Original Article

Neuroendocrine Neoplasms in Rare Locations: Clinicopathological Features and Review of the Literature

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Abstract

Introduction: Neuroendocrine tumors (NETs) occur more often in lungs, gastrointestinal tract, or pancreas. Data about terminology and grading of NETs in rare locations are scarce and variable, and they have been reported mainly as case reports. **Materials and Methods:** We here describe our experience with NETs in unusual locations. We have reviewed all NETs diagnosed in our institution and summarized their clinicopathological features. We have also reviewed the literature and discussed the main characteristics of NETs in each site. **Results:** Two hundred and forty-three primary NETs were diagnosed. About 55.2% of patients were men and the mean age was 62 years. About 90.7% of NETs were located in lungs, gastrointestinal tract, or pancreas, and 50.8% of them were low-grade tumors. We identified 13 NETs in rare locations: breast, ovary, endometrium, vulva, uterine cervix, extrahepatic biliary tract, kidney, sinonasal tract, and thymus. Three additional tumors were diagnosed by the senior author in other institution. Patients were asymptomatic or presented with nonspecific symptoms. All NETs were treated with surgery and 31% of patients received adjuvant therapy. There were 10 Grade 3 (62.5%), 2 Grade 2 (12.5%), and 4 Grade 1 (25%) tumors. Mean follow-up was 72 months. About 60% of G3 tumors recurred or progressed. G2 tumors were located in breast, and both patients are stable. About 50% of G1 tumors recurred or progressed (both renal NETs). **Conclusions:** NETs in rare locations are heterogeneous, and their behavior does not seem to correlate absolutely with tumor grade. More studies are needed to clarify the role of proliferation rate in these tumors.

Keywords: Classification, grade, location, neuroendocrine, rare

Introduction

Neuroendocrine tumors (NETs) are heterogeneous tumors arising from neuroendocrine cells. They were first known as carcinoid tumors, but this term has been replaced by the term "NET" in the last World Health Organization (WHO) and European NET Society (ENETS) classifications of tumors of digestive system.[1] However, NETs in some locations are still classified as typical or atypical carcinoids. NETs are uncommon, with an incidence ranging from 1 to 5/100,000 patients.[2] They occur more frequently in lungs, rectum, small bowel, stomach, and pancreas.[3] They can also be identified in colon, cecum, or appendix, and they are very rare in other locations. In a study of 350,000 patients by Yao *et al*. in 2008, only 15% of all NETs were located in sites other than gastrointestinal tract, pancreas, or lungs.[2]

NETs show different features between locations. Yao *et al*. reported a statistically significant association between primary NET site and sex, race, age, and tumor stage. About 64% of patients with pancreatic tumors showed distant metastasis at diagnosis, as compared with 44%, 33%, 31%, or 30% of the most aggressive nonpancreatic NETs (cecum, colon, thymus, and small bowel NETs, respectively).[2] In fact, tumor location (pancreatic vs. nonpancreatic) is a decisive factor for patient management.[4]

Historically, there has been controversy about the classification of these tumors, and more than 20 different classifications have been proposed, depending on cell of origin, tumor location, histological grade, embryological origin, or secretory activity. The last WHO-ENETs classification was intended

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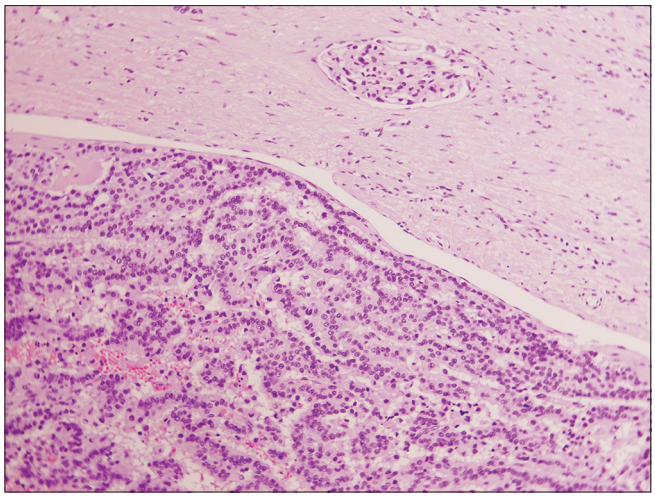

