NUT Carcinoma

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Clinical Features of NUT Carcinoma

NUT carcinoma (NC) is a rare, aggressive cancer. It can affect any gender or age group and occurs equally in males and females from the neonatal period [1, 2] through the eighth decade of life [3, 4]. Fewer than one hundred cases have been reported. At sites outside of the lung NC may represent 4–18% of tumors otherwise diagnosed as poorly differentiated carcinomas or undifferentiated malignant neoplasms [2, 5, 6]. Based on one study, the prevalence of NC amongst primary pulmonary nonglandular carcinomas was less than 1% [7]. There is no known racial predilection.

The cell of origin is not known and no in situ epithelial component has ever been observed. The tumor is usually locally invasive and widely metastatic at diagnosis. Because NCs arise from various anatomical sites, they cannot be categorized by the same system of nomenclature as most other carcinomas, which are traditionally defined by the tissue of origin. Instead, NC is defined genetically by the presence of chromosomal rearrangements involving the *NUT* (aka *NUTM1*) gene [8]. NCs tend to arise from midline anatomical sites, most commonly the upper aerodigestive tract (50%) [9] and the mediastinum (41%) [10]. However, it has been diagnosed within such varied tissues as the parotid gland, pancreas, adrenal gland, subcutis, bladder, and iliac bone [2, 11–14]. Apart from these unique features, NC is best known for its devastating clinical course. NC is characterized by aggressive local invasion and

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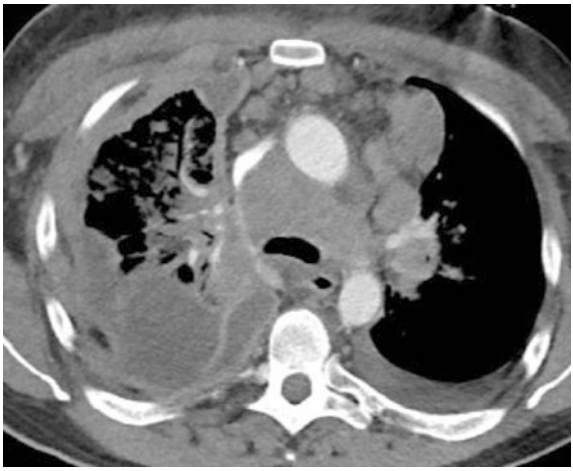

Fig. 7.1 A CT scan shows the appearance of a NUT carcinoma, as a hypoattenuating, heterogenously enhancing, necrotic mass with poorly defined, infiltrative borders

by lymphatic and hematogenous spread [2]. NC is often initially responsive to chemotherapy and radiation, but it invariably recurs rapidly and does not respond to subsequent therapeutic interventions. The median survival is only 6.7 months [4, 10], despite its frequent occurrence in previously healthy children or young adults without comorbid conditions. Thoracic NC usually presents at an advanced stage, with pleural effusions, pleuritic chest pain, nonproductive cough, weight loss, and shortness of breath [15, 16]. Thoracic NC may disseminate to bone, ovaries, liver, and brain [4, 12, 17–22]. Chest X-rays typically demonstrate extremely rapid tumor progression, with complete opacification of the thorax within 2–8 weeks from initial presentation [18]. By computed tomography (CT), NC appears as a hypoattenuating, heterogeneously enhancing, often extensively necrotic mass with poorly defined, infiltrative borders (Fig. 7.1) [15, 18, 23]. Given the age distribution of NC, it is unlikely that smoking plays a pathogenic role; this hypothesis is supported by the absence of a smoking history in many, but not all NC patients [13]. None of the cases tested to date have been associated with Epstein-Barr virus or with human papilloma virus infection [6, 13]. NC has been encountered in many parts of the developed world but is under-recognized in many developing countries.

It was in this rare cancer that the new class of bromodomain (BET) inhibitors were originally developed. BET inhibitors target the chromatin-binding bromdomains of BRD4 (and all other BET proteins) and thus directly inhibit the BRD4-NUT oncoprotein [24]. Clinical use of these inhibitors has demonstrated efficacy in NC [25], and multiple trials are ongoing enrolling NC patients in the United States and Europe. With the development of targeted therapy for NC, there is increased urgency for the early detection and diagnosis of this aggressive cancer.

