ORIGINAL ARTICLE

Long-term Outcomes of Pregnancy-Associated Breast Cancer: A Single Institution Experience

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Abstract

Background: The incidence of pregnancy-associated breast cancer (PABC) is increasing, especially in the developed countries. Herein, we report the long-term outcomes of PABC from a single institution in an Arab country

Methods: Consecutive patients diagnosed to have PABC between 2005 and 2012 at a tertiary referral hospital from a Gulf Cooperation Council country were the subjects of the study. Long-term outcomes are reported, with a minimum follow-up of 8 years.

Results: A total of 16 patients were evaluable for long-term survival analysis. The median age at the time of diagnosis was 31.5 (26-40) years. Nine (56%) patients were multiparous (> 5 previous pregnancies). The mean gestational age at diagnosis was 19.7±7.4 weeks. Immunohistochemistry revealed the following phenotypes: Luminal A 3 (18.8%); HER-2 enriched 8 (50%); triple-negative 5 (31.2%). Three patients underwent modified radical mastectomy as the initial treatment, of which 2 received adjuvant chemotherapy during pregnancy. All other patients received either neoadjuvant or palliative chemotherapy during chemotherapy. The response rate was 75% (pCR 2; CR 1; PR 6). After a median follow-up of 60 months, median progression-free survival was 36 months (95%CI 24.2 to 47.8), while the overall survival was 59 months (95%CI 31.6 – 86.4). Age, marker status, Ki-67 score, clinical stage and differentiation grade did not affect the PFS or OS on an univariate analysis.

Conclusion: Fifty percent of the patient with PABC expressed HER-2/neu protein, and 1/3rd had triple-negative disease. The rate of response to chemotherapy, and long-term survival may help to set a benchmark for studies from the region. Larger cohort studies may help to draw firm conclusions.

Keywords: *Pregnancy; breast cancer, estrogen receptor, HER/2/neu, chemotherapy, Oman.*

INTRODUCTION

Pregnancy-associated cancer (PAC) is defined as cancer diagnosed during pregnancy or within one year post-partum. PAC constitutes 0.07% to 0.1% of all cancers [1]. Breast cancer is the most common PAC, followed by carcinoma of the cervix, lymphoma, leukemia, melanoma, and ovarian cancer [1]. The incidence of breast cancer during pregnancy is reported to be between 1:3,000 – 1:10,000 pregnancies [2]. Between 0.2% – 3.8% of all breast cancers occur co-incidentally with pregnancy [2]. More than 90% of patients with pregnancy-associated breast cancer (PABC) present with a palpable mass, and is self-reported by patients. Less frequently, patients present with erythema, breast swelling, bloody nipple discharge, or local or distant metastasis [3]. The prevalence of PABC has been shown to be increasing with increasing maternal age, especially in the developed countries [4, 5].

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Email: ikramburney@hotmail.com
Received: May 05, 2021; Revised: June 29, 2021; Accepted: July 06, 2021
DOI: https://doi.org/10.37184/lnjcc.2789-0112.2.2

The treatment of breast cancer is multi-modal and often involves surgery, sometimes with radiotherapy, systemic chemotherapy, and hormone therapy. PABC is unusual, and not many surgeons, obstetricians and oncologists have only limited, if any, experience in the management of cancer during pregnancy. An average obstetrician would see 2-3 cases in a 40-year career [1]. For several years, treatment of breast cancer and continuation of pregnancy were considered mutually exclusive. However, with the experience in the past few years with the use of cytotoxic chemotherapy, in the second and the third trimester, it is possible to continue with the pregnancy and the systemic treatment in almost all cases [6].

Whereas there is a plethora of data on the incidence, management and outcomes of PABC from the developed world, there are very little data from the developing countries, especially the middle-east, where the demographic features of breast cancer are different. For example, the mean age at the time of diagnosis of breast cancer in Oman is 47 years, and almost one-third of these patients are in the child-bearing (less than 40 years) age [7]. On the other hand, the fertility rate is high, and the mean number of pregnancies

in the country is more than 78. It is plausible to think that PABC maybe even more common in developing countries. Previously, we reported the clinical features at presentation, response to treatment and short–term outcomes of patients and infants [8, 9]. Herein, we report the incidence, and long-term outcomes of patients treated for PABC at our institution.

