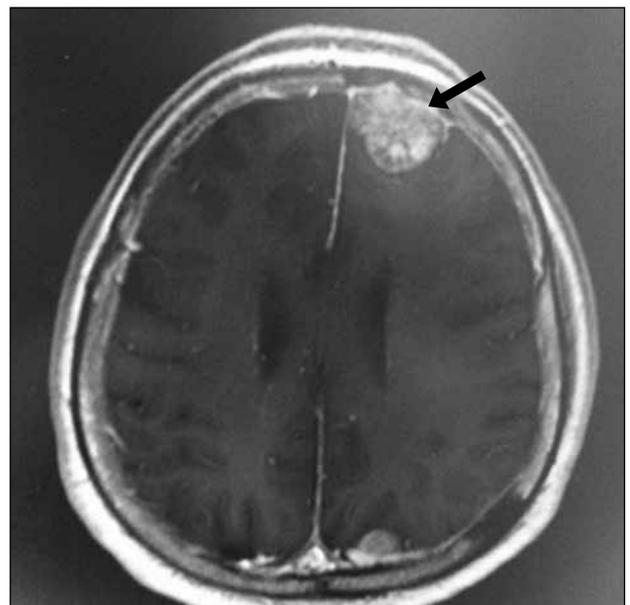


Figure 6. Magnetic resonance imaging of the brain confirmed a 2-cm brain lesion in the left frontal lobe on T2 gadolinium-enhanced image (arrow).

external beam brain radiation. At the 12-month follow-up, the left mandibular lesion decreased in size, and CT brain showed no recurrence (Figure 7). The patient remained well and maintained a good quality of life. Serum chromogranin level dropped to 300 U/l.

DISCUSSION

The annual incidence of clinically significant NET is approximately 2.5 to 5.0 per 100,000 population.² The prevalence may be higher but has been roughly estimated to be 35 per 100,000 population in the literature.³

Pathology

In 2010, the WHO updated its classification of NETs based on tumour site of origin, clinical syndrome, and differentiation.⁴ The tumours have three main categories: well-differentiated NETs, further subdivided into tumours with benign and those with uncertain behaviour; well-differentiated (low-grade) neuroendocrine carcinomas with low-grade malignant behaviour; and poorly differentiated (high-grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas.⁵ The emphasis is on mitotic rate and proliferative index of the tumour. These two parameters are used by pathologists to calculate grade of the tumour. Mitotic rate is assessed by counting mitotic figures, usually expressed as the number of mitoses per 10 high-power microscopic fields. The sensitivity of this technique is limited in small-volume biopsy samples, and is generally considered to

be more applicable to high-grade NETs.⁶ Proliferative index is expressed as the percentage of tumour cells labelled by immunohistochemistry for the proliferation marker Ki-67 (a significant predictor of progression-free survival [PFS]).⁷ This technique is generally considered to be more applicable to low-grade NETs. NETs can also be classified by whether or not they can produce hormonal substances. Functional NETs are associated with symptoms that can be attributed to the secretion of specific hormones or peptides.⁸ Non-functional NETs, on the other hand, are only associated with symptoms related to the size of the mass (eg, pain, obstruction, or bleeding secondary to local invasion or compression). Some NETs may remain asymptomatic for a long time or even indefinitely.⁹ Symptoms caused by functional NETs usually include skin changes, flushing, fatigue, loose stools, hypoglycaemia, pain/discomfort in the abdomen, and wheezing.¹⁰ Approximately 8% to 35% of patients with well-differentiated tumours, typically in the gastrointestinal tract, may present with a syndrome-like picture called carcinoid syndrome.¹¹ It occurs most frequently in patients whose intestinal NET has metastasised to the liver. The hepatic vein carries secreted serotonin and other vasoactive substances to the systemic circulation.¹² Well-differentiated NETs arising in the lungs may also secrete peptides that cause carcinoid syndrome (<5% of cases). These patients may also produce histamine and adrenocorticotropic hormone. Grade-1 and grade-2 NETs are more prone to secrete hormones than higher-grade neuroendocrine carcinomas.¹³ Brain metastasis is rare, and occurs in 1.5% to 5% of the situation. Of all types, bronchopulmonary NETs appear to be the most frequent source of cerebral metastases, and not dural-based deposits as seen in our case.¹⁴

Treatment

Surgery is the mainstay of treatment. The main goal is to perform a complete resection and preserve maximum function of the involved organ.¹⁵ However, it is not always possible to perform a surgical resection. Several chemotherapeutic agents such as cisplatin, doxorubicin, 5-fluorouracil, dacarbazine, etoposide and streptozotocin have been studied in many trials. So far, an objective response rate (ORR) of only 20% to 30% has been achieved with single drugs. In the literature, many chemotherapy combinations have been tried, most commonly with platinum and streptozotocin. In the Eastern Cooperative Oncology Group Study E1281 249, patients with metastatic carcinoid received either 5-fluorouracil plus doxorubicin or streptozotocin. There

