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Original contribution

Dedifferentiated endometrial carcinomas with neuroendocrine features: a clinicopathologic, immunohistochemical, and molecular genetic study☆,☆☆

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Summary Undifferentiated endometrial carcinoma is an aggressive type of uterine cancer, which is occasionally associated with a low-grade endometrioid carcinoma component. This combination is referred to as "dedifferentiated endometrioid endometrial carcinoma." Neuroendocrine expression may occur in undifferentiated endometrial carcinoma, but its significance in dedifferentiated endometrial carcinomas is unknown. To gain insight into the pathogenesis of these tumors we have analyzed the immunophenotype (ARID1A, MLH1, PMS2, MSH2, MSH6, p53, β-catenin, SMARCB1, synaptophysin, chromogranin A, and CD56) and mutational status (*PTEN*, *KRAS*, *PIK3CA*, *TP53* and *POLE*) of 4 dedifferentiated endometrial carcinomas with strong and diffuse neuroendocrine expression. All tumors demonstrated neuroendocrine expression in ≥70% of the cells in the undifferentiated carcinoma areas. Loss of expression of at least 1 DNA mismatch repair protein was observed in 2 cases, and p53 immunoreaction was aberrant (mutated/inactivated) in one case. All carcinomas were negative for β-catenin and maintained nuclear SMARCB1 (INI1) and ARID1A expression. Three tumors shared identical endometrioid molecular profile (*PTEN* and/or *PIK3CA* mutations) in both components. One tumor had *POLE* exonuclease domain mutation in the undifferentiated component. In one case, *TP53* mutation was found exclusively in the undifferentiated component. Two patients died with peritoneal carcinomatosis and abdominal metastases, respectively; one

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patient died of a renal failure without evidence of disease, and the last patient is alive and free of disease at 3.3 years. Dedifferentiated endometrial carcinomas with neuroendocrine features are clinically and molecularly heterogeneous tumors. Probably, these carcinomas might acquire undifferentiated phenotype through mutations in *TP53* and *POLE*.

1. Introduction

Undifferentiated endometrial carcinoma is a very rare but aggressive type of uterine cancer [1]. Occasionally, undifferentiated endometrial carcinoma is associated with a low-grade endometrioid carcinoma component and this combination is referred to as "dedifferentiated endometrioid endometrial carcinoma [2]."

The Cancer Genome Atlas (TCGA) stratified endometrial carcinomas into 4 distinct molecular groups on the basis of molecular genetics alterations: (1) endometrioid carcinomas with *POLE* mutations (ultramutated); (2) endometrioid carcinomas with microsatellite instability (hypermutated); (3) endometrioid carcinomas with low copy number alterations; and (4) predominantly serous but also serous-like endometrioid carcinomas with high copy number alterations and *TP53* mutations [3]. This study, however, includes only 13 cases of mixed endometrial carcinomas, and no information about undifferentiated/dedifferentiated endometrial carcinomas is given. Most of these mixed endometrial carcinomas (8/13; 62%) clustered into the copy number high/serous-like group and 4 cases (4/13; 38%) clustered into the copy number–low group.

Recently, Rosa-Rosa et al studied 10 dedifferentiated endometrial carcinomas by immunohistochemistry and massive parallel and Sanger sequencing [4]. They found that most of these tumors (7/10; 70%) occurred in the setting of mismatch repair deficiency (hypermutated tumors) with accumulation of molecular genetic alterations characteristic of endometrioid carcinomas, such as *ARID1A*, *PIK3CA* or *CTNNB1* mutations in the undifferentiated component. In this study, undifferentiated carcinomas expressing neuroendocrine markers were excluded.

In order to understand the nature of the latter tumors, we studied the clinicopathologic, immunohistochemical, and molecular genetic features of 4 dedifferentiated endometrioid endometrial carcinomas exhibiting strong and diffuse neuroendocrine markers.

2. Material and methods

2.1. Tissue samples

This study includes a total of 4 dedifferentiated endometrial carcinomas, from the consultation files of one of the authors (J.P.) (cases 1 and 4) and the Departments of Pathology of Hospital de la Santa Creu i Sant Pau, Barcelona (case 3) and Hospital Universitario Ramón y Cajal, Madrid (case 2). Tumors were examined and classified using the histopathological criteria recommended by the 2014 World Health Organization (WHO) *Classification of Tumours of the Female Genital Organs* [5] and the 2009 staging classification of endometrial carcinoma proposed by the International Federation of Gynecology and Obstetrics (FIGO) [6]. One case (case 3) has been previously reported as a negative control in a series of *POLE*-mutated undifferentiated endometrial carcinoma [7]. Follow-up information was available for all patients. In 2 of 4 undifferentiated carcinomas, the diagnosis was based not only on conventional morphologic features but also on the characteristic immunohistochemical pattern reported previously; that is, the absence of E-cadherin expression together with ZEB1 nuclear immunoreaction [4]. Twenty-two cases of dedifferentiated endometrial carcinomas without neuroendocrine differentiation, which were used as controls, have been previously reported [4,7]. The cases were anonymized, and the study was approved by the Institutional Ethics Committee.

2.2. Immunohistochemical analysis

Immunohistochemistry was performed using standard semiautomatic platforms.

The following antibodies were used: E-cadherin (cat. no. IR059; Dako, Glostrup, Denmark; ready to use), ZEB1 (cat. no. ab87280; ABCAM, Cambridge, UK; dilution 1:300), p53 (cat. no. IR616; Dako, ready to use), MLH1 (cat. no. M3640; Dako, ready to use), PMS2 (cat. no. IR087; Dako, ready to use), MSH2 (cat. no. M3639; Dako, ready to use), MSH6 (cat. no. M3646; Dako, ready to use), β-catenin (cat. no. IR702; Dako, ready to use), ARID1A (cat. no. HPA005456; Sigma, St Louis, USA; dilution 1:500), SMARCB1 (BD Biosciences, Franklin Lakes, NJ, USA; dilution: 1/100), and neuroendocrine markers including synaptophysin (cat. no. IR660; Dako, ready to use), chromogranin A (cat. no. M0869; Dako, 1/100), and CD56 (cat. no. IR628; Dako, ready to use). Immunostaining was performed using the EnVision detection system (K5007, Dako). P53 immunostain was considered to be aberrant (mutated/inactivated) if the tumor exhibited diffuse moderate to strong uniform nuclear staining in >80% of the tumor cells (diffuse), or the complete absence of nuclear staining in the tumor cells in the presence of focal nuclear staining of the stromal cells (complete absence). Immunostain for p53 was considered normal (wild-type pattern) if any degree of nondiffuse nuclear staining (<80%) of the tumor cells was present.