

**Original contribution**

Placental histologic criteria for umbilical blood flow restriction in unexplained stillbirth

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Summary Approximately 50% of stillbirths are unexplained after fetopsy and placental examination. Fatal hypoxic injury due to restriction of umbilical blood flow (“cord accident”) may be causal in a subset of these stillbirths. We reviewed placental slides of 62 cases of third-trimester stillbirth from our autopsy files over a 5-year period to define criteria and estimate the frequency of cord accident as a cause of stillbirth. By correlating clinical and autopsy information—with placental gross and histologic findings—from a series of index cases with a strong presumptive evidence of cord accident, histologic criteria for cord accident were established. “Minimal histologic criteria,” suggestive of cord accident, were defined as vascular ectasia and thrombosis within the umbilical cord, chorionic plate, and/or stem villi. A definitive diagnosis of cord accident required in addition regional distribution of avascular villi or villi showing stromal karyorrhexis. Of 27 stillbirth cases with a cause of death determined to be other than cord accident, only 3 (11%) met all histologic criteria for cord accident (specificity of 89%). In contrast, of 25 stillbirth cases with an unknown cause of death, a significantly larger subset (13 cases or 52%) met the criteria for cord accident ($P = .0038$). Thus, we find nonacute cord compression implicated in over half of “unexplained” fetal deaths. This is the first report to establish histologic criteria in the diagnosis of cord accident, the application of which could significantly reduce the proportion of unexplained third-trimester stillbirth.

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1. Introduction

Stillbirth, defined as “delivery of an infant with no sign of life between 20 weeks gestation and term,” comprises up to 1% of births in Europe and North America [1]. It is one of the least studied obstetric complications, due in large part to the relatively low percentage of cases consented for postmortem examination [1]. After a complete autopsy and placental examination, the cause of death remains unresolved in as many

as 50% of cases, due in part to variation in the experience levels of pathologists and in part to lack of uniformly applied gross and microscopic protocols for evaluating stillbirth [1].

Many stillborn infants are phenotypically normal and lack evidence of chronic placental lesions (so-called “placental insufficiency”), or more acute mechanisms such as placental abruption or infection, as etiologies for intrauterine demise. One presumed cause of death in these cases is hypoxic injury related to mechanical compression of the umbilical cord. This diagnosis is usually one of exclusion but is supported indirectly by the increased rate of “cord accidents” in association with oligohydramnios and grossly apparent

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umbilical cord abnormalities, including true knots, long cords, hypercoiled cords, narrow cords due to diminished Wharton's jelly, or abnormal cord insertions [2]. Umbilical cord obstruction may occur acutely by umbilical cord prolapse or by nonacute mechanisms such as nuchal cords and hypercoiling. All processes result in fatally compromised blood flow through the umbilical cord [2]. Fetal thrombotic vasculopathy, defined as either absence or degeneration of fetal capillaries (avascular villi or villous stromal karyorrhexis, respectively) in an average of more than 15 contiguous chorionic villi per slide, has been found to be associated with restriction of cord blood flow [3,4]. Both clinical cord entanglements and potentially obstructive abnormalities of the cord are found with an increased incidence in cases of fetal thrombotic vasculopathy [3]. In addition, in up to one third of placentas with this lesion, there is upstream fetal vascular thrombosis, particularly in the muscularized vessels of the chorionic plate or stem villi, further suggesting upstream vascular occlusion [3,5].

The purpose of this study was 2-fold: first, to identify specific criteria for cord accident by analyzing changes in the placental fetal vascular tree in cases with clinical and pathologic stigmata of nonacute umbilical cord compression; second, to test these criteria on cases with either a clear cause of death that was not cord-related or with no known cause of death. The goal was to identify criteria for restriction of umbilical blood flow that would be specific for known cord accident, exclude cases with other known causes of fetal death, and identify cord accidents among stillbirths of unknown/uncertain cause.