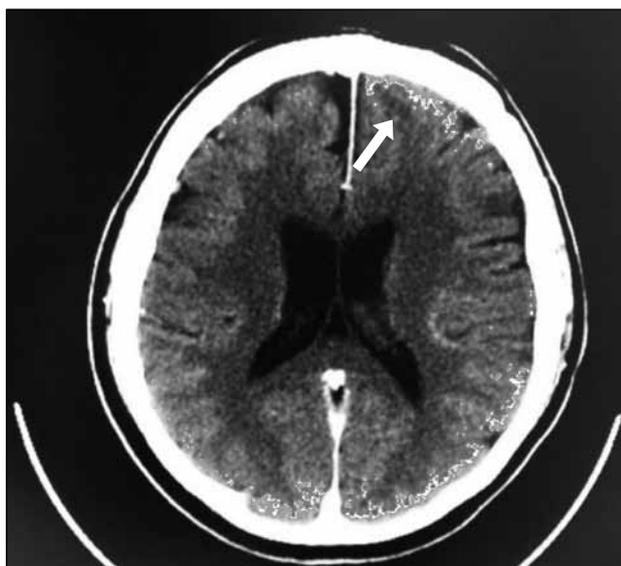


Figure 7. Computed tomography of the brain shows no recurrence in the brain parenchyma (arrow).

was an overall survival (OS) of 24.3 months versus 15.7 months, respectively ($p = 0.0267$).¹⁶

Long-acting peptides have also been used in the past few decades for treating NETs. Octreotide is one of the commonest pharmacological long-acting peptide which has good antisecretory action and is effective in controlling symptoms such as gastrointestinal hypersecretory states (commonly manifesting as loose stools) and abdominal cramping. Lanreotide is a synthetic analogue of somatostatin. Existing data fail to confirm whether long-acting peptide has any value in managing patients who are totally asymptomatic.¹⁷ Recently, radiolabelled somatostatin analogues have been introduced as a new, innovative therapy. Among these, 90Y-DOTATOC and 177Lu-DOTATATE are of interest. 90Y-DOTATOC, also called 90Y-edotreotide, contains a tightly bound yttrium-90 (90Y) atom, which is a high-energy beta emitter, while retaining its high affinity binding properties to both SSTR2 and SSTR3 demonstrating the ability to selectively deliver a tumoricidal dose of radiation to SSTR-positive tumours.¹⁸ In one study, over 500 patients with carcinoids received 177Lu-DOTATATE in a cumulative dose of 750 to 800 mCi (27.8 - 29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Complete response was identified in 2% and partial response seen in 28% of the patients. These were mostly gastroenteropancreatic neuroendocrine patients. Specifically, in the 188 carcinoids patients, ORR was 23%. Time to progression was 40 months while OS was 46 months.¹⁹ Emerging data suggest that these tumours harbour a peculiarly high networking of blood vessels, leading to a path where reducing angiogenesis can be an effective way to inhibit tumour growth. There are many other factors expressed in neuroendocrine neoplasms such as the vascular endothelial growth factors (VEGFs) and some VEGF receptor (VEGFR) subtypes,²⁰ platelet-derived growth factors (PDGFs),²¹ PDGF receptors (PDGFRs), and insulin-like growth factor receptors.²² Sunitinib is a multikinase inhibitor which has been approved for use in renal cell carcinoma. It holds good promise in neuroendocrine neoplasms by inhibiting VEGFR-1, -2, -3, and PDGFR- α , - β .²³

Interferon-alpha is a glycoprotein with antiviral properties which has been found to have antiangiogenic properties with an innate ability to decrease tumour bulk to some extent.²⁴ Many mutations have been identified by immunohistochemistry, of which ErbB3 and ErbB4 are worth mentioning. However, epidermal growth

factor receptor (EGFR) was commonly mutated in lung-based carcinoid neoplasms. Erlotinib can be utilised to potentially inhibit EGFR signal transduction.²⁵

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumour activity in patients with advanced pancreatic NETs.²⁶ Currently, two large phase III studies comparing everolimus 10 mg daily versus placebo in metastatic functional carcinoid tumours (RADIANT 2) and pancreatic NETs (RADIANT 3) have completed accrual. The RADIANT 3 trial demonstrated a statistically significant improvement in PFS from 4 months in the placebo arm to 11 months in the active treatment arm. The RADIANT 2 trial demonstrated an improvement in PFS from 11 months in the placebo arm to 16 months in the active treatment arm. On central radiological review, the statistical significance of this trial was borderline ($p = 0.026$).²⁷

CONCLUSION

Due to paucity of phase II and randomised phase III trials, there is no consensus on treatment standard. The current treatment is based on data from various series, case reports, or very small samples of patients. Most studies in the literature have included carcinoids from different sites which show different clinicopathological behaviours, thus, skewing the data. With modern technology, there will be more emphasis on molecular genetics which will help physicians in predicting the prognosis of NETs, and develop practice guidelines. Overall success lies in taking a multidisciplinary approach towards management.

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