The number of ways in which cells die is broadly characterized into apoptosis and necrosis. The term “apoptosis” has been coined by Kerr et al. [1] to describe a specific morphological aspect of cell death. Apoptosis is accompanied by rounding-up of the cell, retraction of pseudopods, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), classically little or no ultrastructural modifications of cytoplasmic organelles, plasma membrane blebbing (but maintenance of integrity until the final stages of the process), and engulfment by resident phagocytes (in vivo) [1,2].

Factors contributing to necrosis are mostly extrinsic in nature, such as osmotic, thermal, toxic, hypoxic–ischemic, and traumatic insults. The morphology of a necrotic cell is very distinct from that of a cell undergoing classic apoptosis, with ultrastructural changes occurring in both the cytoplasm and the nucleus. The main characteristic features are chromatin flocculation, swelling and degeneration of the entire cytoplasm and the mitochondrial matrix, blebbing of the plasma membrane, and eventual shedding of the cytoplasmic contents into the extracellular space with subsequent inflammation [3]. Unlike in apoptosis, chromatin is not packed into discrete membrane-bound particles, but forms many unevenly textured and irregularly shaped clumps, a feature that is being used for differentiating between the two modes of cell death [3]. The mitochondria undergo inner membrane swelling, cristolysis, and disintegration. Dilation and fragmentation of the cisterns of rough endoplasmic reticulum and Golgi apparatus are frequently observed.

From a histological viewpoint, various morphological forms of tissue necrosis exist. In coagulative necrosis, denaturation of intracytoplasmic protein is the dominant process. In hematoxylin–eosin-stained sections, coagulative necrosis appears acellular and stains homogeneously with red eosin. Careful examination, however, shows retention of the general architectural pattern of the tissue, despite the death of its constituent elements. Coagulative necrosis is also characterized by abrupt transition from viable cells to necrotic cells without an interposed zone of granulation tissue or hyalinized tissue between viable and necrotic cells. After a period of time, this pattern is replaced by colliquative necrosis, in which the cellular structures...
are broken down by proteolytic enzymes released from ruptured lysosomes and similar enzymes released by infiltrating inflammatory cells [4].

**EPITHELIAL NEOPLASIAS CHARACTERIZED BY COAGULATIVE NECROSIS**

Tumor necrosis has garnered increased attention over the last few years, in part because a number of studies have now shown that tumor necrotic tissue represents a significant prognostic marker with an independent influence on metastasis-free survival in patients with neoplasm. Tumor necrosis has been extensively studied in kidney [5–7], breast [8–12], lung [13], thyroid [14], gastric [15], and colorectal carcinomas [16]. Recent studies suggest that surgical pathologic evaluation of tumor necrosis should routinely record its presence or absence [5–7,12,16]. Such an assessment is easily performed through routine histologic evaluation with reasonably high rates of reproducibility among pathologists.

In invasive carcinoma of the breast, necrosis has been shown to correlate with increased tumor size, high-grade disease, microvessel density, macrophage infiltrates, high proliferative fraction, decreased relapse-free survival, and a poor prognosis. More recently, extensive central necrosis has been reported as a common morphological feature of the tumors belonging to the molecular class of basal-like breast cancers [8,9,12]. Recent studies suggest that the presence of tumor necrosis provides information, in addition to routinely reported prognostic factors [11]. Tumor necrosis is associated with a poorer outcome irrespective of histologic grade, and, indeed, all grades had similarly poor outcomes in the presence of tumor necrosis. Instead, in the absence of tumor necrosis, patients with grade 3 tumors had poorer outcome than those with grade 1–2 tumors [11]. These results suggest that the presence of tumor necrosis identifies a biologically distinct subgroup within breast cancer and that the difference is important in determining the efficacy of standard chemotherapy and endocrine therapy [11].

**NONAPOPTOTIC TUMOR CELL DEATH**

In addition to apoptosis and necrosis, various models of tumor cell death have been proposed, including paraptosis, autophagy, and mitotic catastrophe. Thus, tumor cells can die by manifesting massive autophagy (sequestration of large parts of the cytoplasm in autophagic vacuoles, often before the cells undergo apoptosis) [3], as a result of paraptosis (a process of swelling and vacuolization that begins with physical enlargement of the endoplasmic reticulum and the mitochondria) [17] or by mitotic catastrophe.

