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Prognosis of naevoid melanomas

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ABSTRACT

Introduction: There appear to be several variants of naevoid melanoma suspected as having different outcomes, but follow-up studies have been few. We aimed to assess the prognosis of naevoid melanomas in a multi-centre study.

Material and methods: From histopathology records we ascertained patients in the UK, Australia and Italy diagnosed with maturing naevoid melanoma (n = 65; 14; 7 respectively) and nodular/papillomatous naevoid melanoma (12; 6; 0), and patients with superficial spreading melanoma (SSM) from UK (73) and Australia (26). Melanoma deaths in UK patients were obtained from NHS Digital; in Australia, via the National Death Index and cancer registry; and in Italy, through clinical records. For maturing naevoid vs. SSM, we used Cox-proportional hazard regression models to compare survival adjusted for age, sex, tumour thickness, and ulceration, and additionally Fine-Gray regression analysis, to calculate sub-hazard ratios (SHR) in the UK cohort, accounting for competing causes of death.

Results: Among UK patients, there was a non-significantly lower risk of melanoma death in maturing naevoid vs SSM, including after accounting for competing causes of death (SHR 0.40, 95% confidence interval (CI) 0.12–1.31), while among nodular/papillomatous naevoid melanoma patients, there were no melanoma deaths on follow-up. Two melanoma deaths occurred in Australian SSM patients, and none in maturing or nodular/papillomatous naevoid melanoma patients, after 5 years' minimum follow-up. None of the 7 Italian patients with maturing naevoid melanoma died of melanoma after nearly 12 years' average follow-up.

Conclusions: There was no significant difference in risk of death from melanomas with naevoid features, and SSM. Nodular/ papillomatous naevoid melanoma patients did not carry higher risk of death than SSM patients though the very few cases of the papillomatous naevoid variant limited our assessment.

1. Introduction

A small proportion of melanomas known as naevoid melanomas are difficult to diagnose because they resemble one of the many variants of benign naevi. Spitzoid melanoma is the most established of these, and is now considered as an entity in its own right, but the ways of naming

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other malignant simulants vary considerably [1]. Classifications range from nodular and verrucous naevoid [2] to papillated and non-papillated [3,4]. Although some suggest that the outcomes of these other naevoid melanomas are dependent on the standard prognostic measurements of thickness and mitotic count and that sub-classification is not important [2,5], Blessing et al. [6] have suggested that the papillomatous variant is associated with poor prognosis similar to nodular melanoma, while another variant of naevoid melanoma, termed 'small cell melanoma', had a favourable prognosis. Because the term 'small cell melanoma' is problematic (being used for a highly aggressive variant of non-cutaneous melanoma), we have previously described similar melanocytic tumour [6,7] as maturing naevoid melanoma [4] or as melanoma with paradoxical maturation [4]. Like Blessing et al. [6], we also suspected that maturing naevoid melanoma has a better prognosis than other melanomas [4], such as superficial spreading melanomas (SSM).

Our understanding is that there are essentially three variants of naevoid melanoma, namely the nodular, the rare papillomatous, and the maturing (or small cell) naevoid melanoma. Numbers of the rare papillomatous variant of naevoid melanoma are few and since papillomatous and nodular naevoid variants share many similarities, the two types may be considered together, as distinct from maturing naevoid melanoma (Table 1, Figs. 1, 2). The maturing naevoid variant has similarities to a compound dysplastic naevus and has small cells similar to naevus cells. To date, no studies have clearly established whether the separation of naevoid melanoma into subtypes is justified in terms of their behaviour, in particular their overall survival. This study was conducted to address that question, based on patient series from three countries, UK, Australia and Italy.

2. Material and methods

2.1. UK

We ascertained naevoid melanoma cases from the records of Royal Surrey County Hospital and associated hospitals in the period 2004–2018, as well as from cases referred to one of us (MGC) for pathological review in the same period (ethical approval 07/Q190913). In addition, a series of randomly selected patients with SSM > 1 mm in thickness who had undergone sentinel lymph node biopsy (SLNB) 2002–2013 and were subsequently followed-up routinely, were obtained from clinical records of St George's Hospital, London, using a melanoma database (ethical approval 17/NI/0212).

