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Clinicopathological Features, Surgical Outcomes, Oncogenic Status and PD-L1 Expression of Pulmonary Pleomorphic Carcinoma

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Abstract. *Background/Aim: Pulmonary pleomorphic carcinoma (PPC) is rare, and few studies have reported its features. We assessed the clinicopathological features, surgical outcomes, oncogenic status and programmed death-ligand 1 (PD-L1) expression of PPC. Patients and Methods: We retrospectively reviewed data from 22 consecutive patients who underwent resection of PPC between 2007 and 2017. Results: The predominant tissue type of the epithelial component was adenocarcinoma in 15 patients (68%) and the others in 7 patients (32%), and the 3-year disease-free survival rate tended to be better in patients with an adenocarcinoma component compared to patients with another component (40.0% vs. 17.1%, p=0.059). PD-L1 expression was observed in all eight tumors whose PD-L1 status could be examined and high PD-L1 expression (≥50%) was frequent (5/8, 63%). Conclusion: A predominant adenocarcinoma epithelial component in PPC might be associated with better survival outcomes and high PD-L1 expression might be frequent in PPC.*

Pulmonary pleomorphic carcinoma (PPC) is a subtype of sarcomatoid carcinoma according to the 2004 World Health Organization (WHO) histological classification, and it is defined as poorly differentiated non-small cell lung cancer (NSCLC) that contains at least 10% spindle cells and/or giant cells (1). PPC has been reported to be a rare malignant tumor, with an incidence of 0.1-0.4% among all lung cancers (2). In addition, the clinical course of PPC is considered aggressive when compared to that of other NSCLCs (3, 4). There have been several studies regarding the predictors of long-term survival among patients with PPC, such as lymph node metastasis (3-7), pathological stage (3, 4), and tumor size (3). However, the clinicopathological features and prognostic factors influencing overall survival and disease-free survival in patients with PPC have not been well clarified because of its rarity.

One of the reasons for the poor prognosis of patients with PPC is its resistance to chemotherapy (2, 3, 8, 9). Although surgical resection is associated with a good prognosis (9, 10), recurrence after surgery is common regardless of postoperative adjuvant chemotherapy. Therefore, a new systemic therapy, in addition to complete resection, is needed. Recently, several investigators reported that patients with PPC carrying epidermal growth factor receptor (*EGFR*) mutations who were treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) exhibited partial or complete response to these drugs (9, 11). Furthermore, several studies have shown the efficacy of immune checkpoint inhibitors for PPC (12, 13), which is related to a previous finding that PPC expresses programmed death-ligand 1 (PD-L1) very frequently (14). However, there are few reports regarding both the oncogenic status and PD-L1 expression in PPC.

Therefore, in the present study, we assessed the clinicopathological features and surgical outcomes in surgical cases of PPC to elucidate the prognostic factors influencing overall survival and disease-free survival and investigated the oncogenic status and PD-L1 expression in PPC to identify appropriate therapeutic strategies in addition to surgery.

Patients and Methods

Patient selection. A total of 2,513 patients underwent surgery for primary lung cancer at the Aichi Cancer Center Hospital between January 2007 and December 2017. Among these patients, 22

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patients (0.9%) who were diagnosed with PPC after surgery were retrospectively identified and included in the present study. PPC was diagnosed strictly according to the 2004 WHO classification (1). The diagnosis was made according to the light microscopic findings of the resected specimen, and was confirmed with immunohistochemical examination, if necessary. PPC was defined as NSCLC containing at least 10% sarcomatoid components (spindle cells and/or giant cells). Patients with lower than 10% sarcomatoid component and those diagnosed with other sarcomatoid carcinomas of the lung (spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma) were excluded from this study. The present study was approved by the institutional review board of our institute (approval no.: 2018-1-130), and informed consent was obtained from each patient for the use of clinical data in various investigations.