2. Materials and methods

After approval by the internal review board, the pathology departmental database at Brigham and Women's Hospital was searched for cases of stillbirth during the third trimester, defined as intrauterine fetal demise on or after 26 weeks gestational age, received between January 2001 and August 2005. Cases were selected in which both a fetal autopsy and placental examination were performed at Brigham and Women's Hospital, and placental slides could be retrieved (total of 158 cases). Among these cases, 10 had an autopsy diagnosis of cord accident; an additional 27 control (noncord accident) cases and 25 unknowns were randomly selected from the remaining cases (see Table 4). The causes of death in the control cases included abruption (3 cases), maternal vascular disease/placental insufficiency (11 cases), hydrops fetalis (3 cases), congenital abnormalities (mainly involving heart and lungs, 8 cases), chronic villitis (1 case), and intracranial hemorrhage (1 case). The placental slides were reviewed jointly by two authors (M.M.P. and T.K.B.), blinded to all clinical and gross information contained in the autopsy and placenta reports. The presence or absence and location of the following microscopic findings were noted: (1) fetal

vascular ectasia, (2) fetal vascular thrombosis, (3) avascular villi, and (4) villous stromal karyorrhexis. Fetal vascular ectasia was defined as vascular distension to at least four times the diameter of an adjacent muscular vessel of similar caliber (Fig. 1). Fetal vascular thrombosis included not only organizing and organized thrombi in muscular vessels (Fig. 2A) but also early muscular vessel thrombi, identifiable by focal loss of integrity of vascular endothelial lining with erythrocyte fragmentation and extravasation (Fig. 2B). For both ectasia and thrombosis, the types of muscular fetal vessels involved were documented, including umbilical cord, chorionic plate, and/or stem villus vessels. In addition, the presence and distribution (focal, regional, or diffuse) of both avascular villi and villous stromal karyorrhexis were documented. Villous stromal karyorrhexis was recognized by the presence of fragmented erythrocytes and karyorrhectic debris in terminal villi (Fig. 3), while avascular villi represented complete loss of villous vasculature [3]. Notation was made if any of the above findings were associated with other placental pathology, such as infarction, abruption, or chronic villitis. Based on the review of placental slides alone, a consensus impression by both pathologists regarding cause of death was reached for every case as cord accident or other. "Other"

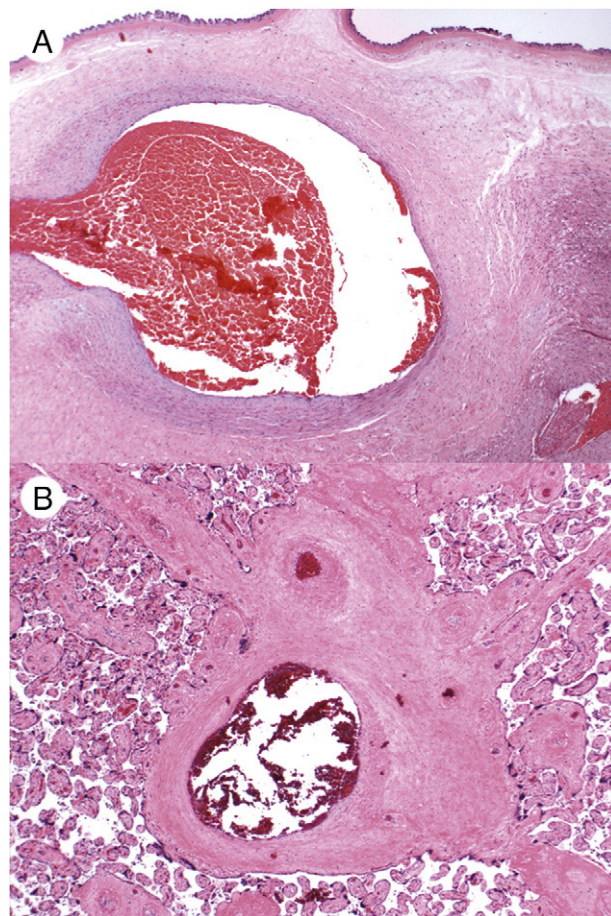


Fig. 1 Fetal vascular ectasia. Examples of ectatic chorionic plate vessel (A) and stem villus vessel (B) are shown. Both (A) and (B) are at the same magnification.