Patient age, sex, details of tumour site (head/neck, trunk, upper limb, lower limb), thickness (mm), ulceration (yes, no), mitoses (number per mm^2) and melanoma subtype (nodular naevoid /papillomatous naevoid / maturing naevoid; SSM) were extracted from diagnostic pathology reports. For maturing naevoid melanomas, the proportion of the overall tumour diameter affected by the maturation-like process was recorded.

Follow-up: All UK study patients had vital status systematically followed-up in NHS Digital till February 2022. The date of death and cause of death were recorded for all study patients. *Australia.*

Personal and melanoma histological characteristics of patients diagnosed with naevoid melanomas and SSM were ascertained from two follow-up studies of high-risk primary melanomas in Brisbane [8,9] with institutional ethical approval (HREC/09/QPAH/217; HREC/11/QPAH/470). Diagnostic slides or tissue blocks were sent for histopathologic review (by MGC, blind to original histological diagnosis) and patients whose tumours on review were confirmed as specific types of naevoid melanoma, or SSM, were included in the study.

Follow-up: Patients in the first cohort were ascertained between 1994 and 2007 and were followed for survival to 2013 via the National Death Index [8]. Those in the second cohort were ascertained from 2010 to 2014 and followed for five years from date of diagnosis by regular searches of Queensland Cancer Registry and hospital records for information on melanoma deaths [9].

2.1.1. Italy

Eligible cases were naevoid melanoma patients diagnosed, treated, and followed-up prospectively at the Department of Dermatology, University of Florence between 2004 and 2011. Cases were extracted from pathology reports and diagnoses were confirmed by histopathological

Table 1
Microscopic features of two subtypes of naevoid melanomas.

Nodular/Papillomatous	Maturing
Raised/papillomatous nodule	Flat or shallow dome
Frequent epidermal strands causing segmentation	Epidermis without segmentation
Little intraepidermal melanocytic proliferation	Intraepidermal severe atypia amounting to melanoma
Hyperchromatic angulated cells	Epithelioid upper, small cells in deep part
Little cytoplasm	More cytoplasm in upper part, less in deep
Sheets showing little variation	Changes in cell type from top to deep nests becoming larger deeper
Mitoses numerous at periphery of nodules	Mitoses few and superficial only

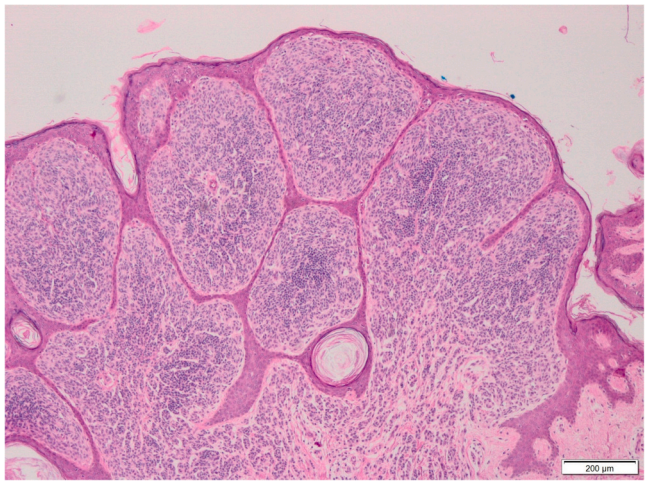

Fig. 1. Typical exophytic papillomatous naevoid melanoma with epidermal strands compartmentalising the tumour cells and showing little junctional proliferation.

