LARGE CELL METASTATIC PANCREATIC NEUROENDOCRINE CARCINOMA TREATED WITH SOMATOSTATIN ANALOGUES - CASE REPORT AND LITERATURE REVIEW

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Abstract

We report the case of a 55-year-old-male with a large cell metastatic pancreatic neuroendocrine carcinoma treated for 14 months with lanreotide autogel having a stable disease (SD) and not responding to chemotherapy.

The somatostatin analogues (SSA) were introduced after an episode of diarrhea and controlled the disease. Progression-free survival (PFS) as determined by Computerized Tomography (CT) scans was obtained for 14 months. After more than a year, the patient's health state deteriorated along with progressive disease. The capecitabine-temozolomide regimen was challenged, but after three cycles, a rapid clinical decline was noted.

Conclusion. This unexpected event (diarrhea) in the course of the disease could represent the beginning of carcinoid syndrome. While the lanreotide autogel helped the episode of diarrhea pass, it also helped gain control over the disease itself.

Key words: Neuroendocrine tumor, Large cell pancreatic carcinoma, lanreotide autogel.

INTRODUCTION

Pancreatic neuroendocrine neoplasms (pNENs) or islet cell tumors or pancreatic carcinoids derived from neuroendocrine cells are heterogeneous tumors, which are in a continuous increase in incidence from one year to another.

The survival rates for newly diagnosed patients with pNENs are estimated at about 42% as far as the 5 year survival rate is concerned (1).

pNENs may be functional (F-pNENs), non-functional (NF-pNEN) or secretory but nonfunctional, depending on their biological behaviour of secreting/

non-secreting active hormones. NF-pNENs represent 30-50% or after others 60-90% (2) of all pNENs. NF-pNENs are discovered incidentally by imaging studies or the patients present symptoms caused by tumor bulk, such as: abdominal pain, weight loss or jaundice (3, 4).

Although NF-pNENs do not secrete peptides which could cause a clinical syndrome, they could secrete other peptides such as: chromogranin A (70-100%), pancreatic polypeptide (50-100%), ghrelin, calcitonin or neurotensin, all of which do not cause symptoms.

There are no proper diagnostic methods to identify the malignant potential in early stages, but this can be appropriately evaluated by pathologic examination after surgery or after the appearance of metastases (5).

The treatment options for pNENs are varied: surgery, locoregional therapy or systemic therapy. Surgery with curative intent is to be considered in all cases if clinically and technically possible (4). Locoregional liver-directed therapies are transarterial chemoembolization, bland embolization, radiofrequency ablation, transcatheter alcohol ablation and microwave ablation, whereas systemic therapies are somatostatin analogues, mTOR inhibitors, tyrosine kinase inhibitors, chemotherapy and immunotherapy.

Poorly differentiated neuroendocrine carcinoma of the pancreas represents rare malignant tumors with a poor prognosis, making it very difficult to approach as far as treatment options are concerned. We believe there is much room to improve in the way we treat this specific tumor and we can start from treating each patient as a separate entity with its

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clinical particularities. By presenting clinical issues in the context of a patient situation, case studies are an effective tool for demonstrating clinical decision making. We strongly encourage listening to patients' goals and preferences by offering a consensus opinion from a multidisciplinary team in order for it to most benefit the patient.

CASE PRESENTATION

In February 2015, a 55-year-old man, 68 kg, 172 cm tall, living in a rural area presented to the gastroenterologist with fatigue for three months. An abdominal ultrasonography (US) followed by an abdominal CT scan showed a tumor of pancreatic head and multiple space occupying lesions in the liver.

The medical history of the patient is as follows: in 1980 he had an appendectomy, in 2000 he was diagnosed with gastroesophageal reflux disease, hyperlipidaemia and chronic B virus hepatitis, for which he received no treatment. He denied alcohol consumption, but smoked ten cigarettes a day for 30 years.