Figure 1: Neuroendocrine tumor of the kidney (G1). H and E, ×200

to standardize NET categorization and provide prognostic information.[5] This system is based on histomorphology and proliferative activity (number of mitoses and Ki-67 index) and divides NETs into three grades. Grade 1 and 2 tumors are considered low-grade tumors. Grade 3 NETs can be divided into small cell and large cell carcinoma. This grading system is applied in gastroenteropancreatic and biliary tract NETs.[6] Its use has not been validated in NETs in rare locations, where data about terminology and grading of NETs are scarce and variable. Based on the last WHO classifications of tumors, biliary tract and gallbladder NETs are classified and named just as gastroenteropancreatic tumors (G1 neuroendocrine – NE tumor, G2 NE tumor, and G3 NE carcinoma), and thymic NETs are classified as their pulmonary counterparts (typical carcinoid, atypical carcinoid, and NE carcinoma).[7] Breast, kidney, and bladder tumors are divided into well-differentiated and poorly differentiated NE neoplasms. Ovarian neuroendocrine neoplasms, low-intermediate grade NETs of sinonasal tract or vulva, and intermediate grade NETs of endometrium are not included in the last WHO classifications. Given the variety of existing terms, we have used the term "NET" for describing all tumors with pure neuroendocrine differentiation. Thus, it encompasses both NETs or carcinoids and neuroendocrine carcinomas.

Our objective is to characterize the clinical, histological, and prognostic features of NETs of rare locations and to review the published criteria for their diagnosis and classification.

Materials and Methods

We have reviewed all NETs diagnosed in our institution (Hospital Clínico San Carlos, Madrid, Spain) between 1999 and 2016. A total of 248 NETs were diagnosed in this period. Of these, we excluded NETs located in lung, large bowel, small bowel, stomach, or pancreas. We have also excluded small cell carcinomas due to their clinical peculiarities and their similarity to their pulmonary counterparts.

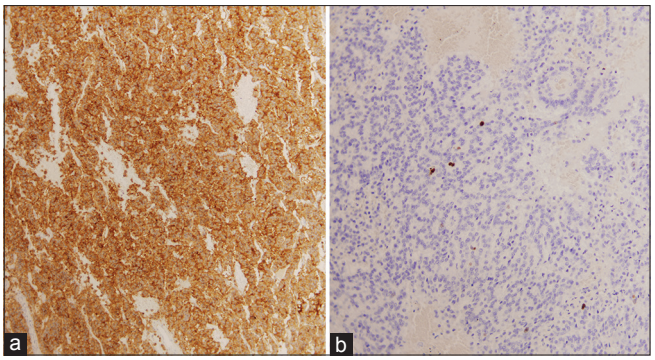

Figure 2: (a) Strong and diffuse expression of synaptophysin. Neuroendocrine tumor of the kidney (G1). Synaptophysin, ×100. (b) Ki-67 of <2%. Neuroendocrine tumor of the kidney (G1). Ki-67, ×200

Main clinicopathological data (sex, age, tumor location, and tumor grade) of gastroenteropancreatic and pulmonary NETs were collected.

Regarding NETs in rare locations, clinical features (sex, age, symptoms, tumor location, tumor size, treatment, prognosis, and duration of follow-up) and histological features (atypia, architecture, mitosis, Ki-67 index, immunohistochemical analysis, and tumor grade) were assessed. All cases were independently reviewed by two pathologists and disagreements were solved by consensus.

Grading of NETs was done according to the last WHO classification of gastroenteropancreatic NETs as follows: Grade 1 (G1) tumors showed <2 mitoses/10 high power fields (hpf) and/or Ki-67 index of <3%, Grade 2 (G2) tumors showed 2–20 mitoses/10 hpf and/or a Ki-67 index of 3%–20%, and Grade 3 (G3) tumors showed more than 20 mitoses/10 hpf and/or a Ki-67 index of more than 20%.

Finally, a literature review was made to summarize clinical and histological features of NETs in each location and to compare previous studies with our results. In addition, the last WHO classifications of tumors were reviewed, and NET classifications were presented in a summary table, which can be useful in daily practice.

