Review Article

Advances in the pathogenesis and treatment of nut carcinoma: a narrative review

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Abstract: *NUT* carcinoma (NC) is a rare, highly invasive and fatal tumor and often misdiagnosed. It typically arises from the mediastinum and midline organs and has complicated pathogenesis and poor outcome. Genetically, its pathogenesis is related to a chromosomal rearrangement involving the *NUTM1* gene. In most cases, the main oncoprotein is *BRD4-NUT* with a translocation between *NUTM1* and *BRD4* genes, but in a few cases, the oncoprotein is *BRD3-NUT*, or *NSD3-NUT*. Studies have shown that the histone hyperacetylation and *BRD4* hyperphosphorylation may lead to the activation of cancer circuits. Abnormal production of microRNA, inactivation of tumor suppressor genes and abnormal activation of several signaling pathways are proposed as potential mechanisms underlying the pathogenesis of NC. Currently, there is no consensus on its standard treatment for NC. Extent of surgical resection with negative margins, initial radiotherapy and part of chemotherapy regimens may significantly associated with the improvement of progression-free survival (PFS) rate and overall survival (OS) rate. Some bromodomain and extraterminal inhibitors (BETis) have shown encouraging results in the clinical trials on NC, but delayed drug resistance is still an important issue that needs to be resolved. Histone deacetylase inhibitors are also found to possess the potential in the treatment of NC. Herein, we summarize recent advances in the pathogenesis and treatment of NC.

Keywords: NUT carcinoma (NC); pathogenesis; gene rearrangement; therapy; bromodomain and extraterminal inhibitors (BETis)

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Introduction

NUT midline carcinoma (NMC) is a malignant tumor with involvement of testicular nuclear gene rearrangement, which has the tendency to arise from midline anatomical sites, and it was initially described as a mediastinal tumor in 1991 (1) with increasing cases reported in non-midline structure such as renal pelvis, pancreas, parotid gland, bladder, sublingual gland and femur (2-7). WHO redefined NMC as *NUT* carcinoma (NC) in 2015 (8). Generally, NC progresses rapidly. Bauer *et al.* investigated the clinical characteristics of 57 patients with NC and found that the median survival time was 6.7 months (9). Pathologically, NC is characterized by variable degrees of squamous differentiation with a predominance of the poorly or undifferentiated component(10,11). The pathogenesis of NC is complex and related to the acquired chromosomal rearrangements involving *NUTM*1 (*NUT* Carcinoma Family Member 1) and other causes leading to the differentiation blocking (12). NC has no preference for gender or age and is often misdiagnosed. The survival rate of NC patients has not been improved significantly

although some strategies have been employed for the treatment of NC, and there is no consensus on the standard treatment for NC currently. Herein, we summarize the advances in the pathogenesis and treatment of NC in recent years. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1884).

Pathogenesis

Exposure factors

The occurrence of NC has not been reported to be associated with any special exposure factors such as tobacco use (13) and infection with Epstein-Barr virus or human papillomavirus (14,15). Whether the occurrence of NC is related to other tumor-causing viral infections is needed to be further studied.

Multiple gene rearrangement

Malignant tumors may be caused by genetic changes, including the acquisition or loss of chromosomes and chromosomal segments, gene translocation, gene transcoding, and gene point mutations, which can lead to the activation of oncogenes or inactivation of tumor suppressor gene (*TSG*). Shiota *et al.* found that *NUT* is expressed in post-meiotic spermatogenic germ cells, and it can recruit p300 and/or CBP and enhance histone H4K5 and H4K8 acetylation, leading to the histone-to-protamine replacement (16). In the rearrangement gene expression of NC, the *NUTM1* (*NUT*) gene usually uses bromodomain-containing protein 4 (*BRD4*) as a fusion partner, sometimes uses BRD3, and, in a few cases, uses NSD3 (17,18). Alekseyenko *et al.* found that *ZNF532* as a chromatin factor could interact with *BRD4-NUT* complexes, and they also identified another fusion oncogene, *ZNF532-NUT* (19). It has been reported abnormal three-way translocations involving t (4;15;19), t(9;15;19), t(11;15;19) and a t(2;9;15) in NC cells (20). A new type of *NUT* fusion partner *MGA* has also been reported (21,22), but this pathology is ultimately classified as a sarcoma; *MXD4*, a novel partner, is reported recently (21,23).