**DEFINITION OF MITOTIC CATASTROPHE**

It should be noted that there is still no consensus definition of mitotic catastrophe. Due to this, there are disagreements and uncertainties about the precise causes, mechanisms, and outcomes of mitotic catastrophe. Some authors have considered mitotic catastrophe as a state generally, but not necessarily, associated with cell death as an outcome [18]. Alternatively, mitotic catastrophe has been classified not as a mode of cell death but as a special example of apoptosis [19]. Other groups have presented evidence indicating that death-associated mitotic catastrophe is not a separate mode of cell death, rather a process (“prestage”) preceding cell death, which can occur through necrosis or apoptosis [20]. Mitotic catastrophe has also been depicted as the main form of cell death induced by ionizing radiation [21,22]. As pathologists, we prefer a morphological definition of mitotic catastrophe [23]. Therefore, in this review, mitotic catastrophe is defined as a cell death mode occurring after a dysregulated/failed mitosis, which can be accompanied by morphological alterations, including micronucleation (which often results from chromosomes and/or chromosome fragments not being distributed evenly between daughter nuclei) and multinucleation (the presence of two or more nuclei with similar or heterogeneous sizes, deriving from a deficient separation during cytokinesis) [3,23]. Multinucleated, bizarre giant cells can be seen in benign (e.g., symplastic leiomyoma of the uterus) or malignant conditions, including carcinomas, sarcomas, and lymphomas [24]. In this review, however, we focus only on the relationship between mitotic catastrophe and malignant epithelial tumors.

**DETECTION METHODS OF MITOTIC CATASTROPHE**

According to the recommendations of the Nomenclature Committee on Cell Death [25], the definition of cell death must be based on precise terms of the parameters that describe the presumed cell death pathway involved. Electron microscopy is the gold standard for detection of these types of cell death [25]. It is now agreed that a rational combination of at least two techniques should be utilized, one to visualize morphological changes and the second to determine biochemical changes, when the modes of cell death are asserted [25]. Therefore, at present morphological detection methods of mitotic catastrophe include light and electron microscopy as well as immunohistochemical markers (p53, Ki-67, pericentrin, gamma-tubulin).

**P53**

In response to a range of stresses, including DNA damage, hypoxia, or proliferative signals, p53 stabilizes, causing cells to undergo either cell-cycle arrest or apoptosis.
The centrosome is a fascinating organelle that resides in many tumor types and is deregulated in many cancers [26]. Although the gene encoding p53 is found mutated in more than 50% of all types of human cancers, mitotic catastrophe has been overlooked until now. Cells lacking p53 function also lack G2 checkpoint function [26]. This is an important fact for cancer treatment outcome as >50% of human tumors (especially solid tumors) are p53 nonfunctional and, thus, lack G2 checkpoint surveillance and are often resistant to cytotoxic and genotoxic treatments. Thus, the ultimate goal of eradicating cancer by subjecting patients to surgical intervention and rounds of radiation and/or chemotherapeutic agent treatments might be compromised by the tumor response to these later treatments. Basically, alterations in p53 can be analyzed by mutation analysis or immunohistochemical staining. Mutations in the TP53 gene can result in either the production of a stable p53 protein, which can be detected immunohistochemically, or production of truncated p53 protein. The latter type of mutations (null mutations) will result in false-negative immunohistochemical staining for the p53 protein and lead to the erroneous conclusion that no mutation is present [27]. Therefore, immunohistochemical staining of p53 suffers both false-negative and false-positive results, compared with p53 gene sequencing, so introduction of additional immunohistochemical parameters can be expected to increase precision.

**KI-67 IMMUNOHISTOCHEMISTRY**

Ki-67 is a nuclear protein that has demonstrable utility as a prognostic marker for several malignancies [28]. Ki-67 is an enormous protein (nearly 360 kDa), encompassing one of the most uniformly and tightly regulated proteins expressed within proliferating eukaryotic cells (cell cycles G1, S, G2, and M), but not quiescent cells (cell cycle G0). Ki-67 is widely accepted as a reliable indicator of cell proliferation within various human tissues, including various forms of cancer. Consequently, Ki-67 has been routinely exploited to assess tumor cell proliferation to gauge the aggressiveness as well as responsiveness to therapy of multiple human malignancies [28].