Results

A total of 248 NETs were identified. There were 137 (55.2%) men and 111 women (44.8%). Patient age ranged from 11 to 90 years (mean: 62, standard deviation: 15.4), and 225 tumors (90.7%) were located in the gastrointestinal tract, pancreas, or lungs. About 50.8% of NETs were low-grade tumors and 49.2% were high-grade tumors (43% of them were small cell carcinomas). Main features of NETs in each location are summarized in Table 1.

Twenty-three tumors occurred in rare sites (9.3%). Ten of them were small cell carcinomas, and they were therefore excluded from our study. The 13 remaining NETs were located in breast (2 cases), ovary (2), endometrium (1), vulva (1), uterine cervix (1), extrahepatic biliary tract (1), kidney (2),

Table 1: Main features of all neuroendocrine tumors diagnosed in our institution

Location	Percentage of cases	Sex	Age Minimum-maximum, mean (SD)	Grade HG/LG
Lung	30.2	64% male	34-86, 64.7 (11.07)	89.3% HG
Pancreas	15.3	52.6% male	29-84, 61.8 (13.52)	81.6% LG
Stomach	12.9	59.4% female	44-81, 66.3 (9.65)	81.3% LG
Colon	10.9	66,7% male	20-84, 63 (15.1)	59.3% HG
Rectum	8.1	60% female	14-88, 57.5 (19.71)	75% LG
Small bowel	8.1	60% male	30-90, 63.2 (15.11)	85% LG
Appendix	5.2	53.8% male	29-84, 61.8 (25.37)	100% LG
Bladder	2.4	83.3% male	72-86, 79 (5.65)	100% HG (small cell carcinoma)
Other locations	6.8	-	-	-

SD: Standard deviation, HG: High grade, LG: Low grade

sinonasal tract (2), and thymus (1). All NETs were treated with surgery and 31% of patients received adjuvant therapy. Median follow-up was 36 months (25th percentile: 29.2, 75th percentile: 118.7). Clinical data are summarized in Table 2. Histopathological data are summarized in Table 3.

Breast NETs (cases 1 and 2) were incidentally discovered in 60–70-year-old patients. They measured about 1 cm. Histologically, they were tumors with no or mild atypia and cells were arranged in trabeculae, acini, nests, or rosettes. No mitoses were identified and Ki-67 index was 5% or lower. They were classified as Grade 2 tumors, and both patients remain stable. Ovarian tumors (cases 3 and 4) occurred in the sixth decade of life, and they were high-grade tumors. One of them showed a large size (15 cm) and tumor progression. The other ovarian NET measured 3 cm, and the patient is stable and being followed up. Endometrial and vulvar NETs (cases 5 and 6) appeared in patients aged 81 and 54 years, with sizes of 4.5 and 2 cm, and they were classified as Grade 3 tumors. Cervical TNE (case 7) was identified in a 48-year-old patient with vaginal pain. It showed severe atypia, necrosis, abundant mitosis, and high Ki-67 index, and the patient died 11 months after diagnosis.

Extrahepatic biliary tract (EBT) NETs (cases 8, 9, and 10) occurred in patients aged 50–70 years. Patients presented with obstructive jaundice or abdominal pain. Tumor size was approximately 3 cm, and they were treated with surgery alone. Two EBT NETs were Grade 3 tumors, and the other EBT NET was a Grade 1 tumor. The patients with Grade 3 tumors died 9 and 24 months after diagnosis and the patient with Grade 1 NET remains stable. Gallbladder NET was identified in a 79-year-old woman with abdominal pain. It showed severe atypia, solid growth, and a high Ki-67 index. However, the patient is free of disease more than 2 years after diagnosis.

Renal NETs (cases 12 and 13) showed different clinical features (male and female patients, 26 and 69 years, 3.8 and 15 cm). No atypia or solid growth was seen, and proliferative activity was low [Figures 1 and 2]. However, both tumors progressed.

Two NETs were located in the head and neck region (sinonasal tract) (cases 14 and 15). These tumors appeared in 60-year-old patients, and they were Grade 3 NETs. One of them showed signet ring cell morphology. One patient is stable, and the other tumor progressed and the patient died 3 years after diagnosis.

Thymic NET (case 16) occurred in a 69-year-old man, and it was a Grade 3 tumor with severe atypia and a high Ki-67 index. The patient was treated by surgery and radiotherapy, but the tumor recurred locally 96 months after diagnosis. No more recurrences have been noted.

