REVIEW

A peculiar mimicker of gastro-entero-pancreatic neuroendocrine tumors: Malignant Gastrointestinal Neuroectodermal Tumor – literature review and one case report

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ABSTRACT

Malignant gastrointestinal neuroectodermal tumor (GNET) is a distinctive and relatively newly described neoplasm that is seldom encountered in routine clinical practice. It is characterized by a predominantly monomorphic population of polyhedral to epithelioid cells, exhibiting pale eosinophilic or clear cytoplasm, rounded nuclei with vesicular chromatin, and occasionally prominent eosinophilic nucleoli. These cells are arranged in a heterogeneous pattern, forming small nests, compact solid areas, and pseudo-papillary or pseudo-microcystic structures. Within the tumor, osteoclast-like giant cells may be a notable feature, although their presence is variable. This tumor consistently demonstrates positivity for S100, SOX10, and vimentin, while it is invariably negative for Melan-A, HMB45, desmin, CD117, and pan-cytokeratin. Additionally, it exhibits variable expression of the following immunohistochemical markers: synaptophysin, chromogranin, CD56, neuron-specific enolase (NSE), and neurofilament protein (NFP). A specific mutation in the Ewing's sarcoma breakpoint region 1 (EWSR1) gene has been described for GNET, characterized by EWSR1-CREB1 and EWSR1-ATF1 fusions. This article discusses the clinical, pathological, immunophenotypic, and genetic features of one clinical case of GNET, followed by a literature review of 127 cases published in the PubMed database, for which full-length articles were accessible. According to this review, approximately 10% of GNETs have been initially misdiagnosed, with about 6% being misclassified as neuroendocrine tumors or neuroendocrine carcinomas.

KEYWORDS: malignant gastrointestinal neuroectodermal tumor (GNET); clear cell sarcoma-like tumor of the gastrointestinal tract (CCSTGT); differential diagnostic of neuroendocrine tumor; NET mimicker; EWSR1 fusions; GIST differential diagnostic; neural crest origin; osteoclast-like giant cells

1. INTRODUCTION

Insights gleaned from historical medical records indicate that the systematic observation of recurring features may facilitate the identification of distinctive new patterns or even previously unrecognized entities. In 2003, Zambrano et al. adopted this approach by compiling six clinical cases of aggressive tumors initially thought to be gastrointestinal stromal tumors (GIST), despite exhibiting differing morphology and immunophenotype from GIST. Following their description, Zambrano et al. proposed the classification of these cases into a new category, termed clear cell sarcoma-like tumor of the gastrointestinal tract (CCSTGT) [1]. A significant milestone in the understanding of this tumor was the study conducted by Stockman et al. in 2012, which reconfirmed and identified additional specific features that underscore its uniqueness, suggesting that it should be referred to as malignant gastrointestinal neuroectodermal tumor (GNET) rather than CCSTGT [2]. Ultimately, in 2019, the fifth edition of the WHO Classification of Tumors of the Digestive System recognized this tumor as a distinct entity, characterized by specific morphological, immunohistochemical, and genetic features, as well as a distinctive aggressive behavior that will be further discussed below [3]. Both terminologies, GNET and CCSTGT, are accepted [3].

Malignant gastrointestinal neuroectodermal tumor (GNET) represents an exceedingly rare entity within clinical practice,

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initially considered to be a manifestation of clear cell sarcoma of soft tissue with gastrointestinal localization, but has subsequently been confirmed as a distinct tumor type [2,4,5]. Macroscopically, this tumor exhibits considerable variation in size and presents a solid, tan-greyish appearance with well-defined contours; it may occasionally be lobulated and has a firm consistency. Instances of focal hemorrhage or necrosis are infrequent, and cystic degeneration is rare. GNET can develop in any segment of the gastrointestinal tract, primarily at the interface between the submucosa and muscularis propria. This location often leads to ulceration of the overlying mucosa, while less frequently, it may manifest as fungating masses that extend into the lumen of the bowel wall [1,2,5,6]. Microscopically, the tumor cells demonstrate a polyhedral to epithelioid morphology, characterized by abundant pale eosinophilic or clear cytoplasm, alongside round to oval nuclei exhibiting vesicular chromatin with peripheral margination. The cells are arranged in various growth patterns, including small nests, sheets, cords, and, to a lesser extent, pseudo-alveolar, pseudo-papillary, fascicular, and reticular configurations [2,5,6]. Although not universally observed, the presence of osteoclast-like giant cells may provide a valuable diagnostic indicator, as these cells exhibit positivity for CD68 [2]. Immunohistochemical (IHC) analyses consistently demonstrate that this tumor is positive for S100, SOX10, and vimentin, while exhibiting uniform negativity for Melan-A, HMB45, Desmin, CD117, and pan-cytokeratin. Additionally, the tumor displays variable expression of several IHC markers, including synaptophysin, chromogranin, CD56, neuron-specific enolase (NSE), and neurofilament protein (NFP) [2,5,6]. Furthermore, a limited series of cases examined via electron microscopy revealed that the tumor cells are interconnected by primitive, simple cell junctions, possess a moderate cytoplasmic volume containing secretory aggregates and occasional synapse-like structures, but lack evidence of melanosomes or melanosome-like structures; however, pre-melanosomes have been documented in rare instances [2,4,7].

