Case Report

Misdiagnosis of malignant gastrointestinal neuroectodermal tumor as Ewing sarcoma: A case report with molecular insights

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ABSTRACT

Malignant gastrointestinal neuroectodermal tumor (GNET) is a rare and aggressive mesenchymal tumor that primarily affects the gastrointestinal tract (GIT). Previously termed clear cell sarcoma (CCS)-like tumor of the GIT, GNET is histopathologically distinct from CCS and lacks melanocytic differentiation. This report details a case of a 45-year-old male who was initially misdiagnosed with Ewing sarcoma based on a core biopsy but was later confirmed to have malignant GNET following surgical intervention and molecular testing. The patient presented with abdominal pain, weight loss, vomiting, and constipation. Imaging revealed a 7.0 cm intra-peritoneal soft-tissue mass with adjacent small bowel involvement. Initial biopsy results suggested Ewing sarcoma, leading to chemotherapy treatment. However, persistent intestinal thickening and hepatic nodular lesions prompted surgical re-evaluation. Histopathological examination of the resected specimen showed sheets of tumor cells infiltrating the mucosa, submucosa, muscularis, and serosa, with extensive necrosis and high mitotic activity. Immunohistochemical analysis demonstrated positivity for S100 protein, SOX10, CD56, synaptophysin, and vimentin while being negative for HMB45, Melan-A, desmin, and CD117. Fluorescence *in situ* hybridization confirmed an EWSR1:CREB1 fusion, confirming the diagnosis of malignant GNET. This case underscores the importance of comprehensive histopathological and molecular assessments to ensure accurate diagnosis and optimal management of rare GI tumors like GNET. Further research is necessary to establish effective targeted therapies and improve patient outcomes.

Key words: Clear cell sarcoma, Ewing sarcoma misdiagnosis, EWSR1:CREB1 fusion, Gastrointestinal mesenchymal tumors, Malignant gastrointestinal neuroectodermal tumor

Malignant gastrointestinal neuroectodermal tumor (GNET), previously known as a clear cell sarcoma (CCS)-like tumor of the gastrointestinal tract (GIT), is an uncommon mesenchymal tumor primarily affecting the (GIT) [1]. This tumor has been recognized as a separate entity from CCS and is classified under the 5th Edition of the World Health Organization digestive system tumors classification. Experts have recommended using the name "CCS" when markers such as Melan-A, HMB45, or MITF are expressed, while the term "malignant GNET" is preferred in their absence [2]. Most cases of GNET are observed in young adults aged 20–40 years [3]. In a 2019 study, Huang *et al*. analyzed the clinicopathological and cytogenetic characteristics of 47 cases, all of which originated within the abdominal cavity, with the small intestine, stomach, and colon being the most commonly affected sites. Patients typically presented with non-specific symptoms, such as weight loss, abdominal pain, intestinal obstruction, or anemia. Histologically, GNET cells exhibit diverse growth patterns, including solid, nested, pseudo-alveolar, fascicular, pseudopapillary, microcystic, or rosette-like architecture [4]. Biologically, GNETs are highly malignant, with a tendency for local recurrence and metastasis [5]. However, their etiology remains unclear.

This case is reported due to its rarity, the initial misdiagnosis as Ewing sarcoma, and the crucial role of molecular diagnostics in distinguishing malignant GNET from other morphologically similar tumors.

Access this article online	
Received - 07 January 2025 Initial Review - 31 January 2025 Accepted - 24 April 2025	Quick Response code
DOI: 10.32677/ijcr.v11i5.4990	

CASE REPORT

A 45-year-old male presented with intermittent and episodic abdominal pain, constipation, loss of appetite, vomiting, and significant weight loss (~15 kg) over 6 months.

Laboratory investigations showed anemia (9 g/dL) and elevated liver enzymes. A computed tomography (CT) scan of the abdomen revealed a 7.0 cm intra-peritoneal soft-tissue mass with adjacent small bowel jejunal wall thickening. A biopsy

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performed on the lesion was initially reported as Ewing sarcoma, and the patient subsequently received 10 cycles of chemotherapy. A follow-up CT scan showed persistent small bowel jejunal wall thickening with some regression compared to the previous study. In addition, nodular lesions were identified in multiple segments of the liver, though the portal vein and hepatic pedicle were uninvolved.

Surgical intervention was undertaken, and the resected specimens were sent to the pathology department for histopathological evaluation. Macroscopic examination of the specimen (Fig. 1) revealed a coiled segment of the small intestine with a 7.0 × 6.0 × 5.0 cm irregular, tan nodular mass within the mesentery, adherent to the small intestinal wall. Sectioning revealed a fleshy, tan-white tumor with areas of necrosis and hemorrhage. The tumor involved the intestinal wall and extended to the mesentery, with mucosal ulceration and multiple enlarged mesenteric lymph nodes.

