

# Gastrointestinal clear cell sarcoma, AKA malignant gastrointestinal Neuroectodermal tumor: an uncommon entity in a young patient presenting with Anemia, Intraabdominal mass and subsequent liver metastasis

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## Abstract

Gastrointestinal clear cell sarcoma is a rare tumor with neuroectodermal differentiation that affects the gastrointestinal tract and involves gene fusion translocations of EWSR1. These tumors predominantly occur in young adults and often display aggressive behavior, with metastases to lymph nodes and the liver. Histologically, the tumor comprises uniform round cells with round nuclei and pale eosinophilic or clear cytoplasm. It exhibits variable mitotic activity and demonstrates positive immunohistochemical staining for S100 and SOX10, while specific melanocytic markers are negative. Currently, no tailored chemotherapy regimen has been identified for this entity. Due to the limited number of reported cases, effective management strategies remain unclear. Here, we present the case of a young adult patient diagnosed with CCS/GNET using immunohistochemistry. The diagnosis was confirmed by next-generation sequencing (NGS), which detected the characteristic EWSR1-ATF1 gene fusion, and liver metastases were identified during follow-up.

**Keywords:** gene fusion EWSR1-ATF1; next-generation sequencing (NGS); EWSR1 (22q12.2); malignant gastrointestinal neuroectodermal tumor; gastrointestinal clear cell sarcoma

## Introduction

Gastrointestinal clear cell sarcoma is a rare mesenchymal tumor with neuroectodermal differentiation that affects the gastrointestinal tract and involves gene fusion translocations of EWSR1. Histologically, the tumor typically consists of uniform round cells with round nuclei and pale eosinophilic or clear cytoplasm, although areas with spindle cell morphology may also be present. Tumor cells are often separated by fibrous septa, and multinucleated osteoclast-like giant cells are observed in approximately half of the cases. Mitotic activity is variable. Positive immunohistochemical staining for S100 and SOX10 is characteristic, while melanocytic markers such as Melan A and HMB45 are, by definition, negative. Staining for synaptophysin and CD56 is commonly observed but may be patchy. In this report, we present a case of jejunal CCS and discuss its clinicopathological, immunohistochemical, and molecular features, as well as the differential diagnoses of CCSs.

## Case presentation

Our patient was a young adult who was previously healthy, a non-smoker, and a social drinker, with no history of drug use. His

family history was non-contributory. The patient presented with progressive fatigue, weight loss, and significantly low hemoglobin levels (4.6 g/dl). Initial investigations, including endoscopy and colonoscopy, were conducted to evaluate a suspected malignancy as the source of bleeding, but no abnormalities were identified. The patient underwent multiple upper gastrointestinal endoscopies, all of which were unremarkable and failed to reveal any abnormalities. Due to persistent concerns about malignancy, a PET/CT scan was performed. The scan revealed focal wall thickening of a small bowel loop in the left abdomen with increased FDG uptake (Fig. 1).

Subsequently, the patient underwent diagnostic laparoscopy with segmental small intestinal resection. Gross examination revealed a 5 cm annular mass involving the full thickness of the jejunal wall (Fig. 2). On cross-section, the mass appeared solid and tan-white, with an unremarkable mucosal surface.

A low-power histologic exam shows clusters and sheets of round epithelioid cells separated by fibrovascular bands. The tumor is mainly submucosal and only focally invades mucosa (Fig. 3A). The intermediate power exam shows sheets and clusters of malignant cells separated by fibrovascular cores. Clear cytoplasmic appearance can be appreciated at this magnification (Fig. 3B). High power exam shows the cells with large round

Received: November 27, 2024. Accepted: February 19, 2025

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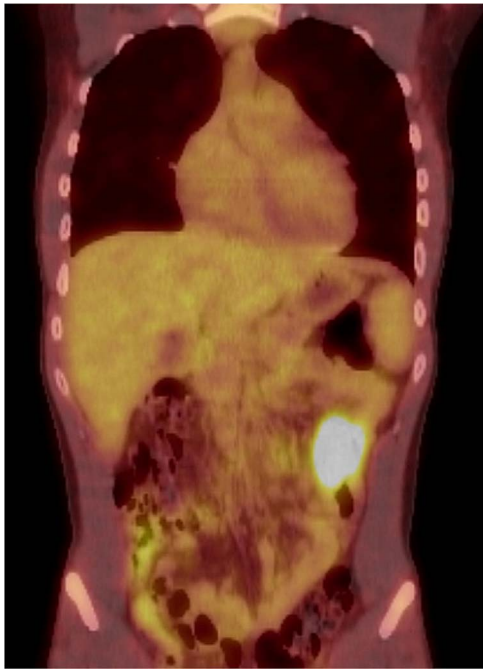


Figure 1. PET/CT scan: Showing focal wall thickening of small bowel loop in the left abdomen with increased FDG uptake (SUV max 8.7).

