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Prevalence of ectopic breast tissue and tumor: a twenty-year single center experience

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6 Title

7 Prevalence of ectopic breast tissue and tumor: a twenty-year single center experience.

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31 Abstract

32 Ectopic breast tissue, which includes both supernumerary breast and aberrant breast tissue, is the most common
33 congenital breast abnormality. Ectopic breast cancers are rare neoplasm, that occur in 0.3-0.6% of all cases of
34 breast cancer. We retrospectively report, accounting a large series of breast abnormalities diagnosed and treated,
35 our clinical experience on the management of the ectopic breast cancer. In two decades, we observed, out of a
36 total of 12,177 subjects undergone to a breast visit, 327 (2.7%) patients with ectopic breast tissue. All patients
37 were classified, in eight classes, according to Kajava's classification and assessed by physician examination,
38 ultrasounds, and when appropriate further integrated with fine needle aspiration cytology and mammography.
39 All specimens were submitted to the anatomic-pathologist. The most frequent benign histological diagnosis was
40 fibrocystic disease. A rare granulosa cell tumor was also found in the right anterior thoracic wall. Four
41 malignancies were also diagnosed in four women, an infiltrating lobular cancer in a patient class I, an infiltrating
42 apocrine carcinoma, an infiltrating ductal cancer, and an infiltrating ductal cancer with tubular pattern, occurred
43 in three patients belonging to class IV. Only one recurrence was observed. We recommended an earlier surgical
44 approach for patients with lesions from class I to IV.

45

46 Micro-Abstract

47 Herein we described our clinical experience on the management of the patients with ectopic breast tissue.
48 Ectopic breast cancers are rare neoplasm, that occur in 0.3-0.6% of all cases of breast cancer. Overall, we
49 retrospectively reviewed 327/12,177 (2.7%) patients with ectopic breast tissue, observed throughout twenty
50 years and classified according to Kajava's classification. Among them, four malignancies were diagnosed. We
51 recommended an earlier surgical approach for patients with lesions from class I to IV.

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57 Keywords

58 ectopic breast cancer; ectopic breast tissue; supernumerary breast, aberrant breast tissue; polymastia; polythelia.

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61 Introduction

62 Ectopic breast tissue (EBT) may develop along all sites of an embryological ideal curved line also defined *milk-*
63 *line*, that goes from the axilla to the groin, and represents the expression of the incomplete involution of this
64 embryological cellular line.

65 EBT may be distinguished as supernumerary breast (SB) with a nipple or an areola, or aberrant breast tissue
66 (ABT) lacking a nipple or an areola.

67 Physiologically, embryonic breast development starts during the 4th week of pregnancy, when bilateral
68 mammary ectodermal tissue forms a ridge, corresponding to the milk-line, on the ventral surface of the body.

69 Later, during the 5th week, this mammary ridge disappears gradually, except only for the 4th intercostal space of
70 the anterior chest wall, where cells continue to proliferate resulting in the primary mammary sketch. Then,
71 between the 7th and 12th week, a dermal solid button will origin with a trend to grow and to differentiate in adults
72 mammary lobules.^{1,2} Failure of this involution can lead to EBT in any portion of the milk line.

73 Since 1915, Kajava et al. classified ectopic breast in 8 classes of presentation: Class I, complete supernumerary
74 breast with nipple, areola and glandular tissue (*polymastia*); Class II, supernumerary nipple and glandular tissue
75 without areola; Class III, supernumerary areola and glandular tissue without nipple; Class IV, aberrant glandular
76 tissue only; Class V, supernumerary nipple and areola without glandular tissue, replaced by fat tissue
77 (*pseudomamma*); Class VI, supernumerary nipple only (*polythelia*); Class VII, supernumerary areola only
78 (*polythelia areolaris*); Class VIII, patch of hair only (*polythelia pilosa*).³

79 Overall, the prevalence of EBT in female ranges 0.4-6% and in male 1-3%, with the highest incidence reported
80 among Japanese patients.^{4,5} These areas of breast tissue suffer physiological changes, may increases in their size
81 after hormonal stimulation periods (puberty, pregnancy, lactation), and represent potential sites to develop
82 benign or malignant breast diseases.⁶⁻⁹

83 Malignant and benign tumors such as carcinoma, intraductal papilloma, and fibroadenoma have all been
84 described.¹⁰ Ectopic breast cancer (EBC) is rare and occurs in 0.3-0.6% of all cases of breast cancer.^{11,12}

85 In this retrospective study, we report our clinical experience on the management of the EBC diagnosed in a large
86 series of breast abnormalities observed and surgically treated.