PATIENTS AND METHODS

Consecutive patients diagnosed to have PABC at a tertiary referral center for cancer diagnosis and treatment in Oman between Jan 2005 and Dec 2012 were included. The database was searched to identify all cases. The number of deliveries in the unit of obstetrics during the time-period was also noted. Demographic information including the age at diagnosis of breast cancer, gravidity, gestational age at the time of diagnosis (assessed both by the last menstrual period and the ultrasound) were recorded. Histopathological features, such as the histological subtype, degree of differentiation, estrogen receptor (ER) expression, progesterone receptor (PgR) expression, HER-2/neu status (using either immunohistochemistry or fluorescent in-situ hybridization) and the proliferative marker Ki-67 were also recorded. Before commencing the treatment, an X-ray of the chest, ultrasound of the abdomen, and blood tests including alkaline phosphatase were carried out, to clinically stage the disease, as accurately as was possible. Patients with clinically localized or locally advanced disease were treated according to the situation and preferences, either with surgery first or with neoadjuvant chemotherapy. Patients with metastatic disease at the time of presentation were treated with palliative chemotherapy. The time and mode of delivery were also recorded. After delivery, breast cancer was staged using a CT scan of the chest, abdomen and pelvis, and a 99Tc bone scan. Further treatment was continued according to the clinical stage, and the presence of predictive markers, such as ER, PgR, and HER-2/neu. Progression-free survival (PFS) was calculated using the method of Kaplan and Meier from the time of diagnosis to progression or death. Overall survival (OS) was calculated from the time of diagnosis to death or 31st Dec, 2020.

RESULTS

Over the study period, a total of 17 patients were diagnosed to have PABC. One patient was diagnosed to have ductal carcinoma in situ and was excluded from the overall analysis. This patient was 31 years at the time of diagnosis, was pregnant a 2nd time, and the gestational age at diagnosis was 10 weeks. The patient was treated with mastectomy, and after the delivery, was commenced on Tamoxifen.

Over the study period of 8 years, a total of 21,717 deliveries were recorded in the obstetrical unit of the hospital, of which 16, coincided with the diagnosis of infiltrating carcinoma of the breast, suggesting an incidence rate of 0.00074 breast cancer cases per pregnancy.

The median age at the time of diagnosis for the evaluable 16 patients was 31.5 (26-40) years. The mean number of pregnancies before the diagnosis of PABC was 4.8 (1-9); 9 (56.3%) patients had been pregnant 5 or more times before the pregnancy. All patients were diagnosed during pregnancy. The gestational age at the time of diagnosis was 19.7 (6-31) weeks. The details, including the mean tumor size, and the degree of differentiation are shown in Table **1**. The predictive and prognostic markers are also shown in Table **1**. Three patients (18.8%) were positive both for ER and PgR and negative for HER-2/neu (Luminal A). On the other hand 5 patients (31.2%) were triple-negative, whereas 8 patients had HER-2 enriched type breast cancer with or without co-expression of ER and PgR.

Table 1: Clinico-pathological features at presentation.

Median age at the time of diagnosis	31.5 (26-40) years
Gravidity	4.8 ± 2.3
Gestational age at diagnosis	19.7 ± 7.4 weeks
Clinical stage at diagnosis	
Locally advanced	15
Metastatic	1
Tumor size	4-14 cm
Multifocal	7
Degree of differentiation	
Well-differentiated	2
Moderately differentiated	6
Poorly differentiated	8
Tumor type	
Luminal A	3 (18.3%)
HER-2 enriched	8 (50%)
Triple negative	5 (31.2%)

The details of the treatment are shown in Table **2**. Out of the 16 evaluable patients, one patient presented with metastatic disease and was treated with palliative chemotherapy. Three patients underwent modified

Table 2: Individual patient data on presentation, treatment, response to treatment and clinical stage.

