RELATO DE CASO

Secretory breast carcinoma in a seven-year-old girl: case report and review of the literature

Carcinoma mamário secretório em criança de sete anos de idade: relato de caso e revisão da literatura

Míriam de Fátima Brasil Engelman[1], Fiorita Gonzales Lopes Mundim[2], Rogério Mendes Grande[2], Angela Flávia Logullo Waitzberg[3]

Keywords

Secretory carcinoma
Breast carcinoma in children
Immunohistochemistry

ABSTRACT

Secretory breast carcinoma is an extremely rare entity initially described in children and in adolescents, but a relatively frequent number of cases has been reported in adults. It is often associated with good prognosis. The present case refers to a seven-year-old girl with a progressively growing tumor in the left breast. Clinical examination identified a hard, mobile, non-painful, subareolar nodule with regular margins; further macroscopy of surgical specimen showed a smooth surface and 1.3 cm in diameter. The final diagnosis of malignancy led to mastectomy and intra-operatively negative sentinel lymph node assessment. Immunohistochemical profile included a strong positive stain for cytokeratins (AE1/AE3) and TP53, and estrogen-receptor and progesterone-receptor and Her-2/neu protein expression negative; and MIB-1 (Ki-67) labeling index was 10%. Further follow-up examinations have shown no evidence of distant metastases, with normal development of secondary sexual characteristics (pubarche, right thelarche, and menarche occurring in July, 2009). Seven years later, the teenager still does not have the disease and waits reconstructive plastic surgery of the left breast.

Descritores

Carcinoma secretório
Câncer de mama em criança
Imunoistoquímica

RESUMO

O carcinoma secretório da mama é uma entidade extremamente rara, inicialmente descrita em crianças e adolescentes, mas um número relativamente frequente de casos foi relatado em adultos. É usualmente associado ao bom prognóstico. O presente caso refere-se a uma menina de sete anos de idade com crescimento tumoral progressivo na mama esquerda. O exame clínico identificou um nódulo subareolar duro, móvel, indolor e margens regulares; macroscopicamente, o espécime cirúrgico mostrou nódulo com 1,3 cm de diâmetro e superfície lisa. O diagnóstico final de neoplasia maligna levou à mastectomia, e a avaliação intraoperatória do linfonodo sentinela foi negativa. O perfil imunoistoquímico incluiu coloração fortemente positiva para citoqueratinas (AE1/AE3) e TP53, expressão negativa para receptores de estrógeno e progesterona e proteína Her-2/neu; o antígeno de proliferação celular Ki-67 (MIB-1) mostrou índice de marcação de 10%. Exames adicionais de acompanhamento não mostraram nenhuma evidência de metástases à distância, com desenvolvimento normal das características sexuais secundárias (pubarca, telarca direita e menarca, que ocorreu em julho de 2009). Sete anos mais tarde, a adolescente ainda está livre da doença e aguarda cirurgia plástica reconstrutiva da mama esquerda.

[1]Doutora pela Universidade do Vale do Sapucaí (UNIVÁS) – Pouso Alegre (MG), Brasil.
[2]Mestres pela UNIVÁS – Pouso Alegre (MG), Brasil.
[3]Doutora pela Universidade Federal de São Paulo (UNIFESP) – São Paulo (SP), Brasil.
Correspondence: Míriam de Fátima Brasil Engelman – Rua São Paulo, 85 – Medicina – CEP: 37550-000 – Pouso Alegre (MG), Brasil – E-mail: mi.engelman@uol.com.br
Financial support: none.
Conflict of interest: nothing to declare.
Received on: 15/12/2011 **Accepted on:** 15/12/2011

Introduction

Secretory breast carcinoma (SBC) is a very rare condition characterized by distinct histomorphology and it was first described by Mcdivitt and Stewart[1]. It comprehends 1% of breast carcinomas, but they are associated with more favorable prognosis compared to the invasive ductal carcinoma of usual type (IDC). Another epidemiological feature is the prevalence in children, but it can also occur in adults[1,2]. Recently, the tumor was associated with the ETV6-NTRK3 gene translocation. The biological consequence of this translocation is the fusion of the dimerization domain of a transcriptional regulator (ETV6) with a membrane receptor tyrosine kinase (NTRK3) gene, which activates the Ras-Mek1 and PI3K-Akt pathways that are important for breast cell proliferation and survival[3,4].