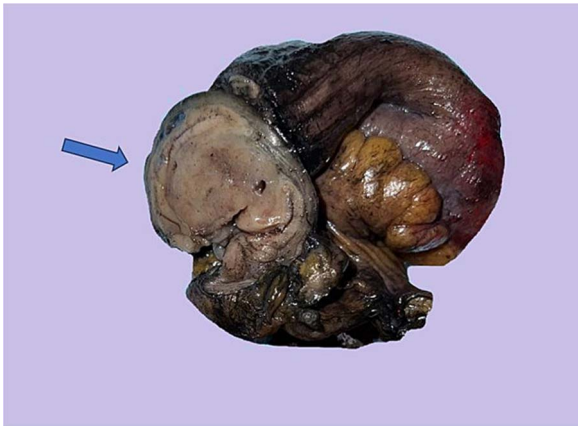


Figure 2. Gross appearance: Show well circumscribed solid tan-pink cut surface.

nuclei, occasional prominent nucleoli and light eosinophilic to clear cytoplasm. Mitotic figures were inconspicuous. Osteoclast-like multinucleated giant cell can also be seen (Fig. 3C).

Immunohistochemistry demonstrated nuclear and cytoplasmic positivity for S100 (Fig. 4A), positive nuclear staining with SOX10 (Fig. 4B), and patchy membranous staining with CD56 (Fig. 4C). The tumor was negative for melanocyte-specific markers (Melan A and HMB-45), SALL4, Synaptophysin, and CD117.

Molecular studies included FISH analysis, which confirmed an EWSR1 (22q12.2) rearrangement (Fig. 5). Next-generation sequencing (NGS) identified an EWSR1-ATF1 chromosomal rearrangement and tumor mutational burden of 4.2 mutations/MB (low).

Post-operatively, the patient did well with improved symptoms and a hemoglobin level that increased to 14.7 g/dl. The patient was presented at a multidisciplinary tumor board conference, which concluded that no adjuvant therapy is indicated at this time due

to the negative lymph node status, and frequent surveillance was recommended. Approximately five months later, during routine surveillance imaging, a whole-body scan was negative except for a newly identified peripherally enhancing lesion in the posterior right hepatic lobe, measuring 1.5 cm, which was not on prior examinations exams. MRI with contrast was performed to better visualize the liver lesion, revealing three small, indeterminate, ill-defined lesions in the posterior right hepatic lobe, measuring up to 13 mm, with surrounding perfusion changes concerning for metastatic disease. The patient underwent a CT-guided liver biopsy. The initial biopsy was negative for metastatic tumor. The second biopsy showed the tumor with histomorphologic features identical to those observed in the jejunal resection (Fig. 6A and B).

The immunohistochemical profile performed and showed positive Sox-10 (Fig. 7A), S-100, focally positive CD56 (Fig. 7B) and negative synaptophysin. The histology and IHC confirmed the diagnosis of metastatic malignant gastrointestinal neuroectodermal tumor.

## Discussion

Gastrointestinal clear cell sarcoma (CCS) of the gastrointestinal tract is a rare entity first described in 2003 [1]. To the best of our knowledge, fewer than 100 cases have been reported in the English literature [1]. This tumor is most commonly found in young adults, with more than 60% of patients being under the age of 45 and a median age of diagnosis of 35 years [2]. Patients typically present with symptoms such as abdominal pain, vomiting, abdominal distension, weight loss, and anemia [2]. The exact etiology of CCS remains unknown; however, some case reports suggest that a history of radiotherapy may contribute to its pathogenesis [3]. Exposure to chemotherapy or radiotherapy during childhood for conditions like neuroblastoma, hepatoblastoma, acute lymphoblastic leukemia, or Ewing's sarcoma has been suggested as a potential trigger for these tumors [4].