87

88 Patients and Methods

89 From January 1995 to December 2014 we observed, out of a total of 12,177 subjects who had a clinical visit for
90 breast lesions, 327 (2.7%) patients with EBT (242 [74%] were females (F) and 85 [26%] males (M), age range

91 16-92 years (mean age 53.6 ± 18.7 Standard Deviation); all patients were classified according to Kajava's 1915
92 classification and all anatomical lesion sites detailed in **Table 1**. All patients with EBT were assessed by
93 physician examination and ultrasound scan (USS); supplementary fine needle aspiration cytology and
94 mammography were performed in 128 and 52 cases, respectively. In 169 patients with EBT class VI, a renal
95 USS was carried out for a screening of the, frequently associated, occult urogenital anomalies. All specimens
96 were submitted for histological evaluation.

98 **Results**

99 Clinically, patients complaining symptoms (i.e.: vague premenstrual discomfort, pain, restriction of upper limbs
100 movement, turgor, anxiety, itching) were 182 (55.7%, 165 females and 17 males), whereas the remaining 145
101 (44.3%) patients were completely asymptomatic (Table 1). No cases of supernumerary areola and glandular
102 tissue without nipple (Kajava's class III) were found. In 27 (8.3%) patients lesions were multiple, and only in 4
103 (1.2%) cases bilateral. In two cases a duplication of the ureter was associated to a polythelia. In 179 (54.7%)
104 cases out of the 327 diagnosed patients, the expression of the EBT presented a familiar pattern. Surgical
105 procedures were performed in 288 cases (88.1%) (253 F and 35 M) and consisted in the excision of EBT. We
106 recommended an earlier surgical approach for patients with lesions from class I to IV (Figure 1A,B); for the
107 other classes the excision was realized either in symptomatic patients or if required for cosmetics reasons (31
108 patients, 19 F and 12 M). Polythelia (or Class VI) was frequently discovered incidentally, during a clinical
109 examination for other symptoms or discomfort, because misunderstood for nevus (Figure 1C). Overall, the most
110 frequent histological findings were stromal fibrous or dermal tissue, gland breast or fat tissue without noticeable
111 disease. In 98 cases, histological examination was consistent with the diagnosis of fibrocystic disease, in 7 cases
112 with fibro-lipomatosis masses, and in 1 case with a granulosa cell tumor. Four malignancies were also diagnosed
113 in four women, i.e.: an infiltrating lobular cancer in a patient class I; moreover an infiltrating sweat glands
114 cancer, an infiltrating ductal cancer, and an infiltrating ductal cancer with tubular pattern, all tumors occurred in
115 three patients belonging to class IV. Three supplementary axillary lymph node dissections were further
116 performed. No mortality was observed. Only one recurrence occurred: the patient treated for a ductal cancer with
117 axillary nodal involvement developed, during the oncologic follow-up and 8 years after surgery, distant liver and
118 lung metastases notwithstanding the adjuvant treatments performed.

119 **Tumors**

120 *Benign tumor lesions*

121 **Granulosa cell tumor:** it was sited on the right anterior thoracic wall, below the breast, and clinically
122 characterized for slight premenstrual tenderness and swelling, its largest diameter was 5 mm. At gross
123 examination, the specimen appeared well-circumscribed and yellowish-white colored when sliced; histology
124 demonstrated the presence of neoplastic cells arranged in nests and cords separated by fibrous bands, surrounded
125 by a pseudo-capsule, with a low proliferative activity. At immunohistochemical analysis, neoplastic elements
126 were positive for anti-cytoplasmic antibodies anti-protein S-100, anti- Neuron Specific Enolase, anti-vimentin
127 and anti-CD-68; no immunoreactivity for anti-Epithelial Membrane Antigen and broad-spectrum cytokeratins
128 (Figure 2A,B,C) was found.