Clinical case report

A seven-year-old girl without family history of breast carcinoma presented in July 29th, 2005, with a nodule in her left breast, which had been discovered about few months previously and had gradually increased slightly in volume during the intervening period.

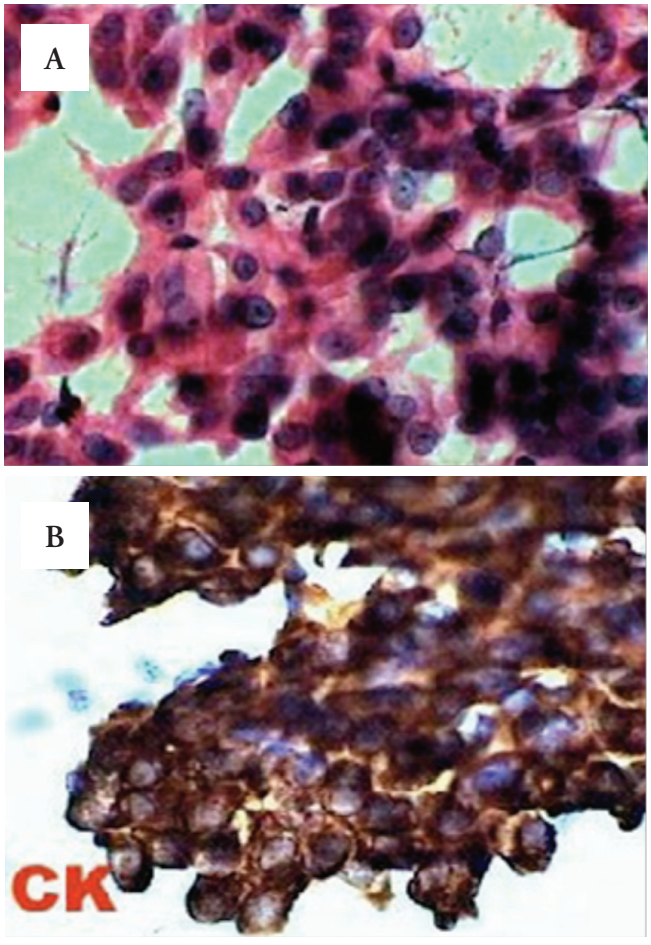

Figure 1. (A) Cytological features of secretory carcinoma; (B) Positive stain for cytokeratins (AE1/AE3) in cytologic smears

Clinical examination showed the presence of a hard, mobile, non-painful, subareolar nodule with regular margins, with smooth consistence and about 1.3 cm in diameter. No clinical alterations were found either in the ipsi- or contralateral axillary lymph nodes.

The nodule was initially addressed through a fine needle aspiration biopsy (FNA), whose cytology result was nonconclusive. A second FNA biopsy was performed and the specimen obtained showed hipercellular smears and these were subsequently submitted to immunohistochemistry, which stained positive for Cytokeratin 40, 48, 50 and 50,6 kDa (Figure 1). Incisional biopsy of the lesion was performed, and histopathological examination concluded as a SBC. Standard microscopic examination in hematoxylin-eosin 5 micra showed solid cell nests, intermingled with tubular structures and separated by fibrous bundles. The neoplastic nests consisted of small, uniform, well-differentiated cells, with granular or vacuolated cytoplasm, and vesicular nuclei containing small nucleoli. Mitoses were scanty and atipia was mild. Eosinophilic, PAS-positive secretory material was observed in the ductular lumina and in the intracytoplasmic vacuoles of many neoplastic cells (Figure 2).

The diagnosis of malignancy led to mastectomy. The sentinel lymph node was intra-operatively negative, which was confirmed afterwards on definitive exam (Figure 3A).

Macroscopically, the breast tissue removed measuring 7.5x5.0x1.5 cm, and it is partially covered by a skin flap, measuring 6.5x3.2 cm, with a scar of 1.2 cm in areolar region. The cut surface shows nodules with maximum 1.3 cm diameter, consisting in a firm and grayish white mass completely enclosed by yellow tissue.