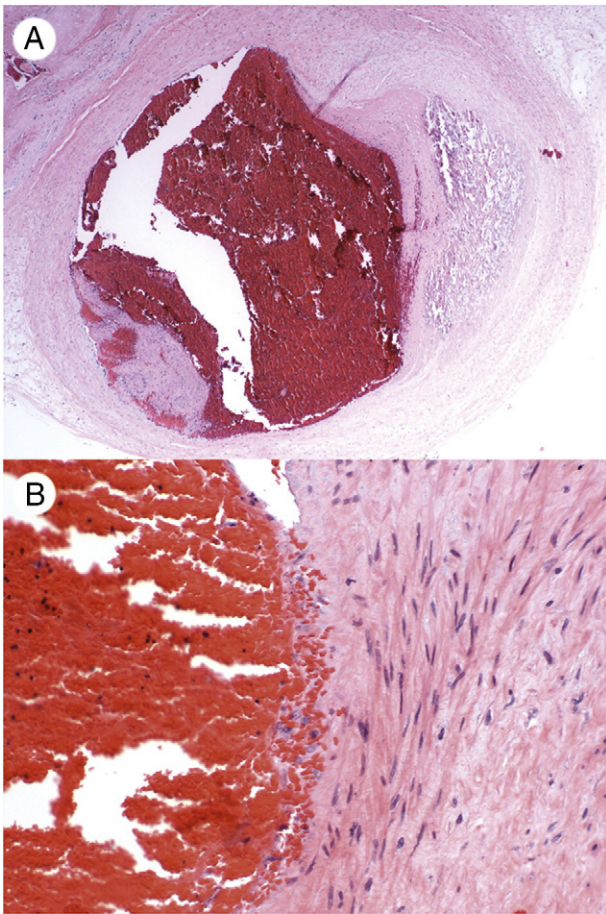


Fig. 2 Fetal vascular thrombosis. Examples of both organizing thrombus (A) and early thrombosis (B) are shown, the latter defined by loss of endothelial integrity with erythrocyte fragmentation and extravasation.

included identifiable causes of death other than cord accident and unknown causes of death, based on placental histology alone. Impressions for every case were then tabulated along with clinical information and gross examination findings extracted from the original autopsy and placenta reports. The extracted information included clinical findings of oligohydramnios and nuchal/body cord, as well as potentially obstructive gross umbilical cord abnormalities, including true knot, hypercoiling, abnormal insertion onto the placental disc, decreased Wharton's jelly, and long cord. Abnormal insertion was further documented as marginal or velamentous. A long umbilical cord was defined as cord length greater than 68th percentile (one standard deviation above the mean) for gestational age [6]. Results were tabulated and analyzed using Microsoft Excel (Microsoft Corp, Redmond, WA).

3. Results

Based on the original autopsy reports, including clinical information contained therein, cases were subdivided into

3 categories: cord accident (10 cases), known cause of death other than cord accident (27 cases), and unknown cause of death (25 cases) (see Table 4). As outlined above, based on our review of the placenta slides alone, we rendered a cause of death for each case as cord accident or other. The overall concordance rate between our histologic scores and the original autopsy reports was 87% (data not shown). All 10 cases with an original clinical/autopsy diagnosis of cord accident, based on either a clinically documented nuchal/body cord or a potentially obstructive gross cord abnormality (Table 1), were also designated by us as cord accident based on our evaluation of placental histology, independent of clinical or gross information. These 10 index cases were used as the "gold standard" to determine criteria for cord accidents (Table 1). All 10 placentas demonstrated vascular ectasia and thrombosis in muscularized chorionic plate and/or stem villus vessels, as well as focal or regional avascular villi and/or villous stromal karyorrhexis (Table 1). These histologic findings thus established the diagnostic criteria for cord accident. We also defined "minimal histologic criteria," suggestive but not diagnostic for cord accident, as vascular ectasia and thrombosis involving the muscular branches of