Multiple studies have investigated the genetic landscape of these tumors, revealing that nearly all cases exhibit mutations in the Ewing's sarcoma breakpoint region 1 (EWSR1) gene, including EWSR1-ATF1 and EWSR1-CREB1 fusions [2,4,8]. Kandler et al. conducted next-generation sequencing (NGS) on 20 cases of GNET, confirming the presence of the aforementioned EWSR1 gene fusions while identifying additional, less frequently encountered alterations. Their findings suggest that, although there is a specific genetic hallmark associated with this tumor, the overall genetic mutational burden is relatively low, with a median of 1.25 mutations per megabase [9]. It is noteworthy that EWSR1 gene rearrangements have also been identified in other tumor types, including Ewing's sarcoma, clear cell sarcoma, hyalinizing clear cell carcinoma of the salivary gland, myxoid liposarcoma, extraskeletal chondrosarcoma, desmoplastic round cell tumors, hemangioma-like fibrous histiocytoma, and myoepithelial carcinoma. Consequently, the diagnosis of GNET should not be solely reliant on molecular assessments [2,10].

Given the predominant localization of these tumors within the submucosal layer of the gastrointestinal tract, alongside findings from ultrastructural studies and the immunohistochemical (IHC) staining patterns indicative of neural differentiation, yet lacking a melanocytic phenotype, the hypothesis suggesting an origin from neural crest cells has gained traction [2,4,11]. It is pertinent to note that the EWSR1 gene is part of the TET/ETS family of RNA-binding proteins, which have been implicated in the oncogenesis of Ewing's sarcoma, a tumor for which a neural crest cell origin has also been proposed. This gene family plays a critical role in the migration of neural crest cells [12]. Neural crest cells are regarded as the fourth germ layer during embryonic development, possessing the capacity to migrate and differentiate into a variety of cell types, including melanocytes, parasympathetic ganglia of the gastrointestinal tract, Schwann cells, components of the neurocranium, and the medulla of the adrenal gland, as well as neuroendocrine cells, such as thyroid ''C'' cells [13,14]. These observations suggest that neural crest cells may follow three distinct pathways of differentiation prior to their migration throughout the body: one leading towards clear melanocytic differentiation, another towards neuroendocrine differentiation, and a third towards mesenchymal specialization. While the latter two pathways may retain neural characteristics, as evidenced by positive staining for neural markers (e.g., synaptophysin, CD56, NSE, S100), a key distinction lies in the fact that cells exhibiting a more pronounced neuroendocrine differentiation progressively begin to express epithelial markers as they become more integrated within the epithelial structure.