When dividing NETs in rare locations into three groups depending on their grade, we observed 10 Grade 3 (62.5%), 2 Grade 2 (12.5%), and 4 Grade 1 (25%) tumors. About 40% of patients with G3 tumors are stable and being followed up (endometrium, vulva, sinonasal tract, gallbladder). In the remaining patients with G3 tumors, the disease recurred, progressed, or the patient died due to tumor. The two G2 tumors were located in breast and both patients are stable and being followed up. Fifty percent of G1 tumors progressed or recurred (kidney), and the remaining two patients with G1 tumors are stable and being followed up (ovary, extrahepatic biliary tract). Classification of NETs in each location according to the last WHO classifications is summarized in Table 4.

In our institution, NETs are treated depending on their histology, Ki-67 index, octreoscan uptake, and patient symptoms. Treatment options for low-grade tumors are somatostatin analogs, mTOR, or tyrosine kinase inhibitors (everolimus and sunitinib). High-grade tumors are treated with carboplatin and etoposide.

Discussion

As shown in our series, NETs are rare and heterogeneous tumors with great variations in their biology, behavior, and treatment.[5] They are located more frequently in the lungs, gastrointestinal tract, and pancreas. Microscopically, well-differentiated NETs (also known as low or intermediate grade, typical or atypical carcinoid tumors, or islet cell tumors) show neuroendocrine morphology: organoid or trabecular patterns, rosette formation, uniform cells with finely granular nuclear chromatin and inconspicuous nucleoli, moderate cytoplasm, and low or moderate mitotic rates. Small cell (high grade) tumors are composed of small tumor cells with finely granular chromatin

Table 2: Clinical data of neuroendocrine tumors in rare locations

Case	Sex	Age	Symptoms	Location	Size (cm)	Treatment	Patient status Follow-up (months)
1	Female	76	Incidental finding	Breast	1.5	Surgery	Stable 186
2	Female	76	Incidental finding	Breast	0.8	Surgery	Stable 36
3	Female	51	Incidental finding after hysterectomy for endometrial hyperplasia	Ovary	3	Surgery	Stable 170
4	Female	46	Abdominal distention, metrorrhagia	Ovary	15	Surgery + ChT	Tumor progression (distant metastases: ChT) Loss of follow-up 30
5	Female	81	Metrorrhagia	Endometrium	4.5	Surgery	Stable 120
6	Female	54	Palpable mass	Vulva	2	Surgery	Stable 196
7	Female	48	Vaginal pain	Cervix	4	Surgery + ChT-RT	Tumor progression Death due to tumor 11
8	Female	72	Abdominal pain Choluria Acholia Pruritus	Extrahepatic biliary tract	3	Surgery	Tumor progression (distant and lymph node metastases) Death due to tumor 9
9	Male	51	Obstructive jaundice	Extrahepatic biliary tract	3	Surgery	Stable 60
10	Male	73	Obstructive jaundice	Extrahepatic biliary tract/ ampulla of Vater	2.5	Surgery	Tumor progression (distant metastases: ChT) Death due to tumor 24
11	Female	79	Abdominal pain	Gallbladder	12	Surgery	Stable 29
12	Female	69	NS	Kidney	3.8	Surgery	Tumor recurrence after 36 months: surgery 35
13	Male	26	Back pain	Kidney	15	Surgery	Tumor progression (distant metastases: ChT) 36
14	Female	59	Nasal respiratory failure Frontal headache Tearing of left eye	Sinonasal (left nostril/maxillary sinus)	5	Surgery + ChT-RT	Stable 63
15	Male	59	Cold-like symptoms	Sinonasal (right nostril/ethmoid, sphenoidal and frontal sinus)	6.3	Surgery + RT	Tumor progression (distant metastases: surgery + ChT) Death due to tumor 31
16	Male	69	Heart palpitations	Thymus	6.5	Surgery + ChT	Tumor recurrence after 96 months: surgery 115

NS: Not specified, ChT: Chemotherapy, RT: Radiotherapy

and absent nucleoli in a diffuse growth pattern. Apoptotic and mitotic rates are high. Large cell (high grade) tumors can show neuroendocrine differentiation, but cells are large with a high mitotic rate. Necrosis is frequent.[7] Immunohistochemical studies show synaptophysin, chromogranin A, and/or CD56 positivity. Ki-67 index is essential to assess tumor grade. Regarding tumor management, resectable NETs are treated by surgery. First-line therapy for unresectable and poorly differentiated tumors consists of platinum with etoposide. Unresectable well-differentiated tumors with asymptomatic or stable disease can be followed up or somatostatin analogs can be administered. Patients with symptoms or tumor progression are usually treated with systemic therapies.[4]