Data collection. Data pertaining to the following demographic and clinical variables were retrospectively extracted from the institutional database and individual medical records: age, sex, smoking history, Brinkman index, preoperative serum tumor marker levels (carcinoembryonic antigen [CEA]), tumor location and size according to preoperative computed tomography (CT), maximum standardized uptake value on fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography, clinical TNM stage (cTNM), resection type and lymph node dissection range. Additionally, data pertaining to the following pathological variables were retrospectively extracted: tumor size, pathological TNM stage (pTNM), pleural invasion, vascular and lymphatic invasion, tissue type of the epithelial component, oncogenic status (*EGFR*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), anaplastic lymphoma receptor tyrosine kinase (*ALK*), v-raf murine sarcoma viral oncogene homolog (*BRAF*), hepatocyte growth factor (*MET*) and human epidermal growth factor receptor type 2 (*HER2*), and PD-L1 expression. Staging was performed according to the 8th edition of the TNM classification for lung cancer (15). Mutation analysis of oncogenes was performed as previously described (16). *EGFR* mutations (exons 18-21) were identified using the cycleave polymerase chain reaction method. *KRAS* (exons 2-3), *BRAF* (exons 11-15) and *HER2* mutations (exon 20) were assessed using fragment analysis, and the results were partially validated with direct sequencing, as previously reported (17). *ALK* rearrangement was screened using immunohistochemistry, and the results were confirmed using fluorescence *in situ* hybridization (FISH), as previously reported (18). Tumor PD-L1 expression was evaluated in the resected specimen using an automated immunohistochemistry assay (Autostainer Link 48, Dako, Santa Clara, CA, USA) that involved mouse monoclonal antihuman PD-L1 antibody (clone 22C3) or rabbit monoclonal antihuman PD-L1 antibody (clone 28-8). PD-L1 was scored according to the percentage of staining of the tumor cell membrane (any intensity) in a section that included at least 100 tumor cells for evaluation. We retrieved only the oncogenic status and PD-L1 expression results that were obtained after surgery.

Surveillance of surgical outcomes. The clinical course after discharge was assessed every month for 3 months, and then, tumor recurrence was evaluated with physical examinations and serum tumor marker tests every 3 or 6 months. Chest CT was performed every 6 months until 2 years after the operation and once a year thereafter as a standard follow-up protocol.

Table I. *Clinicopathological characteristics of 22 patients with PPC.*

Characteristics	n=22 (%)
Age	
Median, range	68 (54-87)
Gender	
Male	15 (68)
Female	7 (32)
Smoking history	
Former or current smoker	13 (59)
Never smoker	9 (41)
Brinkman index	
Median, range	711 (0-1900)
CEA	
Median, range (ng/ml)	2.6 (1.3-194.1)
Tumor location	
RUL	14 (64)
Others	8 (36)
SUV max in PET	
Median, range	26.3 (13.5-57.8)
cStage (8th)	
I-II	17 (77)
III-	5 (23)
Type of resection	
Lobectomy	20 (91)
Others*	2 (9)
Lymph node dissection	
ND2a-1/ND2a-2	21 (95)
ND0	1 (5)
Combined resection with adjacent organ**	
Yes	5 (23)
No	17 (77)
Pathological tumor size	
Median, range (mm)	37 (15-115)
Pathological nodal status	
pN0-X	14 (63)
pN1-2	8 (37)
pStage (8th)	
I-II	14 (63)
III-	8 (37)
Pleural invasion	
Yes	13 (59)
No	9 (41)
Vascular invasion	
Yes	21 (95)
No	1 (5)
Lymphatic invasion	
Yes	22 (100)
No	0
EGFR mutation	
Yes	4 (18)
No	18 (82)
Predominant tissue type of epithelial component	
Adenocarcinoma	15 (68)
Others	7 (32)
Adjuvant chemotherapy	
Yes	5 (23)
No	17 (77)
Recurrence	
Yes	13 (59)
No	9 (41)
Prognosis	
Dead	6 (27)
Alive	16 (73)

PPC: Pulmonary pleomorphic carcinoma; CEA: carcinoembryonic antigen; RUL: right upper lobe; SUV: standardized uptake value; PET: positron emission tomography; ND: node dissection; EGFR: epidermal growth factor receptor. *Including pneumonectomy and wedge resection; **Including parietal pleura, chest wall and phrenic nerve.