The histopathology of the specimen confirmed the diagnosis of SBC with tumor-free surgical margins. Vascular and perineural invasions were not identified.

Immunohistochemical profile of the tumor (Table 1) showed neoplastic cells with a strong positive stain for cytokeratins (AE1/AE3) and TP53, along with triple-negative results (estrogen-receptor and progesterone-receptor and Her-2/neu protein expression negative). MIB-1 (Ki-67) labeling index was 10% (Figure 3B).

Periodic follow-up examinations after the surgical procedure have shown no evidence of distant metastases, and normal development of secondary sexual characteristics occurred (pubarche, right thelarche, and menarche occurring in July, 2009). Seven years later, the teenager is still free of the disease and waits reconstructive plastic surgery of the left breast.

This study was approved by the Committee on Research and Ethics of Universidade do Vale do Sapucaí (UNIVÁS).

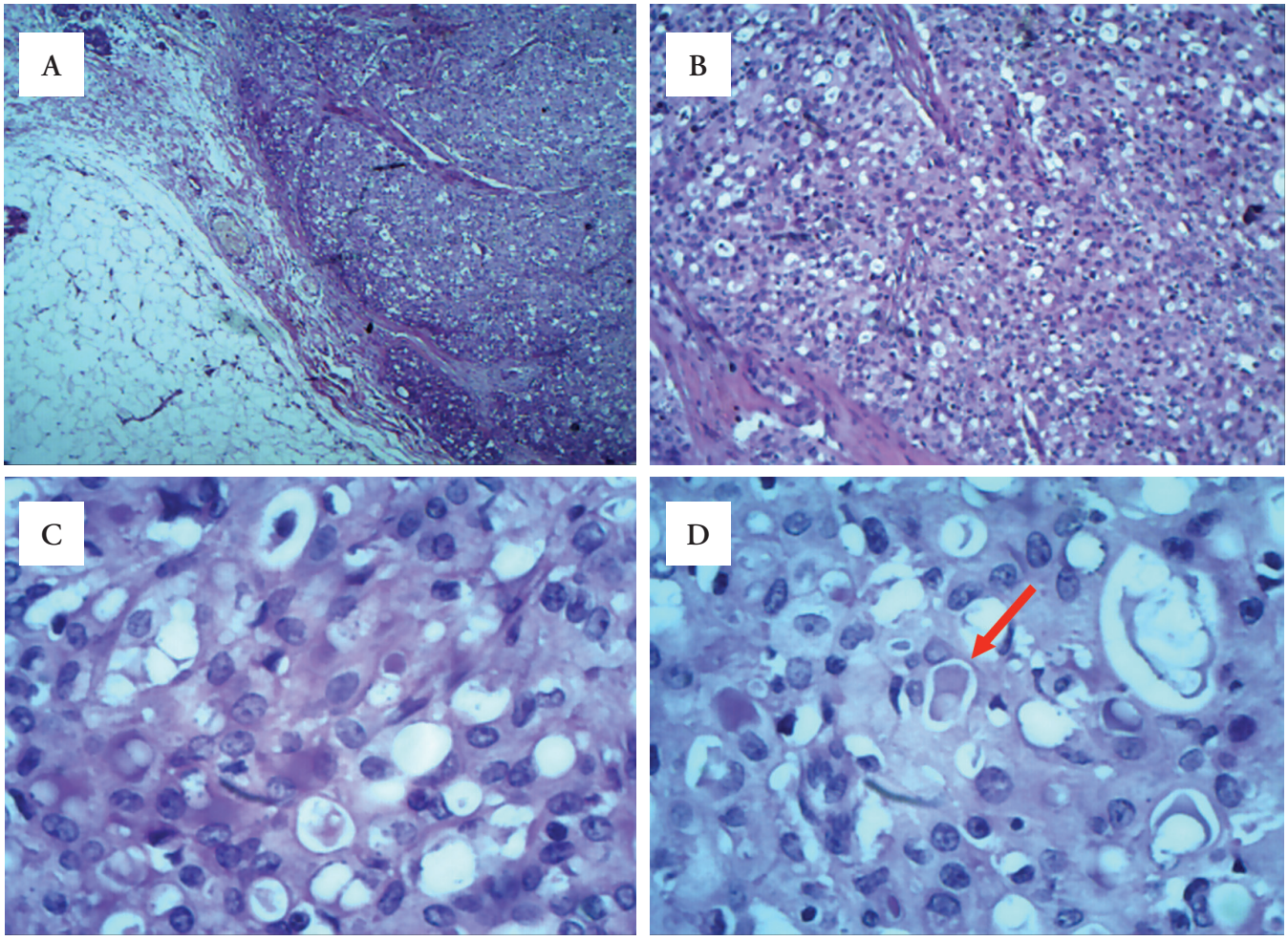