No	GAD	Tumor size (Clinical)	Treatment During Pregnancy	Surgery Post-Delivery	Response	Tumor Size (cms)	Positive Nodes	Final stage after Surgery	Treatment After pregnancy
1	8	10 cm	MRM > ACx4>Docx4	-	Not evaluable	3.5	3/24	pT2N1M1	RFA to liver VNB +Cap
2	17	Inflammatory Peau'd orange	AC x 4	MRM	PR	3	12/12	ypT2N3M0	Docx4 Radiotherapy Trastuzumab Tamoxifen

No	GAD	Tumor size (Clinical)	Treatment During Pregnancy	Surgery Post-Delivery	Response	Tumor Size (cms)	Positive Nodes	Final stage after Surgery	Treatment After pregnancy
3	10	12 x 10 cm	ACx4>Docx4	MRM	pCR	0	0	ypT0N0M0	-
4	31	Multifocal	ACx1	MRM	CR	3mm	0	ypT1aN0M0	ACx3>Docx4 Trastuzumab
5	20	Multifocal	ACx4	MRM	PR	In-situ	3/10	ypTisN1M0	Docx4 Trastuzumab Tamoxifen
6	19	??	ECx4	MRM	PR	1.8	0/9	ypT1cN0M0	Docx4 Trastuzumab Tamoxifen
7	24	10 cm	No Chemotherapy during pregnancy	-	Not evaluable	xx	xx	Stage IV	Doc+Capx 3> Doc+ Ctxx2
8	12	10 cm	ACx4>Docx4	MRM	PR	3	3/17	ypT2N1M0	Trastuzumab Tamoxifen
9	24	Multicentric	ACx4	MRM	SD	6 cm	5/27	ypT3N2M0	Pacliaxelx12w + Carboplatin
10	21	Multicentric	ACx4	-	PR	xx	xx	Stage IV	Docetaxel x 4 Trastuzumab
11	19	Multicentric	MRM FECx4>Docx2		Not evaluable	2.6	6/24	pT2N2M0	Doc x 2
12	25	Multifocal	ACx3	MRM	SD	5.2 x 4.3	13/17	ypT3N3M0	ACx1>Docx4 Trastuzumab
13	8	10 cm	FECx6	MRM	pCR	In-situ	0	ypTisN0M0	-
14	26	7x6 cm	ACx4	WLE+AC	PR	6mm	2/15	ypT1bN1M0	Docx4 Trastuzumab Radiotherapy
15	24	8x8 cm	ACx4	MRM	SD	7cm	13/17	ypT3N3M0	Paclitaxel Radiotherapy
16	29	4 cm cm	MRM	-	Not evaluable	2.5	39/42	pT2N3M0	Did not agree for further Treatment

GAD = Gestational age at Diagnosis; MRM = Modified Radical Mastectomy; AC = Doxorubicin 60mg/m2 + Cyclophosphamide 600mg/m2; Doc = Docetaxel 75mg/m2; EC = Epirubicin 90mg/m2 + Cyclophosphamide 600mg/m2; FEC = 5Fluorouracil 500mg/m2 + Epirubicin 75mg/m2 + Cyclophosphamide 500mg/m2; WLE+AC = Wide local excision + Axillary Clearance; PR = Partial response; pCR = Pathological complete Response; CR = Complete Response; SD = Stable disease; RFA = Radiofrequency Ablation; VNB+Cap = Vinorelbine + Capecitabine; Doc+Cap = Docetaxel + Capecitabine; Doc+Ctx = Docetaxel + Cyclophosphamide.

radical mastectomy (MRM) as the initial treatment; 2 received adjuvant chemotherapy during the pregnancy, while one patient refused further treatment. Twelve patients received neoadjuvant chemotherapy, as shown in the table.

During the pregnancy, patients received between 1 and 8 cycles of chemotherapy, with a median of 4 cycles. (3 patients = 8 cycles, all including anthracyclines and taxanes; 1 patient = 6 cycles of FEC, 7 patients = 4 cycles, all including anthracyclines; 1 patients = 3 cycles; 1 patient = 1 cycle). Of the 12 patients who received neoadjuvant chemotherapy during pregnancy, one patient was subsequently found to have the metastatic disease after delivery, and was continued on palliative chemotherapy, and did not undergo surgery. However, she had a partial response to chemotherapy during pregnancy. Of the 11 other patients, 2 achieved a pathological complete remission (pCR), one patient had a complete clinical remission (CR), 5 patients achieved a partial response (PR), whereas, 3 patients had stable disease (SD). The overall response rate (ORR) was 75%. No patient progressed while receiving chemotherapy.