The differential diagnosis of gastrointestinal neuroectodermal tumor (GNET) is extensive, encompassing a wide array of tumors that may share similar localization within the gastrointestinal tract or exhibit comparable morphological features (Table 1). One of the most significant overlaps is with clear cell sarcoma of soft parts (CCS), which predominantly affects young adults and typically arises in the extremities. Although the cellular morphology is similar, CCS may occasionally present with melanin pigmentation and notably lacks osteoclast-like giant cells. Approximately 90% of CCS cases demonstrate positivity for HMB45 and MelanA [15,16]. The epithelioid variant of gastrointestinal stromal tumor (GIST) can be readily excluded from the differential diagnosis due to lack of positivity for CD117, DOG1, and CD34 [1,2]. The small intestine is also a common site for metastatic melanoma; the clinical history of melanoma, positivity for melanocytic markers, and the absence of EWSR1 gene rearrangements strongly support a diagnosis of metastatic melanoma [2,5]. Confusion may arise with neuroendocrine tumors or neuroendocrine carcinomas (NET/NEC) due to the monomorphic nature of the tumor cells, the arrangement of small nests or compact-solid areas, and the pronounced IHC expression of synaptophysin and CD56 in multiple cases. However, NET/NEC typically exhibit epithelial differentiation by expressing cytokeratin markers, a characteristic not observed in GNET [2,5]. It is important to note that NET/NEC are commonly positive for Ck8 and Ck18 and may occasionally show double negativity for Ck7 and Ck20. Therefore, relying solely on the combination of Ck7 and Ck20 to exclude a NET/NEC diagnosis is insufficient. In such cases, employing multiple pan-cytokeratin cocktails (e.g., AE1/AE3, Cam5.2) is advisable to comprehensively confirm the absence of epithelial differentiation [17]. Due to its strong and diffuse positivity for S100, GNET may be mistaken for the epithelioid variant of malignant peripheral nerve sheath tumor (MPNST), although MPNST typically presents with distinct genetic abnormalities, often involving the NF1 gene [18]. Another potential differential diagnosis includes perivascular epithelioid cell tumor (PEComa), which exhibits positivity for

Table 1. Differential diagnosis for GNET based on clinical features, morphology, immunohistochemistry and molecular characteristics.

Diagnosis	Clinical features	Morphology	Immunohistochemistry	Molecular features
GNET	Affecting young adults, most commonly located in the small intestine	polyhedral to epithelioid cells arranged in small nests, sheets, cords, pseudopapillary structures; osteoclast-like giant cells are often present	constantly positive for S100, SOX10, vimentin and negative for Melan-A, HMB45, desmin, CD117 and pan-cytokeratin; variable expression for synaptophysin, chromogranin, CD56, NSE, NFP	EWSR1 gene rearrangements; EWSR1-ATF1 and EWSR1-CREB1 fusions
Clear cell sarcoma	Affects young adults, with predilection on extremities	Similar morphologic features, more uniform, often contain macronucleoli Lack osteoclast-like giant cells; 2/3 contain melanin pigment	90% of them positive for HMB-45 or Melan A positive for SOX10	EWSR1-ATF1 fusion present
Epithelioid variant of GIST	Affecting young adults, located in the small intestine, gastric wall	Spindle/epithelioid cells with scant fibrillary cytoplasm, monotonous ovoid to spindle nuclei	Positive for CD117, DOG1 and CD34	KIT mutations
NET/NEC	Widespread age predilection and throughout the entire gastro-entero-pancreatic system	Monotonous cells arranged in small nests or compact-solid areas	Strong positive expression for synaptophysin, chromogranin, CD56 show epithelial differentiation by expressing cytokeratin markers	None
Metastatic melanoma	Frequently older adult population	Epithelioid/spindle shaped cells, marked nuclear pleomorphism, large eosinophilic nucleoli	S100 positive, melanoma markers positive	No EWSR1 translocation

melanocytic markers (HMB45, MelanA) and myogenic markers, but is generally negative for S100 [18]. Particularly for GNETs of gastric origin, granular cell tumor may also be considered, although granular cell tumors often display nuclei with denser chromatin compared to GNET and show a diffuse pattern of positivity for CD68, in contrast to the scattered CD68-positive osteoclast-like giant cells characteristic of GNET [19].

Treatment options for GNET remain poorly defined due to its rarity and the limited number of patients involved in clinical trials. Current understanding indicates that for patients with localized disease, excisional surgery may provide a potential benefit. In cases of progressive or metastatic disease, various modalities including chemotherapy, radiotherapy, and targeted therapies - such as tyrosine kinase inhibitors - have been explored, demonstrating some favorable outcomes [5,6]. However, further research is necessary to establish standardized treatment protocols and optimize therapeutic strategies for GNET.

2. CASE PRESENTATION

A 56-year-old female patient, previously diagnosed in 2021 with a grade 3 neuroendocrine tumor (NET) of the ileum, presented in July 2024 during her oncological follow-up with a liver metastasis located in segment VIII, which was exerting compression on the medial hepatic vein. In response to this finding, a transversal hepatectomy was performed in the General Surgery Department of a tertiary hospital. The surgical procedure involved the resection of segments VIII, VII, and the first segment of the liver, with a total excised weight of 250 grams.