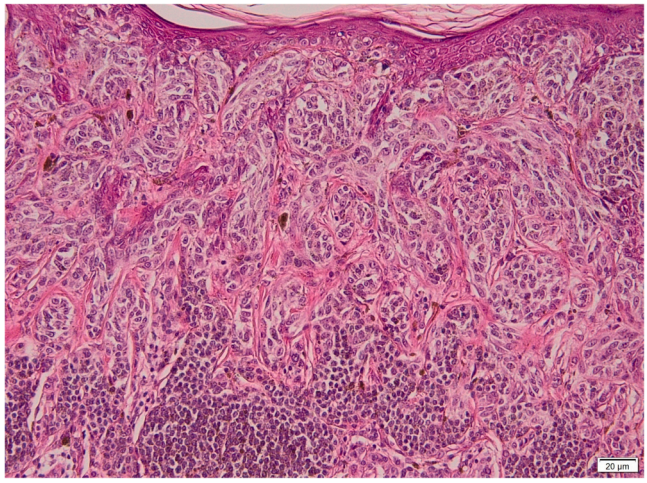

Fig. 2. Maturing naevoid melanoma. Disorderly large, atypical melanoma cells (upper) contrasting with smaller round cells with little cytoplasm (deep).

review by two experienced dermatopathologists (DM and MGC). The clinical and pathological parameters extracted from the hospital database included sex, age, anatomical site, date of diagnosis, Breslow thickness, ulceration, mitotic rate, naevoid melanoma subtype, follow-up and vital status.

Follow-up: Patients were followed, depending on Breslow thickness and according to the Italian Association of Medical Oncology (AIOM) guidelines, until 2022 by clinical review every 4–6 months for the initial 2 years, then every 6 months until the end of year 5 and annually thereafter. For patients who remained alive, survival was censored at the most recent date of clinical assessment. Approval from the Institutional Board Committee and local Ethical Committee (PRO-MEL #ID OSS15124) was obtained.

2.1.2. Statistical analysis

Although all diagnostic slides were reviewed by a single expert histopathologist (MCG), because of heterogeneity of follow-up of study patients in the three centres, data from the respective series, while analysed centrally (by YS), were not combined. End-points obtained from NHS Digital and hospital records (UK); cancer registries and clinical records (Australia); and hospital records (Italy) were alive, dead due to melanoma, or dead due to other causes. Follow-up time for UK naevoid melanoma patients who were alive was computed as the difference between date of diagnosis and date of the NHS digital search (assumed 14 February 2022).

For maturing naevoid vs. SSM comparison, we used Cox-proportional hazard regression models to compare overall survival and melanoma-specific survival adjusted for age, sex, tumour thickness (as a continuous variable) and, where possible, ulceration (yes/no). The assumption of proportional hazards was assessed graphically using log–log plots of the estimated survivor functions, and showed no strong departure from the proportional hazards assumption. To more tightly control for the predominant effect of tumour thickness on outcome, we conducted analyses separately for melanomas ≤ 2 mm and > 2 mm thick. Results were reported as hazard ratios (HR) with their corresponding 95% confidence interval (CIs). In addition, for the larger cohort of UK patients, we used Fine-Gray regression analysis and calculated the sub-hazard ratio (SHR) to compare melanoma-specific survival between the maturing naevoid and SSM groups, where deaths due to causes other than melanoma were treated as competing risks. All adjusted analyses excluded participants with missing thickness data.

3. Results

3.1. UK

There were 65 patients diagnosed with maturing naevoid melanomas (mean age 54, 51% male); 12 patients with nodular/papillomatous naevoid melanoma (mean age 47, 50% male); and 73 patients with SSM (mean age 57, 59% male), all followed up for over 7 years (Table 2). Maturing naevoid and SSM were less frequent on the head and neck (12%, 6% respectively) than nodular/papillomatous naevoid melanomas (33%) and more frequent on the trunk (maturing naevoid, 38%; SSM, 34%) compared with nodular/papillomatous naevoid (8%). SSM tumours were substantially thicker on average (mean 2.4 mm) than either maturing naevoid (1.01 mm) or nodular/papillomatous naevoid (1.78 mm) melanomas. Ulceration was seen in 5% and 8% of maturing and nodular/papillomatous naevoid melanomas respectively, compared with 18% of SSMs, while mitotic rates were $> 3/mm^2$ in 8% of maturing naevoid and 58% in nodular/papillomatous naevoid melanomas respectively, and 34% among SSM (Table 2).