129 *Malignant tumor lesions*

130 **Infiltrating lobular cancer:** it was located in the left axilla, asymptomatic, 9 mm in its largest diameter,
131 histologically it showed a mainly solid growth pattern with infiltration of the peritumoral fat tissue; hormonal
132 status showed a positivity for estrogen (70%) and progesterone (60%) receptors, HER-2 was negative with a
133 proliferative index of 10%. Fourteen axillary lymph nodes removed, resulted all uninvolved with non-specific
134 reactive lymphadenitis findings. The patient underwent adjuvant chemo- and radiotherapy, followed by a 5-year
135 anti-estrogen therapy and at her last follow-up visit she was alive and getting on well.

136 **Infiltrating sweat glands cancer or apocrine carcinoma:** it was located in the right axilla, 10 mm in its largest
137 diameter and caused acute pain. The microscopic appearance on hematoxylin-eosin routine stain highlighted
138 solid nests of neoplastic elements with low-grade malignancies and local infiltration of subcutaneous fat (Figure
139 2D). Immunostainings showed neoplastic elements with a strong cytoplasmic positivity for anti-alfa-Smooth
140 Muscle Actin. No complementary treatments were carried out. At the last follow-up visit, the patient was doing
141 well and free of any clinical local recurrence or distant metastases.

142 **Infiltrating ductal cancer:** it was located in the left axilla and asymptomatic, 19 mm in its largest diameter,
143 presenting at microscopic examination large features of tubulo-papillar cribriform desmoplastic tumor, with
144 images of lymphangitis and dermal infiltration. The carcinoma displayed no nuclear reactivity for estrogen or
145 progesterone receptors and was also HER-2 negative with a proliferative index superior to 20%. Axillary lymph
146 nodes were largely infiltrated, nine nodal metastases out of a total of 15 lymph nodes harvested. Adjuvant
147 treatments were chemotherapy followed by radiation therapy and at her last follow-up visit, the patient was still
148 alive and followed by oncologist for pulmonary and hepatic metastases.

149 **Infiltrating ductal cancer with tubular pattern:** it was located above the normal right breast along the
150 midclavicular line, nearby the region between the upper-inner and upper-outer quadrants, 12 mm in its largest

151 diameter; it presented a tubular pattern and the patient complained only a vague discomfort. Hormonal status
152 showed a high nuclear positivity for estrogen (90%) and progesterone (90%) receptors, HER-2 was positive with
153 a low proliferative index of 5% (Figure 3A,B,C). Twelve axillary lymph nodes we harvested were completely
154 uninvolved. The patient underwent adjuvant radiotherapy followed by a 5-year anti-estrogen therapy, and did
155 well free from recurrences and metastases up to our last follow-up.

156

157 **Discussion**

158 Ectopic breast tissue (EBT), which includes both SB and ABT, is the most common congenital abnormality of
159 the breast. SB and ABT are different on histopathology, because the former consists of an organized ductal
160 system communicating with its overlying skin, whereas the latter is characterized by an unorganized secretory
161 system which has no communication to the overlying skin.^{1,13} EBT is more frequently localized in the axilla,¹⁴
162 even if other localizations have been reported in parasternal, subclavicular, submammary, vulvar and anal
163 regions.^{13,15} Malignancy arising from EBT is a rare entity. However, the cases reported in locations other than
164 milk line may be due to a migratory arrest of breast primordium during chest wall development^{11,16} or may
165 develop from modified apocrine sweat glands.¹² EBT shows autosomal dominant inheritance with incomplete
166 penetrance, even if sporadic cases are most commonly frequent.¹ Since 1915, Kajava classified ectopic breast in
167 8 classes of presentation.³ EBT is an important entity as it is at risk of developing any benign or malignant
168 tumors that can develop in a normal breast. Benign and malignant conditions such as carcinoma, intraductal
169 papilloma, fibroadenoma and fibrocystic disease have been reported in literature.^{5,12} In our series, a rare
170 granulosa cell tumor was found in the right anterior thoracic wall. Moreover, four malignancies were diagnosed
171 in four women, an infiltrating lobular cancer in a patient class I, an infiltrating apocrine carcinoma, an infiltrating
172 ductal cancer, and an infiltrating ductal cancer with tubular pattern, occurred in three patients belonging to class
173 IV. They may be prone to diagnostic challenge till they are biopsied. EBT, that may be bilateral, usually remains
174 not detectable until puberty and is often found only during pregnancy or lactation, when hormonal stimulation
175 can cause engorgement.^{7,17,18} Early diagnosis relies on the lesion histology, since the clinical diagnosis is
176 difficult.¹⁴ Standard mammograms do not usually show EBT because of its location, but with special positioning
177 of the patient, it may sometimes be revealed. The role of MRI in identifying the EBC is well established.⁴ Their
178 diagnosis may be delayed without a high index of suspicion, particularly in cases with no overlying accessory
179 areola or nipple. Therefore, especially when located beyond the periphery of the gland, it may be misdiagnosed
180 as a subcutaneous lesion, i.e. lipoma, lymph node, sebaceous cyst or hidradenitis suppurativa, and diagnosed in