Histopathology

The histopathology of NC is characteristic, but not diagnostic. The most common appearance is that of a poorly differentiated carcinoma with focal, abrupt squamous differentiation (Fig. 7.2). In contrast to many other poorly differentiated carcinomas, which consist of highly pleomorphic large cells, NC cells are usually medium sized, round, and often monomorphic in appearance (Fig. 7.3). Overt areas of squamous differentiation are seen in approximately half of cases [8] but may not always be present, particularly in small biopsies. A peculiar feature seen often in NC is a brisk neutrophilic infiltrate not associated with necrosis (Fig. 7.4). Well documented NC with unequivocal features of adenocarcinoma have not been seen. The histopathologic features of NC overlap with those of several other poorly differentiated cancers, including poorly differentiated squamous cell carcinoma, sinonasal undifferentiated carcinoma [5], Ewing sarcoma, Epstein-Barr virus-associated nasopharyngeal carcinoma, thymic carcinoma, neuroblastoma, pancreatoblastoma [12], and even primary salivary gland carcinoma (Fig. 7.5) [26]. NC is commonly misdiagnosed; it has even been mistaken for acute leukemia (due to the occasional expression of CD34) [2]. Also contributing to the failure to diagnose NC is poor awareness of the disease among clinicians and pathologists, its rarity, and until recently, the absence of widely available diagnostic tests. To counter the lack of awareness of NC among pathologists and oncologists, an Internet-based international NC registry (http://www.NCRegistry.org) has been established. This registry provides access to (a) pathologic review, (b) updated information about the disease, (c) treatment guideline suggestions, (d) a repository for clinical data, and (e) educational information for physicians and patients about this disease.

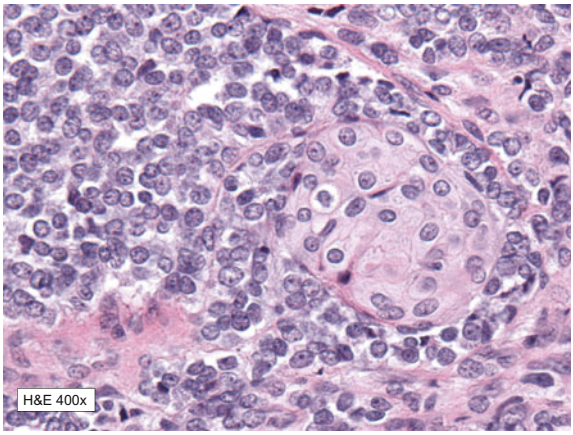

Fig. 7.2 The most common appearance of NUT carcinoma is that of a poorly differentiated carcinoma with focal abrupt squamous differentiation, present on the *right side* of the micrograph

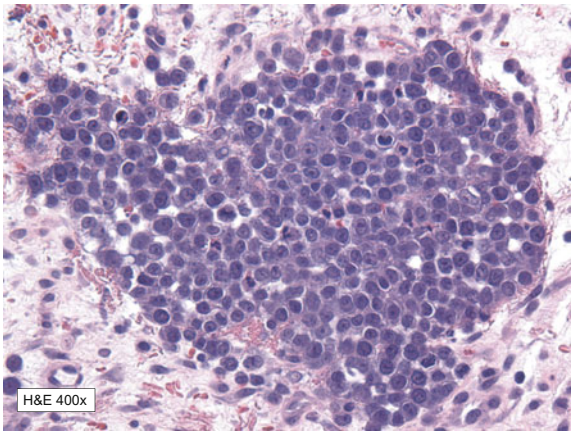

Fig. 7.3 NUT carcinomas cells are usually medium sized, round, and show a characteristic monomorphic appearance

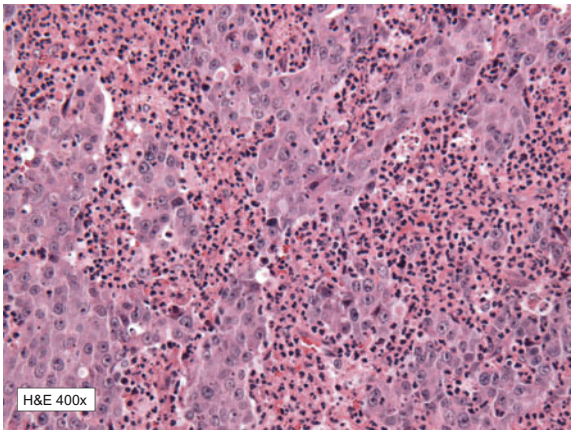

Fig. 7.4 A peculiar feature seen commonly in NUT carcinoma is the presence of a brisk neutrophilic infiltrate

