Quiz Case

Pleomorphic neoplasm in a liver: A potential pitfall for misdiagnosis

Lubna Alattia, Kyle Molberg, Elena Lucas

Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA.

CLINICAL HISTORY TO GUIDE THE QUIZ

A 58-year-old male presented to the emergency department with diarrhea, nausea, and vomiting for 2 weeks. The liver function tests, bilirubin, and alpha-fetoprotein (AFP) were within normal limits. A computerized tomography (CT) scan showed multiple heterogeneous masses replacing the right liver lobe. No suspicious lesions were identified in other organs. A core biopsy was performed. Figure 1a-d shows the CT scan and the cytological and histological features of the tumor.

* Corresponding author: Elena Lucas, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA. elena.lucas@utsouthwestern.edu

Received: 14 June 2019
Accepted: 09 September 2019
Published: 22 April 2020

DOI 10.25259/Cytojournal_81_2019

Quick Response Code:

Figure 1: (a) Computed tomography scan showing multiple liver masses. (b) Touch imprints of the core biopsy showing pleomorphic cells, some with large nuclei, scattered dense intracytoplasmic rhabdoid inclusions, and occasional clear cytoplasmic vacuoles (Diff-Quik stain, ×400). (c) Touch imprints showing neoplastic cells forming rosettes (Diff-Quik stain, ×400). (d) Core biopsy showing pleomorphic cells arranged in sheets with rosettes and pseudoglandular formations. Some cells show rhabdoid features and cytoplasmic inclusions resembling mucinous vacuoles (H and E, ×400).

QUESTION NUMBER 1

What is your interpretation?

A. Adenocarcinoma
B. Hepatocellular carcinoma (HCC)
C. Malignant rhabdoid tumor
D. Pleomorphic well-differentiated neuroendocrine tumor (NET)
E. Large cell neuroendocrine carcinoma (NEC).
ANSWER TO QUESTION NUMBER 1

The correct cytopathologic interpretation is:
D. Pleomorphic well-differentiated NET.

BRIEF DISCUSSION WITH FOLLOW-UP

The touch imprints of the core biopsy were highly cellular with the tumor cells arranged singly and loosely cohesive small groups with rare rosette-like formations. Striking nuclear pleomorphism and multinucleation were seen. Very large hyperchromatic nuclei, some with bizarre nuclear shapes, were scattered among smaller cells with low-grade, eccentric round nuclei. The nuclear-cytoplasmic ratios were low, and the abundant pink cytoplasm contained frequent large, dense, magenta-colored intracytoplasmic inclusions, resembling perinuclear cytoplasmic whorls seen in the rhabdoid cells [Figures 1b and 2a]. Occasional cells had small, clear cytoplasmic vacuoles and rare vacuoles with dense pink secretions. The tissue sections of the cores revealed cells arranged in sheets with occasional rosettes and pseudoglandular formations, a few of which contained lightly basophilic secretions resembling mucoid material. Many cells were columnar, and many had dense, light pink intracytoplasmic inclusions, resembling rhabdoid cells. Occasional cells had cytoplasmic inclusions resembling mucinous vacuoles. The chromatin of large cells was hyperchromatic and mostly smudged; however, occasional cells showed nucleoli, intranuclear inclusions, and coarsely clumped chromatin [Figures 1d and 2b, c]. There were prominent vascularity and rare small foci of necrosis. Mitotic activity was <1 mitosis per 10 high power fields. The differential diagnosis included primary or metastatic adenocarcinoma, hepatocellular carcinoma, or an unusual, pleomorphic NET. By immunohistochemistry, the cells were positive for cytokeratins CAM5.2, CK7, and CK19 and patchy positive for CK20. The cells also were diffusely positive for MOC31, CDX2, synaptophysin, chromogranin, and CD56. The HepPar-1, polyclonal CEA, CD10, glypican 3, AFP, and TTF-1 were negative. The KI-67 proliferation index was approximately 6%–8% [Figure 2d-i]. Based on the strong positivity for neuroendocrine markers, low mitotic count, and relatively low proliferation index, the diagnosis of a well-differentiated NET (Grade 2) was made.