**ROLE OF CENTROSOMES IN MITOTIC CATASTROPHE**

The centrosome is a fascinating organelle that resides near the cell center—hence, its name. The interphase centrosome consists of a pair of orthogonally oriented centrioles surrounded by a pericentriolar matrix. Although pericentriolar material contains hundreds of proteins, gamma-tubulin and pericentrin are the two classical markers of the centrosome where they have specific localizations [29]. The role of centrosomes in a wide range of tumor types has been investigated and centrosome aberration (supernumerary and structurally altered centrosomes) may play a potentially causative role in malignant progression. Some researchers have found centrosome defects in a significant fraction of precursor lesions, including in situ carcinomas of the uterine cervix, prostate, and female breast, by detecting centrosomes proteins, pericentrin, and gamma-tubulin using immunohistochemistry [30–32]. Lingle et al. [33] reported detailed morphological abnormalities in cancer cells, such as supernumerary centrioles, excess pericentriolar material, disrupted centriole barrel structure, unincorporated microtubule complexes, centrioles of unusual length, and mispositioned centrosome. Lingle et al. [33] suggested that differentiated tumors have centrosomes that may be mislocated, as in tumors with inverted cell polarity. Centrosome abnormalities are characteristic of poorly differentiated anaplastic tumors [33]. The presence of excess pericentriolar material was associated with the highest frequency of abnormal mitoses as assessed by Ki-67 immunolabeled paraffin sections of the same tumors [33]. Centrosome abnormalities may result in multipolar spindles, which cause abnormal chromosome segregation and may generate cells with micronuclei and multinucleated giant cells, which are characteristically found in mitotic catastrophe [34,35]. Thus, the study of mitotic catastrophe in human carcinomas should also include electron microscopy and immunohistochemistry (pericentrin and gamma-tubulin) of centrosomes.

**ULTRASTRUCTURAL DEFINITION OF MICRONUCLEI, NUCLEAR BLEBS, AND STRINGS**

The nuclei of the cells of most solid tumors in histopathologic preparations vary in size, shape, and chromatin pattern, both from normal nuclei and from each other. Nevertheless, only a few attempts have been made to classify abnormalities in the morphology of interphase nuclei. The study of Gisselsson et al. [36,37], on primary cultures of solid tumors, suggested a rough classification into three types: nuclear strings, nuclear blebs, and micronuclei. In that study, a nuclear string was defined as a chromatin thread connected to the membrane(s) of one or two nuclei, a nuclear bleb as a round or oval protrusion of the nuclear membrane connected to the main part of the nucleus by a thinner chromatin segment, and a micronucleus as a rounded chromatin located adjacent to a nucleus, with a diameter not exceeding one-third of the diameter of that nucleus.
Nuclear heterogeneity has been documented by Fenech et al. [38] in normal and folate-deprived cultures of human lymphocytes. In addition to micronuclei, they describe nuclear buds and nucleoplasmic bridges, which are synonymous with the nuclear blebs and strings of Gisselsson’s study [37], respectively. Some studies suggest that nuclear blebs might be converted into micronuclei during interphase [39]. According to Utani et al. [40], micronuclei and nuclear buds are important indicators for genome instability.

**PLEOMORPHIC, GIANT CELL CARCINOMA**

Morphologic features compatible with mitotic catastrophe can be seen in pleomorphic, giant cell carcinoma: a tumor lacking any identifiable glandular, squamous, or any other type of differentiation. In fact, it consists of sheets of highly undifferentiated pleomorphic cells, often with areas of necrosis. There may be numerous bizarre/multinucleated cells. Mitotic figures are numerous with many being abnormal. Areas of more differentiated carcinoma can be seen in association with anaplastic areas. Pleomorphic, giant cell carcinomas are usually highly aggressive malignant tumors that are widely found, but most commonly in the lungs, breast [41,42], pancreas, and thyroid [24].

