Human Pathology (2015) **46**, 1799–1807

ELSEVIER

Human PATHOLOGY

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Original contribution

Pitfalls in the diagnosis of adrenocortical tumors: a lesson from 300 consultation cases☆,☆☆

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Received 3 April 2015; revised 6 August 2015; accepted 19 August 2015

Keywords:
Adrenocortical carcinoma;
Adrenal gland;
Differential diagnosis;
Pathology consultation;
Pheochromocytoma

Summary The correct pathologic classification of adrenocortical carcinoma (ACC) is relevant to establish an early therapeutic strategy of this rare malignancy. The aim of the study was to assess the most frequent pitfalls in ACC diagnosis reviewing a large consecutive series of 300 cases with an original diagnosis or a clinical suspect of ACC, which were sent in consultation to our institution between 2004 and 2014. A major disagreement that significantly modified the clinical management of patients was recorded in 26 cases (9%). The most common pitfall (10 cases) was to distinguish ACC from pheochromocytoma and vice versa. Seven other cases diagnosed as ACC were reclassified as metastases from other primaries and primary adrenal soft tissue tumors (including 3 angiosarcomas). Finally, 5 adrenocortical adenomas were reclassified into carcinomas, and 4 ACCs were converted into adenomas. Minor disagreements were mostly related to the identification of ACC variants (up to 32% of cases of adrenocortical tumors in the present series). Moreover, more than 50% of ACC cases lacked Ki-67. In conclusion, our results indicate that, in the presence of a histologically suspected ACC, a special attention should be devoted to exclude metastatic and soft tissue tumors and pheochromocytoma (in this latter case with special reference to the oncocytic variant of adrenocortical tumors). Moreover, pathologists should be aware of the major role of Ki-67 in determining prognosis and in selecting patients to the most appropriate treatment.

1. Introduction

Adrenocortical carcinoma is a rare malignancy with an incidence of approximately 1 case (range, 0.7-2.0) per million population [1]. Because of its aggressive behavior, distant metastases at the time of diagnosis are relatively common, and in this context, the main diagnostic issue is the exclusion of the reverse condition (ie, other malignant neoplasms metastatic to the adrenal gland), which is also relatively common for lung and other cancers. Conversely, in

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☆ Competing interests: All authors have no potential conflicts of interest to declare.

☆☆ Funding/Support: This study is supported by grants from Associazione Italiana per la Ricerca sul Cancro, Milan, Italy (no. IG/14820/2013 to M.P.).

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http://dx.doi.org/10.1016/j.humpath.2015.08.012
0046-8177/

the presence of an adrenal-confined disease, the diagnostic difficulties rely on differentiating adrenocortical from adrenomedullary tumors on the one side and on taking adrenocortical adenomas apart from carcinomas on the other. In this regard, the pathologic diagnosis of "carcinoma" requires the recognition of multiple morphologic parameters combined either in scoring systems [2-4] or in diagnostic algorithms [5-7], suggestive but not pathognomonic per se of malignancy. Moreover, some cases lack enough parameters for reaching a proven diagnosis of malignancy. These cases are worrisome from both pathologic and clinical standpoints, underlying the need of a more unequivocal pathologic classification and posing questions on their appropriate clinical management and follow-up [8]. A revision of 387 patients from the German Registry of adrenocortical carcinoma (ACC) revealed a partial inaccuracy in histopathologic diagnoses. In 161 cases (42%), a second opinion on the tumor specimen was requested by the reference pathologist, and in 21 patients (13%), the diagnosis of ACC was changed to metastases from other malignancies, malignant pheochromocytoma (also termed intraadrenal paraganglioma), renal cell carcinoma, or sarcoma [9]. A correct histopathologic diagnosis is fundamental to define the proper treatment and to improve outcomes. The rarity of ACC and the reported relatively high rate of misdiagnoses underline the importance of referring pathology specimens to specialized centers, particularly in the case of nonfunctioning adrenal tumors.

The aim of this study was to assess the most frequent histopathologic pitfalls in adrenocortical tumor diagnosis by revising a large series of 300 consultation cases from a single institution.

We here show that (*a*) a second opinion on surgically resected adrenocortical tumors can determine changes of the pathologic diagnosis in 9% of cases, which significantly alter the therapeutic strategies and clinical management of patients; (*b*) major pitfalls are related to the misdiagnosis of pheochromocytoma versus ACC, but a high suspicion level is recommended for metastatic and soft tissue tumors, as well; (*c*) among primary adrenocortical tumors, cases with borderline malignant features or the special variants (eg, myxoid or oncocytic) are the most problematic entities.

2. Materials and methods

2.1. Case series

The Divisions of Internal Medicine and Medical Oncology of the San Luigi Hospital and University of Turin serve as a referral center for ACC diagnosis and treatment in Italy. Between January 2004 and July 2014, the pathology unit of this university hospital received 300 consecutive consultation cases, related to patients with proven or suspected ACC that sought medical advice at the center. Cases were submitted with a median of 9 hematoxylin and eosin–stained slides per case (range, 3-20) and 4 immunohistochemical stains per case (range, 0-10). Among them, 256 cases (85%) were sent by clinicians (mostly endocrinologists and oncologists internal at San Luigi Hospital) at the time of first visit for advice and/or cure, and 44 (15%) were submitted by pathologists from Italian or European institutions for the purpose of a second opinion. All cases were reviewed by 4 of us (E. D., M. V., E. B., and M. P.) having a specific experience in endocrine or urologic pathology and were classified according to the appropriate diagnostic system, that is, Weiss score [2] for conventional and myxoid ACC, Lin-Weiss-Bisceglia system [10] for pure oncocytic adrenocortical tumors, and Wieneke classification [11] for the 2 pediatric tumors. In the case of disagreement among the reviewers, each tumor was jointly discussed at a multihead microscope, and a consensus was reached. The present study was approved by the Local Ethical Committee at San Luigi Hospital.

2.2. Histochemistry and immunohistochemistry

Depending on the morphologic features and/or the availability of additional unstained slides or paraffin block(s), a panel of reactions, comprising histochemical reticulin stain and immunohistochemical markers, was applied in 221 of 300 cases. The latter included the adrenocortical-specific molecules melan A, α-inhibin, and steroidogenic factor 1 (SF-1) and the proliferation-associated marker Ki-67 (assessed in hot-spots as the percentage of positive nuclei counting at least 2000 tumor cells), as well as organ-specific markers (Thyroid Transcription Factor 1 [TTF-1], others) and markers of epithelial or mesenchymal lineages, whenever appropriate. The immunohistochemical markers more frequently added to the available slides are listed in Table 1.

3. Results

3.1. Diagnoses after revision

Upon revision, the whole series of 300 cases was reclassified as follows: 269 ACCs, 14 adrenocortical adenomas, 7 adrenocortical tumors of uncertain malignant potential, 3 pheochromocytomas, 5 soft tissue tumors in the adrenal gland, and 2 metastases from lung and breast carcinomas. An agreement between the original and consultation diagnoses was observed in 274 cases (91%), including minor discrepancies on the Weiss score values and/or the exact tumor variant recognition (see below). In the remaining tumors, a change in the diagnosis upon revision was made, which significantly modified the clinical management of patients (Table 2).

The original pathologic report was available in 205 cases (68%). The diagnostic system used (Weiss score or