181 an advanced clinical stage.^{7,9,13,17} In comparison to SB, the ABT is considered to be more susceptible to
182 malignant degeneration probably because of the stagnation in the ductal lumen.^{19,20} A review on 82 cases of EBC
183 published between 1865 and 1994 reported an increasing incidence of cancer in ABT, but no increased incidence
184 of cancer in SB cases. Furthermore, the mean age at diagnosis of patients within EBC was about 54 years, about
185 six years younger than the average age when cancer arises in normal breast.¹³ The most frequently described
186 histotype of EBC is the infiltrating ductal carcinoma (79%), followed by medullary and lobular carcinoma,
187 whereas Paget's disease, cystosarcoma phylloides, papillary carcinoma, leiomyosarcoma and invasive secretory
188 carcinoma are rare.^{13,14} EBC should be treated as typical breast tumor, even if general clinical guidelines are not
189 standardized. In case of benign neoplasm, lumpectomy is the standard of care. If malignant, the principles of
190 postoperative treatment are the same as for cancer arisen in the orthotopic breast.²¹ There is not any role for
191 ipsilateral prophylactic mastectomy.^{16,22} The prognosis of accessory breast carcinoma is difficult to establish due
192 to the limited follow-up data and small sample size. Some Authors consider the same prognostic indices for the
193 orthotopic breast as well.^{11,13} Although no prognostic conclusions are available due to the rarity of this disease,
194 EBC seems to have a poorer prognosis than cancer developed in normal breast parenchyma, because early
195 diagnosis may be difficult.^{17,23,24} In our series, one recurrence was observed: the patient treated for a ductal
196 cancer with axillary nodal involvement developed, 8 years after surgery, distant liver and lung metastases. Other
197 Authors consider the worst prognosis of axillary breast cancer since it spreads earlier to axillary lymph nodes.^{9,14}
198 In conclusion, we have reported our experience in the diagnosis and treatment of the ectopic breast cancer and
199 recommend the importance of keeping in mind this possibility in the evaluation of such masses, so as to provide
200 earlier diagnosis and definitive treatment.

201

202 **Clinical Practice Points**

- 203 • Ectopic breast cancers are rare neoplasm, that occur in 0.3-0.6% of all cases of breast cancer.
- 204 • We retrospectively report, accounting a large series of breast abnormalities diagnosed and treated, our
205 clinical twenty-year experience on the management of the ectopic breast cancer. Among our cohort of
206 patients (327), four malignancies were diagnosed (infiltrating lobular cancer, infiltrating apocrine
207 carcinoma, infiltrating ductal cancer, and infiltrating ductal cancer with tubular pattern).
- 208 • We recommended an earlier surgical approach for patients with lesions from class I to IV.

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210

211 **Disclosure**

212 There was no grant support and no conflict of interest exists to the submitted manuscript.

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300 **Table and figure Legends**

301

302 **Table 1.** Cohort patient characteristics (period: 1995-2014): 327 patients out of (more than) 12,000 subjects
303 who had a clinical visit for breast lesions.