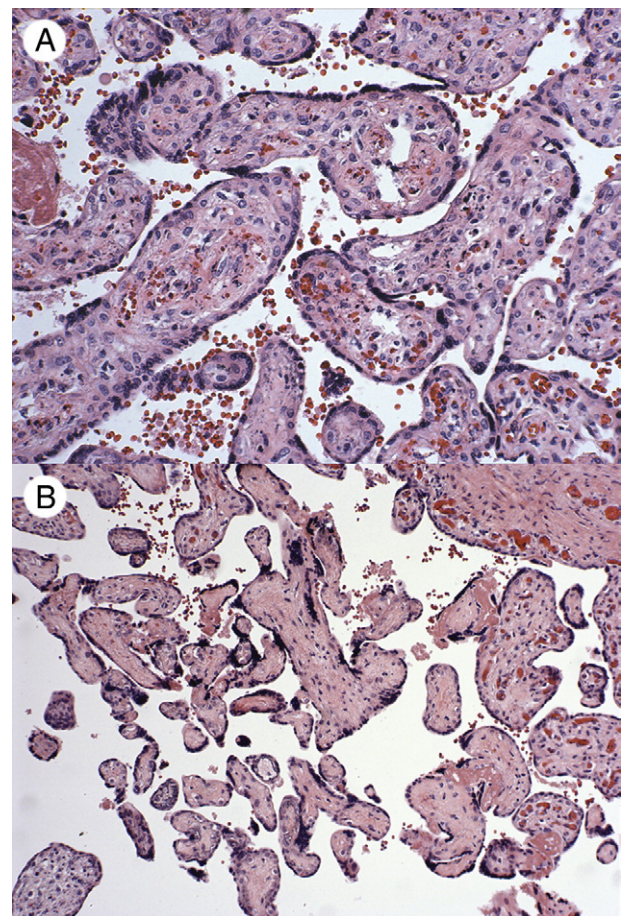


Fig. 3 Villous stromal karyorrhexis (A), defined by the presence of fragmented erythrocytes and karyorrhectic debris in terminal villi, represents an intermediate stage before complete loss of terminal villous vasculature (avascular villi) (B).

Table 1 The index (“gold standard”) cases used to establish criteria for definite cord accident, including their histologic as well as gross and clinical findings.

Case no.	Clinical	Gross	Vascular ectasia*	Thrombosis	Avascular villi	Villous stromal karyorrhexis
13	Nuchal/body cord		UC, SV	UC, SV		Focal
26		Long cord; velamentous Insertion	UC, CP, SV	UC, CP, SV	Focal	Focal
29		Long cord; true knot	UC, SV	CP, SV		Regional
31	Nuchal/body cord		UC, CP	UC, CP	Focal	Focal
34	Nuchal/body cord		UC, SV	CP		Focal
38		Long cord; marginal insertion	UC, CP, SV	UC, CP, SV	Regional	Regional
49	Nuchal/body cord		UC, CP, SV	CP, SV		Regional
52		Long cord; marginal insertion	UC, CP, SV	CP, SV		Regional
57	Nuchal/body cord	Long cord	UC, SV	SV		Regional
58		Marginal insertion	CP	CP		Focal

Abbreviations: UC, umbilical cord; CP, chorionic plate; SV, stem villus.

the fetal vascular tree, which we believe evolve prior to the changes within terminal chorionic villi, in cases leading to fetal death (Table 2). Vascular ectasia was observed in at least 2 chorionic plate and/or stem villus vessels; ectasia in umbilical cord vessels alone was found to be nonspecific (data not shown). Thrombosis had to be present in vessels of the cord, chorionic plate, or stem villi. As stated above, for a definite diagnosis of cord accident, additional histologic findings of avascular villi and/or villous stromal karyorrhexis were required (Table 2). Importantly, these histologic findings within terminal villi were included as diagnostic criteria only if present in a focal or regional rather than a diffuse distribution (see discussion). In addition, these findings could not be associated with other placental pathology because lesions such as infarction, abruption, or chronic villitis can give rise to secondary avascular villi, independent of cord compression, and are generally accepted to infer an alternative cause of stillbirth [3,5].

When the minimal histologic criteria suggestive of cord accident (fetal vascular ectasia and thrombosis, see Table 3) were applied to the 27 cases with a known cause of death other than cord accident, based on the original autopsy report, 7 cases met the criteria, giving a specificity of 74% (20/27) (Table 3). The presence of avascular villi and/or villous stromal karyorrhexis (Table 2) increased specificity

such that only 3 of the 27 cases with original cause of death other than cord accident met these latter criteria (specificity, 89% [24/27]) (Table 3).

Of the 27 cases with known cause of death other than cord accident, 22 were concordant based on the original autopsy diagnoses and our independent histologic review (data not shown). If the above analysis of specificity is applied to this narrower subset of 22 cases, 3 cases meet the minimal histologic criteria, and only 1 of these also had avascular villi (data not shown), raising the specificity of minimal and definite criteria to 86% (19/22) and 95% (21/22), respectively.