Following delivery, patients were staged formally with a CT scan of the chest and the abdomen, and a bone scan. Overall 3 patients were found to have stage IV disease. One patient had pulmonary, hepatic and skeletal metastases, one had hepatic and skeletal metastasis, while one patient had a solitary lesion in the liver, which was treated with radiofrequency ablation, followed by further chemotherapy. The final pathological stage and further treatment after the delivery are also shown in Table **2**.

The mean gestational age at delivery was 35.6 ± 1.6 weeks. The mean APGAR score at 1 and 5 minutes was 8.7 ± 0.9 and 9.5 ± 0.9 respectively. All pregnancies and deliveries were uneventful except one patient who had intrauterine growth retardation (IUGR). For this patient, the gestational age at delivery was 34 weeks, and the APGAR scores at 1 and 5 minutes were 6 and 8 respectively

Two patients developed pregnancy subsequent to the treatment and delivered healthy babies.

After a median follow-up of 60 months, median progression-free survival was 36 months (95% CI 24.2

- 47.8 months) while the overall survival for the entire cohort was 59 months (95% CI 31.6 – 86.4). Five-year PFS was 31%, whereas OS was 50% at 5 years and 27% at 10 years (**Figs. 1A&1B**). On univariate log-rank analysis, age, marker status, Ki67 score, clinical disease stage and differentiation grade did not affect the PFS or OS significantly.

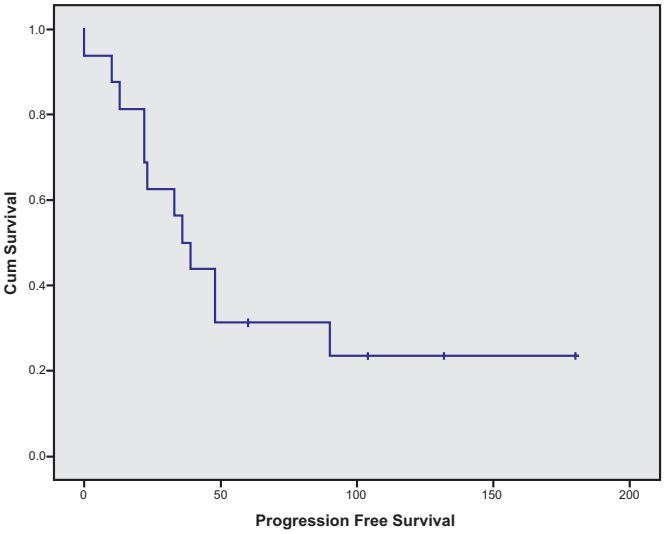

Fig. (1A): Progression-free survival of 16 patients treated for pregnancy-associated breast cancer. After a median follow up of 60 months, median PFS was 36 (95% CI 24.2 – 47.8 months. 5-year PFS was 31%.

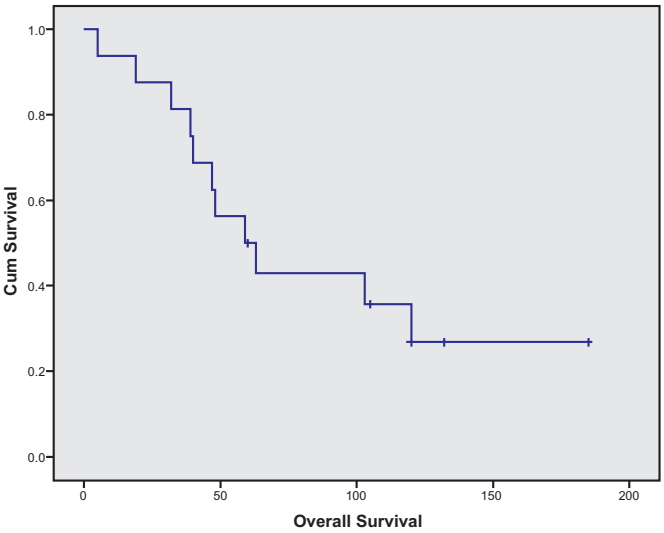

Fig. (1B): Overall survival of 16 patients treated for pregnancy-associated breast cancer. After a median follow up of 60 months, median OS was 59 months (95% CI 31.6 – 86.4 months. 5-year OS was 31%, whereas, 10-year OS was 27%.

