The poor prognosis factors in G2 neuroendocrine tumor

CĂTĂLINA POIANĂ¹,², M. C. NEAMTU³, ELENA TAINA AVRAMESCU⁴, MARA CARŞOTE¹,², RALUCA TRIFĂNESCU¹,², DANA TERZEA¹,²,⁵, OANA MARIA NEAMTU⁴, D. FERECHIDE¹, RUCSANDRA DĂNCULESCU MIULESCU¹)

¹) “Carol Davila” University of Medicine and Pharmacy, Bucharest
²) “Constantin I. Parhon” National Institute of Endocrinology, Bucharest
³) Department of Pathologic Physiology, University of Medicine and Pharmacy of Craiova
⁴) Department of Sport and Kinetic Therapy, University of Craiova
⁵) “Victor Babes” National Institute, Bucharest

Abstract

Background: The G2 neuroendocrine tumors (NET) or well-differentiated neuroendocrine carcinomas (2010 WHO Classification of Tumours of the Digestive System) embrace different types of evolution despite the fact that they actually are included in the same group of prognosis based on mitotic count and the Ki-67 proliferation index. Aim: We studied the pathological and clinical aspects in patients with G2 NET.

Materials and Methods: This is a retrospective pilot observational study in patients admitted between January 2008 and January 2013 in “Constantin I. Parhon” National Institute of Endocrinology, Bucharest, Romania. They were evaluated based on the pathological report, imagistic scan, and neuroendocrine markers.

Results: Nine patients (female/male ratio: 5/4) with G2 NET were included (mean age at diagnosis 54.11 years). Surgery was performed in 66.66% of cases. 44.44% of tumors had unknown origin. 22.22% of patients had negative immunostain for chromogranin A. Synaptophysin was positive in all cases. Neuronal specific enolase (NSE) was performed in 44.44% of cases and it was positive in all these situations. 88.88% of patients had high neuroendocrine markers. Multiple tumors were found in two cases (follicular thyroid adenoma, and a carcinoma of the port vein, respective bilaterally pheochromocytomas). The youngest patient (39-year-old) had atypical onset with bilateral adrenal tumors (positive for CHROMO, EMA, CK-19, CK-20, negative for SOMATO, CK-7, S-100, glucagon, CD57, and a Ki-67 of 15%). Death was registered in two cases, both with bone metastases.

Discussion: Some poor prognosis factors may be taken into account as lack of CHROMO immunostain, young age at diagnosis, genetic background, and lack of therapy options as surgery. Larger databases will provide more information. Conclusions: It is possible that the G2 NET group of tumors actually includes some different subtypes or in fact, a late diagnosis of the tumor might be associated with a poor diagnosis.

Keywords: well-differentiated carcinoma, neuroendocrine tumor, chromogranin A, synaptophysin, Ki-67.

Introduction

The neuroendocrine tumors (NET) became an interesting field of science during the last years but many data are still a matter of debate. The tumors have an increasing frequency because of on one hand the relative aspects as more powerful detection methods, but on the other hand because of absolute aspects as real increased frequency related to genetic or toxic causes (more or better described up to this moment). The classical terms as “cancer” or “carcinoid tumors” are no longer adequate in NET description or terminology [1]. Based on NET classification (2010 WHO Classification of Tumours of the Digestive System) using the tumor grading, the G2 NET (well-differentiated carcinoma) have a medium aggressive profile between G1 NET (well-differentiated neuroendocrine tumors) and G3 NET (poor differentiated neuroendocrine carcinoma) [2]. The mitotic count in G2 NET is situated between 2 and 20 (at 10 High Power Field with at least 40 fields at 40× magnification, considered at highest mitotic density), and a Ki-67 index between 3% and 20% [2]. This classification is very useful in prognosis evaluation but the concept is continuously improved based on new databases and studies. The latest observations are related to the fact that a part of G2 NET actually embraces a very aggressive profile, having rather a G3 NET behavior, thus chemotherapy might become the first option therapy and re-biopsy might be useful to confirm the change of tumor characteristics in these situations. The metastases with a higher Ki-67 value are frequently seen in different cancers including G3 NET, but there also cases reported in G2 NET [3].

Aim

We analyzed a series of G2 NET cases and observed some potential aggressive features. The central issue was related to the fact that some G2 NET may associate metastases early at diagnosis or may associate a short period of time of survival.