Further, diagnostic work-up revealed a markedly elevated serum chromogranin level (1481 ng/ml). Extensive examination of the patient including chest and abdominal CT scans and lower and upper gastrointestinal endoscopy failed to reveal a potential primary tumor origin. Whether

Figure 2: (a) Touch imprint showing pleomorphic cells, some with large irregular nuclei. Some cells demonstrate dense pink cytoplasmic inclusions and inclusions resembling mucinous vacuoles (Diff-Quik stain, ×400). (b and c) Core biopsy shows sheets of pleomorphic cells, some with bizarre nuclei, intranuclear inclusions and dense cytoplasmic inclusions (H and E, b × 600, c × 400). (d) Synaptophysin is positive. (e) Chromogranin is positive. (f) MOC31 demonstrates diffuse membranous staining. (g) CDX2 shows patchy nuclear staining. (h) HepPar1 is negative. (i) Ki-67 proliferation index is low.
this tumor was primary versus metastatic could not be determined with certainty. The absence of identifiable other primary sites suggested that this could be a primary hepatic neoplasm. However, due to the extreme rarity of primary liver NET and questions in the literature of the very existence of hepatic NETs, the tumor in our case was favored to represent metastasis from a small, undetectable, or “burned out” tumor likely originating in the gastrointestinal tract or extrahepatic pancreatobiliary system. The patient underwent palliative therapy with octreotide with a good initial response and symptomatic relief. However, his serum chromogranin level was steadily increasing. He was placed on an oral chemotherapy regimen. Whole-body surveillance scans continued to show stable large liver masses. The patient was lost to follow-up. Two years later, the patient’s friend informed our hospital that the patient developed severe nausea, vomiting, and bleeding and died at outside hospital.

ADDITIONAL QUIZ QUESTIONS

Q2. NETs in the liver are most commonly:
   A. Primary hepatic
   B. Metastatic from the pancreas, small intestine, or stomach
   C. Metastatic from large intestine
   D. Metastatic from lung

Q3. According to the literature, the behavior of pleomorphic NETs comparing to adenocarcinoma is:
   A. More aggressive
   B. Less aggressive
   C. Similar
   D. Unknown

Q4. Electron microscopy demonstrates that rhabdoid inclusions in NET contain:
   A. Round neurosecretory granules with a centrally located electron-dense core
   B. Collection of whorls of intermediate filaments mixed with neurosecretory granules
   C. Collection of electron-dense rhabdoid-shaped crystals
   D. Collection of needle-shaped crystals

ANSWERS TO ADDITIONAL QUIZ QUESTIONS

Q2. (B); Q3. (B); Q4. (B)

Q2. (B) Most NETs in the liver are metastases from the gastrointestinal tract, pancreas, or lung. The liver is rarely the site of origin.[1,2]

Q3. (B) NETs have a better prognosis than adenocarcinoma. Pleomorphic NETs do not seem to behave differently from conventional NETs.[3]

Q4. (B) Ultrastructurally, the cytoplasm of NETs with rhabdoid features shows prominent smooth and rough endoplasmic reticulum, some mitochondria, and round neurosecretory granules with centrally located electron-dense core. The rhabdoid inclusions are composed of whorls of intermediate filaments mixed with variable number of neurosecretory granules.[4]

BRIEF REVIEW OF THE TOPIC

NETs comprise approximately 1%-2% of all gastrointestinal tumors. In the liver, they most commonly represent metastases from other sites.[3] Tumors without an identifiable primary site most commonly originate from small, unrecognized or “burned-out” gastroenteropancreatic NETs, although rare primary hepatic NETs have been reported in the literature.[1,2,6-8] Different hypotheses exist concerning the pathogenesis of purported primary hepatic NET, including the transformation of liver stem cells,[1,9] proliferation of neuroendocrine-type cells from the bile ducts,[1,2] and presence of ectopic adrenal or pancreatic tissue as the source of primary NETs.[1,2]