Table II. *Details of the predominant tissue type of the epithelial component, oncogenic status and PD-L1 expression.*

Patients	Predominant tissue type of epithelial component	EGFR	KRAS	ALK	BRAF	MET	HER2	PD-L1
1	Adenocarcinoma	+	–	NA	NA	NA	NA	NA
2	Adenocarcinoma	–	–	NA	NA	NA	NA	NA
3	Adenocarcinoma	–	–	NA	NA	NA	NA	NA
4	Adenocarcinoma	–	–	NA	NA	NA	NA	NA
5	Adenocarcinoma	+	–	NA	NA	NA	NA	NA
6	Adenocarcinoma	–	–	NA	NA	NA	NA	NA
7	Adenocarcinoma	–	–	NA	NA	NA	NA	NA
8	Squamous cell carcinoma	–	–	NA	NA	NA	NA	NA
9	Adenocarcinoma	–	–	NA	NA	NA	NA	+ (40%)
10	Adenocarcinoma	–	–	–	NA	NA	NA	NA
11	Adenocarcinoma	+	–	–	NA	NA	–	+ (80%)
12	Adenosquamous cell carcinoma	–	–	–	–	NA	–	NA
13	Non-small cell carcinoma	–	+	–	–	NA	–	+ (100%)
14	Adenocarcinoma	+	–	–	–	NA	–	+ (1%)
15	Adenocarcinoma	–	–	–	–	+	–	NA
16	Adenocarcinoma	–	+	–	–	NA	–	NA
17	Non-small cell carcinoma	–	–	–	–	–	–	+ (60%)
18	Non-small cell carcinoma	–	–	–	–	–	–	NA
19	Adenocarcinoma	–	–	–	–	–	–	+ (60%)
20	Squamous cell carcinoma	–	–	–	+	–	–	NA
21	Adenocarcinoma	–	–	–	–	+	–	+ (>90%)
22	Squamous cell carcinoma	–	–	–	–	–	–	+ (45%)

PD-L1: Programmed cell death ligand 1; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homolog; ALK: anaplastic lymphoma receptor tyrosine kinase; BRAF: v-raf murine sarcoma viral oncogene homolog; MET: hepatocyte growth factor; HER2: human epidermal growth factor receptor type 2; NA: not applicable.

Statistical analysis. Group comparisons were performed using the Mann-Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Survival rates were calculated using the Kaplan–Meier method, and differences were assessed using the log-rank test. Overall survival was calculated from the date of surgery to the date of the most recent follow-up. Disease-free survival was calculated from the date of surgery to the date of recurrence or death from any cause. All statistical analyses were performed using SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

The clinicopathological characteristics of all 22 patients are summarized in Table I. Of the 22 patients, 15 (68%) were male and 7 (32%) were female. The median age at the time of surgery was 68 years (range=54-87 years). In this study, no patient received neoadjuvant chemotherapy before surgery. Complete resection of the lesion (R0 surgery) was achieved in all patients. The pathological TNM stage was stage I in eight patients (IA1-3: 2, IB: 6), stage II in six patients (IIA: 2, IIB: 4) and stage III in eight patients (IIIA: 8). Details of the predominant tissue type of the epithelial component, oncogenic status and PD-L1 expression in the patients are presented in Table II. The predominant tissue type of the epithelial component was adenocarcinoma in 15 patients (68%) and others in 7 patients (32%). With regard to the oncogenic status, four patients had *EGFR* mutation (4/22, 18%), two had *KRAS* mutation (2/22, 9%), none had *ALK* rearrangement (0/13, 0%), one had *BRAF* mutation (1/11, 9%), two had *MET* mutation (2/7, 29%), and none had *HER2* mutation (0/12, 0%). The predominant tissue type of the epithelial component in all four patients with an *EGFR* mutation was adenocarcinoma. It was noted that PD-L1 expression was observed in all eight patients whose PD-L1 status could be examined. High PD-L1 expression (≥50%) was frequent (5/8, 63%), and relatively low expression (1-50%) was confirmed in the other three patients (3/8, 37%).