Macroscopic examination of the specimen revealed a solitary, solid tumor measuring 34 mm at its maximum diameter. The tumor was well demarcated and displayed a homogeneous greyish coloration interspersed with brown streaks of hemorrhage (Figure 1). Histopathological processing involved embedding the tumor almost entirely in paraffin blocks, followed by examination of conventional stained slides (Hematoxylin-Eosin, HE).

The microscopic analysis demonstrated a monotonous proliferation of tumor cells exhibiting polyhedral to epithelioid morphology, characterized by a bizarre heterogeneous architecture. This was represented by small nests, compact-solid areas, and, on occasion, pseudo-alveolar or pseudopapillary microcystic formations with the entrapment of small biliary ducts (Figure 2). At higher magnification, the tumor cells displayed abundant eosinophilic or clear cytoplasm, round nuclei with vesicular chromatin and peripheral margination, occasionally featuring prominent nucleoli. The mitotic activity was relatively low, with 7 mitoses observed per 10 high-power fields, and osteoclast-like giant cells were noted infrequently (Figure 3). Notably, there was no evidence of necrosis, though restricted areas of hemorrhage were present.

Immunohistochemistry (IHC) studies were conducted to address the discrepancy between the tumor morphology and the strong clinical suspicion of liver metastases originating from the neuroendocrine tumor (NET) diagnosed in 2021. In the initial series of tests, the tumor cells displayed negativity for various cytokeratin markers, including Ck AE1/AE3, Cam5.2, Ck7, Ck20, EMA, and Ck19. However, the tumor exhibited focal positivity for synaptophysin and CD56, alongside strong positivity for S100, SOX10, and vimentin (Figure 4).

Fortunately, a paraffin block from the initial ileal tumor was received for consultation at this stage. Examination revealed a tumor measuring 23 mm in maximum diameter, primarily developing within the submucosa and muscularis propria, with associated mucosal ulceration (Figure 5a). Microscopically, the tumor exhibited a morphology strikingly similar to that of the liver tumor, characterized by monotonous cells predominantly organized in small nests, with the presence of rare osteoclast-like giant cells. The tumor cells generally displayed clear cytoplasm and vesicular nuclei, although prominent nucleoli were absent (Figure 5b). IHC testing was repeated on this initial tumor, yielding results consistent with those observed in the liver tumor. Furthermore, other tumors that could present with similar morphology - such as neuroendocrine tumor or carcinoma, solid papillary

