

Clinical Case

Malignant Gastrointestinal Neuroectodermal Tumor Mimicking Melanoma in the Small Bowel: A Diagnostic Challenge

Tumor Neuroectodérmico Gastrointestinal Maligno a Simular Melanoma do Intestino Delgado: Um Desafio Diagnóstico

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ABSTRACT

Malignant gastrointestinal neuroectodermal tumor (GNET) is a rare and aggressive mesenchymal neoplasm characterized by S100 and SOX10 expression and *EWSR1* gene rearrangements. Diagnosis is challenging due to overlap with other gastrointestinal tumors, particularly malignant melanoma.

A 53-year-old woman presented with abdominal pain and melena. Physical examination revealed diffuse abdominal tenderness without peritoneal signs. Laboratory tests showed mild anemia (hemoglobin 11.5 g/dL) with no inflammatory markers. Upper endoscopy and colonoscopy were unremarkable. Contrast-enhanced computed tomography (CT) and CT enterography identified a 20 mm lesion in the jejunum. The patient underwent laparoscopic segmental enterectomy without complications.

Initial histopathological evaluation suggested malignant melanoma. However, further analysis demonstrated diffuse S100 and SOX10 positivity with negative HMB-45, Melan-A, CD117, and CD34. Molecular testing confirmed an *EWSR1* gene rearrangement,

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establishing the diagnosis of GNET. The patient was referred to a multidisciplinary oncology team, and surveillance was recommended. Follow-up positron emission tomography at three and six months showed no evidence of recurrence. GNET should be considered in the differential diagnosis of small bowel tumors with melanocytic features, particularly in the absence of conventional melanocytic markers. Although both GNET and melanoma express S100 and SOX10, only melanoma typically shows HMB-45 and Melan-A positivity and lacks *EWSR1* rearrangements. Given the high risk of recurrence and the absence of standardized treatment protocols, accurate diagnosis is essential to guide management and avoid misclassification. This case highlights the importance of integrating histopathological, immunohistochemical, and molecular findings within a multidisciplinary approach.

Keywords: Intestinal Neoplasms; Intestine, Small; Melanoma; Neuroectodermal Tumors

RESUMO

O tumor neuroectodérmico gastrointestinal maligno (GNET) é uma neoplasia mesenquimatosa rara e agressiva, caracterizada pela expressão de S100 e SOX10 e por rearranjos do gene *EWSR1*. O diagnóstico é desafiante devido à sobreposição com outras neoplasias gastrointestinais, particularmente o melanoma maligno.

Mulher de 53 anos, recorreu ao serviço de urgência por dor abdominal e melenas. Ao exame objetivo apresentava dor abdominal difusa, sem sinais de irritação peritoneal. Analiticamente, apresentava anemia ligeira (hemoglobina 11,5 g/dL), sem elevação dos marcadores inflamatórios. A endoscopia digestiva alta e a colonoscopia não revelaram alterações. A tomografia computadorizada (TC) com contraste e a enterografia por TC identificaram uma lesão de 20 mm no jejuno. A doente foi submetida a enterectomia segmentar laparoscópica, sem intercorrências.

A avaliação histopatológica inicial sugeriu melanoma maligno. Contudo, uma revisão da análise histopatológica demonstrou positividade difusa para S100 e SOX10, com negatividade para HMB-45, Melan-A, CD117 e CD34. O estudo molecular confirmou rearranjo do gene *EWSR1*, estabelecendo o diagnóstico de GNET. A doente foi referenciada a uma equipa multidisciplinar de oncologia, tendo sido instituída vigilância. A PET de controlo aos três e seis meses não evidenciou recidiva.

O GNET deve ser considerado no diagnóstico diferencial de tumores do intestino delgado com características melanocíticas, sobretudo na ausência de marcadores melanocíticos clássicos. Apesar de partilharem expressão de S100 e SOX10, apenas o melanoma apresenta positividade para HMB-45 e Melan-A e não apresenta rearranjos do *EWSR1*. Dado o elevado risco de recidiva e a ausência de protocolos terapêuticos bem definidos, o diagnóstico correto é essencial para orientar a abordagem clínica. Este caso destaca a importância da integração de dados histopatológicos, imunohistoquímicos e moleculares numa abordagem multidisciplinar.