Adjuvant chemotherapy after surgery was performed in five patients (23%). Among these patients, four were treated with platinum-based chemotherapy and one was treated with tegafur and uracil. Tumor recurrence was noted in 13 patients (59%), and all recurrences occurred within 18 months after surgery. With regard to therapy after recurrence, nine patients were treated with local control therapy, including two treated with surgical resection (one for lung recurrence and one for brain recurrence), four treated with chemoradiotherapy and three treated with radiotherapy. The median follow-up period was 32 months (range=2-110

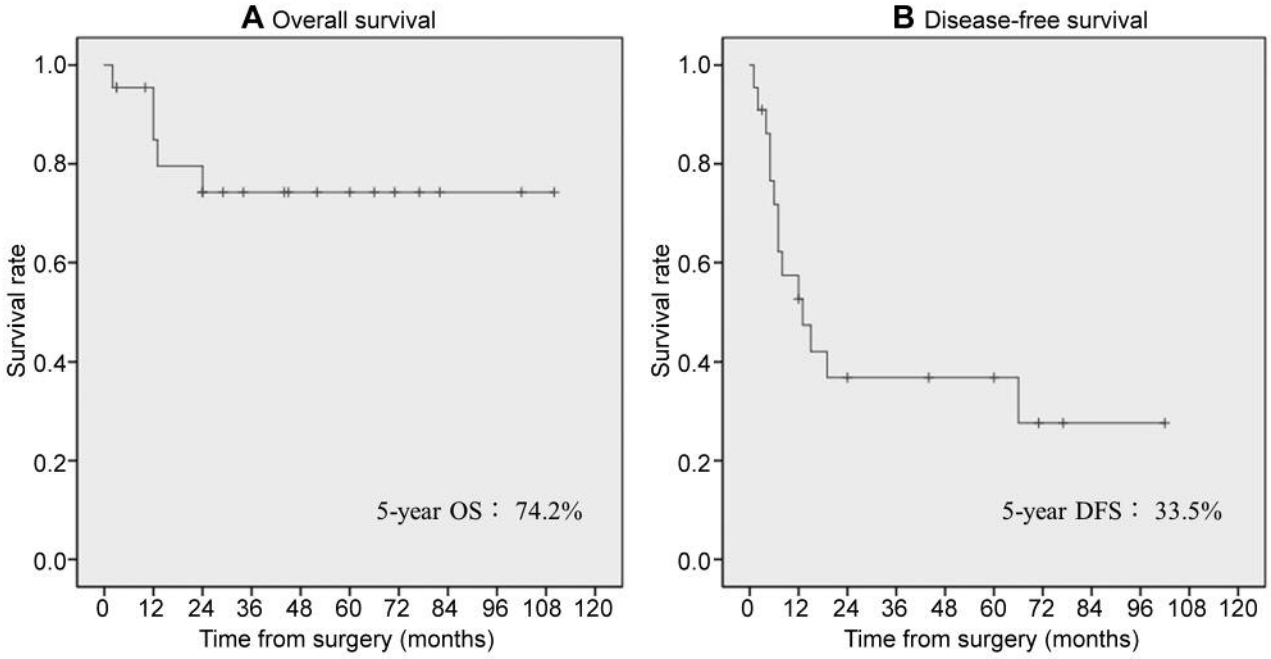

Figure 1. *Overall survival (A) and disease-free survival (B) curves for all patients (n=22).*

months). Death was noted in six patients, and of these, four patients had died of the disease. The overall survival and disease-free survival curves for all 22 patients are presented in Figure 1. The 5-year overall survival and 5-year disease-free rates were 74.2% and 33.5%, respectively. The results of the univariate analysis of clinicopathological prognostic factors are presented in Table III. Although young age and female sex were associated with better overall survival, they were not associated with disease-free survival. The predominant tissue type of the epithelial component (adenocarcinoma) tended to be associated with better overall survival and disease-free survival (p=0.052 and 0.059, respectively).

