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Case and Review

Gastrointestinal Neuroectodermal Tumor/Extraskeletal Ewing Sarcoma of the Ileum with Ulcerative Colitis

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Keywords

Ileum · Inflammatory bowel disease · Sarcoma · Ulcerative colitis

Abstract

Introduction: Malignant gastrointestinal neuroectodermal tumor (GNET), previously known as clear cell sarcoma-like tumor of the gastrointestinal tract, is an extremely rare and aggressive mesenchymal neoplasm characterized by high rates of recurrence, metastases, and mortality. Currently, there are no standardized guidelines for therapy. ***Case Presentation:*** We present a case of GNET in a 32-year-old male with a history of lymphoma and ulcerative colitis (UC), who also had synchronous multiple liver metastasis. To our knowledge, this is the first documented case of GNET in a patient with inflammatory bowel disease. ***Conclusion:*** The narrow time frame in which UC and GNET were diagnosed warrants further investigation into their potential relationship.

Introduction

There are approximately 100 documented cases of gastrointestinal neuroectodermal tumor (GNET) [1]. First described in 1965, GNET was initially associated with tendons and aponeuroses of the distal extremities. It was later discovered as a jejunal tumor containing osteoclast-like giant cells. As more cases were reported, it became evident that most of these tumors involved the subserosa and submucosal layers of the gastrointestinal (GI) tract and could be found throughout the small intestine and stomach [2]. Individuals with chronic atrophic gastritis are more susceptible to developing GNETs [3]. The tumor often resembles

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melanoma and shares many histologic features with it. The most frequent translocation and distinguishing feature is the presence of t(12;22), which results in the fusion of EWSR1-ATF1 and EWSR1-CREB1 genes [4]. It was named clear cell sarcoma-like tumor of the gastrointestinal tract due to its similar morphologic features, but the osteoclastic giant cells and melanin pigment, as evidenced by S100 protein expression, are primary differentiating factors from clear cell sarcoma-like tumor of the gastrointestinal tract [5].

Case Presentation

A 32-year-old male with a history of stage IIB Hodgkin's lymphoma initially diagnosed in 2008 and since in remission after treatment with adriamycin, bleomycin, vinblastine, decarbazine was diagnosed with ulcerative proctitis in 2019 and was subsequently managed on mesalamine and vedolizumab. The patient was initially started on oral and rectal mesalamine but was switched to vedolizumab given persistent symptoms. He was later restarted on rectal mesalamine following breakthrough rectal bleeding after chemotherapy. Both therapies were continued during active chemotherapy to mitigate the risk of an ulcerative colitis flare, which would further immunocompromise the patient.

Five months after continuing both therapies, he was found to have profound anemia prompting further workup, including colonoscopy that yielded negative findings. Given the negative colonoscopy, he underwent capsule endoscopy, which led to the discovery of a small bowel obstruction necessitating exploratory laparotomy. A 3.5 × 2.0 cm circumferential, centrally ulcerated, polypoid, firm mass was removed (shown in Fig. 1). Microscopic examination revealed a malignant neoplasm with positive margins. Tumor cells had oval to polygonal nuclei, prominent nucleoli, clear cytoplasm, 22/10 hpf, and 5% necrosis (shown in Fig. 2). Immunostaining revealed cells that were immunoreactive for SOX-10, EMA, and vimentin, and negative for S100, HMB-45, Melan-A, CD117, DOG1, chromogranin, synaptophysin, SMA, desmin, CAM 5.2, and AE1/AE3. FISH analysis revealed EWSR1-ATF1 rearrangement with a positive t(12;22) translocation.

A staging PET scan revealed a 2 cm right liver mass and hypermetabolic densities in the left liver; biopsies of these areas revealed epithelioid neoplasms with EWSR1-ATF1 fusion. He underwent liver embolization of the right liver metastases and later the left lobe. Despite this, he continued to experience weight loss and enlarging liver masses prompting treatment with pazopanib, followed by doxorubicin, ifosfamide, and mesna. This second regimen decreased the size of the lesions, reduced overall PET avidity, and improved symptoms such as night sweats. However, he experienced a hypersensitivity reaction to doxorubicin, resulting to a switch to trabectedin. Although there was some improvement in symptoms, new and increased bilobar hepatic metastases developed, necessitating a change to high dose ifosfamide and etoposide. Due to the rapid progression of disease and worsening liver function, the patient eventually opted for hospice and comfort care.

