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Letter to the Editor

Clear cell sarcoma-like tumor of the gastrointestinal tract: A clinicopathological review

To the Editor:

Clear cell sarcoma of soft parts (CCS) is a rare melanin-producing soft tissue sarcoma that was originally reported by Enzinger in 1968.[1] Morphological and immunohistochemical features of CCS are similar to those of malignant melanoma. However, CCS is genetically distinct from melanoma as it lacks *BRAF* mutations, and has *EWSR1/ATF1* or *EWSR1/CREB1* fusion transcripts.[2] In 1993, Ekfors et al. reported a case of clear cell sarcoma of the duodenum, which was the first visceral case reported.[3] Following this report, several clear cell sarcomas of visceral cases were reported with a variety of names (including malignant gastrointestinal neuroectodermal tumor, an osteoclast-rich tumor of the gastrointestinal tract with features resembling those of clear cell sarcoma of soft parts). Clear cell sarcoma in the gastrointestinal tract is classified as a poor prognostic subtype of CCS in the World Health Organization Classification of Tumors-Tumors of Soft Tissue and Bone 4th edition.[4] In contrast, it is classified as an independent disease, clear cell sarcoma-like tumor in gastrointestinal tract (CCSLGT) because of its different histological features, immunohistochemical expression, and poor prognosis, as described in Enzinger & Weiss's Soft Tissue Tumors 6th edition.[5] To the best of our knowledge, tumors belonging to the CCSLGT category have been reported in 58 cases in the English literature and in one case in the Japanese literature. Herein, we report our CCSLGT case and review 60 cases.

The patient was a 32-year-old woman who had no history of malignancy. She visited the hospital because of fever and was diagnosed with anemia. She underwent gastrointestinal endoscopy. Lower gastrointestinal endoscopy revealed a tumor of the transverse colon. On admission, tumor marker levels (CA 19–9, $<$2.0 U/mL; carcinoembryonic antigen [CEA], 1.6 ng/mL) were not elevated. Contrast-enhanced computed tomography showed a poorly enhanced tumor in the transverse colon and lymphadenopathy around the colon. Substantial organ metastasis was not found. Positron emission tomography showed that the tumor had an abnormal accumulation (standard uptake value: 13.7). There was no other abnormal accumulation, except in the lymph nodes.

Tumor biopsy showed round to oval cells that were growing in solid sheets. The neoplastic cells contained clear to lightly eosinophilic cytoplasm. The nuclei had small nucleoli. Mitotic activity was brisk. Because the tumor was diagnosed as malignant using biopsy, the patient underwent transverse colon resection and lymphadenectomy. The resected specimen showed a well-circumscribed mass with ulcer formation, having a diameter of $65 \times 40 \times 25$ mm. On cut section, the tumor was a multinodular tan-gray mass. Pathological analysis showed round to oval cells with a high nucleus to cytoplasm ratio; the cells had grown in solid sheets with an area of short spindle cell proliferation. Some osteoclast-like multinucleated giant cells were identified (Fig. 1a–c). There was no pleomorphism or necrosis. Fifteen mitotic figures were noted per 10 high-power fields (HPFs). There were lymph node metastases around the intestinal tract (6/57). Immunohistochemical staining showed that the tumor cells were positive for S100 protein, vimentin, BCL2, and synaptophysin, focally positive for chromogranin A, CD56, and epithelial membrane antigen (EMA), and negative for AE1/AE3, CAM5.2, leukocyte common antigen, CD34, glial fibrillary acidic protein, c-kit, α-smooth muscle actin, desmin, transducer-like enhancer of split 1, CD99, melan A, human melanoma black 45 (HMB45), and neuron-specific enolase (Fig. 1d). The Ki-67 index was approximately 30%. Fluorescence in situ hybridization (FISH) using a Ewing sarcoma breakpoint region (EWSR) 1 probe showed split signals in 76% of tumor cells. The tumor cells contained *EWSR1-ATF1* fusions with exon 11 of *EWSR1* fused to exon 5 of *ATF1*, which were detected using reverse transcription polymerase chain reaction (RT-PCR). Therefore, our case was finally diagnosed as clear cell sarcoma-like tumor of the colon. The patient received postoperative adjuvant chemotherapy (ifosfamide and doxorubicin). Recurrence was confirmed as liver metastasis 38 months after resection, and we are currently considering the possibility of further chemotherapy.

We reviewed 60 cases that were classified into the CCSLGT category (Table S1). There were 32 male and 28 female patients, with ages ranging from 10 to 85 years (median, 40 years). In terms of clinical findings, abdominal pain, anemia and weight loss were reported in many cases. The tumors ranged from 15 to 150 mm (median, 53 mm). CCSLGT occurs everywhere in the gastrointestinal tract, but is most frequent in the small intestine (70%). Only seven patients survived for longer than 3 years, including our case, but there are insufficient cases to conclude that CCSLGT have a worse prognosis than CCS (Fig. S1). The frequency of lymph node metastases at the time of diagnosis of CCSLGT was 62% in comparison with 4% for CCS.[2]

