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Immunohistochemical expression of glypican-3 in adrenocortical carcinoma: A potential cause of diagnostic pitfalls

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Sir,

We read with great interest the paper entitled "Three cases of adrenocortical tumors mistaken for hepatocellular carcinomas/diagnostic pitfalls and differential diagnosis" by Park et al. [1], which was recently published in Annals of Diagnostic Pathology. The authors reported on three interesting cases of adrenocortical tumors arisen from ectopic adrenocortical tissue and mistaken for hepatocellular carcinomas (HCCs) [1]. Of note, while two cases had been diagnosed as HCC at imaging, the third one was an adrenocortical adenoma misdiagnosed as HCC on needle biopsy [1]. Misdiagnosis was due to similar histopathological aspect and to glypican-3 (GPC-3) positivity in the neoplastic cells [1]. Compared to HepPar-1, GPC-3 has higher sensitivity as a diagnostic marker for HCC, as its expression is maintained in poorly differentiated HCC [2,3]. Immunohistochemistry against GPC-3 is mainly used to differentiate preneoplastic and neoplastic hepatocellular disorders [2]. However, use of GPC-3 as a diagnostic marker of HCC versus metastatic tumors is controversial; indeed, GPC-3 expression was observed in other tumors, such as renal cell carcinomas [3]. Herein we report a case of adrenocortical carcinoma (ACC) mistaken for HCC due to histological aspect and GPC-3 positivity. In brief, a 52 year-old man presented with hypercortisolism, systemic hypertension, hypokalaemia and hyperglycemia. Computed Tomography (CT) scan showed a solid, multilobular mass with inhomogeneous enhancement, involving the right adrenal gland and right hepatic lobe. The patient underwent adrenalectomy and hepatic segmentectomy and the surgical specimen was sent for histological examination. The histopathology request form did not provide any clinical information. Gross examination revealed a tumor of 15 cm, partially encapsulated and infiltrating both hepatic and adrenal parenchyma. At histological examination, the tumor was composed of nests and trabeculae of polygonal cells, with eosinophilic or clear cytoplasm, separated by a fibro-vascular network (Fig. 1a and b). Wide hemorrhagic and necrotic areas and numerous atypical mitotic figures were seen. Immunohistochemistry revealed that neoplastic cells were negative for cytokeratin 7, glutamine synthetase, HepPar-1 and alpha-fetoprotein, and positive for GPC-3 (Fig. 1c) and HSP-70 (Fig. 1d). Therefore, HCC was diagnosed. When the endocrinologists received the histopathological report, they relayed their suspicion of a functioning adrenal tumor. Thus, further immunohistochemistry was performed, showing extensive positivity for synaptophysin (Fig. 1e), calretinin and alpha inhibin (Fig. 1f), focal positivity for melan-A and negativity for EMA, broad spectrum cytokeratin and chromogranin. In view of those findings and of clinical information received, the tumor was finally diagnosed as ACC.

Apart from the case described by Park et al. [1], GPC-3 expression was previously reported in a percentage of adrenocortical adenomas [4], but never in ACCs. Thus, this is the first report describing GPC-3 positivity in ACC. ACC may arise from adrenocortical ectopic tissue in the liver [1], but it may also directly extend from the right adrenal gland into the liver or even metastatize to the liver. In all those instances, ACC needs to be differentiated from HCC. Differential diagnosis may be challenging based only on histopathological findings. Indeed, both tumors may show tumor cells with nuclear atypia and eosinophilic/clear cytoplasm, arranged in trabeculae. In the present case, immunohistochemistry targeting HCC alone and the positivity for GPC-3 were further misleading and led to a first diagnosis of HCC. Stains for synaptophysin, melan-A, inhibin-alpha -which are positive in adrenocortical tumors [5,6] – finally allowed to achieve the correct diagnosis.

We found GPC-3 expression in 6/10 adrenocortical adenomas and in 0/7 -apart from the present case- ACCs taken from our archive (unpublished data). Those data indicate that GPC-3 positivity is a rare event in ACC. However, albeit infrequent, the possibility that ACC can express GPC-3 should be kept in mind to avoid incorrect diagnosis relied on such immunohistochemical positivity. Indeed, misdiagnosis of ACC as HCC has relevant clinical consequences, since the post-surgical treatment of the two entities is completely different.

This case also emphasizes the importance of gathering clinical information. Although half of the patients with ACC have non-specific symptoms or are incidentally diagnosed by imaging, the other half have symptoms related to adrenocortical hormone excess, as in the present case. Clinical information can be essential to solve the differential diagnosis between tumors with overlapping histological and immunohistochemical features, such as ACC and HCC.