The surgical specimen was processed using standardized protocols, including fixation in 10% formalin, paraffin embedding, 4-µm sectioning, and hematoxylin and eosin (H&E) staining. Microscopic examination revealed sheets and relatively discohesive clusters of tumor cells (Fig. 2). The tumor extended from the mucosa, causing mucosal erosion, into the submucosa, muscularis, and serosa, with extrinsic invasion into the mesentery. Cellular features included moderate nuclear pleomorphism, coarse chromatin, conspicuous nucleoli, and clear cytoplasm. Mitotic activity was high, with 15 mitoses/10 high-power fields, including atypical mitoses. Necrosis accounted for approximately 50% of the tumor volume, possibly due to prior chemotherapy. Lymphovascular invasion, perineural infiltration, and neoplastic emboli were evident. Among the 18 lymph nodes sampled, 8 showed metastatic involvement.

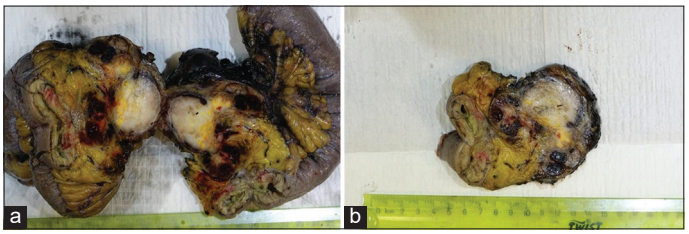

Figure 1: (a) Fleshy tan-white mass centered in the mesentery and (b) extension to the small intestine wall

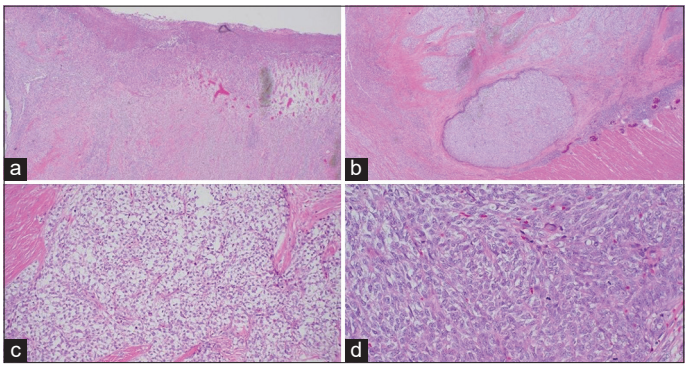

Figure 2: Morphology of neoplastic cells. (a) Neoplastic cells eroding the mucosa and extending to submucosa and muscularis (×100). (b) Neoplastic cells arranged as nests and nodules dissecting the muscularis (×100). (c) Cells in the nests were present in pseudopapillary and pseudoalveolar architectures with vacuolation in many cells (×200). (d) Focally cells were round or short spindle-like in shape, with weak eosinophilic or clear cytoplasm and increased mitosis (×400)

Immunohistochemical (IHC) analysis revealed positive staining for S100 protein (Fig. 3a), SOX10 (Fig. 3b), CD56 (Fig. 3c), synaptophysin (Fig. 3d), and vimentin. CD99 showed patchy positivity. The tumor was negative for HMB45, Melan-A, desmin, c-kit (CD117), leukocyte common antigen, and pan-cytokeratin AE1/AE3. Fluorescence *in situ* hybridization (FISH) analysis confirmed the presence of an EWSR1:CREB1 fusion, solidifying the diagnosis of malignant GNET.

DISCUSSION

GNETs are rare, aggressive tumors with poor prognoses. Stockman *et al*. described 16 cases of GNET in 2012, highlighting their IHC and ultrastructural features. These findings suggested that the tumor originates from autonomic primitive neural cells, lacking melanocytic differentiation [1].

In a comparative study of 96 GNET cases, patients ranged from 5 to 82 years old, with a median age of 36. Most tumors were located in the small intestine (67.0%), followed by the stomach (13.8%) and colon (9.6%) [6]. This case of a 45-year-old male with a tumor in the small intestine aligns with these findings.

Misdiagnosis is a frequent challenge with GNETs, often being mistaken for CCS-GIT lesions. However, studies have established GNET as a distinct entity. Unlike GNET, CCS lesions display melanocytic differentiation, with positivity for HMB45 and Melan-A and the presence of melanin granules on electron microscopy. While CCS can occur in various locations, 90.4% of GNETs are restricted to the GI tract, with occasional cases reported in the esophagus, anal canal, and bronchi [3,7]. Osteoclast-like giant cells, a characteristic feature of some GNETs [6], were absent in this case.