Palavras-chave: Intestino Delgado; Melanoma; Neoplasias do Intestino; Tumor Neuroectodérmico

INTRODUCTION

Malignant gastrointestinal neuroectodermal tumor (GNET) is a rare and aggressive mesenchymal neoplasm of the gastrointestinal tract.¹

Approximately 130 cases have been reported in the literature.^{2,3} First described by Zambrano *et al* as a “clear cell sarcoma-like tumor” of the gastrointestinal tract, it was later recognized as a distinct clinicopathological entity characterized by the absence of melanocytic differentiation and the presence of recurrent *EWSR1* gene rearrangements.^{1,2}

Immunohistochemically, these tumors typically express S100 protein and SOX10 but lack melanocytic markers such as HMB-45 and Melan-A.² Morphological and

immunophenotypic overlap with other tumors, particularly malignant melanoma and gastrointestinal stromal tumors, makes diagnosis challenging.^{2,4}

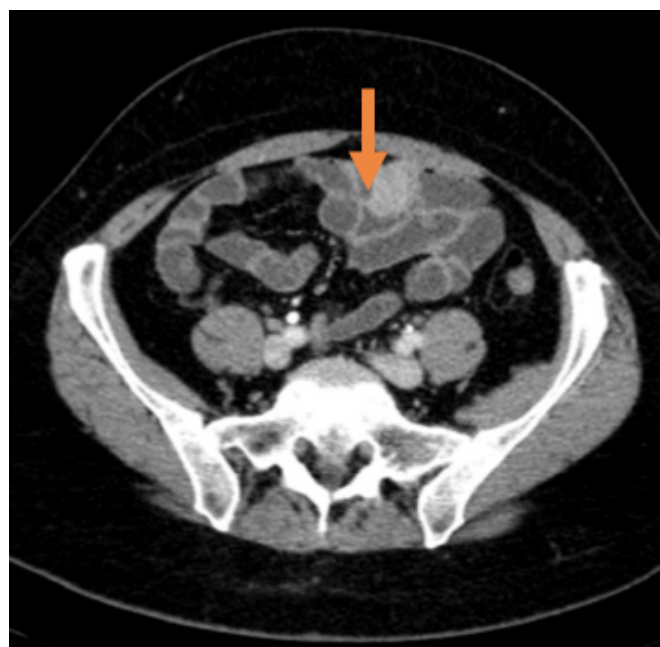
Due to its rarity, the natural history and optimal management of GNET remain poorly defined. Surgical resection is generally considered the mainstay of treatment for localized disease,^{2,3} while the role of systemic therapies remains uncertain.^{2,3}

CASE REPORT

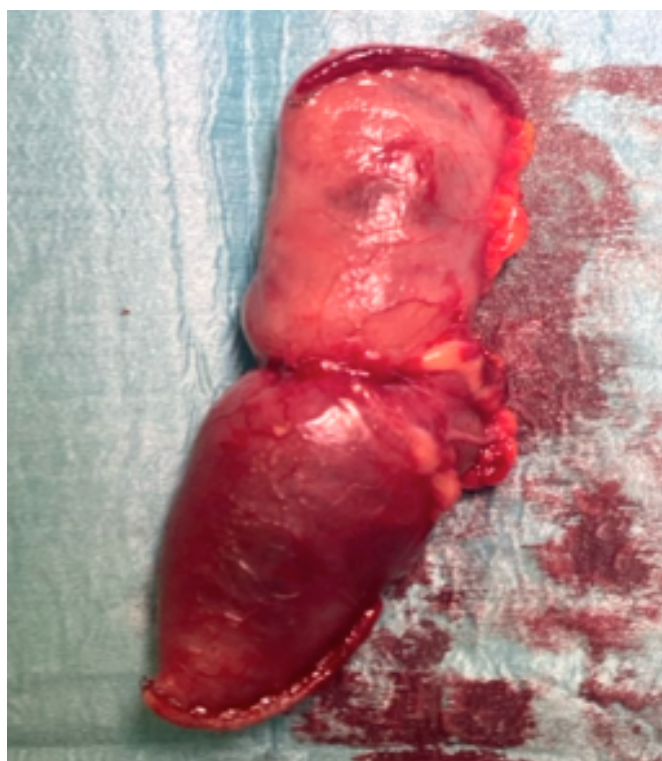
A 53-year-old woman with a history of hypertension, nephrolithiasis, and hemithyroidectomy for benign disease presented to the emergency department with abdominal pain and melena that had developed over several hours. She denied weight loss or other associated symptoms.

On examination, the patient was hemodynamically stable and afebrile. Diffuse abdominal tenderness was noted, but there were no signs of peritoneal irritation. Laboratory studies revealed a hemoglobin level of 11.5 g/dL, slightly below her baseline of 12.5–14 g/dL, with no elevation of inflammatory markers.