The association between histological grade (WHO) and prognosis has been validated by most studies, but NETs in rare locations do not seem to correlate absolutely with

Table 3: Histopathological data of neuroendocrine tumors in rare locations

Case	Atypia Architecture	Mitoses	Ki-67 index (%)	IHC	Grade
1	No or mild atypia Nests/rosettes	1/10	5	Chromogranine^{-}, synaptophysin^{+} Estrogen receptors^{+} (8/8), progesterone receptors^{+} (8/8) S100^{+}	G2
2	No or mild atypia Nests/rosettes	0/10	5	Chromogranine^{+}, synaptophysin^{+} Estrogen receptors^{+}, progesterone receptors^{+}	G2
3	No or mild atypia Trabeculae/acini	0/10	1	Chromogranine^{-}, Enolase^{+}, synaptophysin^{+}	G1
4	Severe atypia Trabeculae/rosettes	4/10	27	Chromogranine+ Estrogen receptors^{+}, progesterone receptors^{+} P53^{-}	G3
5	No or mild atypia Trabeculae/acini	14/10	25	Chromogranine^{-}, enolase^{+}, synaptophysin^{+} Estrogen receptors^{-}, progesterone receptors^{-} Focal weak CD10	G3
6	Moderate atypia Solid	3/10	35	Chromogranine^{+}, synaptophysin^{+} Estrogen receptors^{-}, progesterone receptors^{-} S100^{+}, somatostatin^{+}	G3
7	Severe atypia Solid/necrosis	12/10	60	Chromogranine^{+}, Synaptophysin^{+} Estrogen receptors^{-}, progesterone receptors^{-} P16^{+}, S100^{-}	G3
8	Moderate atypia Cords and acini	17/10	80	Chromogranine^{+}, enolase^{+}	G3
9	No or mild atypia Trabeculae/rosettes	2/10	3	Chromogranine^{+}, synaptophysin^{+}, enolase^{+}	G1
10	Severe atypia Solid	50/10	30	Chromogranine^{+}, synaptophysin^{+}, enolase^{+} Gastrin^{+}	G3
11	Severe atypia Solid	18/10	75	Chromogranine^{+}, enolase^{+}	G3
12	Primary				
	Mild atypia Trabeculae/acini	5/10	2	Chromogranine^{+}, synaptophysin^{+}, focal enolase Somatostatin^{+}	G1 PRI
	Recurrence				
	Moderate atypia Solid	6/10	25	Chromogranine^{+}, synaptophysin^{+}	G3 REC
13	Moderate atypia Trabeculae	0/10	1-2	Chromogranine^{+}, synaptophysin^{+}	G1
14	Moderate atypia Trabeculae/rosettes	100/10	90	Chromogranine^{+}, synaptophysin^{+}, enolase^{+}	G3
15	Goblet cells	-	35	Chromogranine^{+}, synaptophysin^{+}, CD56^{+} S100^{-}	G3
16	Severe atypia Solid	10/10	55	Chromogranine^{+}, synaptophysin^{+}, CD56^{-}	G3

IHQ: Immunohistochemistry, PRI: Primary tumor, REC: Recurrence

tumor grade. In these cases, prognosis could be influenced by location-related factors rather than proliferative activity.

The incidence of primary NET of breast ranges between 1% and 5%, and some authors have reported neuroendocrine differentiation in 10%–20% of all breast tumors.[8,9] Breast NETs are divided into well-differentiated, poorly differentiated, and invasive carcinoma with neuroendocrine differentiation. They are usually estrogen and progesterone receptor positive and HER2 negative, as shown in our series.[10] Studies about their behavior have shown opposite results, and their prognosis is still debated. Proliferative index and lymph node status seem to be the most important prognostic factors.[10] Our two cases were G2 tumors, and the patients did not show recurrences or metastases (cases 4 and 8).