Discussion

Green et al. [6] analyzed 58 cases of GNET and demonstrated a median survival of 9.5 months. A 2019 study by Yagnik et al. [7] conducted an in-depth analysis of GNET to map the occurrence of Extraskeletal Ewing's Sarcoma/Primitive Neuroectodermal Tumor (E-EWS/PNET) within the small bowel across 30 cases. The findings revealed similarly poor survival rates, with the highest incidence observed in individuals aged 10–20 years. The distribution of E-EWS/PNET within the small bowel was as follows: 61.29% of cases in the ileum, 22.58% in

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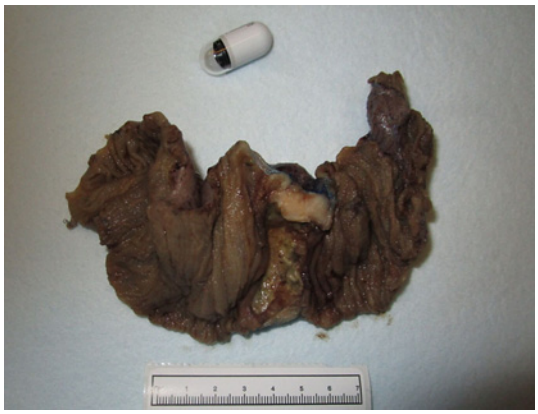

Fig. 1. Resected small bowel after retained capsule causing small bowel obstruction with 3.5 × 2.0 cm mass.

the jejunum, 6.45% in the duodenum, and 9.67% of cases with no specified localization. However, given the relatively recent characterization and rarity of disease, there is no consensus on treatment. The most commonly employed treatment is tumor excision, but high rates of metastases and local recurrence necessitate adjuvant chemotherapy [8]. Doxorubicin is standard first-line treatment of soft tissue sarcoma. Other options include pazopanib, which offers favorable response for 1.5 years, tyrosine kinase inhibitors such as apatnib and anlotinib, or cisplatin and etoposide [9–11]. EWSR1-CREB1 activates melanocyte transcription factors, which in turn activate transcription of c-MET, a factor shown to be involved in GNET. Currently, MET inhibitor trials are underway [12].

In our patient, ulcerative proctitis and GNET were diagnosed 7 months apart. Given this narrow window, there was consideration as to whether his UC was truly a paraneoplastic-like syndrome or if UC was a risk factor for GNET. Neuroectodermal neoplasms exists into two groups: group I containing neuroendocrine carcinomas including pituitary and carcinoid, and group II containing non-epithelial neuroectodermal neoplasms like malignant melanoma and Ewing's sarcoma [13].

Inflammatory bowel disease (IBD) confers an increased risk of colorectal malignancies, most commonly adenocarcinoma. Other epithelial and non-epithelial tumors include lymphomas and sarcomas, which represent the largest group of reported tumors associated with IBD [14]. Melanoma, a non-epithelial neuroectodermal neoplasm, is also associated with IBD. Biologics and immunosuppressives can increase the risk of melanoma in IBD patients; however, our patient did not start vedolizumab until after the diagnosis of GNET [15]. Additionally, there appears to be intrinsic increased risk for melanoma in IBD that is not associated with immunosuppressive agents [16].

Given its selective mode of action in the gut, vedolizumab is the preferred treatment for UC in patients with a prior history of systemic cancers. The question remains whether immunosuppressive therapy in patients with a history of lymphoma will lead to recurrence of their prior disease. In a retrospective study, the incidence of recurrence or development of a new cancer diagnosis in patients using vedolizumab was 2.2 per 1,000 person-years compared to 5.6 per 1,000 person-years in those without immunosuppressive therapy [17]. There is ultimately no significant difference in risk of recurrence with immunosuppressive therapy.

To our knowledge, this is the first case of GNET in a patient with co-committant IBD/UC. Adhya et al. [18] gathered 62 cases of malignant GNET from 1998 to 2019 with cases documenting a past history of hepatoblastoma, leukemia, neuroblastoma, Ewing sarcoma, colon adenocarcinoma, renal cell carcinoma, and seminoma. We have also identified a case of GNET with liver and lymphatic metastases in a patient with a history of malignant lymphoma, similar to our patient [19]. Given the limited literature, it is difficult to determine risk factors

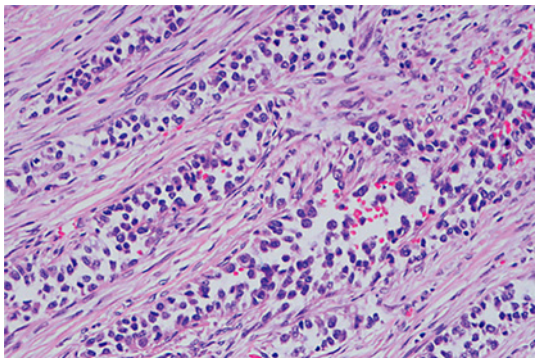

Fig. 2. GNET tumor cells with oval to polygonal nuclei, prominent nucleoli, and clear cytoplasm.

and sequelae to this neoplasm. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542659).

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Statement of Ethics

Written informed consent was obtained from the patient and discussed with next of kin for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local and national guidelines. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tianyu She and Stephanie Ren drafted the manuscript. Seymour Katz conceived and designed the manuscript and reviewed the manuscript critically for important intellectual content in addition to grammatical edits. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

No data were made available with respect to this work. All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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