In February 2015 he had an ECOG performance status of 1, asthenia, scleral jaundice, hyperchromic urine and abnormal liver biochemical and function tests such as: AST 130 U/L (normal value(NV): 10-40U/L), ALT 84 U/L(NV:7-56U/L, TB 1.83mg/dL (NV:0.2-1.2mg/dL), ALP 475U/L (NV:30-130U/L), GGT 186U/L (NV:0-55U/L). Serum CA19-9 level was 45U/mL (NV<37U/mL). An increase in serum calcium levels was also noted (11.5mg/dL, NV: 8.6-10.2mg/dL) An upper gastrointestinal (GI) endoscopy showed grade I oesophageal varices and portal hypertensive gastropathy.

In March 2015, an abdominal CT scan with

iodinated contrast agent showed a hypervascular cephalic pancreatic tumor that invaded the splenoportal confluence, portal vein thrombosis, multiple lesions within the liver measuring 4-6 cm in diameter with dilation of the intrahepatic biliary ducts and common bile duct, retrocephalic, periportal and lomboaortic lymph nodes. Neuroendocrine tumor markers in blood and urine were measured: chromogranin A 686 µg/L (NV: 19-98µg/L); serotonin 313 µg/mL (NV: 80-400 µg/); urinary 5-HIAA 49.7mg/24h (NV: 2-7 mg/24h), NSE-8ng/mL; (NV<16ng/mL).

In April 2015 the patient underwent antegrade cholecystectomy, choledocoduodenal anastomosis and hepatic metastasectomy. A pathological exam of the liver metastasis showed an infiltration with a solid islet, a trabecular tumor with large cells and necrosis and was categorized as large cell neuroendocrine carcinoma (NEC) (Fig. 1 A, B, C). The diagnosis was confirmed by the positive immunoreactivity for chromogranin A (Fig. 2 A), synaptophysin (Fig. 2 B), as well as for CD56 expression (Fig. 2 C, D). Cytokeratin (CK) 19 was positive and suggestive for pancreatic origin (Fig. 3). The Ki 67 proliferation index was 40% (Fig. 4).

From May until June 2015, the patient received two cycles of chemotherapy with cisplatin and etoposide i.v every 4 weeks and lamivudine for chronic B virus hepatitis. In June, the patient was admitted for a CT scan evaluation. While scanning, the patient felt very tired and presented melena with hemodynamic instability – blood pressure (BP) 60 mm Hg, heart rate (HR) 100 bpm in a regular pattern, cold sweats, and haemoglobin concentration decreased at 6g/dL.

Superior GI endoscopy showed bleeding from duodenal ulceration.

Figure 1. Microscopic examination of the liver metastasis showed an infiltration with a solid islet, trabecular tumor with large cells and necrosis large cell neuroendocrine carcinoma (NEC). **A.** long arrow: tumor ; short arrow: peritumoral cholestasis (H&E -hematoxylin and eosin- x200); **B.** general view of the trabecular and solid tumor (H&Ex40); **C.** large sized cells with hyperchromatic nuclei (arrow)(H&Ex400).

Figure 2. Immunohistochemistry(IHC) revealed: A. diffuse strong and uniform cytoplasmic staining for chromogranin A in tumor cells (IHC chromogranin; $\times 200$); B. an intense positive staining for synaptophysin in tumor cells (IHC synaptophysin; $\times 100$); C. an intense positive staining for CD56 in tumor cells (long arrow) and positive control for CD 56 in biliary duct cells(short arrow) (IHC CD56; $\times 100$); D. an intense positive staining for CD56 in tumor cells-detail (IHC CD56; $\times 200$).

Figure 3. Cytokeratin (CK) 19 was positive in tumor cells (IHC CK19; $\times 200$).

Figure 4. Ki-67 proliferation index was 40% (IHC Ki67; $\times 200$).