CCS most commonly arises from the wall of the small intestine and less frequently from the walls of the stomach, colon, or peritoneum [5]. At the time of diagnosis, most cases present with regional lymph node involvement or distant metastases, or patients develop recurrence following surgical excision. The liver, peritoneum, and omentum are the most common metastatic sites [1]. Consequently, the clinical course of gastrointestinal CCS appears more aggressive than that of clear cell sarcoma of the soft tissue [5]. As a malignant tumor originating in the interstitium of the gastrointestinal tract wall, it must be differentiated from gastrointestinal stromal tumors (GISTs), synovial sarcoma, and malignant peripheral nerve sheath tumors [6]. Histologically, CCS can be misinterpreted as other non-epithelial gastrointestinal tumors or metastatic tumors, such as seminoma. Awareness of the diagnostic criteria is crucial to avoid misdiagnosis. Strong S-100 staining in most tumor cells is atypical for GISTs and helps exclude leiomyosarcoma. Furthermore, GISTs typically express CD117 (c-Kit), DOG1, and CD34, which are absent in CCS, and c-Kit fusion is a common feature in GISTs [7]. Another important differential diagnosis is clear cell sarcoma of soft tissue; however, CCS lacks melanocytic markers such as HMB-45 and Melan-A, which are commonly found in the soft tissue variant [7]. Identifying the t(12;22)(q13;q12) translocation through FISH analysis further aids in distinguishing CCS from other tumors. Microscopically, CCS is characterized by uniform epithelioid cells arranged in various patterns, including solid formations, nests, and pseudopapillary architectures. Osteoclast-type giant cells are frequently observed,



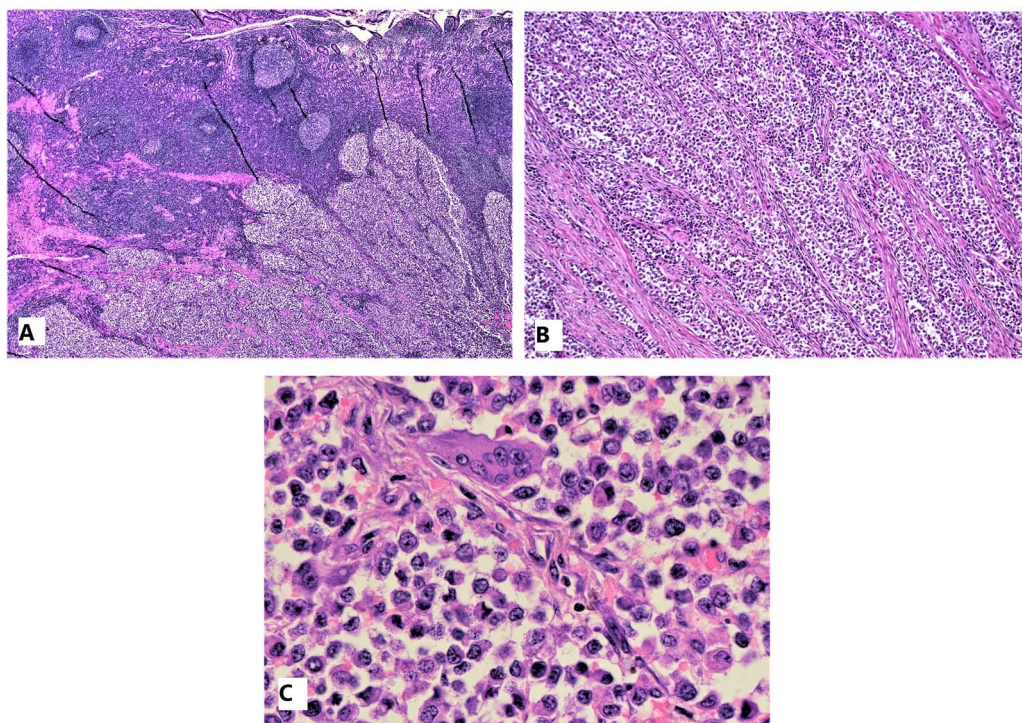


Figure 3. Microscopic pictures: Clusters of malignant cells show upward invasion of the mucosa (A), clusters of malignant cells separated by fibrovascular cores (B), high-power view of tumor cells and a single multinucleated giant cell (C).