☆ Declarations of interest: none.

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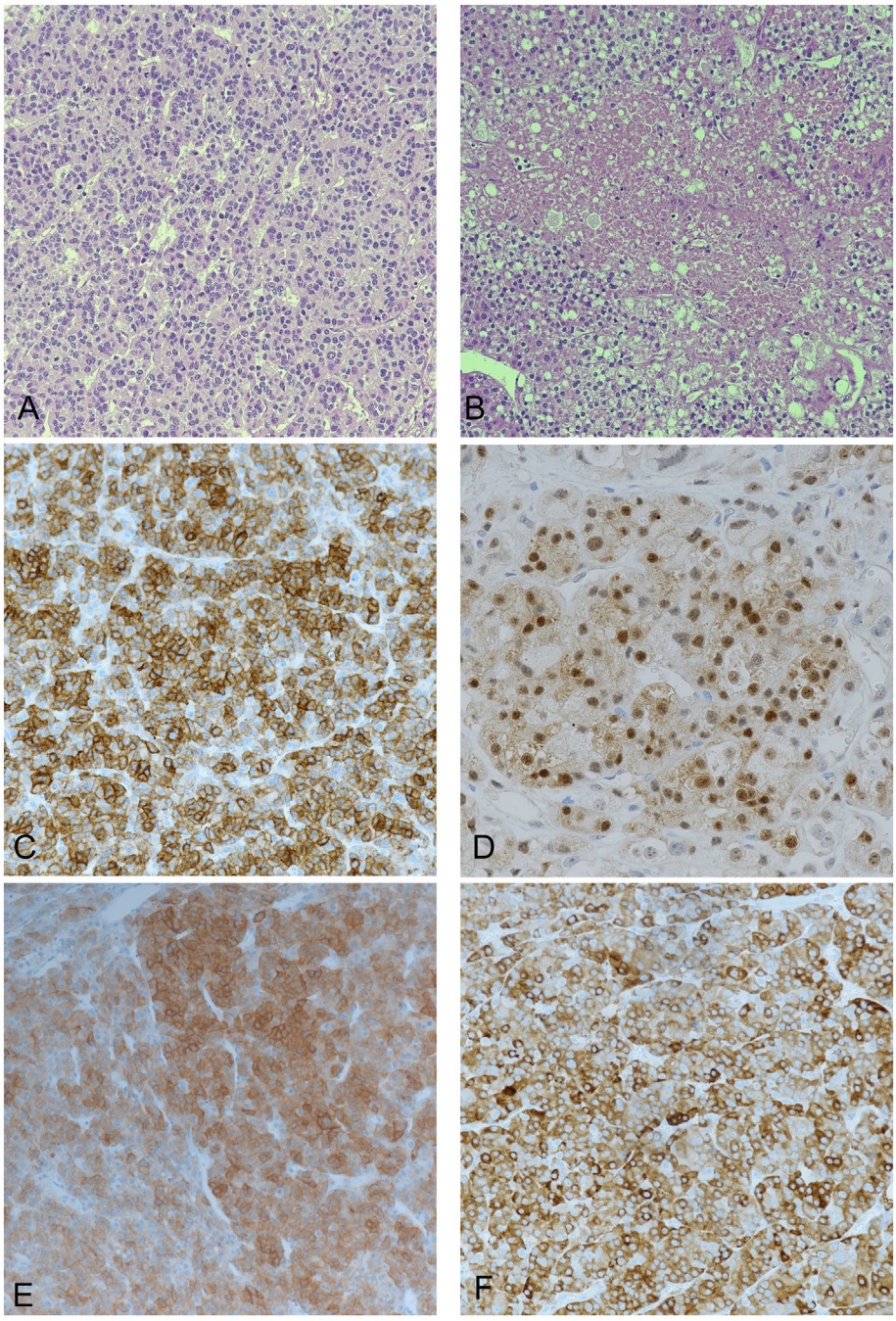

Fig. 1. A. Tumor composed of cells with eosinophilic cytoplasm, arranged in cords and trabeculae, separated by a fibro-vascular network. Numerous mitotic figures were seen (Haematoxylin and eosin stain; original magnification, ×200). B. Areas with clear cells and necrosis (Haematoxylin and eosin stain; original magnification, ×200). C. Cytoplasmic diffuse positivity for GPC-3 (GPC-3 stain; original magnification, ×200). D. Nuclear and cytoplasmic positivity for HSP-70 (HSP-70 stain; original magnification, ×200). E. diffuse positivity for synaptophysin (synaptophysin stain; original magnification, ×200) and (F) inhibin-A (inhibin-A stain; original magnification, ×200).

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