The CT scan from June 2015 (Fig. 5) showed progressive disease: increase of all liver metastases (Fig. 5 A), regression of biliary ducts dilation, thrombosis of portal vein with portal cavernoma (Fig. 5 E, F), pancreatic tumor of the same size that invades the duodenum, and higher lymph nodes (Fig. 5 B) compared to the baseline CT scan (March 2015). The interventional radiologist proceeded to the transcatheter embolization of the gastroduodenal artery with coils and a gelatine sponge and the bleeding stopped completely (Fig. 5 C, F). PET-CT with ^{18}F -FDG showed an intense focal area of FDG uptake in the head of pancreas and in other multiple liver areas. The patient had neither octreoscan nor ^{68}Ga -DOTATATE PET/CT because it was not reimbursed by the National Health Insurance House.

From July to August 2015, the patient was given two more cycles q4w of cisplatin/etoposide. In September 2015, he was emergently hospitalized for grade III diarrhea (7-9 watery stools), fever 38°C , abdominal pains, nausea, oliguria, pallor and ankle edema.

The test for *Clostridium difficile* toxin was positive, so the patient received the standard treatment with Metronidazole and Vancomycin. After 14 days of treatment, the stool CD toxin assay was negative, but diarrhea persisted (2-4 semiconsistent stools/day). The patient started octreotide 50 mcg s.c. twice daily with normalization of stools after two weeks of treatment and octreotide s.c. was no longer given.

During October 2015, grade II diarrhea returned and the patient was treated with octreotide 50mcg s.c. twice daily with the control of stools again. In November 2015, he began the treatment with lanreotide autogel 120mg at four weeks interval. We also tested our patient for MEN1 (Multiple Endocrine Neoplasms type 1) by mutations in the menin gene but the test was negative.

Figure 5. Abdominal CT from June 2015 - evaluation with iodinated contrast agent: multiple liver metastases (A-arrows), pancreatic tumor with large adenopathy (B-arrow) and biliary obstruction, embolization of gastroduodenal artery with coils (C, F-arrow), thrombosis of the portal vein associated with portal cavernoma (E, F-arrow).

Figure 6. Abdominal CT scan from Oct 2015 showed stable disease compared to the CT exam from June 2015.

Figure 7. Abdominal CT scan from Jan 2017 showed progressive disease-larger liver metastases and larger pancreatic tumor compared to the abdominal CT scan from June 2015.

Figure 8. Evolution of serum tumor marker Chromogranin A levels.

The CT scan performed in October 2015 (Fig. 6) and February 2016 showed SD according to RECIST 1.1 criteria *versus* CT exam from June 2015, along with a decrease in chromogranin A levels (17.1µg/dL; NV:27-94µg/mL), but with normal NSE value.

In August 2016, a reevaluation was made and the CT scan showed an increase in liver metastases but was still considered SD. Serum chromogranin A was 356 µg/L and the lanreotide autogel was increased to 120mg every two weeks.

In January 2017, another CT scan was conducted and showed progressive disease (Fig. 7), while serum chromogranin A was 278 µg/L (Fig. 8). ECOG performance status was 2 and the patient presented asthenia, upper and mid-abdominal pains controlled with oral opioids, normal stools and abnormal laboratory tests (grade I anaemia and cytolysis, grade II cholestasis). The patient had SD for 14 months with tumor control response from November 2015 until January 2017.

After this, deterioration of the patient's clinical status and weight loss were observed, along with an increase in the size of the liver lesions and of the abdominal lymph nodes. The capecitabine-temozolomide was challenged, but after three cycles, a rapid decline in the patient's quality of life was noted. Within one month, the patient deceased due to progressive disease.

DISCUSSION

Neuroendocrine carcinomas of the pancreas are defined by a mitotic count > 20 mitoses/10 HPF and/or Ki67 index > 20%. They are very aggressive and can be further divided into small- and large-cell subtypes (6, 7). In the revised version of the "World Health Organisation (WHO) Classification of Tumours of Endocrine Organs" published in 2017, the high grade pancreatic neuroendocrine neoplasms are divided into well-differentiated NETs (PanNETs) and poorly differentiated NE carcinomas (PanNECs) histo-morphologically (8). Grading of PanNETs into three tiers (G1, G2, and G3) is based on proliferation assessed by mitotic count and Ki-67 index. In the 2017 WHO classification, PanNECs are also designated as G3, whereas in the current proposal NECs are not specifically graded, as they are regarded all to be high grade by definition. In the case of our patient we used the "2010 WHO Classification of Gastro-Entero-Pancreatic Neoplasms" (9). The NETs G3 are associated with a better prognosis by comparison to NECs G3 and do not significantly respond to cisplatin-based chemotherapy (10).