3.1.1. Maturing naevoid vs SSM

Of the 65 patients with maturing naevoid melanomas, 9 (14%) died during follow-up, compared with 21 (29%) of SSM patients (Table 3). On comparing their risks of dying, there was no difference in regard to all-cause mortality after adjusting for age, sex, tumour thickness and ulceration (HR = 1.00, 95% CI 0.40–2.48), but a lower estimated risk of melanoma death (not significant) was seen in the maturing naevoid group vs SSM (Supp Fig), including after adjusting for age, sex, tumour thickness and ulceration and accounting for competing causes of death (SHR 0.40, 95% CI 0.12–1.31) (Table 3).

We further explored the effect of melanoma thickness on risk of dying by comparing mortality in maturing naevoid melanoma vs SSM patients within tumour thickness bands of ≤ 2 mm and > 2 mm. Of 61 maturing naevoid melanoma patients with data on thickness, 58 (95%) were ≤ 2 mm thick, of whom 9 (16%) died, compared with 43 (of 73; 59%) SSM ≤ 2 mm thick, of whom 6 (14%) died of all causes (adjusted HR= 1.79, 95% CI 0.60–5.34). Among the 58 with maturing naevoid ≤ 2 mm, there were 4 melanoma deaths (7%) vs 6 melanoma deaths among 43 SSM patients (14%) (Table 4; Fig. 3), amounting to no difference in risk of dying from melanoma (adjusted HR =1.01, 95% CI 0.26–3.99). Of the four maturing naevoid melanomas ≤ 2 mm that

Table 2
Patient and tumour characteristics by histologic subtype of the primary melanoma.

	U.K.			Australia			Italy
Patient characteristics	Naevoid Maturing N = 65	Nodular/ papillomatous N = 12	SSM N = 73	Naevoid Maturing N = 14	Nodular/ papillomatous N = 6	SSM N = 26	Naevoid Maturing N = 7
Age at diagnosis, mean (± SD)	53.89 (17.49)	47.39 (24.40)	56.80 (14.77)	64.50 (16.27)	61.00 (17.82)	57.88 (13.58)	61.50 (23.86)
Male sex, n (%)	33 (51)	6 (50)	43 (59)	4 (29)	3 (50)	17 (65)	5 (71)
Follow-up time (yrs), mean (± SD)	7.67 (2.85)	7.56 (3.97)	7.67 (3.10)	5.23 (1.15)	5.89 (2.18)	5.50 (1.73)	11.85 (3.61)
Tumour characteristics							
Site of melanoma, n (%)							
Head and neck	4 (6)	4 (33)	9 (12)	1 (7)	1 (17)	5 (19)	1 (14)
Trunk	25 (38)	1 (8)	25 (34)	4 (29)	4 (67)	10 (38)	5 (71)
Upper limb	11 (17)	2 (17)	7 (10)	2 (14)	1 (17)	5 (19)	1 (14)
Lower limb	19 (29)	4 (33)	31 (42)	7 (50)	0 (0)	6 (23)	0 (0)
Missing (Not stated)	6 (9)	1 (8)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Thickness (mm), mean (± SD)	1.01 (0.53)	1.78 (0.82)	2.40 (2.02)	1.19 (0.61)	1.37 (0.36)	1.29 (0.59)	0.82 (0.28)
Missing (thickness)	4 (6)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulceration, n (%)	3 (5)	1 (8)	13 (18)	1 (7)	0 (0)	6 (23)	0 (0)
Mitotic rate high, n (%)							
< 1	37 (57)	0 (0)	14 (19)	6 (40)	2 (33)	6 (24)	5 (71)
1–3	11 (17)	3 (25)	32 (44)	6 (40)	3 (50)	11 (44)	2 (29)
> 3	5 (8)	7 (58)	25 (34)	3 (20)	0 (0)	6 (24)	0 (0)
Missing	12 (18)	2 (17)	2 (3)	0 (0)	1 (17)	2 (8)	0 (0)

Table 3
Frequency (%) of mortality outcomes for maturing naevoid and nodular/papillomatous naevoid melanomas and SSM by thickness of primary tumour by country.