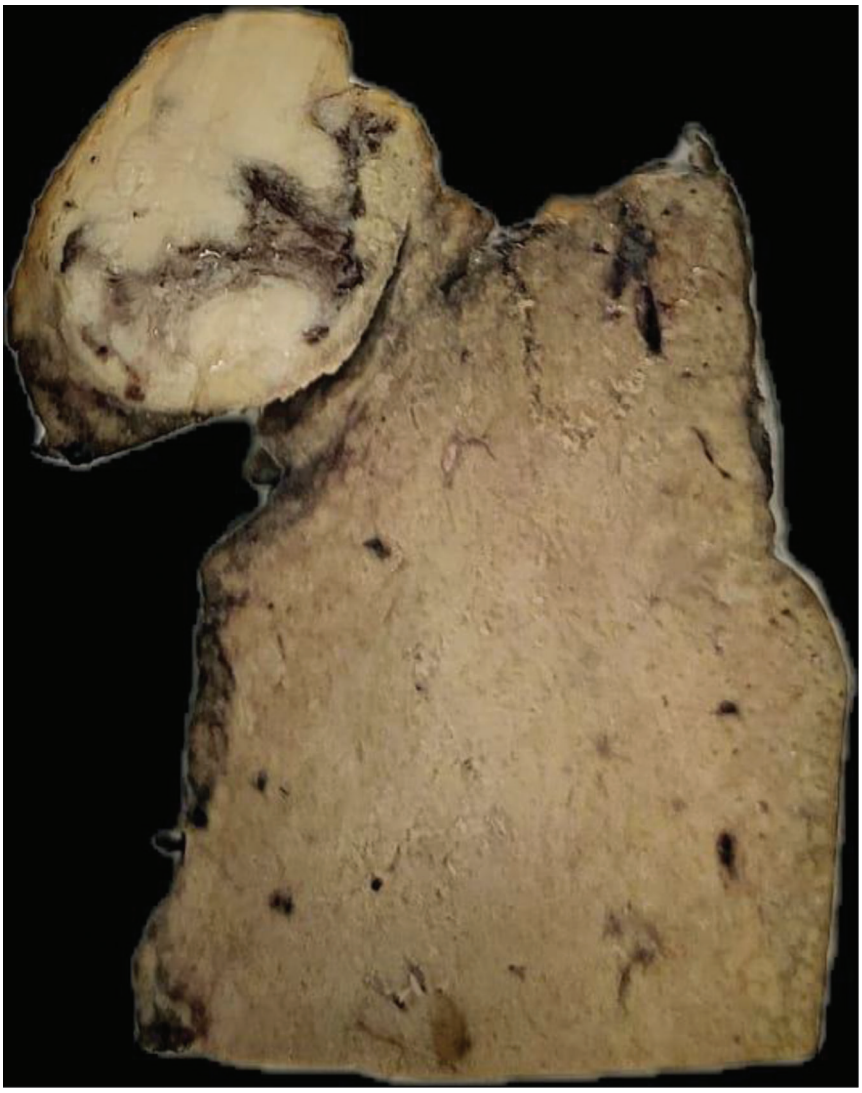

Fig. 1. Macroscopic appearance of the liver malignant GNET: a solitary, solid tumor, 34 mm in maximum diameter, quite well demarcated, homogenous greyish color with brown strips of hemorrhage.

neoplasm (SPN), malignant peripheral nerve sheath tumor (MPNST), paraganglioma, gastrointestinal mesenchymal tumor (GIST), dysgerminoma, or embryonal carcinoma - were excluded based on the negativity of the tumor cells for several markers, including INSM1, chromogranin, beta-catenin, progesterone receptor, CD10, GATA3, HMB45, MelanA, CD117, PGP9.5, OCT 3.4, and D2-40.

The Ki67 proliferative index was evaluated for both tumors, revealing that the liver tumor had a higher index of 8%, compared to 1% for the ileal tumor. These findings led to a preliminary diagnosis suggesting that the liver tumor is most likely a metastasis from a malignant gastrointestinal neuroectodermal tumor (GNET) or a clear cell sarcoma-like tumor of the gastrointestinal tract (CCSTGT). However, additional molecular studies were deemed necessary to confirm this diagnosis. Subsequently, fluorescence in situ hybridization (FISH) testing demonstrated EWSR1 gene rearrangements in approximately 70% of the tumor cells, thereby supporting the presumptive diagnosis of GNET/CCSTGT. In this case, surgical excision was the chosen treatment approach for both the ileal tumor and the liver metastasis. The patient has undergone close oncological follow-up, which has shown no evidence of active disease or progression at the time of writing this article.

3. LITERATURE REVIEW

This review aims to synthesize the available literature on malignant gastrointestinal neuroectodermal tumor (GNET). The literature search was conducted using databases such as PubMed and PubMed Central, utilizing the keywords "GNET" and "malignant gastrointestinal neuroectodermal tumor". Only full-text articles available in English, French, or Spanish were included to ensure clarity and consistency in interpretation. From a total of 134 reported clinical cases identified through the literature and the aforementioned clinical case, 127 cases were included in the final analysis. Cases with incomplete data or insufficient clinical detail were excluded from the review [1,2,5,6,9,11,12,16,18,20–65].

The analyzed patient cohort exhibited a broad age distribution, ranging from 5 to 79 years, with a median age of 41 years. There was a notable female predominance, with

