Poorly differentiated thyroid carcinoma: an evolving entity

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Abstract

The term Poorly Differentiated Thyroid Carcinoma (PDTC) was first proposed in the early eighties to describe a heterogeneous group of neoplasms, of follicular cell origin, dwelling in an intermediate clinicopathological position between well-differentiated follicular or papillary carcinomas and undifferentiated carcinomas. Over the following two decades defenders and sceptics have sustained an unsurmountable debate pertaining the nature of PDTC, its morphological diagnostic features, its clinical relevance and the most suitable management. In 2004, the WHO Committee on Thyroid Tumours agreed to recognize PDTCs as a distinct entity in thyroid follicular cell tumourigenesis. The proposed diagnostic criteria resulted however difficult to apply on daily practice. Four years ago, in an attempt to streamline the diagnosis of PDTC, a panel of experts met in Turin and developed a simple algorithmic approach for PDTC identification. This paper aims to review the state of the art on PDTC from a morphological, clinical and molecular standpoint.

Keywords architecture; cytological features; diagnosis; pathobiology; poorly differentiated thyroid carcinoma; prognosis

Introduction

Poorly differentiated thyroid carcinoma (PDTC) was officially recognized as a distinct pathologic entity and included in the WHO classification of thyroid tumours only 6 years ago.[1]

Over decades, thyroid carcinomas of follicular cell derivation had been formally divided into two main groups: differentiated carcinomas of papillary or follicular histotype and undifferentiated carcinomas (UC).[2] This framework constituted an exception to the common rule in oncology of a continuous range of malignancy. There was a broad gap between the mildly aggressive differentiated carcinomas, which usually carry a good prognosis, and the highly aggressive undifferentiated carcinomas, which entail a dismal prognosis. For a long time, thyroid pathologists, endocrinologists, surgeons and oncologists filled the gap either stressing the importance of tumour staging or emphasizing the degree of differentiation. Those supporting the former approach regarded differentiated carcinomas disclosing invasive and/or metastatic properties, such as extrathyroidal papillary thyroid carcinomas (PTC) and widely invasive follicular thyroid carcinomas (FTC), as carcinomas with an intermediate degree of aggressiveness. Those advocating for the second approach, which usually correlates also with staging, posited the existence of a separate group of thyroid carcinomas of intermediate degree of differentiation and behaviour, which encompassed different terminologies.[3] In 1974, the European Organization for Research and Treatment of Cancer (EORTC) included on its classification of thyroid cancer the concept of "moderately differentiated" trabecular carcinoma as a class of thyroid carcinoma with a morphological appearance and natural history somewhere in between the well-differentiated papillary or follicular carcinomas and the UC.[4] Almost 10 years later, independently and quasi simultaneously, Sakamoto et al.[5] and Carcangiu et al.[6] proposed the concept of PDTC. Much of the historical controversies and troubles dealing with the diagnosis of PDTC can be traced back to its original description in these two papers. The authors completely unaware of the study that was going on in the other group employed a similar nomenclature but markedly dissimilar histopathological criteria. Carcangiu et al.[6] defined PDTC as a tumour of follicular cell derivation composed by a monotonous population of small cancer cells, with scant cytoplasm, small round hyperchromatic nucleus and inconspicuous nucleoli. The PDTC cells appear arranged in "*insulae*" with interspersed microfollicles and/or in solid cell nests outlined in either case by a thin fibrovascular layer. Hence the term "*insular carcinoma*" devised to describe a prototypical representative of PDTC.[3,6,7] Additional features relevant to the diagnosis of "*insular carcinoma*" are the mitoses which are always present, though in variable number, the infiltrative pattern of growth and the existence of foci of necrosis. The latter may be located in the center of the "*insulae*" or around blood vessels resulting in a characteristic peritheliomatous appearance, with preservation of the tumour cells that are closer to the nutrient vessels.[3,6,7] At variance with this, cytological features such as the appearance of the cancer cells or their nuclei, the mitotic index and the presence of necrosis played no role in the description that Sakamoto et al.[5] made of PDTC. The proposal of the Japanese group focused on the architectural pattern of growth, gathering, under the concept of PDTC, barely related, morphologically diverse tumours such as aggressive PTC and FTC that had recurred within 5 years of first excision. The most distinctive histological feature was the arrangement of the cancer cells, even focally, in a solid/sheet-like, trabecular/cord-like or scirrhous/sclerotic pattern.[5,8] Based on the architectural pattern of growth observed in PTC and FTC, including Hürthle cell carcinomas, Sakamoto et al.[5] intended to establish a grading system among thyroid carcinomas of follicular cell origin, whereas Carcangiu et al.[6] clearly attempted to depict a new tumour entity, separated from, albeit nosologically akin to, conventional PTC or FTC from either which may originate.