Molecular diagnostics are crucial for identifying this rare tumor. The most common genetic fusion event in GNET is EWSR1:ATF1, followed by EWSR1:CREB1 [8]. In this case,

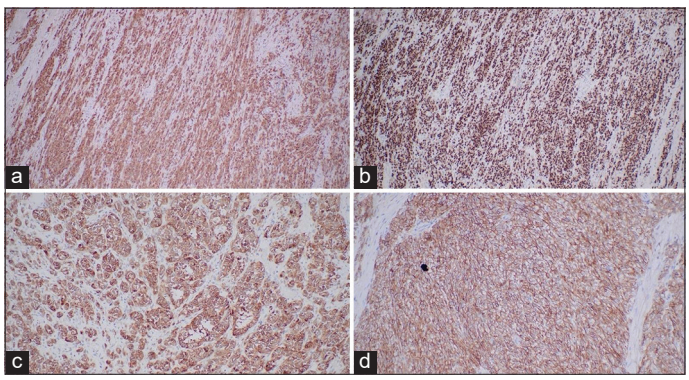

Figure 3: Immunohistochemical of neoplastic cells. Neoplastic cells were diffusely and strongly positive for (a) S100 and (b) SOX10. (c) CD56 and (d) synaptophysin also showed patchy strong positivity (×200)

the initial diagnosis of Ewing sarcoma on biopsy was based on FISH results that confirmed only EWSR1 rearrangement. However, subsequent FISH analysis after surgery identified the EWSR1:CREB1 fusion, underscoring the need to consider GNET in cases of atypical GI tumors with EWSR1 rearrangement.

Li *et al*.'s study on TNM staging and Kaplan–Meier analysis revealed that histological grade, metastasis at diagnosis, and lymph node involvement significantly influence survival. Extensive lymph node metastasis, as seen in this case, is associated with recurrence and poor prognosis. In addition, lower mitotic activity and the absence of necrosis correlate with better outcomes [6]. In this case, persistent hepatic metastasis was noted post-surgery, reflecting the aggressive nature of GNET.

Treatment for GNET typically involves radical surgical excision, followed by close monitoring and adjuvant therapies. However, drug resistance and the lack of specific targeted treatments pose significant challenges [3]. Chemotherapy or radiotherapy can extend survival but may not prevent recurrence or metastasis. Routine endoscopic examination has been suggested as a preventive measure [6].

Our case of malignant GNET shares some similarities with the osteoclast-rich gastrointestinal tumors described by Zambrano *et al*., including small bowel involvement, aggressive behavior, high mitotic activity, necrosis, and metastatic spread. However, while both tumors exhibit S100 positivity, our case showed strong SOX10, CD56, and synaptophysin expression and harbored an EWSR1:CREB1 fusion, distinguishing it from Zambrano's cases, which lacked neuroendocrine markers and instead featured osteoclast-like giant cells and a t(12;22)(q13;q12) translocation, linking them to CCS of soft parts [9,10].

Our case of GNET shares key features with the case reported by Kong *et al*., including EWSR1 rearrangement, S100 positivity, and the absence of melanocytic markers, further supporting the classification of GNET as a distinct entity. However, differences in tumor location, metastatic spread, and neuroendocrine marker expression highlight potential variations in biological behavior and underscore the need for further studies to better define prognostic factors and optimal treatment strategies for this rare tumor type [11].

Among the three cases reported by Shenjere *et al*. there were small bowel involvement, aggressive clinical behavior, S100 positivity, and EWSR1 gene rearrangement similar to our case. However, even though two of the tumors did not show melanocytic markers by immunohistochemistry, they were still classified as CCS in the study, making an accurate comparison difficult [12].

GNET is frequently confused with other tumors, such as Ewing sarcoma and gastrointestinal stromal tumors (GISTs). Diffuse CD99 expression, typical in Ewing sarcoma, is absent in GNET, while molecular studies for specific rearrangements, such as EWSR1:ATF1 or EWSR1:CREB1, are diagnostic. GISTs can be differentiated by their positivity for CD117, DOG1, and CD34, as well as their molecular evidence of c-kit fusion.

CONCLUSION

In summary, GNET is a rare and aggressive malignancy of the GI tract that warrants early diagnosis and prompt management. The present case highlights the potential for misdiagnosis, as the tumor was initially identified as Ewing sarcoma on a small core biopsy. Comprehensive immunohistochemistry and molecular studies, including the detection of EWSR1:ATF1 or EWSR1:CREB1 fusions, are essential for an accurate diagnosis. Further research is needed to improve therapeutic strategies and outcomes for GNET patients.

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Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Shamsuddin F, George SA, Misdiagnosis of malignant gastrointestinal neuroectodermal tumor as Ewing sarcoma: A case report with molecular insights. Indian J Case Reports. 2025; 11(5):232-234.