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CASE REPORTS

Pancreatic glucagonoma presenting as a pulmonary mass

Álvaro Pinto Marín · Elena Hernández Agudo · Jaime Feliú · Manuel González Barón

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Abstract Glucagonoma is an uncommon disease, a neuroendocrine tumour that develops from glucagon-producing pancreatic cells. They are usually slow-growing, but generally advanced at diagnosis, and metastatic disease is virtually incurable. Liver is the most common site of metastatic disease. We present the case of a 48-year-old man with a glucagonoma being diagnosed from a pulmonary mass. This case had no liver affection in the whole evolution of the disease, and showed a particularly aggressive course, with very little response to all therapies administered, and a survival from diagnosis of just 16 months.

Keywords Glucagonoma · Neuroendocrine tumours · Chemotherapy · Somatostatin

Introduction

In the "neuroendocrine tumours" (NET) category we include a wide variety of neoplasms derived from the neuroendocrine cells, but they can be divided into two subgroups: the well differentiated ones (with often indolent behaviour) and the poorly differentiated ones, typified by small-cell lung cancer. These two subgroups have a completely different evolution, treatment and prognosis.

A. Pinto Marín · E. Hernández Agudo · J. Feliú · M. González Barón
Medical Oncology Department
Hospital La Paz
Madrid, Spain

A. Pinto Marín (✉)
C/ Vereda del Carmen, 19 - 1º D
ES-28017 Madrid, Spain
e-mail: alvaro_pinto_marin@hotmail.com

Glucagonomas, as well as other well differentiated NETs, are very unusual. They tend to be disseminated at diagnosis, usually with liver metastasis and an indolent clinical course. They are associated with some typical clinical features, but these are not present in all patients.

We report the case of a 48-year-old man diagnosed with pancreatic glucagonoma with affection of lung and mediastinal and supraclavicular nodes, without liver metastasis. We discuss the clinical course and the therapy given, and review the evidence on this issue.

Case report

We report the case of a 48-year-old man with no significant medical history except for mild hyperglycaemia diagnosed in 2005, who was admitted to the Neurology Department of our institution due to a pulmonary mass located in the left hilum, in December 2006. He was completely asymptomatic. In the computerised tomograph (CT) there was a left hilar mass measuring 4×3.5 cm (Fig. 1), accompanied by at least four lung nodules, two of them in the right lung and the other two adjacent to the hilar mass. There were also lymphadenopathies, located in the left supraclavicular area (largest diameter 2.5 cm) and in the mediastinum (largest diameter 1.5 cm). In the tail of the pancreas, there was a 2-cm nodule with peripheral contrast enhancement and central necrosis. The PET-CT confirmed these findings, showing a pulmonary mass in the left lower lobe, supraclavicular and mediastinal lymphadenopathies and a mass in the tail of the pancreas.

The bronchoscopy revealed a mass with bronchial obstruction in the left upper lobe bronchus. Biopsy was performed, showing a neuroendocrine carcinoma, possibly related to metastatic spread of pancreatic glucagonoma. The somatostatin receptor scintigraphy (SRS) confirmed pathologic uptake of octreotide in lung, lymph nodes and pancreas. No abnormal findings were seen in the blood and urine biochemical study.

In January 2007 the patient was referred to our department, and we decided to begin therapy with streptozocin, doxorubicin and octreotide, receiving three full-dose cycles, the last one in May 2007. In June 2007 the patient was admitted to the Traumatology Department because of a left hip fracture. The CT showed a lytic lesion in the left hip, as well as progressive disease in pancreas and lung. Surgery was performed, with the placement of a hip prosthesis.

Due to progressive disease, chemotherapy was stopped and therapy with interferon and octreotide was initiated in July 2007. In Octo-