Following the original description of PDTC, worldwide thyroid experts have adopted different attitudes towards the issue. Some pathologists and clinicians decided to disregard the

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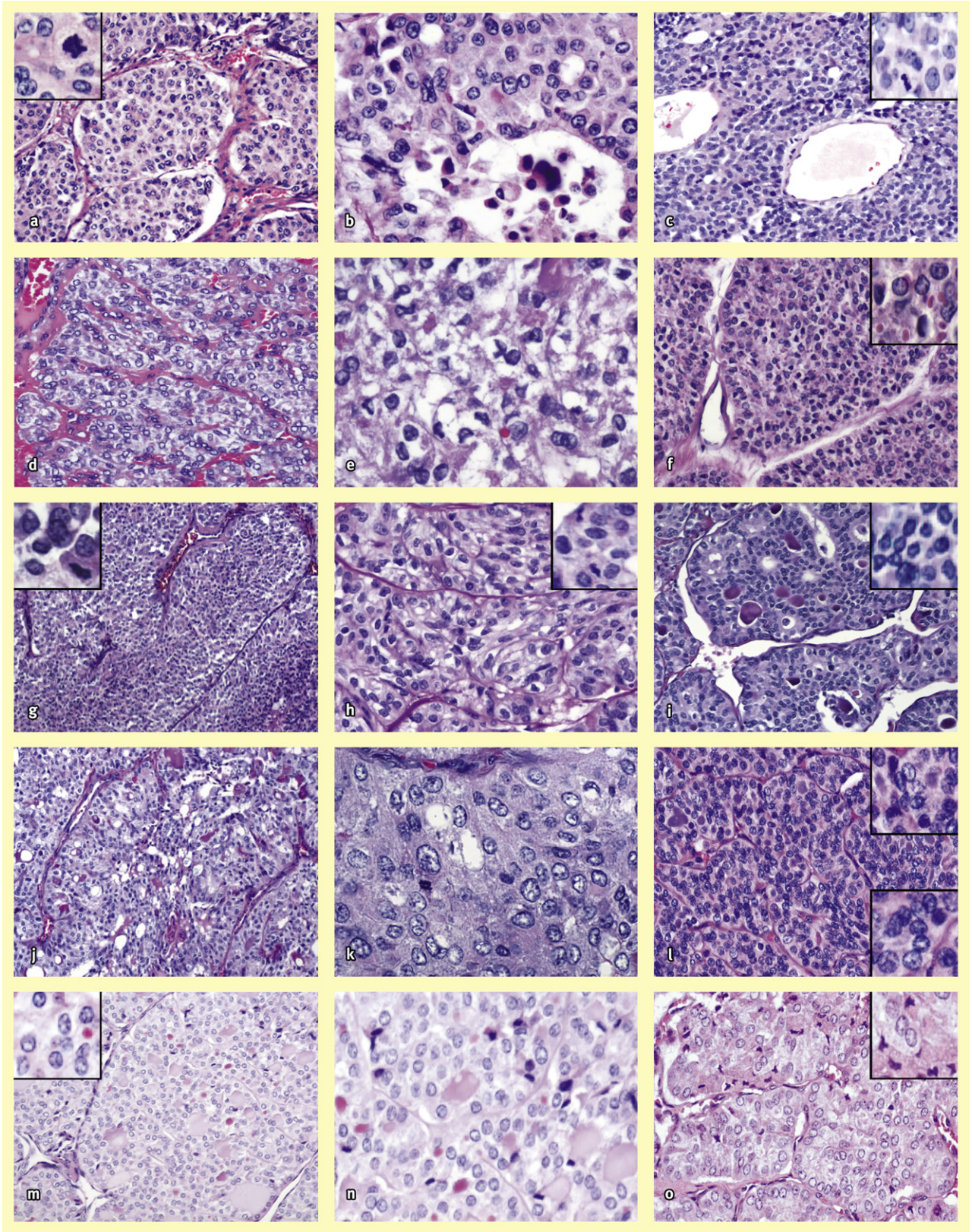

Figure 1 Histological appearance of PDTCs. **a** Insular PDTC disclosing well-defined nests/*insulae* and oncocytic features. The *insulae* are composed of uniform-appearing cells with small, round, dark nuclei and scant cytoplasm. The inset illustrates the presence of mitotic activity. This tumour is mutated at *RAS* and wild type at *BRAF*, *PIK3CA* and *β-catenin* (*CTNNB1*). P53 protein expression, which is expected to correlate with the presence of gene mutation, is positive. **b** High magnification view of the tumour shown in **a** illustrating the presence of an incipient area of necrosis and hyperchromatic nuclei. **c** PDTC featuring a solid/sheet-like growth pattern, prominent vascularization, monotonous hyperchromatic nuclei and frequent mitoses (inset). This tumour is mutated at *RAS* and wild type at *BRAF*, *PIK3CA* and *β-catenin* (*CTNNB1*). P53 is negative. **d** PDTC with intermingled solid, trabecular,