Cytology

NUT carcinoma has a cytopathologic appearance that is nonspecific and mimics other primitive small round cell tumors or basaloid neoplasms [27–30]. Samples are highly cellular with monotonous, primitive-appearing small-to-mid-sized cells distributed most often singly and only occasionally in groups (Fig. 7.6). Vacuolated cytoplasm, corresponding with intracytoplasmic glycogen, is frequently seen, creating artifactual separation of cells and imparting a "fried-egg"-like appearance (Figs. 7.7 and 7.8) [27, 28, 31]. Chromatin ranges from open and pale, to hyperchromatic and neuroendocrine-like (Figs. 7.9 and 7.10) [32]. Mitoses, necrotic debris, and crush artifact are common [28, 33]. Overall, the cytologic characteristics overlap considerably with other poorly to undifferentiated carcinomas.

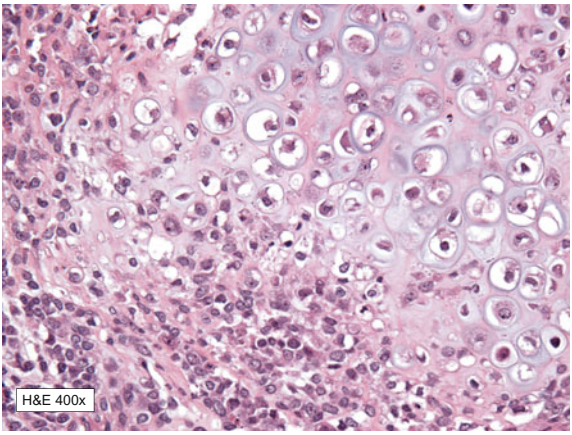

Fig. 7.5 This photomicrograph shows a NUT carcinoma originating in the parotid gland. Initially this tumor was thought to be a carcinoma ex pleomorphic adenoma because of the chondroid differentiation shown in this photomicrograph (i.e., originating from a pleomorphic adenoma)

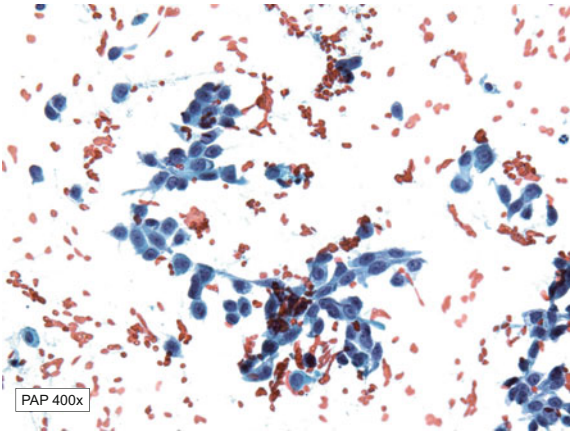

Fig. 7.6 Cytology sample from a patient with NUT carcinoma showing monomorphic, primitive-appearing small cells most often single and less commonly in groups

Macroscopy

NCs often present at advanced stages and therefore are not frequently amenable to surgical resection. NC typically grows as a large mass extending into hilar structures or along the pleura and chest wall (Fig. 7.11) [17]. NC has a fleshy, tan-white cut surface with or without prominent geographic necrosis.

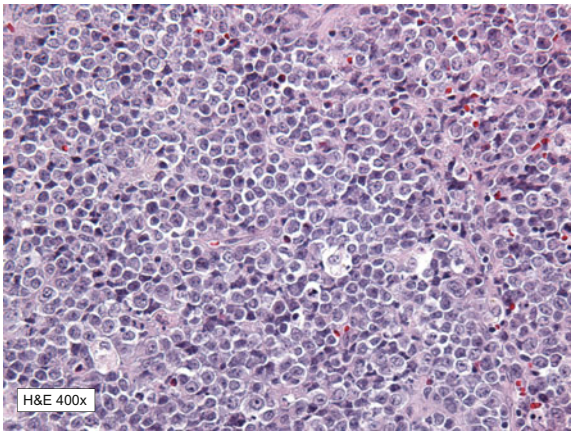

Fig. 7.7 Vacuolated cytoplasm with intracytoplasmic glycogen showing the artifactual separation of cells (fried egg appearance)