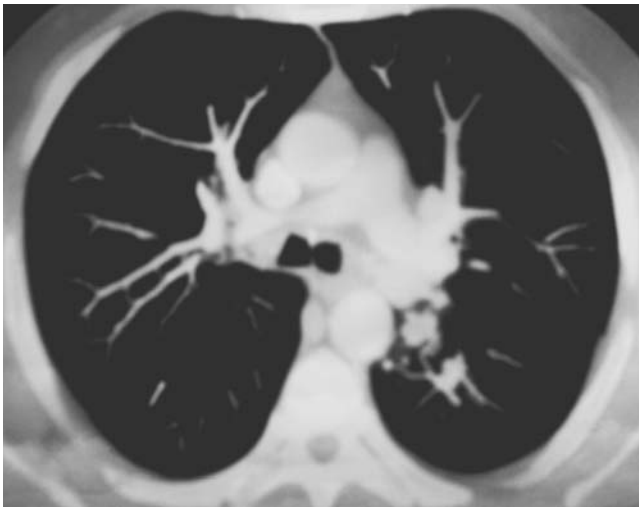

Fig. 1 CT image of the left hiliar mass

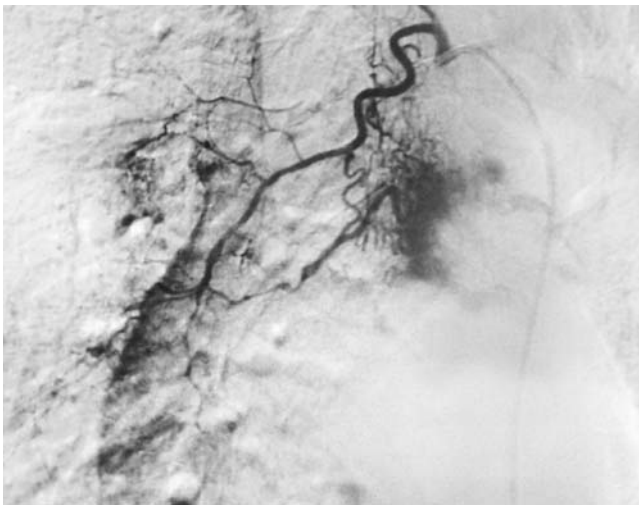

Fig. 2 Embolisation of the bronchial vessels

ber 2007 the disease worsened, with growth of the supraclavicular and mediastinal lymph nodes. He was offered entry to a clinical trial with sunitinib, but it could not be started because of persistent thrombopenia. Given the progressive growth of the supraclavicular mass, with pain and ulceration of the skin, he was referred to the Radiotherapy Department, receiving palliative treatment over this field, with symptomatic improvement. He continued therapy with octreotide.

In February 2008 a bone marrow biopsy was done, due to persistent thrombopenia, and it showed infiltration by malignant cells. Then we began therapy with uracil/tegafur and bevacizumab, but the patient had an episode of severe haemoptysis after the second cycle and bevacizumab had to be stopped. Embolisation was performed and the bleeding stopped in the next few days (Fig. 2). As the disease had been unresponsive to most of the therapies given, we decided to treat it like a small-cell carcinoma, even though the analysis of the tissue obtained at diagnosis revealed a well differentiated neoplasm with a Ki-67<10%. We began treatment with cisplatin, planning to add etoposide if side effects were acceptable and thrombopenia remained stable. Nevertheless, the patient had a new episode of severe haemoptysis in April 2008, not responding to re-embolisation, and died because of massive haemoptysis.

Discussion

NETs of the gastrointestinal tract are relatively uncommon, and present typically in the fifth decade. Pancreatic NETs account for less than 5% of all pancreatic tumours [1]. They can present in a typical clinical syndrome, consisting of necrolytic migratory erythema, diabetes mellitus due to glucagon secretion, anaemia, weight loss, cheilitis, deep venous thrombosis and neuropsychiatric disorders (the so-called "4-D's": diabetes, depression, deep venous thrombosis and dermatitis) [2]. Nevertheless, this clinical feature does not appear in all the cases. At the time of presentation the tumour is usually large (>4 cm) and up to 50% of the patients will have metastatic disease, usually affecting liver. Its commonest location is the tail of the pancreas.

A genetic syndrome that can be associated to glucagonoma is multiple endocrine neoplasia-1 (MEN-1), characterised by pancreatic, parathyroid and pituitary malignancies. It is inherited following an autosomal dominant pattern, with the responsible gene traced in chromosome 11q13 [3].

Diagnosis is usually made by CT [4], revealing a pancreatic mass, usually in the tail of the pancreas. As stated before, if the disease is metastatic, its spread commonly affects the liver. Magnetic resonance imaging (MRI) can be of great help when planning a surgical approach, as it may better define vascular invasion and has a greater sensitivity for detecting liver metastasis [5]. Other imaging techniques, such as transabdominal or endoscopic ultrasound, can also be useful [6]. SRS using radiolabelled octreotide is very sensitive for glucagonomas, and besides confirming the diagnosis and localising the tumour, it is also useful for detecting metastasis, predicting response to treatment with somatostatin analogues and monitoring response to treatment [7].

Laboratory tests may contribute to complete the diagnosis of this disease. Elevation of serum glucagon is common, but some other causes of these elevated glucagon levels must be excluded, such as hypoglycaemia, renal or hepatic failure, trauma, sepsis, acute pancreatitis, abdominal surgery or Cushing's syndrome [8]. However, glucagon levels in glucagonoma are much more elevated (more than 500 pg/ml) than in other conditions.