Materials and Methods

We included patients diagnosed with G2 NET based on pathological and immunochemistry reports after...
surgery of the originating tumor or hepatic, respective lymph nodes biopsy. The major aspects were the mitotic count (that was between 2 and 20, considered at highest mitotic density) and the Ki-67 value (that was appreciated between 3% and 20%). The medullar thyroid cancer cases (regardless they were associated with carcinoid syndrome) were not included. This is an observational retrospective study in patients evaluated in “Constantin I. Parhon” National Institute of Endocrinology, Bucharest, Romania, between January 2008 and January 2013. The patients were further evaluated by imagistic scan as computed tomography, the neuroendocrine markers as serum serotonin, serum chromogranin A, and urinary 5-hydroxy-indol acetic acid. In selected cases, Whole Body Bone Scintigraphy was performed in order to obtain information related to the bone metastasis presence. The informed consent of each patient was obtained. We included the patients who were confirmed as G2 NET, regardless the follow-up: if they remained G2 NET or become more aggressive, embracing a G3 NET phenotype. The therapy with somatostatin analogues as Octreotide or Lanreotide or chemotherapy or interferon was not an including criteria but most of the patients were treated with associated therapy, based on pathological and clinical diagnosis. The immunohistochemistry included also tests for SYN or NSE, somatostatin, somatostatin receptor (in selected series) or specific antibodies for different tissue types, considering the site of the first lesion.

Results

Nine cases (four men and five women) of G2 NET patients were analyzed. Mean age at diagnosis of NET was 54.11 years (SD 16.14 years, ranges between 39 and 87 years).

The pathological report suggested that all the patients had the criteria for G2 NET) [2]. Lymph nodes or hepatic biopsy was performed in one third of cases where no surgery (neither radical nor debulking surgery) was performed. Our observations did not point a more aggressive evolution in cases with no primary surgery. Related to the NET origin, we had 44.44% of cases with unknown origin, 22.22% were originating from pancreas, respective duodenum and 33.34% from rectum. The immunohistochemistry pointed various aspects, as following: 22.22% of patients had negative reaction for chromogranin A (one with a very rapid evolution). Synaptophysin was positive in 100% of cases. Somatostatin was not performed in all cases. Somatostatin receptor status was performed in only one case and it was negative. Neuron specific enolase (NSE) was performed in 44.44% of cases and it was positive in all cases. Vimentin was positive in 22.22% of cases.

88.88% of patients had serum and urinary neuroendocrine markers above the normal limit but true carcinoid syndrome was found only in 44.44% of all cases and this was associated with a more advanced disease.

A second tumor with apparently different origin was found in two cases: one female with pancreatic NET had a follicular thyroid adenoma and a carcinoma of the port vein wall was diagnosed while she had stable NET disease for more than four years from diagnosis. Her immunohistochemistry profile was a Ki-67 of 10%, positive CHROMO, SYNAPTO, NSE, CK-19, CK-7, vimentin. One male with type 1 neurofibromatosis associated bilaterally adrenal tumors that were probably pheochromocytomas) [4].

A particular type of evolution was registered in two cases: one female of 61-year-old with unknown origin of the neuroendocrine tumor and no surgery, who had cervical vertebra metastases while she was treated for osteoporosis (the immunohistochemistry report showed: a Ki-67 of 10%, negative CHROMO, as well as MUC1 and 2, CD117, CEA, CK-7, and positive NSE, CK-8, VEGF, VEGFR), and another patient with bilaterally adrenal tumors as the first sign of the neuroendocrine disease (the antibodies stain pointed positive reaction for CHROMO, EMA, CK-19, CK-20, negative for SOMATO, CK-7, S-100, glucagon, CD57, and a Ki-67 of 15%) (Figure 1). This last patient was also the youngest as age at diagnosis; based on our observations he had stable disease for more than four year under medical therapy. On the other hand, the oldest patient included in the study was first diagnosed with disseminated disease at age of 87 years. He had a Ki-67 of 10%, positive reaction for CHROMO, LEU7, and negative for CK-20, CK-7, CDX2.

Two male patients died within one year from diagnosis. One of these two cases was a type 1 neurofibromatosis associated somatostatinoma in a male patient. This case was previously reported [4]. Generally, the hereditary neuroendocrine tumors associate a poor prognosis, and also in this particular case we mention the highly aggressive features of somatostatin staining neuroendocrine tumors [5]. The other case was a 64-year-old male patient with G2 NET and unknown primary site. The immunohistochemistry was based on hepatic biopsy in this well-differentiated neuroendocrine carcinoma (Figure 2). The CHROMO was positive (Figure 3). Also, positive stain was for SYNAPTO (Figure 4). The Ki-57 was of 15% (Figure 5). Also, positive stain was for TTF1, CK-19, CDX2, CEA, and negative for CA125, MUC5.