	UK					Australia				
	≤ 2 mm Maturing	Nodular/ papillomatous	SSM	> 2 mm Maturing	Nodular/ papillomatous	SSM	≤ 2 mm Maturing	Nodular/ papillomatous	SSM	> 2 mm Maturing	Nodular/ papillomatous	SSM
	(N = 58)	(N = 7)	(N = 43)	(N = 3)	(N = 4)	(N = 30)	(N = 13)	(N = 6)	(N = 24)	(N = 1)	(N = 0)	(N = 2)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mortality												
Alive	49 (84)	7 (100)	37 (86)	3 (100)	3 (75)	15 (50)	11 (85)	6 (100)	22 (92)	1 (100)	0 (0)	1 (50)
All-cause[a]	9 (16)	0 (0)	6 (14)	0 (0)	1 (25)	15 (50)	2 (15)	0 (0)	2 (8)	1 (100)	0 (0)	1 (50)
Melanoma[b]	4 (7)	0 (0)	6 (14)	0 (0)	0 (0)	15 (50)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	1 (50)
Non-melanoma	5 (9)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	2 (15)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)

a, UK only Hazard ratio= 1.79, 95% CI (0.60–5.34), p = 0.296 for all-cause deaths in Maturing naevoid vs SSM group with tumour thickness ≤ 2 mm, estimated from Cox-proportional hazard model adjusted for age, sex, tumour thickness and presence of ulceration

b, UK only Hazard ratio = 1.01, 95% CI (0.26–3.99), P = 0.988 for melanoma deaths in Maturing naevoid vs SSM group with tumour thickness ≤ 2 mm, estimated from Cox-proportional hazard model adjusted for age, sex and tumour thickness

caused death, one showed 80% maturation, and the remaining three showed maturation across the full width of the tumour. Among patients with thicker tumours (>2 mm), none of the 3 maturing were fatal, but 50% of thicker 30 SSM caused death (Table 3).

Nodular/papillomatous naevoid Among 11 nodular/papillomatous naevoid melanoma patients, there were 7 with tumours ≤ 2 mm and 4 with tumours > 2 mm, and no melanoma deaths during follow-up.

3.1.2. *Australia*

There were 14 patients with maturing naevoid (mean age 65, 29% male), 6 with nodular/papillomatous naevoid (mean age 61, 50% male) and 26 patients with SSM (mean age 58, 65% male) (Table 2). All were followed-up for at least 5 years. Maturing naevoid melanomas were less frequent on the head and neck (7%) than SSM (19%) and nodular/papillomatous naevoid melanomas (17%) and were most frequent on the lower limb (50%) compared with SSM (23%) and nodular/papillomatous naevoid (0%). Mean thicknesses were < 2 mm and similar across all subtypes. Ulceration was seen mostly in SSM (23%) and only 7% (one case) and 0% of maturing and nodular/papillomatous naevoid respectively, while mitotic rates were > 3/mm^2 in 24% of SSM, in 20% of maturing naevoid, and 0% of nodular/papillomatous naevoid melanomas respectively (Table 2).

Naevoid melanoma vs SSM All-cause mortality at follow-up was low in Australian study patients. Two melanoma deaths occurred in SSM patients (one in each thickness category) and none in maturing or nodular/papillomatous naevoid melanoma patients (Table 4).

3.1.3. *Italy*

Seven Italian study patients (mean age, 62; 71% male) were diagnosed with maturing naevoid and mean follow-up was almost 12 years (Table 2). The majority (5 of 7) occurred on the trunk, with overall mean thickness of 0.82 mm, no reported ulceration, and none with a mitotic rate > 3/mm^2.

Maturing naevoid outcomes There was one non-melanoma death during follow-up.