304

305 **Figure 1.** **A)** Aberrant glandular tissue only (class IV); **B)** Ultrasound features: circumscribed hypoechoic
306 roundish mass, approximately 64 mm in largest diameter, located above the orthotopic breast; **C)** Supernumerary
307 nipple (class VI).

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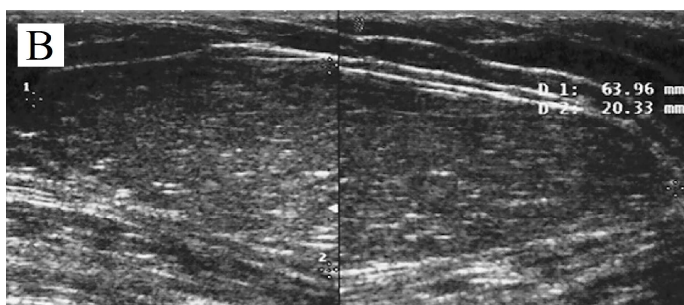
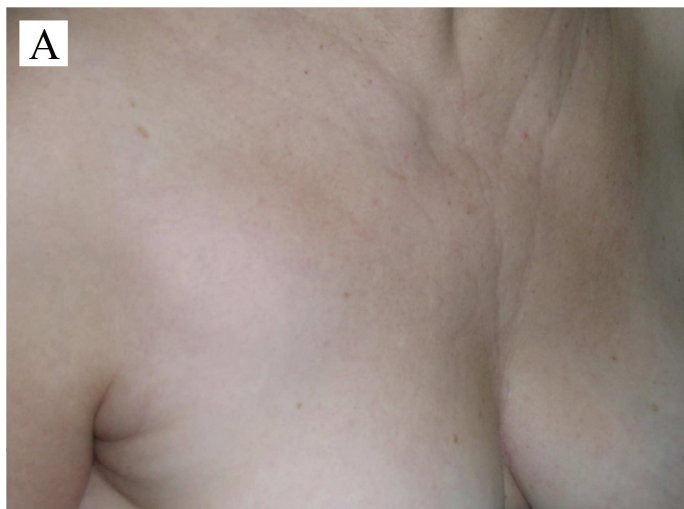
309 **Figure 2.** **A)** Granulosa cell tumor: neoplastic cells organized in nests and cords divided by fibrous tissue, with a
310 small proliferative index (Hematoxylin Eosin stain, x 200); **B)** Intense cytoplasmic immunoreactivity for CD-68
311 antibody (Immunoperoxidase, x 100); **C)** Cytoplasmic immunoreactivity for Neuron Specific Enolase antibody
312 (Immunoperoxidase, x 400); **D)** Apocrine carcinoma: neoplastic cells grouped in solid nests, with focal
313 subcutaneous fat infiltration (Hematoxylin Eosin stain, x 200).