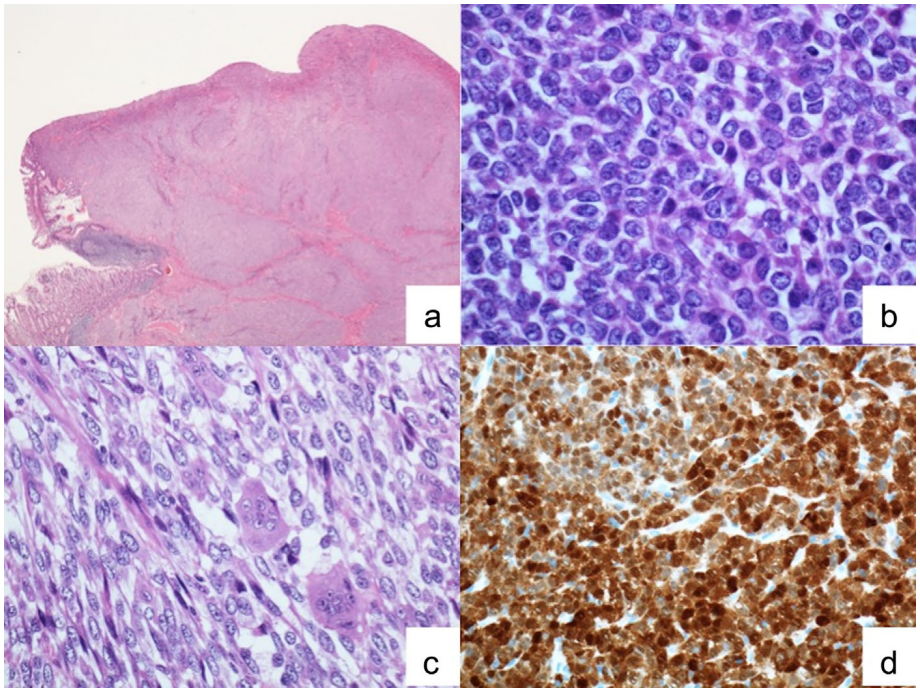

Figure 1 Low-power view of the tumor, which displayed nested architecture (**a**) hematoxylin and eosin staining. The tumor was composed of sheets of small, rounded cells with clear to lightly eosinophilic cytoplasm (**b**) hematoxylin and eosin staining. Spindle cells grew with osteoclast-like multinucleated giant cells (**c**) hematoxylin and eosin staining. Neoplastic cells expressed S100 protein, as assessed using immunohistochemistry (**d**).

The liver was the most frequent metastatic site in CCSLGT (27%: 12 cases), while it was the lung in CCS.[2] Six cases of CCSLGT had peritoneal dissemination at the time of diagnosis. Liver metastasis may be caused by transvenous metastasis in the bloodstream of the intestinal tract wall. The high ratio of liver metastasis and peritoneal dissemination may be related to the anatomical position of CCSLGT.

Overall survival was prolonged in the melanoma marker-negative group compared with the melanoma marker-positive group in univariate analysis by the proportional hazard model ($P = 0.037$); however, multivariate analysis could not confirm significant differences between the two groups (Table S2). We could not detect any significant prognostic factors, as not enough cases had long-term prognosis data. As far as we searched, there are no report that melanoma marker expression is associated with a poor prognosis in CCS.

CCSLGT showed dissimilar features from CCS, including inapparent or small nucleoli and osteoclast-like giant cells, instead of Touton-type neoplastic giant cells.

At the immunophenotypic level, all CCSLGT cases expressed S100 protein and often tested negative for melanoma markers (melan A, HMB45). However, it has been reported that positive SOX10 expression is a sensitive and specific marker for the diagnosis of melanocytic tumors. EMA or neuroendocrine markers are also often positive.

In 48 cases, the *EWSR1* fusion gene was examined; 24 of these involved the *EWSR1/ATF1* and 9 involved the *EWSR1/CREB1* fusion genes. Although *EWSR1-ATF1* and *EWSR1-CREB1* fusions continue to be reported in an increasing variety of neoplasms, the mechanisms by which they contribute to oncogenesis are yet to be understood.

Simple excisions were performed as treatment in many cases. Sixteen cases were treated with postoperative adjuvant chemotherapy mainly composed of ifosfamide and doxorubicin. There are insufficient cases to prove the usefulness of the chemotherapy regimen. However, there were reports that the tumor reduced after chemotherapy and that patients survived without the exacerbation of the tumor even though there was metastasis to the liver or peritoneum at the first surgery. Therefore, chemotherapy may be beneficial in such cases.

In conclusion, CCS and CCSLGT have the same fusion gene; however, their pathological features, immunohistochemical expression, frequency of liver metastasis and peritoneal dissemination are different. Therefore, it is necessary to plan a different treatment strategy for CCSLGT compared with that for CCS. CCSLGT is a relatively recent disease category and is an extremely rare tumor. CCSLGT can be diagnosed based on its characteristic histological features and expression of the S100 protein. Identification of more cases is important for the establishment of a disease classification and an appropriate therapeutic strategy.

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DISCLOSURE STATEMENT

None declared.

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5 Goldblum JR, Folpe AL, Weiss SW, eds. *Enzinger & Weiss's Soft Tissue Tumors*, 6th edn. Philadelphia, PA: Elsevier Saunders, 2014.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Figure S1 Kaplan–Meier overall survival curves for the cases of clear cell sarcoma-like tumor of the gastrointestinal tract.

Table S1 Review of cases of reported clear cell sarcoma of the gastrointestinal tract (60 cases).

Table S2 Univariate and multivariate Cox regression analyses of different prognostic variables in patients with clear cell sarcoma-like tumor of the gastrointestinal tract.