In respect of female genital tract tumors, NETs of the uterine cervix constitute <2% of all cervical tumors.[11,12] Previous studies have shown an association with HPV 16 and 18, and it is estimated that HPV can be detected in 50% of them.[12] Cervical NETs are supposed to be derived from metaplastic and hyperplastic cervical neuroendocrine cells.[11] Most of them are

Table 4: Neuroendocrine tumors: classification and grading according to the last World Health Organization classifications of tumors

Location	Low grade (Grade 1)	Intermediate grade (Grade 2)	High grade (Grade 3)	
GEP	NET Grade 1	NET Grade 2	SCC	LCC
	LGN morphology	LGN morphology	SC morphology	LC morphology
	PR: <2 mit/10 hpf	PR: 2-20 mit/10 hpf	PR: >20 mit/10 hpf	PR: >20 mit/10 hpf
	Ki-67≤2%	Ki-67 3%-20%	Ki-67 >20%	Ki-67 >20%
Lung	Typical carcinoid	Atypical carcinoid	SCC	LCC
	LGN morphology	LGN morphology + necrosis	SC morphology	LC morphology
		PR: 2-10 mit/^{2} mm^2	PR: >10 mit/^{2} mm^2	PR: >10 mit/^{2} mm^2
Cervix	Low-grade NET (carcinoid)	Low-grade NET (atypical carcinoid)	SCC	LCC
	LGN morphology	LGN morphology + greater atypia and mitoses. Possible necrosis	SC morphology	LC morphology
	PR: No evidence	PR: No evidence	PR: No evidence	PR: No evidence
Endometrium	Low-grade NET (carcinoid)	-	SCC	LCC
	LGN morphology	-	SC morphology	LC morphology
	PR: NS		PR: NS	PR: NS
Ovary	-	-	-	-
	-	-	-	-
Vulva	-	-	SCC	LCC
	-	-	SC morphology	LC morphology
			PR: NS	PR: NS
Breast*	Well-differentiated NET		Poorly differentiated NEC	
	Nests/trabeculae of spindle or plasmacytoid cells, clear cells. Delicate fibrovascular stroma		SC morphology	
	PR: NS		PR: NS	
Kidney	Well-differentiated NET		SCC	LCC
	LGN morphology		SC morphology	LC morphology
	PR: <4 mit/10 hpf		PR: NS	PR: NS
Bladder	Well-differentiated NET		SCC	LCC
	LGN morphology		SC morphology	LC morphology
	PR: NS		PR: NS	PR: NS
Ampulla	NET Grade 1	NET Grade 2	SCC	LCC
	LGN morphology	LGN morphology	SC morphology	LC morphology
	PR: <2 mit/10 hpf	PR: 2-20 mit/10 hpf	PR: >20 mit/10 hpf	PR: >20 mit/10 hpf
	Ki-67 ≤2%	Ki-67 3%-20%	Ki-67 >20%	Ki-67 >20%
Biliary tract gallbladder*	NET Grade 1	NET Grade 2	SCC	LCC
	LGN morphology	LGN morphology	SC morphology	LC morphology
	PR: <2 mit/10 hpf	PR: 2-20 mit/10 hpf	PR: >20 mit/10 hpf	PR: >20 mit/10 hpf
	Ki-67 ≤2%	Ki-67 3%-20%	Ki-67 >20%	Ki-67 >20%
Sinonasal tract	-	-	SCC	LCC
	-	-	SC morphology	LC morphology
			PR: NS	PR: NS
Thymus	Typical carcinoid	Atypical carcinoid	SCC	LCC
	LGN morphology	LGN morphology + atypia, necrosis, focal diffuse growth or desmoplasia	SC morphology	LC morphology
	PR: <2 mit/^{2} mm^2	PR: 2-10 mit/^{2} mm^2	PR: >10 mit/^{2} mm^2	PR: >10 mit/^{2} mm^2

*We have not included mixed NETs such MANEC of the biliary tract or carcinomas with neuroendocrine differentiation of the breast. NET: Neuroendocrine tumor, SCC: Small cell carcinoma, LCC: Large cell carcinoma, LGN morph: Low-grade NET morphology (well-differentiated NET), PR: Proliferation rate, NS: Not specified, MANEC: Mixed adenoneuroendocrine carcinoma, GEP: Gastroenteropancreatic

high-grade tumors, and they are usually mixed with other types of tumors.[13] Patients present with vaginal bleeding discharge or pelvic pain.[14] They are more aggressive than conventional squamous cell carcinoma, and stage at diagnosis and lymph node invasion are the most relevant prognostic factors.[15] The clinicopathological features of our case are in accordance with the previous literature since it was a G3 tumor and the patient died less than a year after diagnosis.