Lee *et al.* sequenced the whole genome and transcriptome of three NC patients and found that, except for *BRD3/4-NUT* oncogene rearrangement, no canonical oncogenes or tumor suppressor genes were affected, but it caused NC, a fatal disease (13). French *et al.* for the first time reported the fusion oncogene, *BRD4-NUT* in 2003 (24). The expression of *NUT* fusion oncogenes has great heterogeneity at different ages and tumor locations, which indicates that NC may eventually be divided into clinically related subgroups with different clinical outcomes and therapeutic responses (25). Chau *et al.* grouped 124 out of 141 NC patients by anatomic location and fusion type, and nonthoracic primary NC group with non-*BRD4-NUT* fusion had the best outcome (26). Testing for NC rearrangement may be not enough, and the identification of specific fusion partners may be necessary to develop therapeutic strategies.

Histone hyperacetylation and BRD4 hyperphosphorylation

NUT is exclusively expressed in the testis of human and mice, and p300 and/or CBP are the only acetyltransferases present in the *NUT* interactome. *NUT* recruits p300 and/or CBP to control histone H3 and H4 acetylation. In NC cells, a chromosomal translocation induces *NUT*-mediated forced cooperation between p300 and/or CBP and *BRD4*, forming the hyperacetylated histone chromatin foci (16). This acetylation further affects *BRD4-NUT* in a synergistic manner, ultimately forming a large number of acetylated chromatin regions covering various topologically relevant domains of the entire genome, called the megadomain (27). The megadomain contains approximately 100 chromatin domains, ranging from 100 to 2,000 kb, across the gene and intergenic regions (28).

BRD4 is a member of the bromodomain and extraterminal (BET) family. The tandem bromodomains of *BRD4* (BD1 and BD2) can specifically recognize acetylated histones H3 and H4 on chromatins (29). *BRD4* has been implicated in the pathogenesis of a variety of cancers, including hematological malignancies and solid tumors (30-33). It is also the target of genetic translocation between chromosomes 15 and 19, expressed as t(15;19), which leads to the formation of a novel fusion oncogene *BRD4-NUT* (24). *BRD4-NUT* can induce the abnormal activation of oncogenes such as SOX2 (34) and c-MYC (35) in the hyperacetylated chromatin in NC cells. Wang *et al.* found that a unique cellular environment induced *BRD4* hyperphosphorylation in HCC2429 NC cells. The hyperphosphorylation of *BRD4* induced by *BRD4-NUT* may contribute to the transactivation of oncogenes, which accounts for NC transformation (36).

SOX2 is a sex-determining region Y-box protein 2 and mainly expressed in the stem cells. SOX2 is an essential transcription factor for the self-renewal and pluripotency

of stem cells (37). SOX2 mutations induce abnormal self-renewal of stem cells, leading to the abnormal differentiation of stem cells (37,38). *BRD4-NUT* induces abnormally high SOX2 expression in the NC cells to promote the abnormal stem cell-like growth, which is the basis for the highly invasive transformation activity of the t(15;19) translocation (34).

MYC up-regulation is a common driving event in some human cancers. *MYC* can maintain the transcriptional programs to promote cell growth and proliferation. Grayson *et al.* found that *BRD4-NUT* prevented the differentiation of NC by maintaining *MYC* expression (35). The ability of *BRD4-NUT* to diffuse and fill the entire regulatory region of *MYC* gene and other genes may explain the aggressiveness of NC.

MicroRNA (miRNA) amplification

miRNAs play a key role in regulating target genes and are involved in the development and progression of cancers. miRNAs refer to a group of non-coding RNAs approximately 21 nucleotides in length that can inhibit the expression of target genes by binding to complementary mRNA. A single miRNA can regulate the expression of some different mRNAs (39,40). Pathak *et al.* compared the miRNAs that target *BRD4* and *NUT* transcribed regions before and after *BRD4-NUT* gene fusion event. Because of the formation of fusion transcripts, the regions of fusion gene deletion will no longer be the targets for their respective miRNAs. Many such ex-miRNAs will be significantly amplified in cancer cells, resulting in abnormal cell behaviors (41). miR-3140 (a novel tumor suppressor miRNA) directly inhibits the expression of *BRD4* by binding to its coding sequence; it also inhibits the *BRD4-NUT* fusion protein and its downstream target *MYC* in the NC cell lines (42).