Pancreatic NECs are rare tumors, accounting for about 5% of all pancreatic neuroendocrine neoplasms. They usually arise in adults in the sixth decade of life with a higher prevalence in males (6,7). Some patients may present paraneoplastic syndromes such as Cushing's syndrome, hypercalcemia and carcinoid syndrome. Most patients with NEC have associated symptoms similar to ductal adenocarcinoma

such as back pain, weight loss and jaundice (11), symptoms that were also exhibited by our patient.

Plasma chromogranin A may be increased in two thirds of patients with advanced NEC, but with lower levels than those observed in well-differentiated tumors. By contrast, the levels of other tumor markers such as neuron-specific enolase (NSE) are higher in poorly differentiated tumors than in NET, and they are significantly associated with survival (our patient had an increase of chromogranin A level and not of the NSE). However, the role of circulating tumor markers to predict and monitor outcome has not been properly assessed in extrapulmonary NEC (6,12). Chromogranin A variation as a predictive marker of treatment efficacy was analysed in RADIANT 1,2 and CLARINET studies. In RADIANT 2, early chromogranin A responders had longer PFS *versus* the nonresponders (13), whereas in the CLARINET trial a decrease in chromogranin A level was associated with a reduced risk of disease progression (14, 15). In the case of our patient, we decided to increase the frequency of Lanreotide Autogel 120 mg q2w when chromogranin A increased by an important amount (from 17.1 to 356 µg/L). This approach is also used in the CLARINET Forte trial, the results of which we expect in 2020 (16).

In a NEC it is important to perform both a 18 FDG-PET and a 68 Ga PET for staging and confirmation of endocrine features (7). Somatostatin receptor scintigraphy is not generally recommended in poorly differentiated NECs, but in the case of functioning tumors, confirming the expression of somatostatin receptors warrants the use of SSA treatment to control symptoms caused by hormone overproduction (17, 18). Also, the expression of somatostatin receptors (SSTRs) in NETs, shown by immunocytochemistry, led to the application of somatostatin inhibitor in the treatment of patients with NETs (10). SSTRs have lower expression in G3 pNENs and are important for the efficacy of peptide receptor radionucleotide therapy (PRRT). G3 well-differentiated tumors have a similar SSTR expression to that of G1 and G2 pNETs tumors. There are only two studies which included all grades of NENs with analyses by grade; and three studies limited to patients with G3 GEP NEN (19). The median PFS and OS with 177Lu-DOTATATE PRRT for patients with G3 NEN were between 7-14 and 23-31 months, respectively (20). Retrospective studies of PRRT with 177Lu-DOTATATE or 90Y-DOTATATE which included patients with pNEC showed a better disease control

rate if Ki-67 is $\leq 55\%$ (21). Some case reports have communicated long-lasting responses to PRRT in NEC with high expression of somatostatin receptors, but this therapeutic strategy is generally not successful in the majority of G3 tumors (6, 22). The antineoplastic activity of SSA occurs through direct and indirect activity and it depends on the receptor subtypes to which they are bound to. Direct activity is mediated by somatostatin receptors 2 and 5 and indirect activity depends on the growth factor inhibition through antiangiogenic mechanism and immune-modulating activities. The treatment with octreotide could reduce the VEGF level. Immunomodulation is not very clearly explained but probably it is correlated with the increase of natural killer cells (23, 24).

