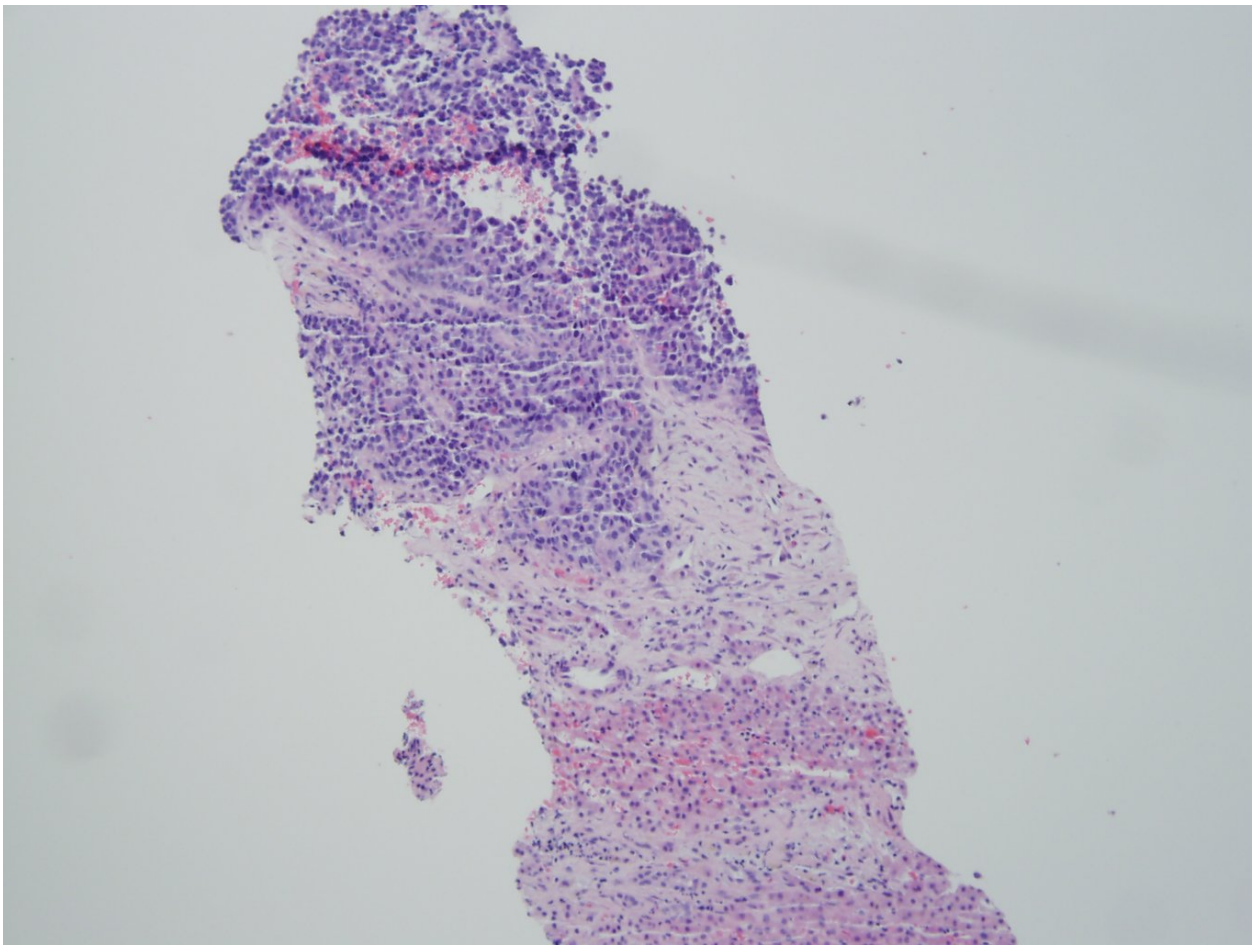
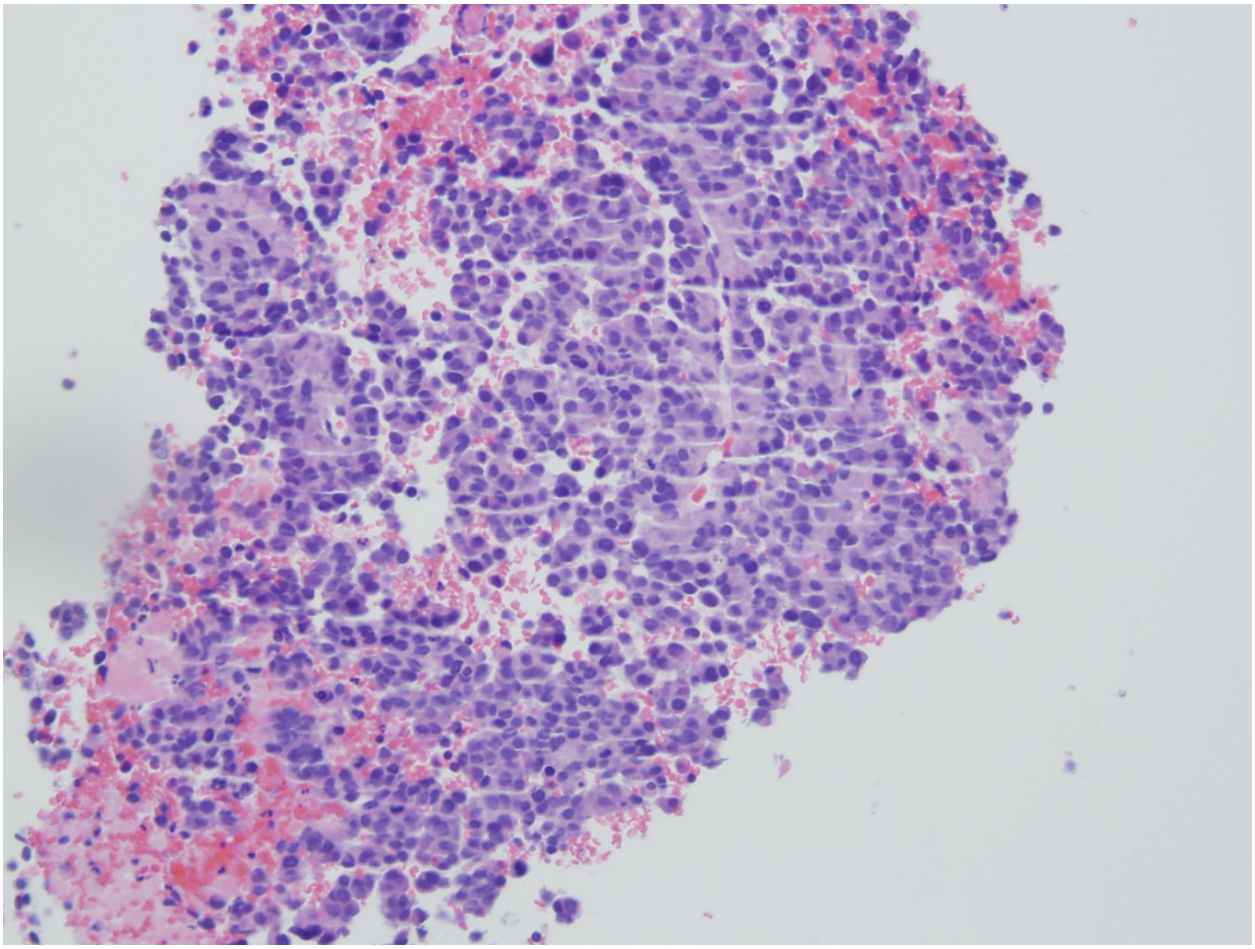
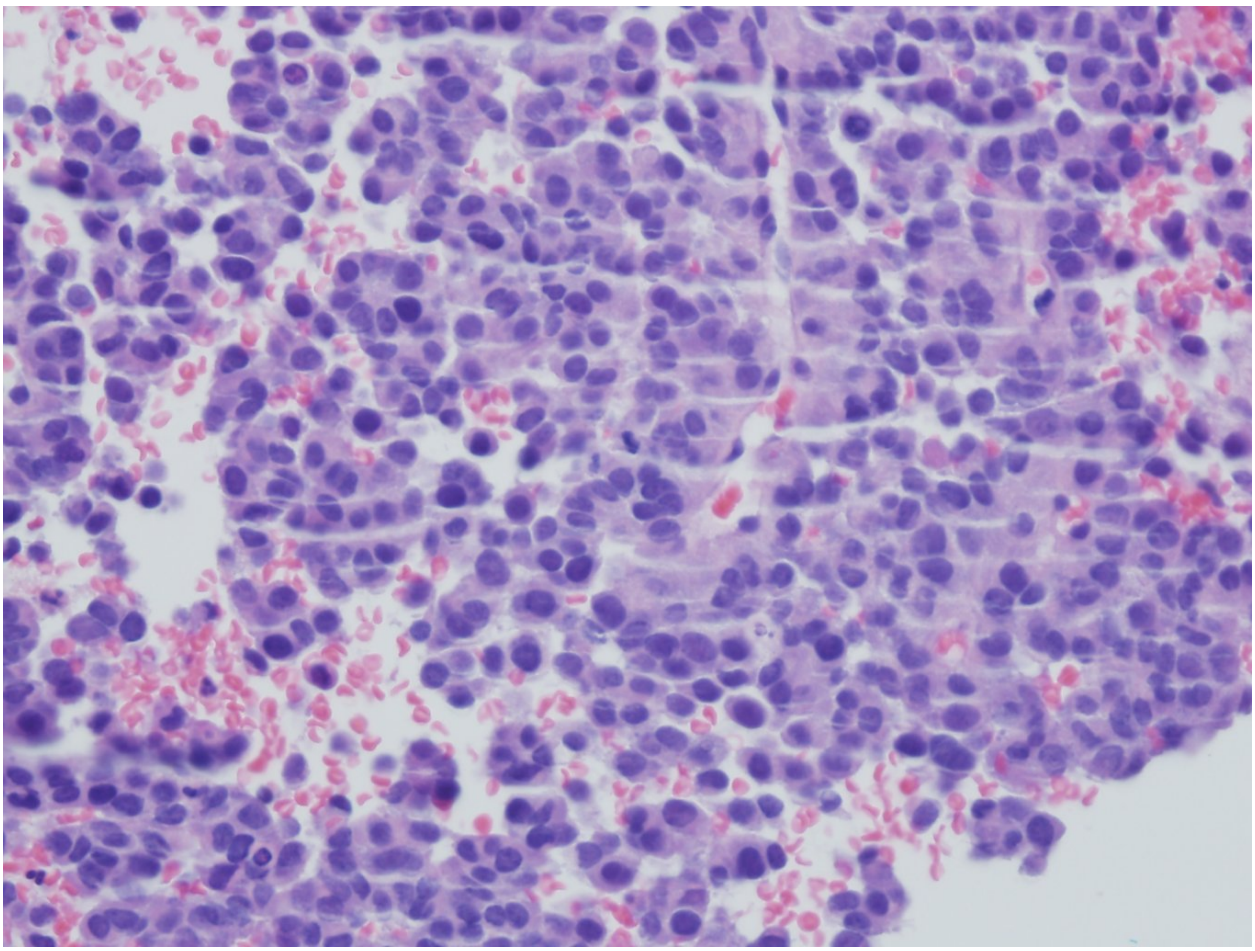