Inactivity of TSG

TP53 is a powerful tumor suppressor gene that prevents mutation via DNA repair and inducing apoptosis. There is evidence showing that *BRD4-NUT* promotes acetylation of p53 via p300, resulting in the chelation and inactivation of *BRD4-NUT* (43). It inhibits SOX2 significantly by inhibiting the p300 activity (44); mRNA and protein expressions of *c-MYC* are also reduced. Alekseyenko *et al.* found that the expression of TP53-associated squamous cell gene *TP63* was regulated by the *BRD4-NUT* megadomain in all tested NCs, which supports a possible mechanism by which *BRD4-NUT* can evade the gatekeeper function of p53 (27).

Abnormal activation of signaling pathways

MYC maintains the proliferation and undifferentiated state of tumor cells in NC. The blockade of PI3K signaling pathway may inhibit MYC activity by suppressing *MYC* gene transcription and protein activity or down-regulating apoptosis of *MYC*-dependent NC cells (44). The activation of RTK, GPCR, and cAMP/PKA signaling pathways are also found to mediate the resistance to BET inhibitors (BETis) in NC cells (45).

Treatment

Surgery and radiotherapy

NC is a highly invasive tumor for which there is no consensus on its standard treatment (6,46-56) (*Table 1*). It has been reported that extent of surgical resection and initial radiotherapy are the independent predictors of progression-free survival (PFS) rate and overall survival (OS) rate of NC patients (9). A recent study on 48 patients with head and neck NC reported that the only long-term survivors in the study were patients who achieved an early complete remission after initial surgery (57). Radiotherapy as a part of the initial treatment may has a positive impact on the OS rate. However, studies shows that radiotherapy has a positive effect on tumors that originate from the head, neck and lungs, but not on the mediastinal primary tumors (58).

Chemotherapy

Currently, several drugs have been used for the chemotherapy of NC, including cisplatin, carboplatin, cyclophosphamide, etoposide, doxorubicin, actinomycin D, vinorelbine, vinblastine, paclitaxel, docetaxel, 5-fluorouracil, S1, bleomycin, vincristine, ifosfamide, gemcitabine and BETis (58). Beesley *et al.* found that vincristine significantly reduced the tumor burden in NC xenografts and was, therefore, an effective drug for the treatment of NC. However, although vincristine significantly slowed tumor growth in these models, it was not sufficient to prevent tumor recurrence (59). Etoposide and vorinostat have also been used in NC patients. Vincristine, doxorubicin, and