Well-differentiated NETs typically have characteristic morphologic features. On cytologic smears, the cells are poorly cohesive and distributed singly or in loose clusters. They tend to be monotonous, small, and uniform and have round, polygonal, or spindle shapes, scant-to-moderate cytoplasm, round or elongated nuclei, and granular, evenly distributed chromatin. In tissue sections, the cells are mainly arranged in trabecular, ribbon-like, acinar, nested, or solid patterns. The diagnosis is confirmed by expression of at least one neuroendocrine marker, such as chromogranin, synaptophysin, CD56, or neuron-specific enolase. According to the World Health Organization (WHO) 2010 classification, gastroenteropancreatic NETs were graded based on the mitotic count and Ki-67 proliferation index and classified into three types: low-grade well-differentiated tumors (Grade 1, <2 mitoses/2 mm², Ki-67 <3%); which typically demonstrate indolent behavior and generally have a good prognosis; well-differentiated tumors of intermediate grade (Grade 2, 2–20 mitoses/2 mm², Ki-67 3%-20%); and poorly differentiated or high-grade neoplasms that have a poor prognosis (Grade 3, >20 mitoses/2 mm², Ki-67 >20%).[10] However, the Grade 3 category of neuroendocrine neoplasms (NENs) is, in fact, heterogeneous. In 2017, an updated WHO classification for pancreatic NENs formally recognized this heterogeneity and included both well-differentiated NETs and poorly differentiated NECs within the Grade 3 category. The former has typical morphology of well-differentiated NETs and shows fewer than 20 mitoses/2 mm² but is associated with high Ki-67 proliferation indices (typically >20% but <55%). Poorly differentiated NECs, on the other hand, have extremely high Ki-67 (usually >75%).[11] Morphologically, they less closely resemble nonneoplastic neuroendocrine cells and have a
more sheet-like or diffuse architecture, irregular nuclei, higher nucleus-to-cytoplasm ratios, and less cytoplasmic granularity. Grade 2 well-differentiated NETs have worse prognosis than Grade 2 NETs but are not as aggressive as poorly differentiated NECs. Because of the characteristic morphologic features, well-differentiated NETs typically do not pose a diagnostic challenge.

On the other hand, one rare morphologic variant, pleomorphic NET, is not well-recognized and has features that can be easily confused with other neoplasms. Only rare studies, including a small series on pancreatic pleomorphic NET and case reports, have been published in the literature. These tumors show exaggerated atypia that may be misleading and suggestive of a high-grade malignancy. It is characterized by large cells, with enlarged or even gigantic nuclei, often with an irregular, bizarre shape, resembling degenerative changes of symplastic leiomyomas and ancient schwannomas. The chromatin may range from smudgy or finely stippled to coarsely clumped. Nucleoli, including macronucleoli and eosinophilic nucleoli, may be present. The cells often show rhabdoid features and demonstrate round, glassy, eosinophilic cytoplasmic globules displacing the nuclei to the periphery. These cytoplasmic inclusions have been previously shown to be negative for both vimentin and desmin, and their rhabdoid phenotype has been defined ultrastructurally as dense cytoplasmic collections of intermediate filaments intermixed with neurosecretory granules. Signet ring-like cells have been also described. In addition to the characteristic growth patterns of typical NET, patterns mimicking glandular and acinar differentiation can be seen. These features can be so extensive that in several reported in the literature cases, they had led to a misdiagnosis of adenocarcinoma. Distinction of these tumors from adenocarcinoma is important because NETs have a much better prognosis and longer survival rate, even in the presence of metastatic disease. The most important characteristic morphologic feature helping to differentiate NETs from adenocarcinoma is the tendency of pleomorphic bizarre cells to be superimposed on a background of relatively uniform, low-grade cells with the characteristic nuclear neuroendocrine features. The neuroendocrine nature of these tumors can be confirmed by one or more neuroendocrine markers, such as chromogranin, synaptophysin, or CD56.

Pleomorphic NETs in the liver can also be confused with HCC. HCC is usually associated with cirrhosis and often has an associated elevation of serum AFP. HCC typically expresses one or more hepatocellular markers, including HepPar-1, arginase-1, AFP, and glypican-3, and is usually negative for neuroendocrine markers. However, HCC with neuroendocrine features and expression of markers of both hepatic and neuroendocrine differentiation in the same population of cells has been described. Pleomorphism combined with positivity for neuroendocrine markers raises the differential diagnosis of high-grade NEC, including its large cell variant. However, NEC typically shows higher nuclear-cytoplasmic ratio, crush artifact, nuclear molding, diffuse growth pattern, apoptotic debris, and high mitotic activity. Pleomorphic NET, on the other hand, shows low mitotic activity, relatively low proliferation index, moderate-to-abundant cytoplasm, and architectural features characteristic of a well-differentiated NET. Other differential diagnoses for pleomorphic NETs originating in the pancreas include acinar cell carcinoma, solid pseudopapillary tumor, and pancreatoblastoma. Significant nuclear pleomorphism is not a characteristic feature of any of these tumors, and the correct diagnosis can be established with the help of the immunostains, if the possibility of a NET is considered. The prognosis of pleomorphic NET has not been well documented because of the rarity of this variant, but based on the limited data, the behavior of these tumors does not appear to differ from that of their conventional counterparts.