When the criteria were applied to the 25 cases originally designated as unknown cause of death, significantly higher number of cases fulfilled the criteria: 18 met the minimal histologic criteria ($\chi^2 = 9.27$; $P = .0023$). Of these 18 cases, 13 met all the criteria for cord accident ($\chi^2 = 8.359$; $P = .0038$) (see Table 3). Reassigning this subset of 13 cases decreased the number of stillbirths with unknown cause of death by over 50% (Table 4).

Finally, using our defined criteria, the number of cases with definite cord accident as cause of death more than

Table 2 Criteria for definite diagnosis of cord accident

Criterion	Definition
Minimal histologic criteria	Vascular ectasia (CP and/or SV) and thrombosis (UC, CP, and/or SV)
Additional histologic findings in terminal villi	Avascular villi and/or villous stromal karyorrhexis ^a

^a These findings have to be present in a regional, not diffuse, distribution and be independent of other placental lesions, including infarction, abruption, and chronic villitis.

Table 3 The number of cases that met the minimal histologic criteria versus definite criteria for cord accident.

Cause of death (per autopsy report)	No. of cases	Minimal histologic criteria	Definite cord accident ^a
Cord accident	10 ^b	10	10
Unknown	25	18	13
Other known	27	7	3

^a These cases in this column are a subset of those listed in the “minimal histologic criteria” column, with the additional histologic findings of avascular villi and/or villous stromal karyorrhexis (see Table 2).

^b These are the index cases used as a gold standard to determine criteria for definite cord accident (see Table 1).

Table 4 Cause of death: comparison between *original autopsy diagnosis* (middle column) and *diagnosis based on definite criteria* (right column) for cord accident.

Cause of death	No. (%) of cases per original diagnosis	No. (%) of cases reclassified per criteria
Cord accident	10 (16%)	26 (42%)
Unknown	25 (44%)	12 (19%)
Other (known)	27 (40%)	24 (39%)

doubled, from 10 (16%) to 26 cases (42%) (Table 4). In sum, the data suggest, by consistent trends among subgroups of stillbirths, that in this set of 62 fetal autopsies, cord accident was a significantly underdiagnosed cause of third-trimester stillbirth.

4. Discussion

Intrauterine demise due to restriction of umbilical cord blood flow, or cord accident, is generally a diagnosis of exclusion, due in part to the lack of established pathologic criteria. We reviewed placental slides from a randomly selected set of third-trimester stillbirths in an effort to determine whether a set of histologic criteria correlated with the diagnosis of cord accident as the cause of death.

Vascular obstruction of the umbilical cord has been suggested as one potential mechanism for the placental lesion of fetal thrombotic vasculopathy (FTV). FTV has been linked to various fetal abnormalities including intrauterine growth restriction, perinatal encephalopathy and neurologic impairment, neonatal liver disease, as well as an increased risk of stillbirth [3-5,7-9]. We evaluated placental slides for the presence of various FTV-related lesions, including vascular ectasia and thrombosis, avascular villi, and villous stromal karyorrhexis.

The minimum requirements for the diagnosis of cord accident were established to be fetal vascular ectasia and thrombosis. Vascular ectasia must be present in the muscularized vessels of the chorionic plate and/or stem villi; on the contrary, thrombosis anywhere in the large fetal vessels was significant, whether in the umbilical cord or its major tributaries within the chorionic plate and stem villi.

In addition to the minimal criteria, the definitive diagnosis of cord accident also requires the presence of avascular villi and/or villous stromal karyorrhexis in a *focal* or *regional* distribution. It is important to distinguish these findings from the *diffuse* vascular changes associated with prolonged interval between intrauterine demise and delivery [10]. Post mortem, the cessation of fetal circulation leads to passive, progressive, and global involution of the placental fetal vascular tree, resulting histologically in erythrocyte extravasation, karyorrhexis, and eventual avascular villi [10]. Although it is our observation that postmortem passive

involution of muscularized chorionic plate and stem villus vessels does not manifest the prominent ectasia of ante-mortem thrombosis, in practice, the diffuse changes that occur with prolonged intrauterine demise preclude optimal histologic evaluation for assessing likelihood of a cord accident. In our series, only 3 cases showed such diffuse changes in the chorionic villi, and not surprisingly, all of these cases were in the “unknown cause of death” category. Of these 3 cases, one also showed dilated and thrombosed chorionic plate and stem villus vessels. However, as noted above, because of the diffuse nature of changes in the terminal villi, this case could not be assigned as cord accident.