Table 1 Clinical therapy and outcome of NC

Study or subgroup, year	Gender	Age (years)	Surgery	Complete resection	Radiotherapy	Dose (Gy)	VCR	5-FU	PTX	DDP/CBP	ADM
Lee *et al.*, 2017	M	34	No	–	No	–	Yes	–	Yes	Yes	Yes
	F	33	No	–	No	–	–	–	Yes	Yes	–
Elkhatib *et al.*, 2019	F	47	Yes	No	Yes	72.5	–	–	–	Yes	–
Albrecht *et al.*, 2019	M	48	Yes	Not sure	Yes	–	–	–	–	–	–
Stirnweiss *et al.*, 2015	F	14	Yes	Yes	–	–	–	–	–	–	–
Shioto *et al.*, 2015	F	36	No	–	Yes	–	–	–	–	Yes	–
Baras *et al.*, 2018	M	39	Yes	No	Yes	–	–	–	Yes	Yes	Yes
Shatavi *et al.*, 2016	F	23	No	–	–	–	–	–	–	Yes	–
Klijanienko *et al.*, 2016	M	20	Yes	Yes	Yes	–	–	–	–	–	–
	F	21	Yes	–	Yes	–	–	–	–	–	–
Li *et al.*, 2018	M	17	No	–	No	–	–	–	–	–	–
Gökmen-Polar *et al.*, 2016	F	22	Yes	Yes	Yes	– –	–	–	Yes	Yes	Yes
	F	37	No	–	No		–	–	Yes	Yes	–
Stathis *et al.*, 2016	F	39	Yes	Yes	Yes	–	–	–	Yes	–	–
	M	22	No	–	No	–	–	Yes	Yes	Yes	–
	F	66	No	–	Yes	45	–	–	Yes	Yes	–
	M	20	No	–	Yes	60	–	–	–	Yes	Yes
Arimizu *et al.*, 2018	M	49	Yes	No	Yes	70+50	Yes	–	–	Yes	Yes
Ueki *et al.*, 2014	F	12	Yes	Yes	No	–	–	–	Yes	Yes	Yes
Lorenzo *et al.*, 2017	Unknow	21	No	–	Yes	28	–	–	Yes	Yes	–
Aizawa *et al.*, 2019	F	38	Yes	Yes	Yes	60	–	–	–	Yes	–
Teo *et al.*, 2011	F	26	No	–	–	–	–	–	–	–	Yes
Seim *et al.*, 2011	M	25	No	–	Yes	–	–	–	–	Yes	–
Oliveira *et al.*, 2019	M	42	No	–	Yes	70	–	Yes	Yes	Yes	–
Agaimy *et al.*, 2018	F	39	Yes	–	Yes	66+30	–	–	–	Yes	–
Samples *et al.*, 2016	F	2	Yes	No	No	–	–	–	Yes	Yes	–
D'Souza *et al.*, 2014	M	32	Yes	Yes	Yes	60+32	–	–	–	Yes	–
Ding T *et al.*, 2019	F	60	Yes	Yes	Yes	60	–	–	–	Yes	–
Maher *et al.*, 2015	F	17	No	–	Yes	45	–	Yes	–	Yes	–
Storck *et al.*, 2017	M	9	No	–	Yes	54	Yes	–	–	Yes	Yes
	M	9	No	–	Yes	59.4+50.4	Yes	–	–	Yes	Yes

Table 1 (*cobtinued*)

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Study or subgroup, year	CTX/IFO	DOC	VP-16	GEM	BETis	HDACi/others	Early relief	OS
Lee *et al.*, 2017	Yes	–	–	–	–	–	No	4 months
	–	–	–	–	–	–	Yes	8 months
Elkhatib *et al.*, 2019	–	Yes	–	–	–	–	Yes	5 months
Albrecht *et al.*, 2019	–	–	–	–	–	–	–	–
Stirnweiss *et al.*, 2015	–	–	–	–	–	–	–	3 months
Shioto *et al.*, 2015	–	Yes	–	–	–	–	–	9 months
Baras *et al.*, 2018	Yes	–	–	–	–	–	–	3 months
Shatavi *et al.*, 2016	–	Yes	–	–	–	Vorinostat	No	21 days
Klijanienko *et al.*, 2016	–	–	–	–	–	–	Yes	8 months
	–	–	–	–	–	–	–	5 months
Li *et al.*, 2018	–	–	–	–	–	–	–	–
Gökmen-Polar *et al.*, 2016	Yes	–	–	–	–	–	–	1 year
	–	–	–	–	–	–	No	6 months
Stathis *et al.*, 2016	Yes	–	–	–	OTX015/MK–8628	–	Yes	19 months
	–	Yes	Yes	–	OTX015/MK–8628	–	Yes	7 months
	–	–	Yes	–	OTX015/MK–8628	–	Yes	18 months
	–	–	–	–	OTX015/MK–8628	–	Yes	5 months
Arimizu *et al.*, 2018	Yes	–	–	–	–	–	Yes	9 months
Ueki *et al.*, 2014	Yes	Yes	–	Yes	–	–	Yes	6+ months
Lorenzo *et al.*, 2017	Yes	–	–	–	–	HDAC	Yes	3 months
Aizawa *et al.*, 2019	–	Yes	–	–	–	–	Yes	7 months
Teo *et al.*, 2011	Yes	–	–	–	–	–	Yes	3 months
Seim *et al.*, 2011	–	Yes	–	–	–	–	No	4 months
Oliveira *et al.*, 2019	–	Yes	–	–	–	–	No	2 months
Agaimy *et al.*, 2018	–	–	–	–	Unsure	–	No	4 months
Samples *et al.*, 2016	Yes	–	–	–	TEN010	Vorinostat	No	3 months
D'Souza *et al.*, 2014	–	–	–	–	–	–	Yes	9 months (in follow-up)
Ding T *et al.*, 2019	–	Yes	–	–	–	Anlotinib hydrochloride	Yes	15 months (in follow-up)
Maher *et al.*, 2015	–	Yes	–	–	–	Vorinostat	Yes	10 months
Storck *et al.*, 2017	Yes	–	–	–	–	–	Yes	6 years (in follow-up)
	Yes	–	–	–	–	–	Yes	8 months (in follow-up)