SUMMARY
Pleomorphic NETs are very rare and may be misdiagnosed as adenocarcinoma, HCC, or other malignancies. Awareness of this unusual morphologic variant and its features is necessary to avoid misclassification and aid with the correct treatment and prognostication.

COMPETING INTERESTS STATEMENT BY ALL AUTHORS
The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS
LA collected the details of the case, carried out literature review, and drafted and edited the manuscript. EL conceptualized the case, performed additional literature review, performed photomicrographs, and edited the manuscript. KM edited the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT BY ALL AUTHORS
This report does not require approval from the Institutional Review Board.

LIST OF ABBREVIATIONS (In alphabetic order)
CT - Computerized tomography
H and E - Hematoxylin and eosin
HCC - Hepatocellular carcinoma
HPF - High power fields
NET - Neuroendocrine tumor
WHO - World Health Organization.
EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (the authors are blinded for reviewers and vice versa) through automatic online system.

REFERENCES

1. DeLuzio MR, Barbieri AL, Israel G, Emre S. Two cases of primary hepatic neuroendocrine tumors and a review of the current literature. Ann Hepatol 2017;16:621-9.
2. Kaya G, Pasche C, Osterheld MC, Chaubert P, Fontolliet C. Primary neuroendocrine carcinoma of the liver: An autopsy case. Pathol Int 2001;51:874-8.
3. Zee SY, Hochwald SN, Conlon KC, Brennan MF, Klimstra DS. Pleomorphic pancreatic endocrine neoplasms: A variant commonly confused with adenocarcinoma. Am J Surg Pathol 2005;29:1194-200.
4. Perez-Montiel MD, Frankel WL, Suster S. Neuroendocrine carcinomas of the pancreas with ‘rhabdoid’ features. Am J Surg Pathol 2003;27:642-9.
5. Shia J, Erlandson RA, Klimstra DS. Whorls of intermediate filaments with entrapped neurosecretory granules correspond to the “rhabdoid” inclusions seen in pancreatic endocrine neoplasms. Am J Surg Pathol 2004;28:271-3.
6. Song JE, Kim BS, Lee CH. Primary hepatic neuroendocrine tumor: A case report and literature review. World J Clin Cases 2016;4:243-7.
7. Morishita A, Yoneyama H, Nomura T, Sakamoto T, Fujita K, Tani J, et al. Primary hepatic neuroendocrine tumor: A case report. Mol Clin Oncol 2016;4:954-6.
8. Gurung A, Yoshida EM, Scudamore CH, Hashim A, Erb SR, Webber DL. Primary hepatic neuroendocrine tumour requiring live donor liver transplantation: Case report and concise review. Ann Hepatol 2012;11:715-20.
9. Garcia MT, Bejarano PA, Yssa M, Buitrago E, Livingstone A. Tumor of the liver (hepatocellular and high grade neuroendocrine carcinoma): A case report and review of the literature. Virchows Arch 2006;449:376-81.
10. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumors of the Digestive System. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
11. Lloyd RV, Osamura R, Klöppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017.
12. Cubilla AL, Hajdu SI. Islet cell carcinoma of the pancreas. Arch Pathol 1975;99:204-7.
13. Danforth DN Jr, Gorden P, Brennan MF. Metastatic insulin-secreting carcinoma of the pancreas: Clinical course and the role of surgery. Surgery 1984;96:1027-37.
14. Eckhauser FE, Cheung PS, Vinik AI, Strodel WE, Lloyd RV, Thompson NW, et al. Nonfunctioning malignant neuroendocrine tumors of the pancreas. Surgery 1986;100:978-88.
15. Lu JG, Farukhi MA, Mayeda D, French SW. Hepatocellular carcinoma with neuroendocrine differentiation: A case report. Exp Mol Pathol 2017;103:200-3.
16. Zhao M, Laisse JA, Zimmermann A. “Neuroendocrine” differentiation in hepatocellular carcinomas (HCCs): Immunohistochemical reactivity is related to distinct tumor cell types, but not to tumor grade. Histol Histopathol 1993;8:617-26.

How to cite this article: Alattia L, Molberg K, Lucas E. Pleomorphic neoplasm in a liver: A potential pitfall for misdiagnosis. CytoJournal 2020;17:8.