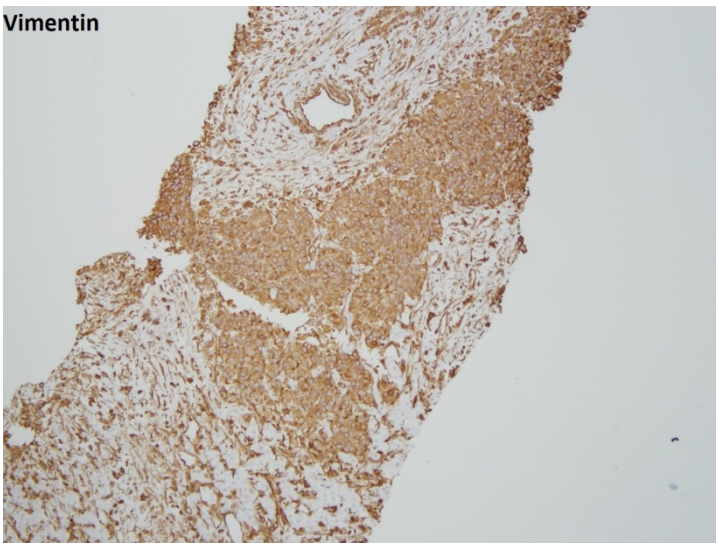
Case: A 54-year-old woman presented with melena. On examination she was found to have abdominal tenderness. A CT scan revealed a large left upper quadrant mass arising from the jejunum with diffuse hepatic metastases.