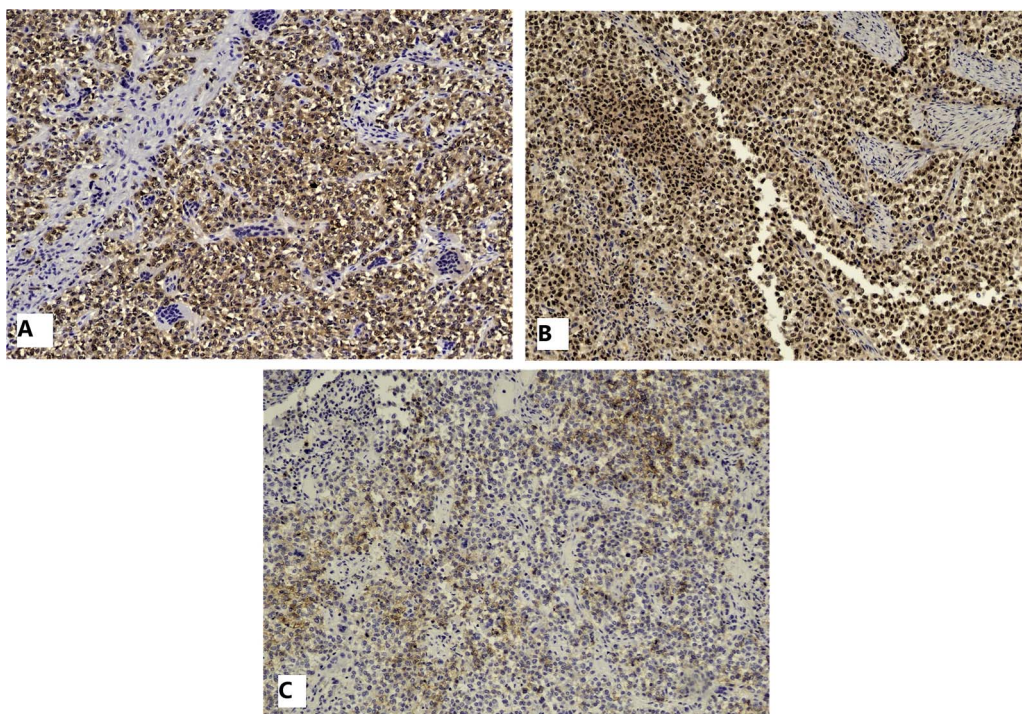


Figure 4. IHC: Tumor cells are strongly and diffusely positive for S-100 (A), Sox-10 (B), and patchy positive for CD56 (C).

but melanin pigment or evidence of melanocytic differentiation is usually absent [4]. The tumor cells are positive for S-100 and SOX-10, with at least focal positivity for CD56. However, melanocytic markers such as Melan-A and HMB-45 are consistently negative [3]. Diagnosis is challenging due to the absence of specific clinical manifestations and the limitations of gastrointestinal endoscopy, making imaging a critical tool for detecting abnormal-

ities. CCS should be considered when significant enhancement of gastrointestinal tumors is observed in the venous phase, particularly if accompanied by liver or lymph node metastases [8]. MRI, with its high-resolution and functional imaging capabilities, offers unique advantages, often providing early indications of disease and prompting timely biopsy. However, definitive diagnosis of CCS relies primarily on pathological evaluation [8].



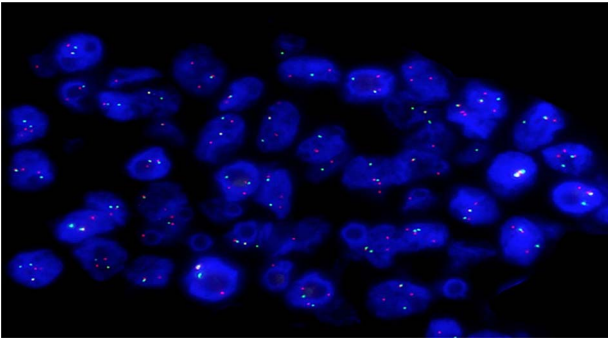


Figure 5. Molecular study with FISH analysis: Positive FISH result for EWSR1 (22q12.2) rearrangement.

## Conclusions

CCSs are highly aggressive malignancies with a high likelihood of local recurrence and distant metastasis, posing significant challenges to patient management and outcomes. Nearly 50% of patients succumb to the disease within three years of diagnosis, reflecting its aggressive clinical course and the limitations of current treatment approaches. The cornerstone of diagnosis lies in the identification of genetic alterations, particularly the hallmark EWSR1-ATF1 or EWSR1-CREB1 gene fusions. These fusions are pivotal for distinguishing CCS from other morphologically similar malignancies. Advanced molecular diagnostic techniques such as fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR),

and next-generation sequencing (NGS) have revolutionized diagnostic accuracy, enabling pathologists to confirm CCS with high specificity. Despite these advancements, the rarity of the tumor and its histopathological overlap with other neoplasms often lead to delayed or misdiagnosed cases, which further complicates patient management and impacts prognosis. Early and accurate diagnosis plays a critical role in guiding treatment decisions and improving patient outcomes. Given the aggressive nature of CCS, identifying the genetic signature not only confirms the diagnosis but also facilitates the development of tailored surveillance and therapeutic strategies. Timely detection and intervention can significantly impact the prognosis, providing a potential window for more effective disease control and better quality of life for affected patients.