**OUR EXPERIENCE**

Recently, we reported a case of a 70-year-old woman with an anaplastic giant cell thyroid carcinoma, along with immunohistochemical and electron microscopic findings [43]. In addition to coagulative necrosis as well as nuclear overexpression of p53 and Ki-67, the tumor was characterized by atypical mitoses and multinucleated and multinucleated giant cells (Figure 1a). Tumor cell nuclei showed heterogeneous size ranging from micronuclei to large-size (giant) nuclei. Micronuclei were confirmed by electron microscopy (Figure 1b) that also showed the presence of nuclear blebs and strings. Pale, swollen nuclei could be seen in some multinucleated giant cells, suggesting an association with nonapoptotic necrosis-like features (Figure 1b).

We also reported a case of pleomorphic, giant cell carcinoma of the stomach (Figure 2) that showed a pleomorphic population of tumor cells with multinucleated giant cells and focal areas of tissue necrosis (less than 5% of the tumor) [44]. Multipolar, atypical mitoses were frequent (Figure 2). There was p53 and Ki-67 immunohistochemical overexpression. In 3 other cases, we have studied gastric neoplasms consisting of uniform tumor cells arranged in a trabecular or solid pattern with extensive tissue necrosis (more than 40% of tumor area) (Figures 3a, 3b) [15]. Bizarre, giant cells were often observed singly or in small groups among the trabecular areas. p53 and Ki-67 were overexpressed (Figure 3c), and multipolar mitoses were also seen (Figure 3b). These preliminary data suggest a variable expression of necrotic phenomena in gastric carcinomas, emphasizing the need for further research.

**FIGURE 1** Anaplastic giant cell carcinoma of the thyroid. (a) Some multinucleated giant tumor cells contain a pale swollen nucleus. Semithin section, Giemsa ×400. (b) Anaplastic carcinoma cell showing multiple nuclei and micronuclei (curved arrow). Note the presence of a pale, swollen nucleus with necrosis-like features (arrow). ×10,000. (c) Anaplastic carcinoma cell characterized by nuclear blebs (arrows) and a micronucleus (double arrow). ×10,000.

**FIGURE 2** Anaplastic giant cell carcinoma of the stomach. Solid sheet of poorly cohesive mononucleated and multinucleated giant cells. Note the presence of mitotic multipolarity. Semithin section, Giemsa ×400.
They also reflect the uncertainties about the precise causes and mechanisms of mitotic catastrophe. In fact, as reported above, mitotic catastrophe has also been considered as a state generally, but not necessarily, associated with cell death as an outcome. Moreover, there are several problems in the identification of mitotic catastrophe in carcinoma tissue samples. One of these is the percentage of pleomorphic giant cells in tumor tissue. For example, breast carcinomas are classified according to WHO as pleomorphic, if characterized by proliferation of pleomorphic and bizarre tumor giant cells comprising more than 50% of the total neoplastic proliferation in a background of adenocarcinoma with spindle and squamous differentiation [43,44]. If a breast carcinoma shows less than 50% of pleomorphic giant cells, can it still be considered a morphological expression of mitotic catastrophe? Thus, the application of the mitotic catastrophe concept in histopathology could be considered a work in progress, and, in addition, efforts to improve the existing schemes are obviously necessary. In particular, it is important to define the cutoff values of percentage of pleomorphic giant cells and tumor necrosis.

**IMPLICATIONS AND PERSPECTIVE**

The term mitotic catastrophe refers to a syndrome characterized by a constellation of morphologic features, including multinucleation, micronucleation, abnormal mitoses, centrosome aberration, tissue necrosis, as well as p53 and Ki-67 overexpression. Features compatible with mitotic catastrophe may be found in pleomorphic giant cell carcinoma of the thyroid, lung, pancreas, and stomach. Probably, they may also be demonstrated in aggressive, high-grade breast carcinomas (basal-like carcinomas) and in grade 4 undifferentiated carcinomas. We think that mitotic catastrophe may be a unifying concept useful for studying the extreme end of the morphologic spectrum of grades in infiltrating carcinomas in order to identify a distinct, although rare, subgroup within carcinomas, characterized by unfavorable prognosis. Therefore, we suggest that the presence or absence of mitotic catastrophe, as defined in previous reports and in the current paper, becomes assimilated into a score that gives more precise prognostic information.

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