Neuroendocrine differentiation is uncommon in endometrial neoplasms. Most endometrial NETs are small cell carcinomas, and only 13 cases of large cell NET have been reported to date.[16] We have found only one endometrial intermediate-grade NET, which showed good prognosis.[17]

As for the ovary, most reported NETs are low grade, and their incidence ranges between 0.5 and 1.7% of all ovarian

tumors. They are usually observed in mature teratomas,[18] and carcinoid syndrome develops in one-third of patients. In our series, we report two ovarian NETs (cases 2 and 12). In these cases, proliferative activity seemed to be correlated with patient outcomes (the patient with a G1 tumor is stable and being followed up and the patient with a G3 neoplasm showed tumor progression).

Regarding EBT and gallbladder NETs, the largest studies have been published by Carter, Squillaci, Etawil, and Lee *et al*., which included a total of 513 patients.[19-22] NETs comprise approximately 0.5% and 0.01% of all tumors in EBT and gallbladder and 3% of gastrointestinal NETs.[20,23] Their pathogenesis is unknown, and there are only scarce enterochromaffin or Kulchitsky cells in the EBT. Some authors have suggested that EBT NETs could be originated from metaplastic endocrine cells or biliary duct cells and hepatocytes acquiring neuroendocrine features, probably under inflammatory conditions.[20,22,24] A female predominance has been described in both locations. Mean age ranges from 12 to 79 years (mean: 45 years).[25] They are usually small tumors, and patients present with nonspecific symptoms (jaundice, pain, pruritus, weakness, or lethargy).[23] There is no specific classification for EBT and gallbladder NETs, so gastrointestinal NETs classification is used. Most gallbladder NETs are poorly differentiated or anaplastic.[22] In respect to molecular features, previous studies have shown alterations of k-Ras gene, loss of expression of wild-type p16, and no mutations of p53.[26] EBT and gallbladder tend to show good prognosis even if they metastatize, with the exception of mixed type and high-grade tumors.[20] In our experience, EBT NETs behavior correlated well with tumor grade. However, gallbladder NET was a high-grade tumor which showed neither metastasis nor recurrences.

As for renal NETs, <100 NETs have been reported in the world literature.[27] Their rarity could be due to the fact that enterochromaffin cells are not identified in adult kidneys in normal conditions. These tumors could be derived from pancreatic tissue, neural crest, multipotent stem cells, urothelial metaplasia, or metastases from an unknown primary.[27,28] They tend to occur in association with congenital and acquired renal abnormalities, patients do not usually develop carcinoid syndrome, and around 30% of tumors are incidentally diagnosed.[29] They are solitary, unilateral, and slow-growing masses larger than 4 cm and advanced at diagnosis.[27] Stage at diagnosis, advanced patient age, and larger tumor size are supposed to be important prognostic factors. Histological features have not demonstrated a clear prognostic value. In fact, our two cases of NET of the kidney showed a low Ki-67 index and a well-differentiated morphology, but they both recurred or progressed.

There are approximately 700 cases of sinonasal NET reported in the literature.[30] Mean age is 53 years and tumors are usually advanced at diagnosis. Tumor type is a strong predictor of survival, and undifferentiated carcinomas show the worst prognosis. We have found two cases of sinonasal NETs. They were G3 tumors, but one patient is stable while the other died. Interestingly, the last patient showed a more locally advanced tumor at diagnosis.

Finally, thymic NETs constitute 2%–5% of all thymic tumors and usually show a poor prognosis.[31] Features such as surgical resection, Masaoka stage, or tumor size have been suggested to be prognostic factors.[32] Our case was a G3 NET which recurred locally. However, the patient is still alive more than 9 years after diagnosis.

Conclusions

NETs in rare locations are heterogeneous and their behavior does not seem to correlate absolutely with tumor grade. However, differences in grading and terminology make it difficult to compare between NETs in different locations. We think that a standardization of classification of NETs is necessary to reduce the confusion and allow a better clinical and pathological understanding of these tumors. More studies are needed to clarify the role of proliferation rate of NETs in rare locations.

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Conflicts of interest

There are no conflicts of interest.

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