The treatment for NETs such as glucagonoma can be grouped in three categories [9]: supportive treatment, surgery and nonsurgical cytoreduction (chemotherapy, radiotherapy, biotherapy). Surgery is the only curative treatment nowadays, and metastatic spread of the disease does not completely contraindicate a surgical approach. Even though in most cases surgery cannot be radical, it can achieve long-term remissions due to the indolent nature of this disease [10, 11]. In selected cases, liver transplantation can be an option but, as there are very few cases reported, this must still be considered an investigational treatment [12]. Some other liver-directed therapies, such as embolisa-

tion [13] or radiofrequency ablation [14], can be useful in selected patients.

Somatostatin analogues, as well as interferon, are useful to control symptoms related to glucagon hypersecretion, but regression of the tumour is rare [15]. This is the reason why the use of these treatments is controversial in asymptomatic patients. Chemotherapy with the classical agents in monotherapy, such as flurouracil, doxorubicin, streptozocin, dacarbazine or etoposide, is associated with a modest response rate, about 10–15%, dacarbazine being the one with a slightly higher response rate [16]. Combination chemotherapy is usually based on streptozocin, combined with doxorubicin and/or fluoruracil, obtaining response rates of about 35%, and an overall survival around 26 months [17]. The combination of temozolomide and thalidomide seems promising, but is still under investigation [18].

Molecularly directed agents are still in a research phase in this disease. The most consistent studies are those related to angiogenesis inhibition, either with bevacizumab, sunitinib or sorafenib. Other research directions, such as mTOR inhibition or tyrosine-kinase (TK) inhibition with small molecules, have very few data up to now.

Summarising, glucagonoma is an uncommon disease, which in some cases may present with a typical clinical feature, and is usually metastatic at diagnosis, in most of the cases with liver metastasis. Its clinical course can be indolent, with long-term survivors. There is no therapy that can be considered standard, and further research is necessary to optimise and individualise the treatment of this selected group of patients.

Conflict of interest The authors declare no conflict of interest.

References

1. Moldow RE, Connolly RR (1968) Epidemiology of pancreatic cancer in Connecticut. Gastroenterology 55:677–686
2. O'Grady HL, Conlon KC (2008) Pancreatic neuroendocrine tumors. Eur J Surg Oncol 34:324–332
3. Chandrasekharappa SC, Guru SC, Manickam P et al (1997) Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 276:404–407
4. Brizi MG, Natale L, Manfredi R et al (2001) High resolution spiral computed tomography of the pancreas. Rays 26:111–115
5. Dromain C, de Baere T, Lumbroso J et al (2005) Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography and magnetic resonance imaging. J Clin Oncol 23: 70–78
6. McLean AM, Fairclough PD (2005) Endoscopic ultrasound in the localization of pancreatic islet cell tumors. Best Pract Res Clin Endocrinol Metab 19:177–193
7. Frilling A, Malago M, Martin H, Broelsch CE (1998) Use of somatostatin receptor scintigraphy to image extrahepatic metastases of neuroendocrine tumors. Surgery 124:1000–1004
8. Wermers RA, Fatourechi V, Wynne AG et al (1997) The glucagonoma syndrome. Clinical and pathologic features in 21 patients. Medicine (Baltimore) 75:53–63
9. Warner R (2005) Enteroendocrine tumors other than carcinoid: a review of clinically significant advances. Gastroenterology 128:1668–1684
10. Touzios JG, Kiely JM, Pitt SC et al (2005) Neuroendocrine hepatic metastases: does aggressive management improve survival? Ann Surg 241: 776–783
11. Schurr PG, Strate T, Rese K et al (2007) Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. Ann Surg 245:273–281
12. Florman S, Toure B, Kim L et al (2004) Liver transplantation for neuroendocrine tumors. J Gastrointest Surg 8:208–212
13. Gupta S, Yao JC, Ahrar K et al (2003) Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J 9:261–267
14. Berber E, Flesher N, Siperstein AE (2002) Laparoscopic radiofrequency ablation of neuroendrocrine liver metastases. World J Surg 26:985–990
15. Aparicio T, Ducreux M, Baudin E et al (2001) Antitumor activity of somatostatin analogues in progressive metastatic neuroendocrine tumors. Eur J Cancer 37:1014–1019
16. Bukowski RM, Tangen CM, Peterson RF et al (1994) Phase II trial of dimethyltriazenoimidazole carboxamide in patients with metastatic carcinoid. A Southwest Oncology Group study. Cancer 73: 1505–1508
17. Kouvaraki MA, Ajani JA, Hoff P et al (2004) Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 22:4762–4771
18. Kulke MH, Stuart K, Enzinger PC et al (2006) Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 24:401–406