The patient was admitted for further investigation. Upper gastrointestinal endoscopy and colonoscopy were unremarkable. Contrast-enhanced computed tomography (CT) demonstrated a 20 mm contrast-enhancing pseudonodular lesion within a small bowel loop. CT enterography confirmed a vegetative lesion located in the jejunum.



Figures 1 and 2 – CT enterography demonstrating the lesion.



Figures 3 and 4 – Surgical specimen with suspicious lesion.

Based on these findings, the patient underwent laparoscopic segmental enterectomy. The procedure was completed without complications. Intraoperative inspection of the surgical specimen revealed an ulcerated lesion suspicious for malignancy, leading to extension of the resection margins of the small bowel and mesentery.

The postoperative course was uneventful, and the patient was discharged four days after surgery.

Initial histopathological evaluation suggested malignant melanoma. Immunohistochemical staining showed positivity for S100, SOX10, and synaptophysin, with negative staining for HMB-45, CK (CAM5.2), chromogranin A, CD117, DOG1, and CD45. Melan-A was not assessed in this initial evaluation. The Ki-67 proliferation index was approximately 20%, and the surgical margins were free of tumor.

A comprehensive dermatological and mucosal examination, including evaluation of the perianal region, did not reveal any suspicious primary lesion. Ophthalmologic examination excluded an ocular primary melanoma, and positron emission tomography (PET) showed no evidence of metastatic disease.

The patient was subsequently referred to a multidisciplinary oncology team at a national reference center. Expert pathological review led to a revised diagnosis of malignant gastrointestinal neuroectodermal tumor.

Histologically, the tumor displayed an infiltrative growth pattern composed of epithelioid cells with moderate nuclear pleomorphism and extensive ulceration. The lesion invaded the mucosa, submucosa, and muscularis propria, with focal extension to the subserosa. Surgical margins were free of tumor, and all eleven regional lymph nodes were negative for metastasis. No lymphovascular or perineural invasion was identified. The mitotic rate was 18 mitoses per 10 high-power fields. Immunohistochemistry demonstrated diffuse positivity for S100 and SOX10, while staining for HMB-45, Melan-A, chromogranin A, cytokeratin AE1/AE3, desmin, caldesmon, smooth muscle actin, CD34, CD117, and DOG1 was negative. Molecular testing confirmed the presence of an *EWSR1* gene rearrangement, supporting the diagnosis of GNET.

Given the high risk of recurrence, the multidisciplinary tumor board recommended close clinical and radiological surveillance with periodic imaging. PET scans performed at three and six months after surgery showed no evidence of recurrent or metastatic disease.

DISCUSSION

Malignant gastrointestinal neuroectodermal tumor (GNET) is a rare and recently recognized mesenchymal neoplasm of the gastrointestinal tract. It was initially described by Zambrano *et al* as a clear cell sarcoma-like tumor of the gastrointestinal tract and was later characterized as a distinct clinicopathologic entity by Stockman *et al* in 2012.^{1,4} GNET predominantly affects adults, most commonly in middle age, although reported cases range from 10 to 81 years of age.⁴ No specific risk factors or gender predilection have been identified to date.²

The small intestine represents the most frequent site of origin (approximately 58%), followed by the stomach (16%), colon (11%), ileocecal junction (5%), esophagus (5%), and anal canal (5%).³ Clinical presentation is often nonspecific, with commonly reported symptoms including abdominal pain, distension, intestinal obstruction, abdominal mass, weight loss, and anemia.² To date, no familial cases or associations with hereditary syndromes have been described.

Macroscopically, these tumors typically appear as firm, solid mural masses that may show hemorrhagic, necrotic, or cystic areas on the cut surface. Histologically, GNETs are composed of epithelioid to spindle-shaped cells arranged in nests or solid sheets, often accompanied by osteoclast-like multinucleated giant cells, which represent a characteristic but nonspecific feature.² The tumor generally originates in the muscularis propria and may secondarily infiltrate the submucosa and mucosa, with possible extension to the serosa in advanced cases. In contrast, melanoma of the gastrointestinal tract is believed to arise from melanocytes located in the mucosa and typically presents as polypoid or ulcerated lesions, often with pigmentation, although amelanotic variants may occur.⁵

Immunohistochemically, GNETs typically express S100 and SOX10, reflecting neural differentiation, while lacking melanocytic markers such as HMB-45, Melan-A, and tyrosinase.³ Positivity for CD56 has also been reported in up to 70% of cases, consistent with a primitive neuroectodermal phenotype.²