Discussion

In general, patients with PPC show an aggressive clinical course and a poor prognostic outcome. In the present study involving sufficiently long follow-up, the 5-year overall survival rate among all 22 patients with PPC was 74.2%, which is higher than the rates reported in previous studies (3-7). On the other hand, the 5-year disease-free survival rate among all 22 patients was 36.8%, which is similar to or lower than the rates reported in previous studies (4-7). Although young age and female sex were associated with better overall survival, these factors were not associated with disease-free survival, and only the predominant type of the epithelial component (adenocarcinoma) tended to be associated with better disease-free survival. Although these findings are consistent with the results of a previous study by Okuda *et al*. (7), they are not consistent with the results of other previous studies (3-5), and thus, predictors of the long-term survival of patients with PPC are controversial. A large-scale study is required to elucidate which clinicopathological features are accurate prognostic factors in patients with PPC.

There have been few studies regarding the oncogenic status in patients with PPC. We reviewed these previous studies and present the results in Table IV (10, 11, 19-23). With regard to *EGFR* and *KRAS* mutations, the frequencies in our study are similar to those reported previously (approximately 15%-20% and 10%, respectively) (10, 11, 19-23). *MET* mutations were detected relatively frequently (approximately 20%) (19, 22, 23). *BRAF* mutations had frequencies of 4%-9% according to our study and a previous study by Forest *et al*. (22). Although they reported that the frequency of *HER2* mutations was 13% (3/24) (22), no patient carried a *HER2* mutation in our study. These details on the oncogenic status are necessary to determine which molecular-targeted therapies can be applied to patients with PPC. However, we should pay attention to differences in the frequencies of gene mutations associated with disparities in the PPC diagnosis, types of epithelial components, and the assessment methods used to detect gene abnormalities among studies. Moreover, specific data on the

Table III. *Results of univariate analysis of prognostic factors influencing overall and disease-free survival with log-rank test.*

Characteristics	Overall survival		Disease-free survival	
	3-year survival (%)	*p*-Value	3-year survival (%)	*p*-Value
Age (y), ≤70 *vs.* >70	90.9 *vs.* 50.8	0.023*	25.2 *vs.* 44.4	0.69
Sex, Male *vs.* Female	59.4 *vs.* 100.0	0.035*	28.9 *vs.* 42.9	0.21
Smoking history, Never *vs.* Former	77.8 *vs.* 70.0	0.49	33.3 *vs.* 33.6	0.64
Clinical stage, I-II *vs.* III-	73.3 *vs.* 80.0	0.84	31.3 *vs.* 40.0	0.94
Combined resection, Yes *vs.* No	60.0 *vs.* 79.6	0.42	40.0 *vs.* 31.5	0.87
Pathological tumor size, ≤5 cm *vs.* >5 cm <	74.2 *vs.* 75.0	0.93	29.6 *vs.* 50.0	0.50
Pathological N status, N0 *vs.* N1-2	69.2 *vs.* 87.5	0.35	42.9 *vs.* 15.0	0.33
Pathological stage, I-II *vs.* III	75.0 *vs.* 72.9	0.84	42.9 *vs.* 14.6	0.37
Pleural invasion, Yes *vs.* No	64.6 *vs.* 87.5	0.16	33.6 *vs.* 33.3	0.83
Predominant tissue type of epithelial component, Ad *vs.* Others	86.2 *vs.* 40.0	0.052	40.0 *vs.* 17.1	0.059

EGFR: Epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homolog; Ad: adenocarcinoma. *Statically significant value.

Table IV. *The previous studies regarding the oncogenic status in patients with PPC.*

Author	Year	Patient number	*EGFR*	*KRAS*	*ALK*	*BRAF*	*MET*	*HER2*
Kaira (10)	2010	17	3/17 (18%)	NA	NA	NA	NA	NA
Lee (19)	2011	61	12/61 (20%)	6/61 (10%)	NA	NA	11/61 (18%)	NA
Chang (20)	2011	42	10/42 (24%)	2/42 (5%)	NA	NA	NA	NA
Jia (21)	2014	70	11/70 (16%)	10/70 (14%)	NA	NA	NA	NA
Tamura (11)	2015	14	2/14 (14%)	3/14 (21%)	0/14	NA	NA	NA
Forest (22)	2016	35	1/28 (4%)	2/28 (7%)	NA	1/24 (4%)	6/35 (17%)	3/24 (13%)
Kwon (23)	2017	45	4/43 (9%)	0/12	0/20	NA	9/45 (20%)	NA
Our data	2018	22	4/22 (18%)	2/22 (9%)	0/13	1/11 (9%)	2/7 (29%)	0/12
Total			47/297 (16%)	25/249 (10%)	0/47	2/35 (6%)	28/148 (19%)	3/36 (8%)