Unfortunately, there is no consensus or standardization of adjuvant therapy for CCS. The effectiveness of chemotherapy and radiotherapy remains limited, with most cases showing minimal or no benefit. Although tyrosine kinase inhibitors have been administered postoperatively in some cases, their efficacy has not been extensively studied. The lack of robust clinical evidence highlights the need for collaborative research and clinical trials to explore novel therapeutic strategies. Targeted therapies, immunotherapy, or other precision medicine approaches may hold promise for addressing the limitations of current treatments.

As CCS continues to be a diagnostic and therapeutic challenge, there is an urgent need for increased awareness among clinicians and pathologists. Multidisciplinary collaboration, incorporating molecular diagnostics, imaging, and advanced

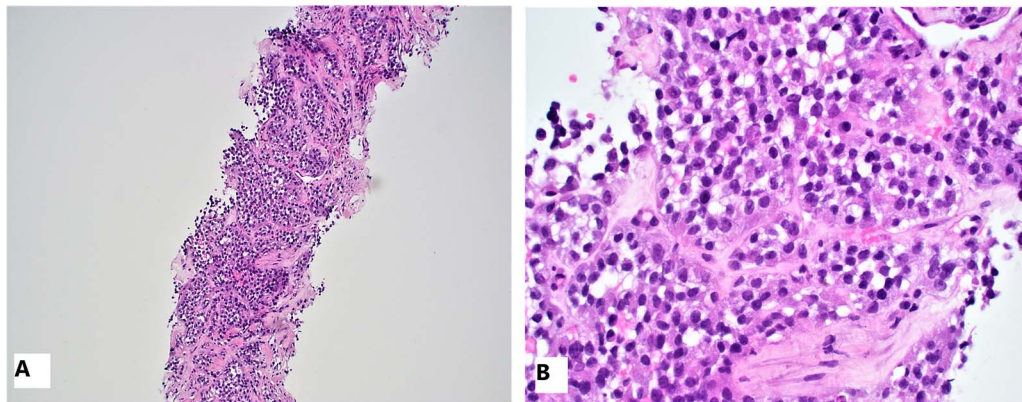


Figure 6. Microscopic image of the liver biopsy mass: H&E shows similar microscopic features of clear cell sarcoma, which shows clusters of uniform tumor cells with clear cytoplasm that replace the liver parenchyma, 20x (A) and 40x (B).

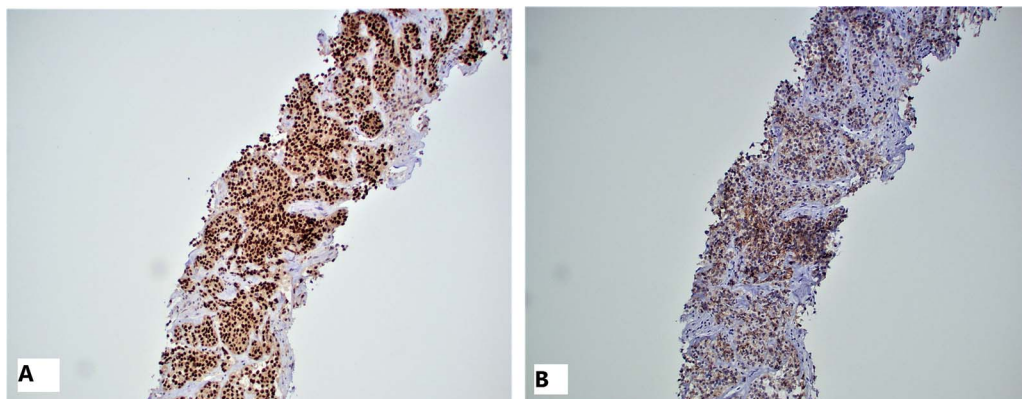


Figure 7. IHC of the liver mass: Tumor cells are strongly positive for Sox-10 (A) and patchy positive for CD56 (B).

surgical techniques, can aid in better understanding and managing this rare malignancy. Future research efforts should focus on elucidating the underlying biology of CCS, identifying actionable targets for therapy, and standardizing treatment protocols to improve survival rates and overall patient care.

## Contributors

All authors contributed to planning, literature review and conduct of the review article. All authors have reviewed and agreed on the final manuscript.

## Funding

None declared.

## Conflict of interest

Authors have no conflict of interest.

## Patient consent for publication

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Availability of data and materials

Not applicable.

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