The main differential diagnoses include metastatic malignant melanoma, clear cell sarcoma, gastrointestinal stromal tumor (GIST), epithelioid schwannoma, granular cell tumor, and perivascular epithelioid cell tumor (PEComa).^{2,3}

Distinguishing primary mucosal melanoma of the small intestine from metastatic melanoma represents a particular diagnostic challenge. Primary small intestinal melanoma

is exceedingly rare, with only a limited number of cases reported in the literature, whereas metastatic melanoma involving the small bowel is considerably more frequent, being clinically detected in approximately 1.5%–4.4% of patients with melanoma. Indeed, the small intestine represents the most common site of gastrointestinal metastasis from melanoma.^{6,7}

When morphological and immunophenotypic findings overlap, molecular testing becomes decisive. Melanomas commonly harbor mutations in *BRAF*, *NRAS*, or *KIT*, whereas GNETs are characterized by rearrangements involving the *EWSR1* gene, most frequently *EWSR1-ATF1* or *EWSR1-CREB1* gene fusions detectable by fluorescence in situ hybridization (FISH) or next-generation sequencing.^{2,8} Both tumors show expression of S100 and SOX10; however, unlike melanoma, GNET typically lacks melanocytic differentiation and is negative for HMB-45, Melan-A, and tyrosinase. The identification of *EWSR1* rearrangements is a key diagnostic feature that strongly supports GNET in the appropriate histopathological context.

The diagnosis of GNET therefore relies on the integration of morphological, immunohistochemical, and molecular features. According to a recent meta-analysis including 127 reported cases, approximately 10% of GNETs are initially misdiagnosed, highlighting the diagnostic complexity of this entity and the importance of expert pathological review.⁹

Clinically, GNET is considered an aggressive tumor with a high risk of local recurrence and distant metastasis, with some series reporting recurrence rates of up to 76%.³ Metastatic spread most frequently involves the liver and regional lymph nodes and, less commonly, the bone.^{2,3}

Radical surgical resection remains the treatment of choice for localized disease.^{2,3} The role of adjuvant therapies remains unclear, as conventional chemotherapy has not consistently

demonstrated clinical benefit. In advanced or refractory cases, several therapeutic strategies have been explored, including chemotherapy, immunotherapy, and targeted agents such as apatinib, a VEGFR-2 inhibitor, with limited but promising preliminary results.⁸

Given the rarity of this entity and the absence of standardized treatment guidelines, management decisions should ideally be made within a multidisciplinary framework. Close clinical and radiological surveillance is recommended due to the significant risk of recurrence and the potential for delayed metastatic spread.

This case highlights the diagnostic challenges associated with GNET and underscores the importance of integrating molecular testing into the diagnostic workup of gastrointestinal tumors with a melanocytic immunophenotype.

CONCLUSION

Malignant gastrointestinal neuroectodermal tumor is a rare and diagnostically challenging neoplasm that may closely mimic malignant melanoma both morphologically and immunohistochemically. Accurate diagnosis requires integration of clinical evaluation, histopathological findings, and molecular confirmation of *EWSR1* rearrangements.

Complete surgical resection remains the primary treatment for localized disease, while the role of systemic therapy in advanced or refractory cases remains uncertain. This case highlights the importance of multidisciplinary collaboration and molecular diagnostics in the evaluation of rare gastrointestinal tumors.

PRIZES AND PREVIOUS PRESENTATIONS

This work was previously presented as a poster at the Portuguese National Congress of Surgery (Congresso Nacional de Cirurgia), held on March 19–20, 2026.

ETHICAL DISCLOSURES

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CONTRIBUTORSHIP STATEMENT

BG: Bibliographical search, study design, data collection, analysis and interpretation of results, drafting of the article, critical review of the content.

EVM: Bibliographical search, study design, analysis and interpretation of results, critical review of the content of the article.

DB, AMF and ELC: Bibliographical search, analysis and interpretation of results, critical review of the content of the article.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

DECLARAÇÃO DE CONTRIBUIÇÃO

BG: Pesquisa bibliográfica, conceção do estudo, recolha de dados, análise e interpretação dos resultados, redação do artigo, revisão crítica do conteúdo.

EVM: Pesquisa bibliográfica, conceção do estudo, análise e interpretação dos resultados, revisão crítica do conteúdo do artigo.

DB, AMF e ELC: Pesquisa bibliográfica, análise e interpretação dos resultados, revisão crítica do conteúdo do artigo.

Todos os autores aprovaram a versão final do manuscrito para publicação e assumem responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

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