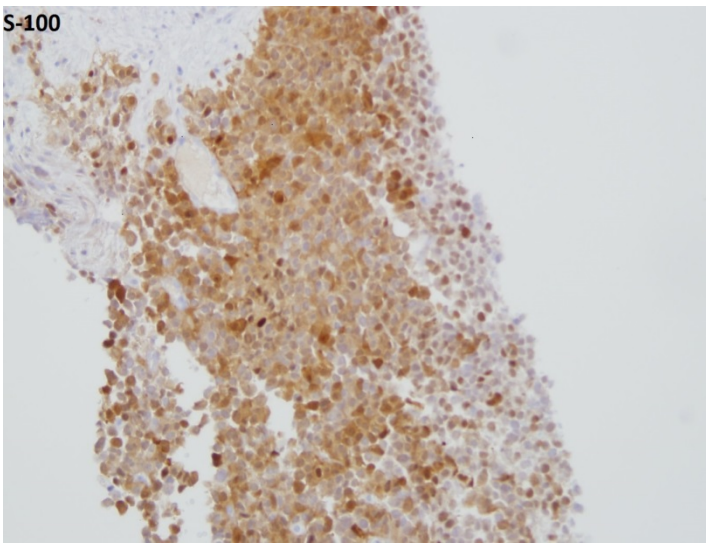
A biopsy of one of the liver lesions was performed. Representative images are shown below including IHC results and FISH.