DISCUSSION

The aims of this retrospective analysis were two-fold. First of all, to report on the outcomes of PABC from Oman, a developing country, situated in the east of the Arabian Peninsula. Whereas there is a plethora of literature on the outcomes of PAC from the Western world, there are only a handful of reports from the developing countries, some of which are relatively old, and reported on very few women treated with the current standards of management [10, 11]. The second aim was to report the long-term outcomes of patients with PABC treated at a single institution on uniform clinical pathways, using modern chemotherapeutic agents, including taxanes.

Overall, the occurrence of cancer during pregnancy is not common and the incidence ranges between 0.07 – 0.1 of all malignant tumors [1]. However, more recently, an increase in the incidence of PABC from 16 to 37.4 per 100,000 deliveries has been observed [4, 12]. The reason for the increasing incidence, at least in the western world, is the trend to delay pregnancy into later reproductive years. However, the same may not be true for developing countries, and countries with a high fertility rate. Although the median age at the time of diagnosis (31.5 years) in our series is comparable to what has been reported from Jordan [11], Saudi Arabia [10], the United States [13, 14], and Europe [15, 16]. However, in our series, the majority of women were multiparous, and 9/16 women were pregnant a 5th or more times when the breast cancer coincided with the pregnancy. This observation may be explained by the high fertility rate in Oman, estimated to be 7.12 births in ever-married women [8]. A total of 21,717 deliveries were recorded at our institution over the 8 years, of which 16, coincided with the diagnosis of infiltrating carcinoma of the breast, suggesting an incidence rate of 7.4 x 10-4. This is in comparison with the study from New South Wales, Australia [5]. Using a population-based cohort study design, the authors reported 1798 new cases of cancer in 1,309,501 maternities over a 15 year period, of whom 499 were diagnosed during pregnancy, and 95 had breast cancer, giving an incidence rate of PABC to be one magnitude of order lower at 7.25 x 10-5.

The protective effect of a full-term pregnancy on breast cancer, and further protection by additional pregnancies is well known [17]. However, the biology of PABC may be different from non-PABC. For example, there were important biological differences in this series, when compared to breast cancer in Oman in general [7]. All patients in the current series presented with either locally advanced or metastatic disease, compared to 54%, who had presented with stage III/IV disease in the period 2003-2008. The tumor size ranged between 4 and 14 cm, almost half of the patients had a multifocal disease. Fifty percent of patients had grade III infiltrating ductal carcinoma, compared to 35% in the general population. The proportion of patients with HER-2 positive disease was especially high (50%, compared to 21.3%), and almost 1/3rd of the patients had a triple-negative disease, compared to 15%.

There are conflicting reports on the impact of pregnancy on the biological features of breast cancer. On the one hand, Azim *et al.* compared 65 patients with PABC with twice the number of non-PABC patients matched for age, year of diagnosis, stage and neo-adjuvant chemotherapy, and did not find any significant differences in tumor characteristics between the two groups [18].

On the other hand, there are several reports that PABC may be associated with aggressive biological features. For example, Genin *et al.* compared the biological characteristics of 41 PABC with 241 non-PABC in women aged 43 or less [19]. The tumors were twice more likely to be larger (T3 or T4), express HER-2/neu protein, and were hormone receptor-negative. Murphy *et al.* compared 99 patients with PABC with twice the number of non-PABC, matched for age and the year of diagnosis [20]. Patients with PABC were more likely to have larger tumor size at presentation, a higher tumor grade, more nodal involvement, and to be negative for ER, and PgR. However, there was no significant difference in the OS. Pilewskie *et al.* used a slightly different definition of PABC, and included patients up to 2 years after the pregnancy [21]. Patients with PABC, using this definition were more likely to have grade 3 tumors, positive lymph nodes and triple-negative tumors compared to 114 nulliparous women.