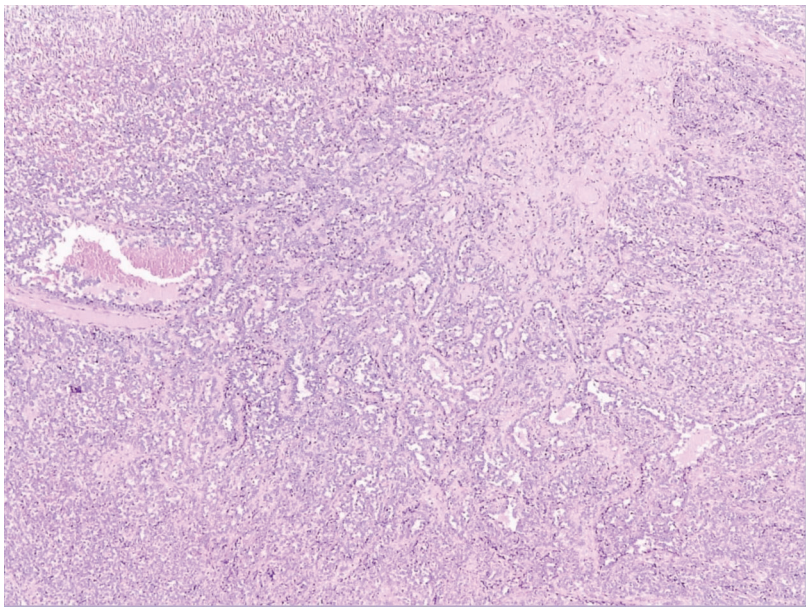

Fig. 2. Liver malignant GNET: microscopic features showing the pseudo-alveolar or pseudopapillary microcystic architecture; upper left corner, showing compact solid growth pattern (HE, 40x).

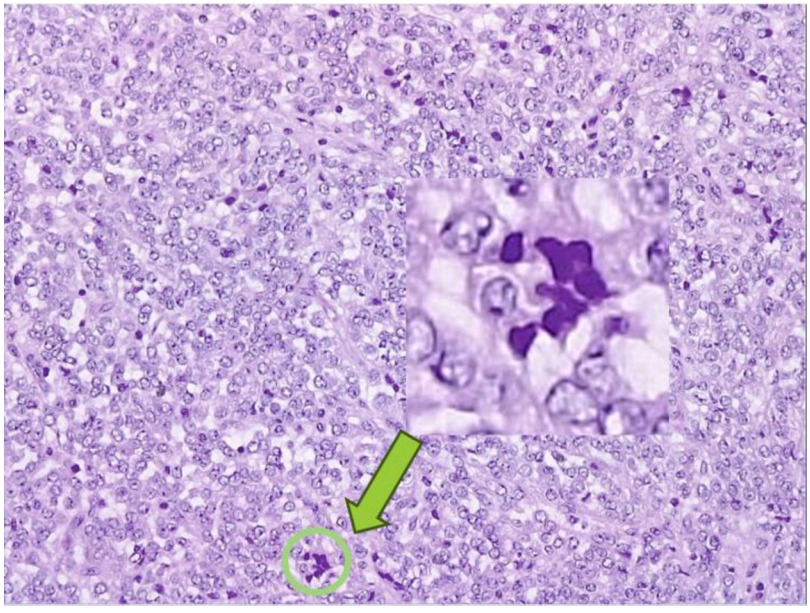

Fig. 3. Liver malignant GNET: tumor cells exhibit abundant eosinophilic or clear cytoplasm, with roundish nuclei displaying vesicular chromatin and peripheral margination. Occasionally, prominent nucleoli are observed. An osteoclast-like giant cell is highlighted within the green circle. (HE, 400x).

65 female patients compared to 51 male patients; however, gender information was not provided for some cases. Most tumors were located in the small bowel (55%), followed by gastric (14%), colonic (7%), esophageal (3%), neck (3%), and tongue (3%) localizations. Approximately 15% of cases had other localizations, including the liver, anal canal, duodenum, extrahepatic bile duct, ileocecal valve, heart, urinary bladder, chest wall, larynx, orbit, parapharyngeal area, shoulder, thigh, buttock, gluteus, and even retroperitoneal sites. This distribution suggests that while most malignant GNETs are found within the gastrointestinal tract, there are indeed cases with extra-enteric localization. Ulici et al. reported 11 non-intestinal GNETs affecting patients with a median age of 33 years, which were localized in soft tissue regions of the visceral neurocranium, shoulder, neck, parapharyngeal area, urinary bladder, and falciform ligament. All these cases exhibited identical morphological, immunohistochemical, and genetic characteristics as malignant GNETs with intestinal localization [44,51]. The diverse distribution of malignant GNETs throughout the body, as highlighted in this review, reinforces the hypothesis that these tumors may originate from neural crest cells. This