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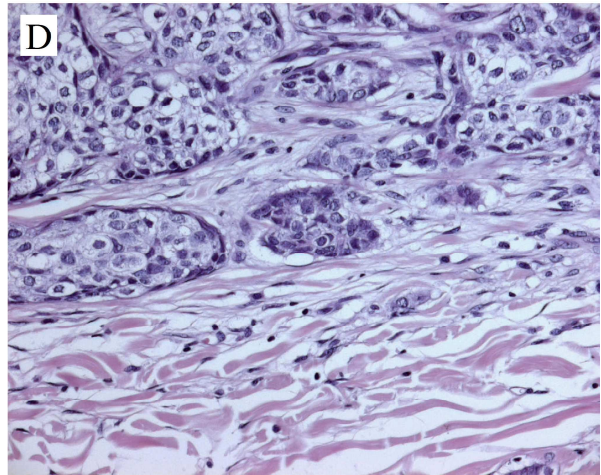
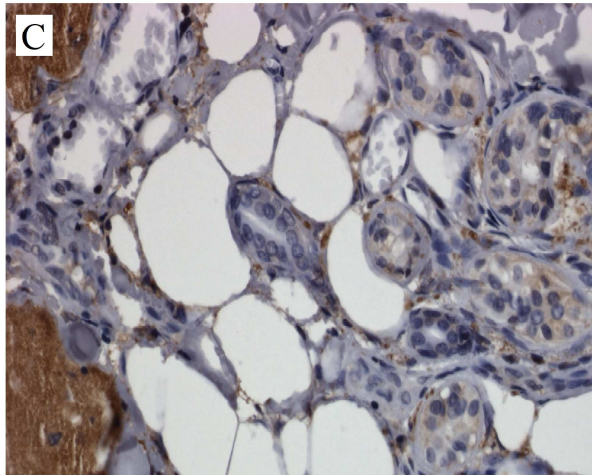
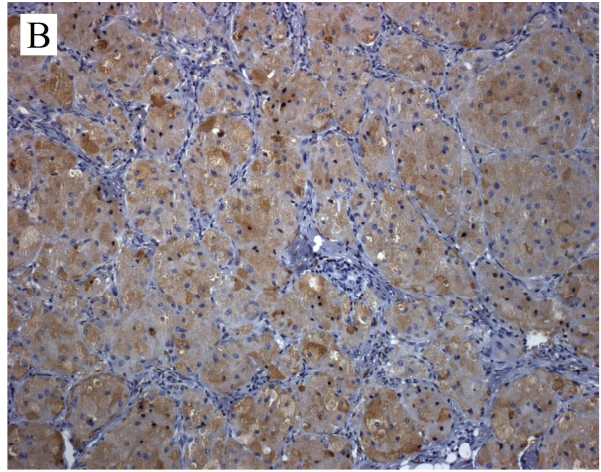
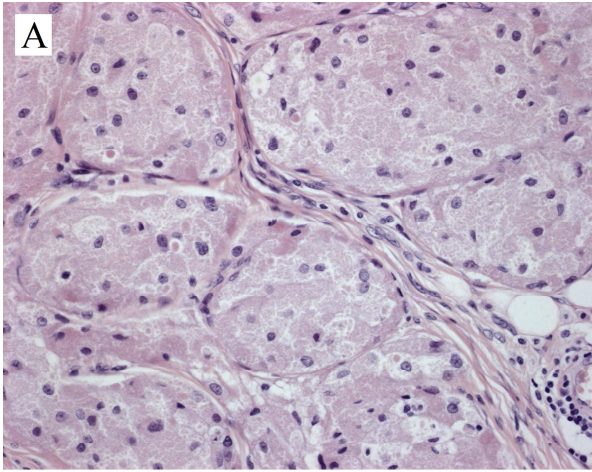
315 **Figure 3.** Infiltrating ductal carcinoma with tubular pattern: **A)** Gross appearance; **B)** Ultrasound features:
316 hypoechoic ovalar lump, approximately 12 mm in largest diameter, sited nearby the region between the upper-
317 inner and upper-outer right breast quadrants; **C)** Typical histological features (Hematoxylin Eosin stain, x 200).

Table 1. Cohort patient characteristics (period: 1995-2014): 327 patients out of (more than) 12,000 subjects who had a clinical visit for breast lesions..

	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII	Class VIII
Number of patients	48	26	/	57	13	174	8	1
Sex ratio (F/M)	46/2	26/0	/	57/0	13/0	93/81	7/1	0/1
Symptomatic patients (F/M)	41/0	11/0	/	37/0	7/0	67/17	2/0	/
Localizations								
Trunk	11	23	/	8	12	143	8	1
Axilla	37	1	/	49	1	11	/	/
Groin	/	1	/	/	/	13	/	/
Other sites	/	1	/	/	/	3	/	/
Surgical Procedures								
Excision	48	26	/	57	13	139	5	/
Axillary lymph node dissection	1	/	/	3	/	/	/	/
Tumors								
Benign	1 granulosa cell tumour							
Malignant	1 infiltrating sweat glands cancer			1 infiltrating lobular cancer N0 (0/14)				
* Nodal involvement: Number of lymph nodes with metastases / total harvested				1 infiltrating ductal cancer N1 (9/15)				
				1 infiltrating ductal cancer, tubular pattern N0 (0/12)				



ACCEPTED MANUSCRIPT



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