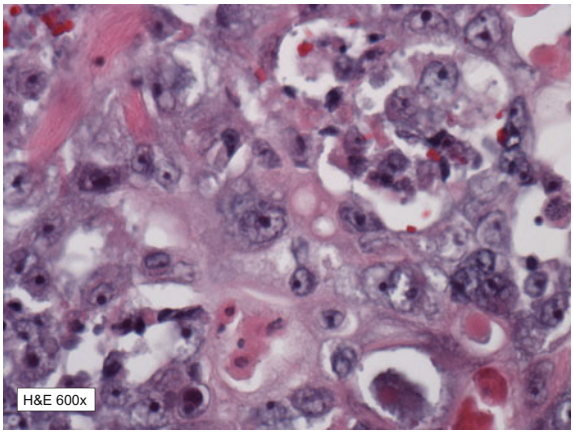

Fig. 7.8 High power magnification showing the fried egg appearance

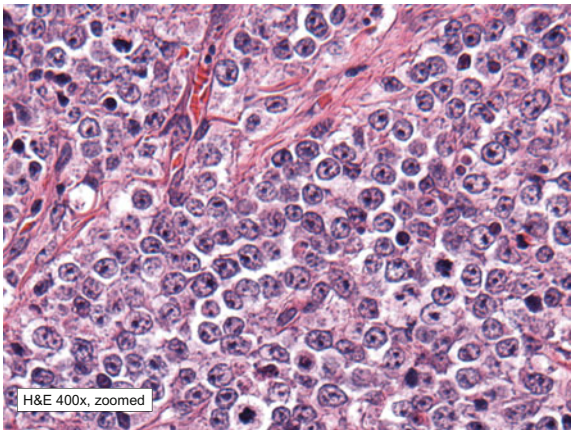

Fig. 7.9 NUT carcinoma cells, example of a pale open chromatin

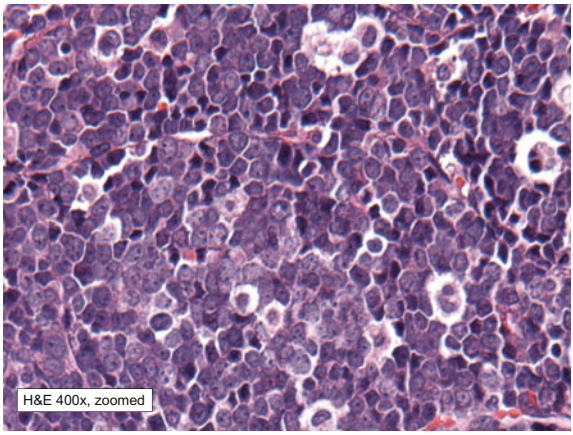

Fig. 7.10 Hyperchromatic, neuroendocrine-like chromatin, with similar appearance as in high grade neuroendocrine carcinomas

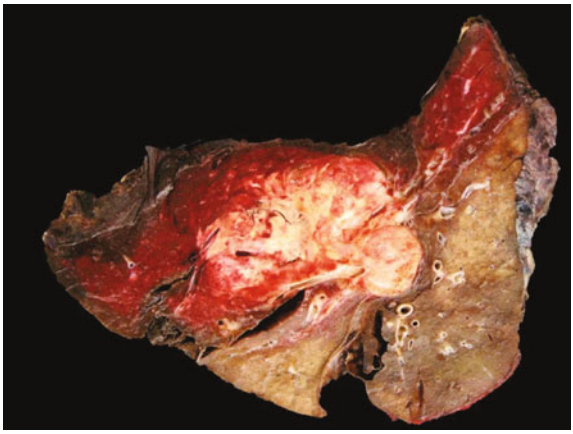

Fig. 7.11 Sagittal section from a pneumonectomy specimen of NUT carcinoma, typically growing as a large mass extending into other structures

Histopathologic Features in Biopsy Specimens

NUT carcinoma typically presents as sheets and nests of undifferentiated cells with a monomorphic appearance. The nuclei have irregular contours and granular to open chromatin (Figs. 7.9 and 7.10). The characteristic presence of abrupt foci of keratinization (Fig. 7.2) could be absent in small biopsy specimens [11, 16, 34]. Tumor cells infiltrate and expand the interstitium and may appear contiguous with bronchial epithelium (Fig. 7.12) [17]. Prominent geographic necrosis might be present (Fig. 7.13).