Tumor shrinkage with SSA treatment was demonstrated in $<10\%$ of the patients, but stabilization occurs in up to 50% of the patients, as was in our case as well (25). The results of the CLARINET trial for patients with metastatic and unresectable GEP NET G1 and G2 (Ki-67 $< 10\%$), regardless of the degree of liver involvement, who received lanreotide at a dose of 120 mg every four weeks showed that PFS was significantly prolonged in the cases of a stable disease course, but without significant differences in the OS (26). A recent observational study suggested a link between prolongation of PFS and OS in a large cohort of patients with metastatic NET treated with somatostatin analogues (27).

Patients with locally advanced or metastatic NEC should undergo chemotherapy (28). The Ki-67 index is important to establish the most appropriate chemotherapy regimen. Ki67 cut-off of 55% was predictive for response to first-line platinum-based chemotherapy in different trials (6,11). Patients with poorly differentiated NEC with ki67 $>55\%$ had a response rate of 42%-67% to the treatment with cisplatin/etoposide while those with ki67 $< 55\%$ had a response rate of 15%. The regimen consisted of VP-16 130 mg/m² per day for three days and CDDP 45 mg/m²per day for two days, on days two and three respectively, every 3 weeks (29) or CDDP 100 mg/m² per day + VP-16 100 mg/m² per day for three days, every three weeks (30) or VP-16 100 mg/m² per day for three days + CDDP 45 mg/m² per day for two days, every four weeks (31) or CDDP was administered at 80 mg/m²day 1 and VP-16 at 100 mg/m² per day for three days, every three weeks (32, 33). Second-line chemotherapy after platinum-containing regimens has not been well defined. FOLFIRI regimen (5fluorouracil + leucovorin+ irinotecan) or

temozolomide in combination with capecitabine +/- bevacizumab showed a response rate of 33%, with a median PFS of six months and a median OS of 22 months (33, 34).

Another cytotoxic agent used in the first line in the treatment of pancreatic NEC is temozolomide as a monotherapy, or in combination with bevacizumab and capecitabine. It seems most effective in patients with Ki-67 between 20–55% (29, 30, 34). In 2011, a retrospective study showed that the combination of capecitabine and temozolomide (CAPTEM) was associated with a 70% objective response rate, with a median PFS of 18 months and an OS of 92% at two years (35). Recently, it was reported that PFS in advanced pancreatic NETs improved significantly with the addition of capecitabine to temozolomide in a randomized trial. The phase II trial ended after a planned interim analysis showed that the combination treatment met the primary endpoint, as median PFS improved from 14.4 months with temozolomide alone to 22.7 months with the combination CAPTEM. Common significant adverse events occurred twice as often in the combination arm (44% vs. 22%), and the most common events were neutropenia, thrombocytopenia, nausea/vomiting, diarrhea, fatigue, and lymphopenia (36).

Patients with NECs have a poor prognosis, with an expected survival of less than two years, and 6–12 months for patients with liver metastases (17) with the performance status representing a significant prognostic factor (7, 12). Patients with poor performance status receive only best supportive care and have a median survival time of only two months.

For patients with inoperable high-grade tumors (Ki-67 $>20\%$) first-line chemotherapy with cisplatin-etoposide is recommended. However, this approach was not effective in this case. Our patient exhibited hormone overproduction that caused diarrhea, a symptom of carcinoid syndrome. NECs are typically non-functional, but in this patient, it was presumed that the tumor increased at a certain level and contained a combination between poorly differentiated cells responsible for its aggressiveness and moderately differentiated cells accountable for the clinical signs.

In conclusion, for the presented case, Lanreotide Autogel contributed to a fair quality of life for 14 months, despite the aggressive nature of the tumor. These results suggest that even patients with poorly differentiated NECs exhibiting symptoms caused by hormone overproduction can benefit from

SSA. Therefore, the treatment should be individualized by taking into account each patient's goals and preferences and offering a consensus opinion from a multidisciplinary panel of medical oncologists, surgeons, radiation specialists and interventional radiologists.

Conflict of interest

The authors declare that they have no conflict of interest.

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