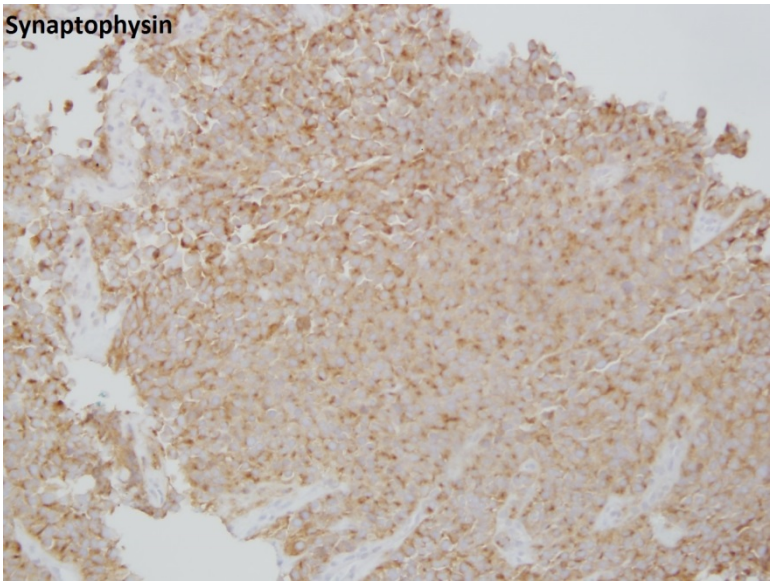






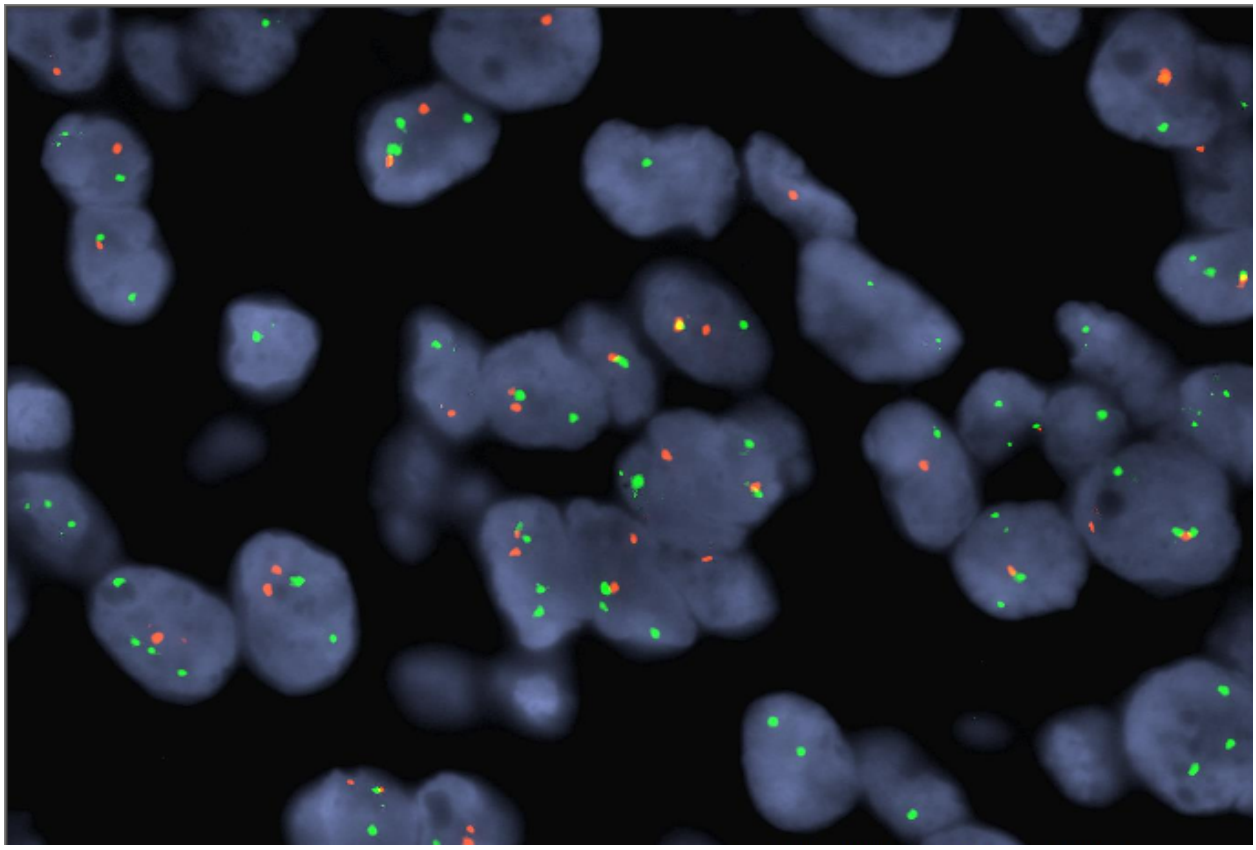






Immunohistochemical Stain	Result
S-100 protein	Positive
Synaptophysin	Positive
Vimentin	Positive
Broad spectrum keratins	Negative
chromogranin	Negative
HMB45	Negative
Melan-A	Negative
PAX-8	Negative
CD56	Negative
CD34	Negative
WT-1	Negative
DOG-1	Negative
CD117 (c-kit)	Negative

