Histopathology and Immunohistochemistry of adrenal cortical adenoma and carcinoma

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The major diagnostic problems which surgical pathologists face in adrenocortical pathology at this juncture are whether resected lesions are benign or not and if malignant, whether cortical origin or not. In this brief review, these two areas will be covered including the potential contribution of immunohistochemistry on this differential diagnosis.

I. Discerning malignancy in adrenocortical tumors

When the patients with adrenocortical mass are detected, the most important clinical aspect in the management of these patients is whether that adrenal mass represents malignant or not. The most important and critical point in adrenocortical pathology is therefore the differential diagnosis between adrenocortical adenoma and carcinoma.

I-1 Macroscopic Evaluations

When evaluating malignancy of adrenocortical neoplasms, gross or macroscopic evaluation is very important. Firstly, the weight of the neoplasm should be determined as carefully as possible. In our experience, the tumor with more than 100g in weight comprised 93% of carcinoma but only 6% of the adenoma. However, it is also very important to note that small adrenocortical tumor can metastasize and some large tumors do not. Therefore, the weight of the tumor is very important in evaluating malignancy of adrenocortical neoplasms but, as is expected, the weight itself is not a reliable prognostic indication of the resected adrenocortical tumor. The next important thing is the macroscopic features of the cut surface of the tumor. Ominous hemorrhage and necrosis are rarely observed in adrenocortical adenoma. Necrosis is sometimes associated with cystic changes. The presence of necrosis and hemorrhage, therefore, strongly indicates the diagnosis of adrenocortical carcinoma. However, it is also true that many adrenocortical carcinoma were not associated with foci of necrosis and hemorrhage. In addition, it is also important to sample the specimens from the areas adjacent to the foci of necrosis and hemorrhage when grossing the specimens.

I-2 Histopathological Evaluations

An increasing number of small adrenocortical neoplasms has been discovered
with the development of CT and MRI scan. Therefore adrenocortical carcinomas not associated with these ominous macroscopic features above have recently increased in number. The distinction of these "well-differentiated" adrenocortical carcinoma from adenoma could be one of the most diagnostic difficulties in surgical pathology practice. There are no single histological criteria which can reliably differentiate adrenocortical carcinoma from adenoma like capsular or vascular invasion of thyroid follicular carcinoma. Only the systems which evaluated multiple histological and/or non-histological criteria of the resected cases can provide reliable histological diagnosis. Among various criteria used, the criteria proposed by Weiss, which requires only histopathological findings and evaluated nine histological features of the tumors most frequently associated with poor clinical outcome of the patients, have been most widely employed due to the straightforwardness of the criteria and easy applicability. These nine histological criterias are as follows: 1. High nuclear grade, 2. Mitotic figures more than 5/50 hpf, 3. Atypical mitotic figures, 4. Eosinophilic or compact tumor cell cytoplasm (>75% of tumor cells), 5. Diffuse architecture (>33% of tumor), 6. Necrosis (confluent necrosis), 7. Venous invasion (smooth muscle in wall), 8. Sinusoidal invasion (no smooth muscle in wall) and 9. Capsular invasion. In the report of Weiss, 20 of 23 cases that fulfilled three histologic criteria died of disease and it is currently considered that the tumors which met more than three of these criteria should be considered adrenocortical carcinoma. The system is straightforward and relatively easy to use, and a good correlation was observed between results and clinical outcome of the patients including the tumor of 19g. However, it is also true that the tumors which behaved not in a malignant fashion in their postoperative course, including the cases of adrenocortical oncocytoma were considered as adrenocortical carcinoma, although these adrenocortical oncocytomas may recur or metastasize in a long period of time. In addition, among these nine criteria, we experienced that nuclear grade, architecture and cytoplasm were likely to be subjective, i.e., the interobserver differences were relatively marked unless observers were well-informed prior to histological examination of adrenocortical tumor.

I-3. Potential contribution of immunohistochemistry in differentiation between adrenocortical adenomas and carcinomas

At this juncture, only the analysis of cell proliferation using Ki67 or MIB1 and topoisomerase IIalpha antibodies can provide any additional meaningful information to carefully performed histopathological analysis. The adrenocortical neoplasms with more than 5-6% of MIB1 labeling index can be considered adrenocortical malignancy. However, the same precautions such as fixation, intratumoral heterogeneity and interobserver differences should be noted in applying MIB1 LI in differential diagnosis.
II. Differential diagnosis between adrenocortical and non-adrenocortical origins.

In the patients who do not manifest any clinical hormonal abnormalities, the malignancies that may be associated with histopathologic differential diagnosis of adrenocortical carcinoma at both primary and metastatic sites are renal cell carcinoma, hepatocellular carcinoma, clear cell carcinoma of the ovary and uterus, malignant melanoma, and large cell carcinoma of the lung and pheochromocytoma. Diagnosis of adrenocortical carcinoma is important in these patients because op'-DDD treatment results in a small but significant increase in mean survival times in the patients with adrenocortical carcinoma. Among these tumors, the two most important primary neoplasms in the differential diagnosis of primary adrenocortical carcinoma are renal cell and hepatocellular carcinoma, especially when the lesions are large. Careful histological examination and detection of biological features of these tumors can resolve the diagnostic dilemma between adrenocortical carcinoma and other tumors in most cases. However, it is also true that specific adrenocortical tumor marker can contribute greatly to the differential diagnosis of these tumors.

Ad4BP/SF-1 is a transcription factor of all steroidogenesis and exclusively expressed in steroidogenic cells except for stromal cells in spleen and some gonadotrophic cells in anterior pituitary glands. Ad4BP/SF-1 immunoreactivity was demonstrated in almost all the tumor cells of adrenocortical carcinoma, both histological sections and cytology specimens regardless of the degrees of differentiation, but not in renal cell carcinoma, hepatocellular carcinoma, malignant melanoma, ovarian and uterine clear cell carcinoma, large cell carcinoma of the lung and pheochromocytoma. An antibody against Ad4BP/SF-1 which may be of use in surgical pathology materials is currently commercially available. Application of Ad4BP/SF-1 immunohistochemistry can greatly contribute to the differential diagnosis of adrenocortical carcinoma from other malignancies both at primary and metastasis sites even in the evaluation of needle biopsy specimens.

References


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