Just as the data on the biological features of PABC is conflicting, the outcomes are also variable. For example, Murphy *et al.* showed that although PABC was biologically more aggressive, there was no significant difference in the OS20. On the other hand, Moreira *et al.* compared the outcomes of 87 patients with PABC with pairwise matched controls and showed that the median OS and the 5 and 10-year survival were significantly shorter for patients with PABC, and concluded that pregnancy was an independent poor prognostic factor in addition to tumor size, grade and stage [22]. Ali *et al.* compared 40 patients with 40 matched controls and demonstrated a significantly inferior DFS and OS for patients with PABC [14]. Johansson *et al.* using a population-based cohort study and a slightly different definition of PABC (including patients up to 2 years post-partum), compared the outcomes of 1,110 patients with PABC with non-PABC, aged between 15-44 years, and showed an inferior long-term survival of patients with PABC [23]. A meta-analysis consisting of 30 studies, including 3,628 cases and 37,100 controls reported on the survival of PABC [24]. Controls were either matched or were selected either from the hospital or the population. The primary outcome measure was 1 year OS and the secondary end-point was 1 year DFS after the diagnosis and treatment of PABC. Overall, patients with PABC had a higher risk of death compared to the controls [24]. On the other hand, a more recent meta-analysis of 54 studies showed that PABC was associated with a poor prognosis for OS, DFS, and causes specific survival. Heterogeneity in terms of the relationship of time of diagnosis with pregnancy was suggested to be an important factor, and the authors argued that the definition of PABC should be extended to include patients diagnosed up to 6 years postpartum [25].

The outcomes of patients diagnosed and treated during pregnancy or in the post-partum period are also beginning to emerge. For example, in the meta-analysis, the difference in survival was not significant in the sub-group of patients diagnosed to have breast cancer during pregnancy compared to controls, however, patients diagnosed to have cancer in the post-partum period had a poor outcome compared to the controls [24]. Halaska *et al.* compared the presentations and outcomes of 32 patients with PABC with matched controls and found the OS to be similar [15]. However, the sub-group of 16 patients diagnosed to have cancer in the post-partum period had a shorter time to relapse than either the controls, compared to the patients diagnosed during pregnancy. On the other hand, the median DFS was 70.6 months in women who started chemotherapy during pregnancy, compared with 94.4 months in women who received the entire chemotherapy treatment after delivery in a large observational study from seven European countries [16].

The effects of chemotherapy on the fetus were also studied. The mean gestational age at delivery was 35.6±1.6 (33-38) weeks; there was only one case of low birth weight, but no case of fetal malformation, or newborn complications. The mean APGAR score was almost 9 and 10 at 1 and 5 minutes. The prospective observational study from Europe suggests that the birth weight was lower for the infants who were exposed to chemotherapy after adjustment for gestational age, but was not influenced by the number of cycles received. Also, there were no significant differences in the birth weight of pre-term (less than 37 weeks of gestation) infant, whether or not they had been exposed to chemotherapy in utero. However, the pre-term infants were more likely to develop malformations and newborn complications [12, 16]. It has been suggested that the fetal complications were the result of premature delivery, rather than exposure to chemotherapy.

Two patients in our series developed a subsequent pregnancy after successful treatment of PABC. There is an ongoing debate about the safety of patients becoming pregnant in such circumstances. The major concerns are the occurrence of new cancer, recurrence of initial cancer, and decreased survival, especially for the ER-positive tumors. Azim *et al.* compared the outcomes of patients who became pregnant after treatment of PABC with those who did not and found no difference in DFS, and even an improvement in the OS in those who became pregnant, in the small cohort of patients [26]. The results were further substantiated by Amant *et al.* who found similar OS between pregnant and non-pregnant women with breast cancer [27].

CONCLUSION

We report long-term outcomes of patients with PABC from an Arabian country, where the fertility rate is high. Whereas the mean age at presentation was comparable to the published literature, biologically the disease was more aggressive, as suggested by a large tumor size, multifocal disease, fewer patients were ER/PgR

positive, and more patients were HER-2/neu positive, or triple-negative. Although the response to treatment was comparable, the long-term survival was inferior to the general population of comparable age. The study may help to set a benchmark for studies from the region.

ETHICS APPROVAL

At the time, the study was conceived and the data were accrued (2005-2012), an explicit approval from ethics committee was not required for retrospective analysis, especially as patient identity was completely concealed.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

No funding was applied/available for this retrospective analysis

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the services of all physicians and nursing staff involved in the management and care of the patients, whose data are presented here.

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