FISH:
Positive for rearrangement of the Ewing sarcoma (*EWSR1*) gene, using a dual color break-apart probe.



What is your diagnosis?

a. Melanoma
b. Gastrointestinal stromal tumor (GIST)
c. Clear cell sarcoma-like tumor of the gastrointestinal tract/Malignant gastrointestinal neuroectodermal tumor
d. Well differentiated neuroendocrine tumor
e. Clear cell sarcoma of tendons and aponeuroses

Answer and Discussion:

C. Clear cell sarcoma-like tumor of the gastrointestinal tract/Malignant gastrointestinal neuroectodermal tumor

Discussion:

Hopefully you picked the longest diagnosis (this is usually the correct answer)

This tumor is characterized by mildly discohesive small monotonous epithelioid cells with round hyperchromatic nuclei, inconspicuous nucleoli, and fine evenly dispersed chromatin. There is moderate amphophilic cytoplasm and the eccentric nuclei seen in many cells impart a plasmacytoid appearance. Duct formation and cytoplasmic pigmentation are absent. Positive stains include S-100, synaptophysin, and vimentin.

Clear cell sarcoma-like tumors of the gastrointestinal tract (CCSLTGT) are similar to their soft tissue counterparts, clear cell sarcoma of tendons and aponeuroses (CCSTA), in that they share some morphologic and immunohistochemical features and both are characterized cytogenetically by a recurrent translocation, t(12;22)(q13;q12)/*EWSR1-ATF1.*[1,2] However, CCSLTGT lacks ultrastructural and immunohistochemical evidence of melanocytic differentiation typically seen in CCSTA[1,2]. Recently, ultrastructural features of a subset of CCSLTGT were evaluated and were shown to have neural differentiation in the form of dense-core granules, multiple interdigitating cell processes, and clear vesicles resembling synaptic bulbs[1]. The authors proposed the term *malignant gastrointestinal neuroectodermal tumor* (GNET) to describe these tumors and thus better reflect their neural origin. Electron microscopy was not performed in our case; therefore a diagnosis of CCSLTGT/GNET was rendered. In practical terms, both are considered aggressive tumors with a very poor prognosis as most patients present with metastatic disease and die within 2 years of initial diagnosis.

The differential diagnosis includes all tumors listed in the above multiple choice question. Melanoma is excluded by a lack of other supporting immunohistochemical stains and appropriate clinical history. An epithelioid GIST is certainly a diagnostic consideration given the mural GI involvement of the primary tumor but negative stains for CD117, DOG-1, and CD34 rule out a GIST. The bland cytology, plasmacytoid appearance, and synaptophysin positivity seen in the current case raises the possibility of a well differentiated neuroendocrine tumor but negative staining for broad spectrum keratins is not seen in neuroendocrine tumors. The most difficult diagnosis to exclude is CCSTA. However, these tumors commonly arise in the deep soft tissue of the extremities[2] and our liver lesion was accompanied by a large mass in the jejunum which represented the primary site of involvement. In addition, most CCSTA express antigens associated with melanin synthesis such as HMB-45 and Melan-A which our tumor did not.

References:

1. Stockman DL, Miettinen M, Suster S. et al. Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract. *Am J. Surg. Pathol.* 2012. 36(6):857-68.
2. Weiss S W, Goldblum J R. (2008) *Enzinger and Weiss Soft Tissue Tumors 5th ed.* Philadelphia, PA: Mosby.

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