VCR, vincristine; 5-FU, 5-fluorouracil; PTX, paclitaxel; DDP/CBP, cisplatin/kabisa; ADM, amycin; CTX/IFO, cyclophosphamide/isocyclophosphamide; DOC, docetaxel; VP-16, etoposide; GEM, gemcitabine; BETis, bromine-domain proteins inhibitors; HDACi, histone deacetylase inhibitor; OS, overall survival.

flavopiridol (CDK9 inhibitor) show significantly better activity than etoposide and vorinostat; statins and anti-metabolites exhibit moderate monotherapy efficacy (59).

In two case reports, three pediatric NC patients were treated with a comprehensive protocol for sarcoma (SSG IX), involving surgery, chemotherapy and focal radiotherapy. These three patients experienced remission for 6 years, 14 years, and 13 years, respectively (60,61).

Targeted therapy

BET inhibitors

A BETis is an acetyl histone mimetic that specifically binds to the BET bromodomain and competitively inhibits its binding to the chromatin (62). In early studies, BETis were shown to be effective against murine hematological malignancies (63). In recent years, many studies have shown that BETis is also effective to inhibit the progression of non-hematological malignancies (64,65). The anti-tumor effect of BETis has also been confirmed in NC. NC cells always have at least one intact *BRD4* locus and express normal *BRD4* and BRD-*NUT* oncoproteins. A variety of BETis are used in clinical trials for the treatment of NC, such as OTX105/MK-8628, GSK525762 and others (such as BAY1238097, GSK2820151, and TEN-010) (62,64,66). Early clinical trials have shown encouraging results (67,68), especially for hematologic malignancies (34). Pathological examination after tumor biopsy revealed a decreased *NUT* expression in areas of differentiation in a NC patient after BETis treatment. This indicates that NC cells may switch to a more differentiated squamous cell phenotype after BETis treatment is initiated. The degree of squamous cell differentiation after BETis treatment may be caused by a number of factors, including the duration of treatment and the site of recurrence (69).

JQ1 is a first-generation BETis. CDK4/6 inhibitors and JQ1 have been used synergistically *in vitro* in NC. Endogenous CDK4/6 plays an important role in regulating JQ1 sensitivity, and CDK4/6 inhibitors may exert synergetic effect with JQ1 (45). A study shows that BET inhibitor JQ1 can induce the differentiation and growth arrest in NC cell lines, and also exert anti-tumor effect in xenograft models of NC (70-72).

The small-molecule BETis birabresib (OTX015/MK-8628) shows anti-tumor activity in patients with hematological malignancies. Lewin *et al.* evaluated the safety and effectiveness of OTX015 in a dose escalation study. Three of 10 patients with NC achieved partial remission. Pharmacokinetic analysis showed that OTX015 exposure and rapid absorption were associated with a dose ratio increase, which suggests OTX015 has good safety in the treatment of solid tumors (66,67). BETis in patients with BRD3-*NUT* or NSD3-*NUT* has similar pharmacodynamic effects; this is the first proof of concept for the clinical activity of bromodomain inhibitors targeting NC (66).

BETis have reversible adverse effects, including fatigue, headache, thrombocytopenia (66), diarrhea, fatigue, nausea, dyspepsia, and hyperglycemia. The pervasive apoptosis in intestinal cells has also been observed after treatment with BETis, which may exacerbate the chemotoxic damage or radiation induced injury (73).