Tumor cells may be associated with a reactive pneumocyte proliferation, leading to diagnostic consideration of an adenosquamous carcinoma.

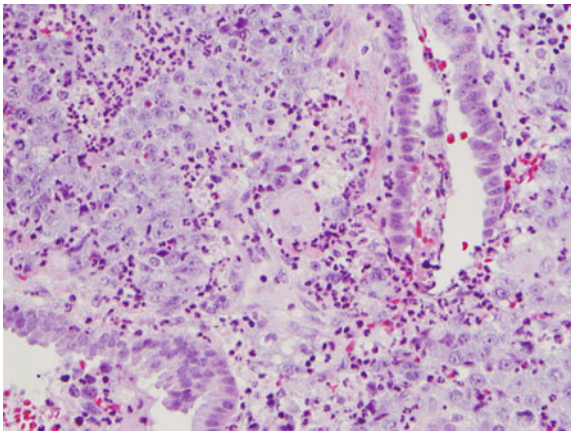

Fig. 7.12 Endobronchial biopsies from patients with NUT carcinoma show tumor cells infiltrating and expanding the interstitial spaces under the bronchial epithelium

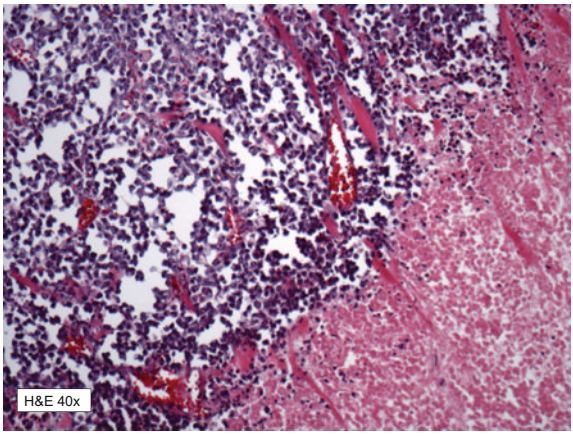

Fig. 7.13 A NUT carcinoma with small monomorphic cells (*left side*) and prominent geographic necrosis (*right side*)

Diagnosis

The diagnosis of NC depends on the demonstration of *NUT* (aka *NUTM1*) gene rearrangement or mis-expression. Although cytogenetic demonstration of a t(15;19) by karyotyping is sufficient for a presumptive diagnosis of NC, most diagnoses are based on formalin-fixed, paraffin-embedded (FFPE) tissues because few suspected carcinomas are submitted for karyotyping. To fill this diagnostic need, one of the authors developed a fluorescence in situ hybridization (FISH) assay that uses dual-color, break-apart bacterial artificial chromosome probes flanking the *NUT* and *BRD4* loci (Fig. 7.14) [35–37]. This assay can be used on virtually any specimen preparation, including frozen tissue, acetic acid-fixed cytogenetic preparations, thin (4–5 μm) sections of FFPE tissues or disaggregated cells, and air-dried or

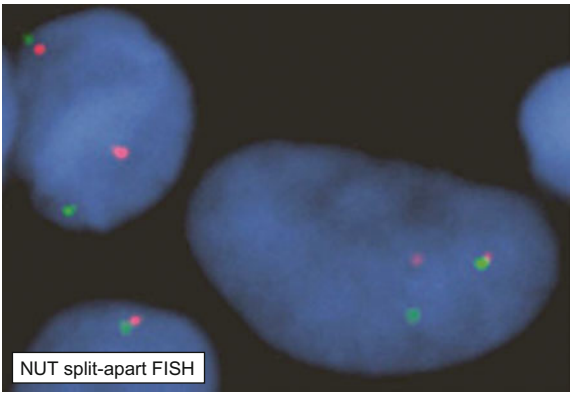

Fig. 7.14 Florescent in situ hybridization (FISH) using a dual color, break-apart probes flanking the NUT, and BRD4 loci. The typical translocation of a NUT carcinoma would result in separating (breaking apart) the probes with two distinctive separate signals: *red* and *green*

ethanol-fixed slides. Because this approach works on archival, formalin-fixed tissue, retrospective analysis can be performed on samples that are decades old [2].