The bone metastases were found in three patients and also at the death moment all the patients had bone metastases. We did not perform bone biopsy in neither of these cases.

Discussion

One major issue is to define in specific terms “the poor prognosis”. The rapid progressive disease to general metastases or rapid fatal outcome represents such aspect. Also, an interesting issue is the changing of the features from the primary tumor into more aggressive profile as found in metastases (the dedifferentiation process) [3]. A retrospective analyze in cases with rapid evolution shows that lack of surgery for primary tumor is a poor prognosis factor since this type of treatment is the only one with curative potential [6].

Related to the pathological report the lack of chromogranin stain might be a poor prognosis factor. This is often found in G3 NET [7]. Also, the intense somatostatin stain as seen in somatostatinomas might be correlated to a rapid evolution [4].

The genetic background as type 1 neurofibromatosis or multiple endocrine neoplasia are related to more aggressive tumors and a younger age at diagnosis [5].
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Figure 1 – Abdominal computed tomography: bilateral adrenal tumors (G2 NET).

Figure 2 – Pathological exam: hepatic metastasis in G2 NET (HE staining, ×100).

Figure 3 – Immunohistochemistry: hepatic metastasis, positive CHROMO in G2 NET (×200).

Figure 4 – Immunohistochemistry: hepatic metastasis, positive SYNAPTO in G2 NET (×200).

Figure 5 – Immunohistochemistry: hepatic metastasis, Ki-67 of 15% in G2 NET (×200).

The bone metastases were present at death moment, this probably is a marker of advanced disease and not necessary a poor prognosis factor. This observation was sustained in a larger series of cases, not necessary only G2 NET [8].

Many observations from literature sustain different prognosis factors related to the site of the neuroendocrine tumors. For example, in jejunal and ileal carcinoids the death is related to distant metastases at diagnosis, the carcinoid syndrome, the presence of multiple tumors or female sex [9]. Our series of cases was too small to point such differences.

Despite the various immunohistochemistry markers, a sensitive and specific marker for predicting the tumor poor outcome does not exist. The chromogranin A is the most sensitive for sustaining the diagnosis, the synaptophysin is expressed independently of the other markers especially in poorly differentiated NET, while the proliferation index Ki-67 is the major tool in prognosis [10].

Our series included G2 NET having the duodenum as primary. Generally, this type of tumors varies from benign behavior to extremely aggressive with increased malignancy features. Sometimes the carcinoid syndrome is found, and some of them have the profile of a pancreatic NET [11]. The duodenum is included in large category called “foregut” NET, as well as stomach, and pancreas [12]. Except for somatostatinoma, the duodenum cases from our study had a medium aggressive profile. The NET with primary site the pancreas is classified based on histopathological report, and also based on functioning or non-functioning profile [13]. This last aspect is mostly related not to the pathological report but to the clinical aspect since there are tumors displaying immunohistochemistry positive reaction on some markers but negative biochemistry profile, as in our study [14]. The functional aspect in pancreatic NET is not tidily related to the prognosis [15]. Since no define correlation is established between pathological exam, as well as hormone profile in order to appreciate the tumor evolution, all the three aspect are useful for follow-up [16]. Neither could we
establish such connections to set up the aggressive features in G2. Another useful tool, which needs to be attached to the pathological and endocrine evaluation, is the imaging studies [17–19]. All the patients from our series had at least one such evaluation. These aspects are important in patients with distant metastases and in order to diagnose a second tumor. As we mentioned before, we had patients with two different tumors diagnosed while managing the NET. Thus, an interdisciplinary approach is needed, including pathological, surgical, medical, endocrine, oncologic, radiological methods [20].

Conclusions

The G2 neuroendocrine tumors associate a variant phenotype and future observations will decide if they may be considered as a totality of different subgroups. Several prognosis factors are described in neuroendocrine tumors, including the well-differentiated neuroendocrine carcinomas but sometimes a poor prognosis is in fact a late diagnosis of the disease.

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Corresponding author
Mara Carșote, MD, "Constantin I. Parhon" National Institute of Endocrinology, 34–36 Aviatorilor Avenue, 011863 Bucharest, Romania; Phone +40744–851 934, e-mail: carsote_m@hotmail.com

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