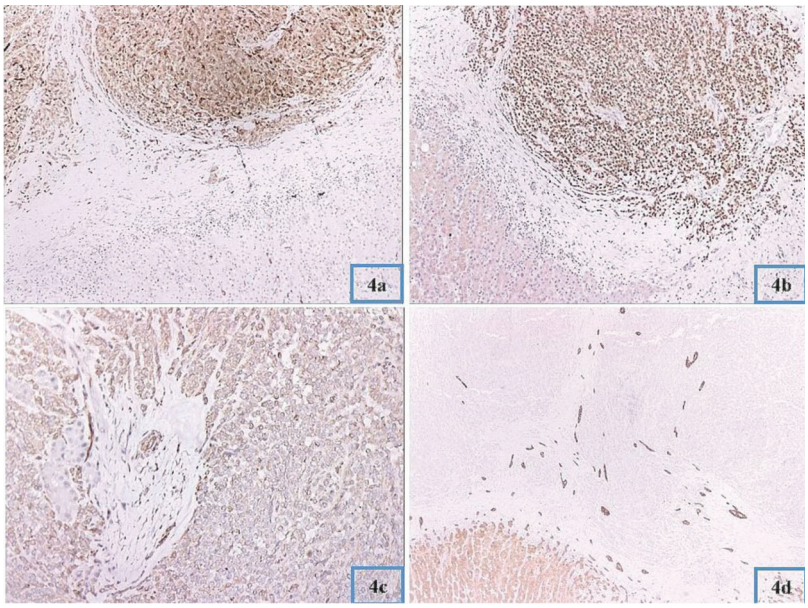

Fig. 4. IHC expression in liver malignant GNET: **a.** diffuse, strong cytoplasmic staining for S100; **b.** diffuse, strong nuclear staining for SOX10; **c.** diffuse cytoplasmic and focal membranous staining for Vimentin; **d.** diffuse negativity for pan-Ck AE1/AE3, with internal control in the small biliary ducts entrapped within the tumor (IHC, 40x).

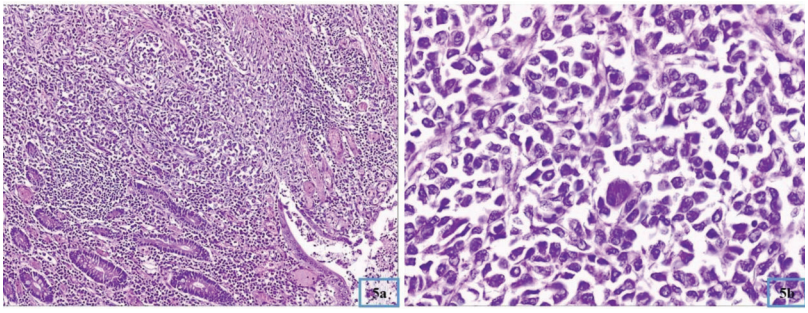

Fig. 5. Ileal malignant GNET: **a.** ulceration of the overlying mucosa (HE, 100x); **b.** monotonous cells predominantly organized in small nests, cells generally displaying clear cytoplasm and vesicular nuclei, but lacking prominent nucleoli (HE, 400x).

perspective emphasizes the need for further research into the developmental pathways and etiological factors contributing to the formation of GNETs across different anatomical sites.

The clinical presentation of patients with malignant GNETs tends to be nonspecific, with various symptoms reported, including weight loss, intestinal obstruction, abdominal pain, fatigue, dizziness, melena, secondary microcytic anemia, and occasionally high-grade fever. Tumor sizes varied significantly, ranging from 12 mm to 135 mm, with a median size of 40.5 mm. Histologically, all cases exhibited similar features, except for one instance where the tumor cells demonstrated oncocytic morphology [55]. Notably, the presence of osteoclast-like giant cells was documented in approximately 36% of cases. In terms of immunophenotype, malignant GNETs consistently displayed strong positivity for S100 and SOX10. Additionally, about 37% of cases showed positivity for synaptophysin, while 43% were positive for CD56. There was persistent negativity for chromogranin, HMB45, MelanA, and smooth muscle actin (SMA). Although it has been previously established that GNETs are typically negative for cytokeratin markers, this review highlights an uncommon finding: five cases exhibited focal positivity for epithelial membrane antigen (EMA) or AE1/AE3 pan-cytokeratin, with moderate to strong intensity. Nonetheless, based on the morphology, strong expression of S100 and SOX10, lack of melanocytic marker expression, and the presence of the EWSR1-ATF1 fusion, the diagnosis of GNET was still confidently made [2,59,60]. Regarding the Ki67 proliferative index, it was found to range from 1% to 60%, with a median of 20%.