4. Discussion

This study is the first to assess the death rates of a number of patients with a range of naevoid melanomas and the first to formally compare these to death rates from SSM. According to the literature [10–13] we might have expected either a similar or worse prognosis for nodular and papillomatous melanomas, compared with SSMs of comparable thickness and mitotic rate, and a similar or better prognosis for maturing naevoid melanoma. In practice however, we found that the death rates due to nodular/ papillomatous naevoid melanomas and SSMs did not differ, though these data still were not conclusive due to case numbers. Equally unexpected was the finding that mortality outcomes of maturing naevoid melanoma and SSM did not differ. Despite their tumours' relative thinness (1.01 mm) on average, 14% of maturing naevoid melanoma patients died during follow-up compared with 29% of SSM patients (2.14 mm average thickness). When stratified by thickness, the death rate of maturing naevoid melanoma < 2 mm thick was less than 7%, whereas that of SSM < 2 mm was 14%, which does not amount to a real clinical difference.

We have previously noted that the small cell component of maturing naevoid melanoma did not always involve the full width of the lesions, and we suspected therefore that deaths might be more frequent in those with only partial small cell change. In contrast to what was expected, 3 of the 4 patients with fatal maturing naevoid melanomas < 2 mm thick showed the small cell component across the full width of the tumour, and the fourth showed a small cell component affecting 80% of the tumour diameter. It therefore seems that this small cell change simulating maturation does not confer a survival advantage.

A weakness of the study was the limited number of cases with nodular/papillomatous naevoid variants. The strengths of the study

Table 4
Comparison of mortality outcomes in UK patients with Maturing naevoid vs. SSM.

			Cox-proportion hazard estimates		Fine-Gray	
	Maturing (N = 65	SSM (N = 73)	Unadjusted	Adjusted[1]	Unadjusted	Adjusted[1]
Outcome	N (%)	N (%)	HR (95% CI)	HR (95% CI)	SHR (95% CI)	SHR (95% CI)
Mortality						
Alive	56 (86)	52 (71)	1.00‡	1.00‡	1.00‡	1.00‡
All-cause	9 (14)	21 (29)	0.48 (0.22–1.05)	1.00 (0.40–2.48)	-	-
Melanoma	4 (6)	21 (29)	0.21 (0.07–0.61)	0.41 (0.13–1.33)	0.20 (0.07–0.60)	0.40 (0.12–1.31)
Non-melanoma	5 (8)	0 (0)	-	-	-	-

CI=Confidence Interval, HR=Hazard, SHR=Sub-hazard ratio
1Adjusted for age, sex, tumour thickness, presence of ulceration
‡Referent category, includes all the patients that were alive regardless of recurrence status

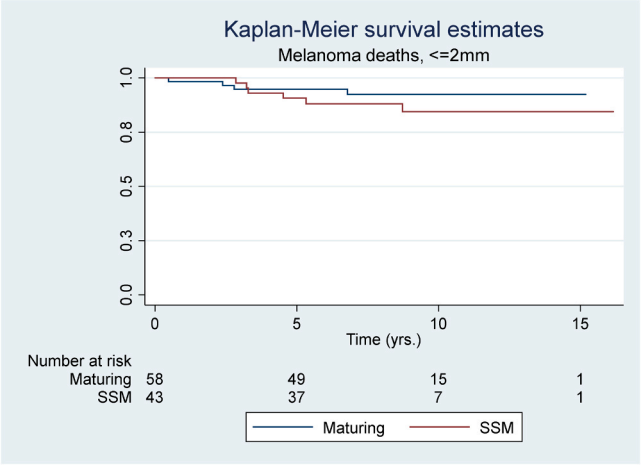

Fig. 3. Survival probabilities of UK patients with maturing naevoid melanomas ≤ 2 mm compared with patients with SSM ≤ 2 mm.

were its multi-centre design, the histopathological review and classification of all naevoid melanoma subtypes by one expert, and the centralised data analysis by discrete subtype.

5. Conclusions

In summary, we did not observe a better prognosis for maturing naevoid features in general, and nor did we find worse outcomes in nodular / papillomatous variants, despite the high mitotic count. Specifically, the naevoid melanoma resembling a dysplastic naevus and anecdotally said by some to be a severely atypical form of that naevus, had a death rate similar to SSM and therefore should be recognised and managed as cautiously as all other invasive melanomas.

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CRediT authorship contribution statement

Conception and design: ACG and MGC. Collection and/or assembly of data: All authors. Manuscript drafting: ACG, MGC, YS. Manuscript review: All authors. All authors have read and approved the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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