The presence of a clinical history of nuchal/body cord or potentially obstructive gross abnormalities of the cord can strengthen the inference from histologic criteria for cord accidents. Of the 3 cases in the “known cause of death other than cord accident” category, based on the original autopsy report, that met all the histologic criteria for cord accident, only 1 had additional clinical or gross cord abnormalities; thus, if the clinical/gross findings are combined with histologic criteria, specificity is increased from 89% (24/27 cases) to 96% (26/27 cases). Of note, the single case in this category that met both gross and histologic criteria for cord accident had an original cause of death of congenital heart disease; however, based on the histologic changes in the placenta, as well as the gross finding of a marginally inserted umbilical cord, we suspect superimposed umbilical cord blood flow restriction caused or contributed to fetal death, thus explaining the apparent diagnostic discrepancy.

In practice, at 74%, the specificity of the minimal histologic criteria for cord accident is high enough to warrant consideration of cord accident as the cause of stillbirth, in cases without other identifiable pathology. In such cases, coincident clinical or gross cord abnormalities may warrant attributing cause of death to suspicious or probable cord accident. On the other hand, a definitive diagnosis of cord accident should be strongly considered based on histologic grounds alone (specificity of 89%). Even so, the added presence of clinical or gross cord abnormalities may assuage lingering doubt regarding the cause of death, by increasing specificity to 96%.

Applying the above criteria to our set of 62 cases more than doubled the number of cord accidents, primarily due to assigning a cause death to the unknown cases. This further underscores the importance of establishing histologic criteria for “cord accident” as a cause of death, in order to prevent underdiagnosis of this important entity.

There are some limitations to using these criteria in evaluating stillbirth. First, our criteria cannot diagnose acute cord accidents, such as can occur with cord prolapse. Acute occlusion of umbilical blood flow can lead to fetal demise before sufficient time has elapsed for the characteristic vascular changes of ectasia and thrombosis to evolve. Therefore, that this study establishes histologic criteria, which must be present for the diagnosis of cord accident,

restricts confident diagnoses to those cases involving subacute and chronic restriction of umbilical blood flow. Second, we believe there is a subset of stillbirths due to "early" nonacute cord accidents, where striking vascular ectasia is present but where thrombosis has not yet evolved to be recognizable histologically. It is our own practice in these cases, providing there are clinical or gross cord abnormalities, to suggest cord accident as a potential mechanism of death, but to stress that the absence of minimal histologic criteria precludes confident diagnosis.

A few additional pathologic observations warrant mention. All stillbirth fetuses and placentas that met the histologic criteria for cord accidents exhibited marked normoblastemia. This observation reflects subacute to chronic hypoxic stress prior to demise, and although normoblastemia is by no means specific for cord accident, it is a constant finding in nonacute fatal restriction of umbilical blood flow. Meconium, while commonly present, is not a universal feature in this clinicopathologic setting. We postulate that, in some cases where umbilical blood flow restriction is chronic, the fetus compensates for slowly evolving hypoxia until the threshold for viability is exceeded and fetal death results. In these cases, there may be no discrete point in time where hypoxic stress increases in intensity sufficient enough to elicit meconium discharge. Finally, grossly flattened and/or microscopically ovoid umbilical cord may be present with mechanical cord compression but, as with umbilical vascular ectasia, is not specific for cord accident (data not shown).

The concept that *cord accident can be inferred by pathologic examination of the placenta and umbilical cord* remains controversial. Notwithstanding the need for larger

studies, we believe the proposed histologic criteria hold promise as a tool to determine the likelihood of nonacute fatal restriction of umbilical blood flow in third-trimester stillbirth. Whether used to identify probable or definite cord accident, these histologic criteria can be objectively applied, and if confirmed by other studies, will underscore fatal umbilical blood flow restriction as a common mechanism of intrauterine demise.

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