If fresh or frozen tissue is available, reverse-transcriptase polymerase chain reaction can be employed by use of primers flanking the known *BRD4* and *NUT* break points [38]. However, this method overlooks *NUT*-variant fusion genes. To develop a diagnostic test for NC that can be used routinely in the community, a monoclonal antibody to NUT (clone C52B1, Cell Signaling Technologies, Danvers, MA) that detects NUT expression by immunohistochemistry was developed by one of the authors (CAF, Fig. 7.15) [39]. NUT expression is normally restricted to post-meiotic spermatids of the testes (Fig. 7.16) [40]. In a study that included a large number of control tissues, predominantly other forms of carcinoma, nuclear reactivity with this antibody was 100% specific and 87% sensitive for the diagnosis of NC when present in greater than 50% of cells [41]. The nuclear reactivity with the NUT antibody in NC frequently, though not invariably, displayed a speckled pattern of staining (Fig. 7.17). In this same study, the authors also observed NUT nuclear staining in a large percentage of germ cell tumors (seminomas, dysgerminomas, and embryonal carcinomas), though the staining was weak, not speckled, and present in less than 10% of cells.

Immunohistochemistry

Most cases of NC have nuclear expression for p63/p40 consistent with squamous differentiation (Fig. 7.18). Broad spectrum cytokeratins are positive in the majority of cases (Fig. 7.19), although rare cases are negative [6, 33]. The other epithelial markers such as EMA, BerEP-4, CEA are expressed variably in NCs. Occasionally

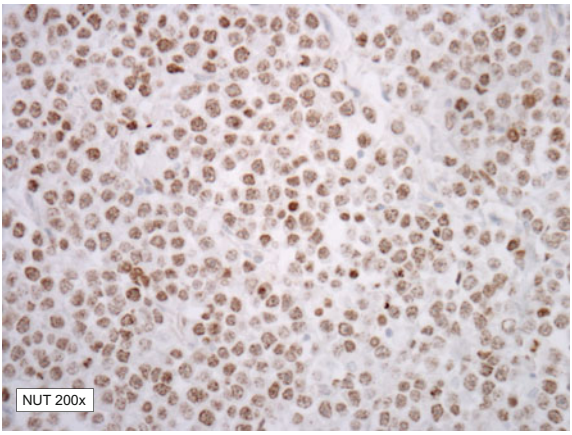

Fig. 7.15 Immunohistochemistry with a monoclonal antibody for NUT showing diffuse positivity for the antibody

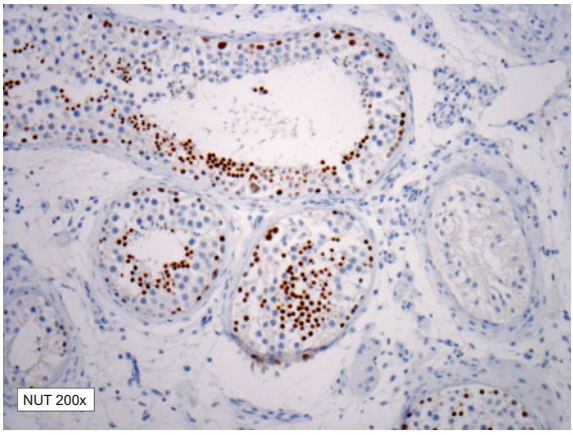

Fig. 7.16 NUT expression is normally restricted to post-meiotic spermatids of the testes

NCs can stain for chromogranin, synaptophysin, or even TTF-1 (Fig. 7.20) [17]. NCs are often positive for CD34, which may lead to a misdiagnosis of acute leukemia [2]. Germ cell, lymphoid, and myeloid markers are negative.

Differential Diagnosis

Since NC potentially look like any other poorly differentiated neoplasm, testing for NUT expression by immunohistochemistry should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology [34]. NC may be misdiagnosed as squamous cell carcinoma, undifferentiated

