Clear Cell Hepatocellular Carcinoma: A Potential Histologic Mimicker of Clear Cell Renal Cell Carcinoma

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Introduction

- Cutaneous metastasis of hepatocellular carcinoma (HCC) is exceedingly rare, occurring in about 3% of HCCs and accounting for less than 0.8% of all known cutaneous metastasis [1].
- In particular, cutaneous metastatic clear cell HCC is difficult to diagnose because it can mimic other clear cell neoplasms such as those in renal cell carcinoma (RCC).
- In this case report, we describe a patient who was found to have cutaneous metastasis of clear cell HCC as the first clinical presentation of disease. It was initially thought to be clear cell RCC.

Case Summary

A 69-year-old male with a history of smoking, dyslipidemia, obesity, and treated stage II colonic adenocarcinoma at age 63 presented to our dermatology clinic for a 0.6 cm pink lesion on his right temple that had been present for three months.

A shave biopsy was done for a suspected benign nevus, and histologic sections revealed a dermal nodule consisting of atypical neoplastic cells with clear cytoplasm, arranged in nests and separated by fibrous septae. Based on the histologic features and location of the lesion on the head, metastatic clear cell renal cell carcinoma was suspected.

On IHC evaluation, the neoplastic cells were positive for AE1/AE3, EMA, beta catenin, and CD10 and negative for BCL-2, CEA-M, p63/CK9043, CK 5/6, CK 7, CK 20, BerEP4, PAX-8, and RCC.

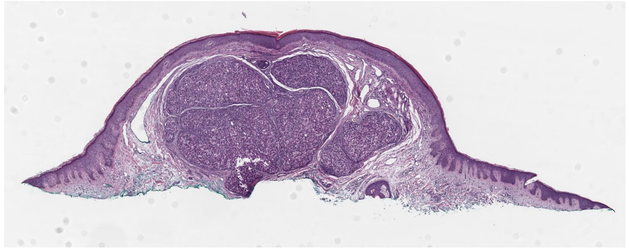

Figure 1: 10X; well-circumscribed dermal nodule.

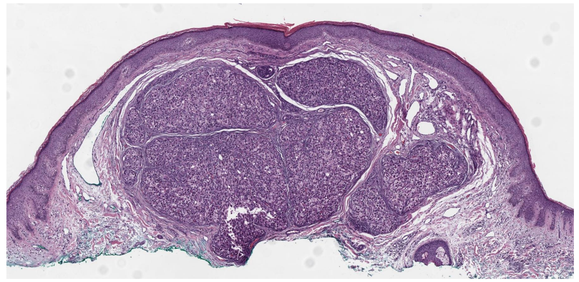

Figure 2: 20X; nested architecture with fibrous septae.

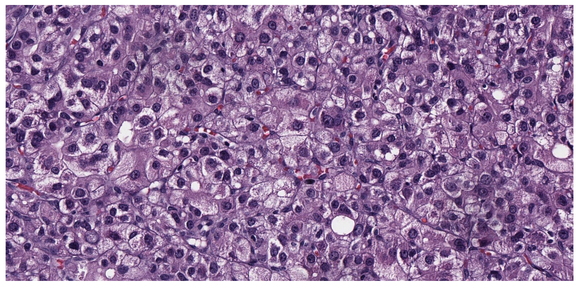

Figure 3: 200X; pleomorphic cells with clear cytoplasm.

Case Summary, Cont.

Since PAX-8 was negative in the initial workup, an additional renal marker (PAX-2) was evaluated and determined to be negative, making metastatic clear cell renal cell carcinoma less likely.

HepPar1, CEA-P, and CK19 immunostains were performed to evaluate alternative origins. HepPar1 and CEA-P stained positively in the neoplastic cells, while CK 19 was negative.

The positive HepPar1 and CEA-P, in addition to the morphologic features of clear cell carcinoma and negative immunostains for RCC, supported a diagnosis of metastatic clear cell hepatocellular carcinoma.

The patient was referred to oncology and a PET scan and MRI showed a hepatic segment VII mass, further supporting a metastatic clear cell carcinoma of hepatic origin.

Table 1: Immunophenotypes of clear cell HCC and RCC

	Clear Cell HCC	Clear Cell RCC
Positive Stains	Hepatocellular Markers: • HepPar1 [1, 2] • Glypican-3 • Arginase-1 • Polyclonal CEA, villin, CD10 • AFP	• PAX8 & PAX2 • AE1/AE3 • EMA/MUC1 (better sensitivity than AE1/AE3) • Vimentin • CD10 • RCC • CA9
Negative Stains	• Cytokeratins: Pankeratin, CK7, CK19 • PAX8	• CK7 • AMACR • CD117

Discussion

While cutaneous metastasis of clear cell HCC may be difficult to distinguish from other clear cell neoplasms such as clear cell RCC, there are some clues we can use to help distinguish the two:

Morphology: Not very useful, as both present as cells with clear cytoplasm that may be arranged in nests, tubules, or sheets and are surrounded by branching fibrovascular septae.

Immunophenotype: Summary of IHC for clear cell HCC and RCC can be found on **table 1**. These can be a powerful tool to narrow down the differential when morphology and clinical history are not enough.

Clinical clues:

- Cutaneous spread of HCC: most commonly on the face, scalp, chest, and abdomen [1].
- Cutaneous spread of RCC: most commonly on the face and scalp [3].
- Always check for a history of malignancy, although a negative history does not rule the possibility out.

Conclusion

When evaluating a cutaneous metastasis of a clear cell neoplasm, it is important to keep HCC on the differential. Immunostains for hepatocellular markers, such as HepPar1 and glypican-3, can help distinguish this entity from other clear cell neoplasms such as RCC.

References

[1] Cazzato, *et al*., 2021. PMID: 34198568.
[2] Terada, *et al*., 2010. PMID: 18499685.
[3] Ferhatoglu, *et al*. 2018. PMID: 30680270.