Resistance to BETis

BETis are effective against NC. However, not all NC patients respond to BETis, and the responders will eventually develop resistance and relapse (45). Studies have shown that some refractory cancers are resistant to BETis (74), including NC (42). In some models, resistant cells continue to rely on *c-MYC* to drive proliferation, but in case of BETis resistance, resistant cells will switch from *BRD4*-mediated *MYC* expression to other pathways, including GLI2 or WNT-β-catenin signaling, to maintain *MYC* expression (45). NC cells have many potential pathways for maintaining *MYC* function. ERK and AKT inhibitors can inhibit the expression of downstream signaling pathways of RRAS2 (Ras-associated GTPase). JQ1 can significantly reduce the expression of *c-Myc* and *cyclin D1*, whereas RRAS2 largely restores the phosphorylation of ERK and increases the expression of *c-Myc* and *cyclin D1*. KLF4 (a transcription factor containing a zinc finger structure) mediates JQ1 resistance in NC cells, and KLF4 cells are able to maintain *MYC* and *E2F* gene expression under JQ1 treatment and bypass JQ1-induced cell cycle arrest (45). The activation of RTK signaling pathway or GPCR/cAMP/PKA signaling pathway can also mediate BETis resistance in NC cells. Cell cycle regulators also play an important role in mediating the carcinogenesis of *BRD4-NUT* (45). Treatment with PI3KCA inhibitors can induce the sensitivity of drug-resistant cells to JQ1 (75). Binding of a BET inhibitor to a PI3K inhibitor maintains PI3K inhibition and enhances cell killing activity (76). In the drug-resistant cells, the bromodomain of *BRD4* is activated and thus it is unaffected by BETis (77).

Histone deacetylase inhibitor (HDACi) and small molecules

Preclinical studies have shown that the upstream modulators, targeting *MYC* alone, such as histone deacetylase (HDAC) and phosphoinositide 3-kinase (PI3K), can reduce *MYC* protein expression and inhibit *MYC*-driven carcinogenesis. CUDC-907 is a small-molecule, double-acting inhibitor of class I and class II HDACs and class I PI3K. It is effective to inhibit the growth and survival of *MYC*-modified or *MYC*-dependent cancer cells and may be used as a potential therapy for *MYC*-dependent cancer. At present, the safety, tolerability, and pharmacokinetic assessments of CUDC-907 have yielded encouraging results in clinical trials (44).

Vorinostat is a histone deacetylase inhibitor (HDACi), and studies have shown that vorinostat can induce tumor cell differentiation and inhibit tumor growth, including NC (78,79).

CDK9 is a potential kinase that mediates *BRD4* hyperphosphorylation. CDK9 inhibitors can block *BRD4* hyperphosphorylation in the NC cells, and a dominant negative inhibitor of *BRD4* and *CDK9* interaction has been found to abolish *BRD4* hyperphosphorylation, oncogene expression, and cell transformation in NC (36). CDK9i and bromodomain inhibition lead to the decrease of *MYC* protein expression, but only bromodomain inhibition induces cell differentiation (80).

Anlotinib hydrochloride is a novel small-molecule, multi-target tyrosine kinase inhibitor that potently inhibits kinases such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, and c-Kit. A patient with NC was relieved after radiotherapy combined with anlotinib hydrochloride. However, more evidence is needed to confirm the therapeutic effect of anlotinib hydrochloride on NC (81).

NC can develop of all ages without gender preference. Only a few patients responded to the treatment, including pediatric cases (52,60,61,66,82). Wang *et al.* found that children with salivary gland NUT carcinomas represented a distinct subset with male predilection and better overall survival (83). However, due to the small number of cases responding to the treatment, it is not enough to explain the difference in the therapeutic effect between children and adults, and more evidence is needed to confirm this result.

Conclusions

NC is a rare disease and often misdiagnosed due to non-specific pathological and clinical manifestations. It should be considered to avoid misdiagnosis and delayed treatment once poorly differentiated tumor is encountered. The pathogenesis of NC is complicated. At present, there is no consensus on the standard clinical treatment for NC. Extent of surgical resection, initial radiotherapy and chemotherapy may have positive impact on OS rate, although strong conclusion cannot be drawn because of the insufficient number of cases. Comprehensive protocol for sarcoma (SSG IX) and targeted therapy may offer promising options for the treatment of NC.

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Footnote

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