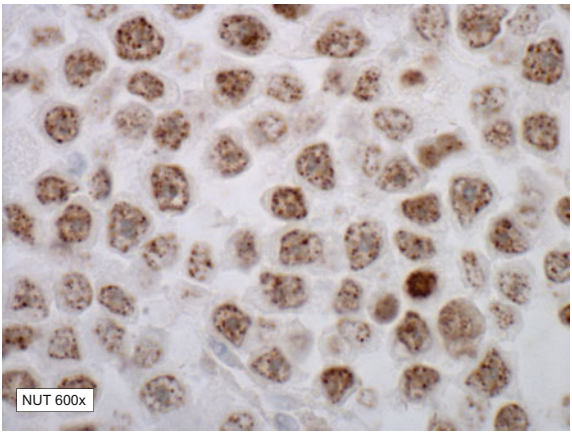

Fig. 7.17 Characteristic-speckled pattern of staining of NUT carcinoma cells (with the clone C52)

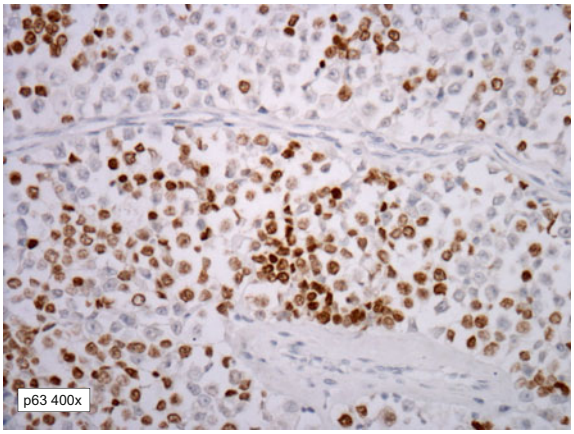

Fig. 7.18 NUT carcinoma cells positive for p63, consistent with squamous differentiation

carcinoma, small cell carcinoma, adenosquamous carcinoma, Ewing sarcoma, metastatic germ cell tumor, and acute leukemia [4, 35].

Summary

NC is a genetically defined, highly aggressive, and incurable squamous cell carcinoma associated with chromosomal rearrangements of *NUT*, most commonly resulting in *BRD4-NUT* fusion oncogenes or, less commonly, *BRD3-NUT*, *NSD3-NUT* or *NUT*-variant fusion oncogenes. Once a difficult diagnosis to make, NC is now diagnosable in most cases by immunohistochemical staining with an anti-NUT

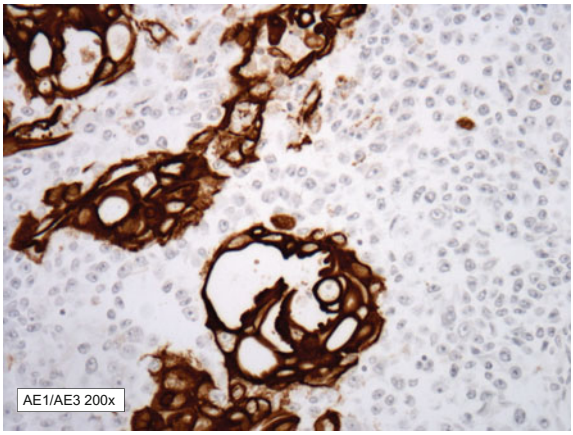

Fig. 7.19 NUT carcinoma cells positive for expressing broad spectrum cytokeratins in the majority of cases

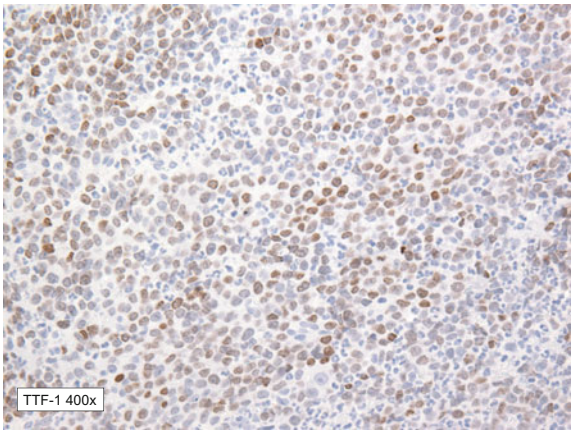

Fig. 7.20 Occasionally NUT carcinoma cells have nuclear TTF-1 expression

monoclonal antibody. Given the emergence of promising targeted therapy for this otherwise incurable cancer, there is an urgent need for increased awareness and early diagnosis of NC. Since NC resembles other poorly differentiated neoplasms, testing for NUT expression by immunohistochemistry should be considered in all poorly differentiated carcinomas with p63 or p40 nuclear expression that lack glandular differentiation or specific etiology.

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