PPC: Pulmonary pleomorphic carcinoma; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homolog; ALK: anaplastic lymphoma receptor tyrosine kinase; BRAF: v-raf murine sarcoma viral oncogene homolog; MET: hepatocyte growth factor; HER2: human epidermal growth factor receptor type 2; NA: not applicable.

clinical efficacy of molecular-targeted therapies are limited. Therefore, a prospective study in a large population is required to confirm the efficacy of molecular-targeted therapy in patients with PPC.

In the present study, although most patients did not have pathological lymph node metastasis (14/22, 63%), recurrence was confirmed in most patients within 18 months after surgery (8/14 patients, 57%). Yuki *et al*. considered that recurrence, including distant metastasis, was frequent, even in early-stage disease, because of frequent vascular invasion in patients with PPC, including those with pN0 disease (5). Although in this study many patients had recurrence after surgery, overall survival was relatively favorable, and we consider that the multidisciplinary treatment after recurrence, including EGFR-TKI therapy and aggressive local control (especially surgical resection), might have contributed to the prolongation of survival. One patient (patient 14) with EGFR mutation was treated with gefitinib for bone metastasis that occurred 12 months after surgery, and the patient achieved a good response and showed survival for a long duration after recurrence (40 months with stable disease). Another patient (patient 11) with *EGFR* mutation was treated with erlotinib for metastases in the liver and small intestine that were confirmed 12 months after surgery, and the patient achieved a partial response. However, the effect was temporary, and the liver metastasis worsened. Surgical resection of recurrent lesions in the liver and small intestine was performed, and the patient had a long survival (no disease at 52 months after initial surgery). With regard to anti-PD-1 therapy, nivolumab was used in only one patient (patient 17) with metastasis in the small intestine. However, the response to nivolumab was poor and metastasis in the small intestine progressed despite the high PD-L1 expression. This result might be related to the heterogeneity of PD-L1 expression in primary and

metastatic lesions. Consistent with previous findings (14), PD-L1 expression was frequently observed in patients with PPC in our study. In addition, high PD-L1 expression (≥50%) was frequent. However, to date, the efficacy of immune checkpoint inhibitors for PPC remains unknown. Further studies in a large population are required to confirm the efficacy of these inhibitors. A phase II study on nivolumab therapy in patients with advanced sarcomatoid carcinoma, including PPC, is being performed in Japan (UMIN000023433).

The present study has several limitations. First, our retrospective study was performed at a single institution with patients having a similar ethnic background. Data on the oncogenic status and PD-L1 expression were obtained from a limited number of patients. Second, our study had a small sample size. Thus, our analysis might have been underpowered to identify differences in several values. In fact, we could not perform multivariate analysis owing to the small sample size. Therefore, the results of the present study need to be interpreted taking into account various possible biases.

In conclusion, a predominant adenocarcinoma epithelial component in PPC might be associated with better disease-free survival and high PD-L1 expression might be frequent in PPC. Our findings from the investigation of the oncogenic status (*EGFR, KRAS, ALK, BRAF, MET* and *HER2*) and PD-L1 expression in resected PPC specimens may help in the development of future therapeutic strategies, including those involving molecular-targeted therapy and anti-PD-1/PD-L1 therapy, for patients with PPC in clinical practice.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

KN and NS coordinated the entire study. Patient clinical data collection was performed by KN, NS, TM, HU, JS, TH, and HK. Data analysis was performed by KN and HU. The article was prepared by KN. Corrections and improvements were suggested by NS, TM, HU, TN, YO, JS, TH, WH, and HK. All Authors reviewed and approved the final article.

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