Approximately 10% of malignant GNETs have been initially misdiagnosed, with the correct diagnosis often made upon examination of metastatic specimens. More than half of these misdiagnosed cases (about 6%) were incorrectly classified as neuroendocrine tumors or neuroendocrine carcinoma [5,35]. Less frequently, GNETs have been misdiagnosed as benign or malignant granular cell tumors, metastatic malignant melanoma, Ewing's sarcoma, malignant peripheral nerve sheath tumors (MPNST), and even schwannomas.

EWSR1 gene rearrangements were found in 94% of the cases of malignant GNETs. The majority of these alterations were attributed to the EWSR1-ATF1 gene fusion, while EWSR1-CREB1 fusion was observed less frequently. Notably,

there was one case that exhibited a rarer fusion: EWSR1-PBX1 [51]. In addition to these fusions, GNETs rarely present with associated mutations, such as those in the BRAF gene. Yagi et al. reported a clinical case involving a 66-year-old woman with a history of desmoplastic melanoma who developed progressive disease after 8 years, leading to multiple metastases, one of which was located in the small bowel. This metastatic lesion exhibited morphological, immunohistochemical, and genetic features consistent with GNET, including the EWSR1-ATF1 fusion associated with a BRAF mutation [41]. Furthermore, there were three clinical cases where patients diagnosed with malignant GNET had a history of other malignancies, including adrenal neuroblastoma, hepatoblastoma, and Ewing sarcoma [32,63,64].

Approximately 59% of patients with malignant GNET presented with metastatic disease, with about 41% having only one metastatic site, while most had two or multiple sites. The liver was the most frequent site of metastases (38%), followed by lymph nodes (31%), peritoneum (11%), lungs (10%), and bone (5%), along with other sites such as the spleen, adrenal gland, pleura, and skin (5%). Notably, around 33% of cases were already metastatic at the time of initial diagnosis, with a median period of 12.5 months to the first metastasis for the remaining cases. The overall survival rate for patients ranged from 1 month to 161 months, with a median survival of 17 months. Patients with limited disease (without metastases at diagnosis and without development of metastases during follow-up) were treated solely with surgery in about 52% of cases, while the others received a combination of surgery, chemotherapy, or radiotherapy. The mean follow-up period for those treated with surgery alone was approximately 26 months, compared to around 22 months for those who received additional treatments. All patients in these groups showed no evidence of disease at the end of the follow-up, except for three patients - one who underwent surgery alone and two who received surgery plus chemo-radiotherapy - who experienced local recurrence. For advanced cases (those with metastases at initial diagnosis or those that developed during the follow-up), treatment typically involved a combination of surgery, chemotherapy, radiotherapy, and immunotherapy in about 56% of instances; in the remaining cases, a surgical approach with negative margins was chosen. The mean follow-up period for patients receiving multiple lines of therapy was 31 months, while those treated exclusively by surgical means had a follow-up of 16.5 months. Within the group treated with multiple therapies, six patients were declared dead due to the disease, whereas only two patients treated solely by surgery succumbed. It is noteworthy that some patients with advanced disease exhibited good response rates to multi-tyrosine kinase inhibitors (TKIs), showing either regression or stable disease. For instance, Subbiah et al. reported a clinical case of GNET harboring the EWSR1-CREB1 fusion that demonstrated a sustained near-complete response to crizotinib and pazopanib for 1.5 years [36,48].

4. CONCLUSION

As of 2021, only 111 cases of malignant gastrointestinal neuroectodermal tumors (GNET) had been published [9]. With the current review, the total number of cases documented has reached 135. This underscores the significant interest in this tumor type, which could potentially enhance the accuracy of diagnoses. It emphasizes the importance of thorough histopathological evaluation and immunohistochemical profiling in the accurate diagnosis of GNETs, especially considering their potential to mimic other tumor types. The complexities of their clinical presentation and histological features necessitate a meticulous diagnostic approach to avoid misclassification and ensure appropriate management. Furthermore, extended research involving larger cohorts of clinical cases could improve treatment options for these patients.

Written informed consent

Written informed consent has been obtained from the patient whose clinical information has been disseminated.

Conflict of interest

Nothing to declare.

Financing

Nothing to declare.

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