Figure 2. Secretory carcinoma standard microscopic examination in hematoxylin-eosin (A) HE 40x, (B) HE 100x, (C) HE 400x, (D) Secretory granule

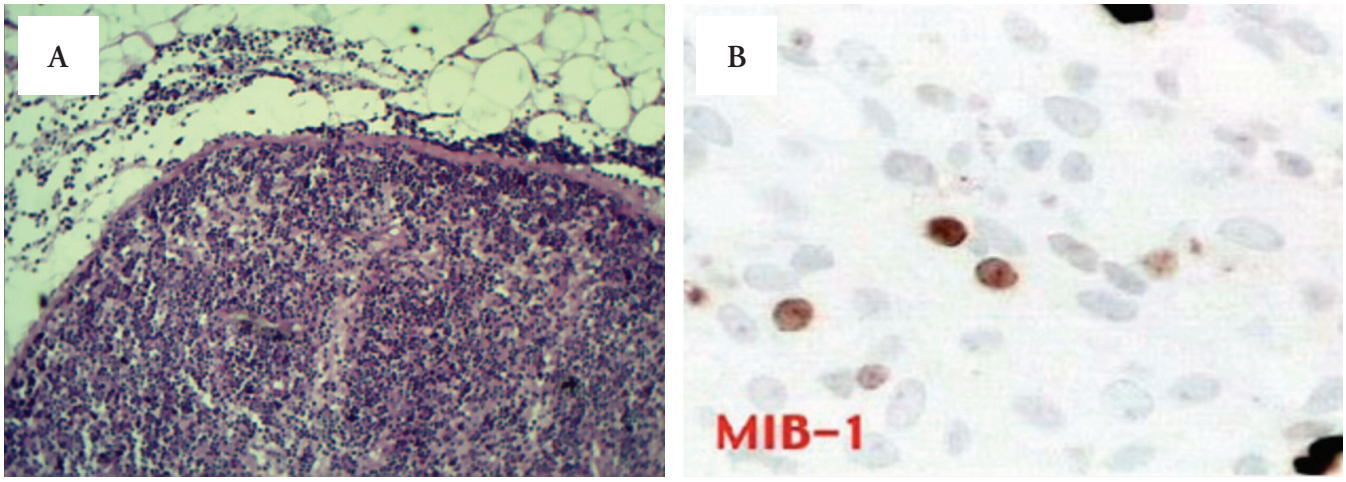

Figure 3. (A) Intra-operatively negative sentinel lymph node; (B) MIB-1 (Ki-67) labeling index was 10% in secretory carcinoma

Table 1. Immunohistochemistry in breast secretory carcinoma in children

Antibodies	Clone	Result
Cytokeratins 40, 48, 50 and 50,6 kDa	AE1/AE3	Positive
Desmin	D33	Negative
Cell proliferation antigen	MIB-1	10% positive
Tumor suppressor gene product TP53	DO7	Positive
Product oncogene HER-2/NEU (c-erbB2)	Policlonal	Negative
Estrogen-receptor	SP1	Negative
Progesterone-receptor	PR636	Negative

Discussion

In the pathogenesis of breast cancer, two sets of influences seem to be important: genetic changes and hormonal influences. Breast carcinoma is rare in women under 20 years of age, probably because their exposure to estrogen (promoter of breast carcinogenesis) is limited. Rivera-Hueto et al.[5] reported meager four cases (0.9% of all 4,341 cases in 24 years). Aceto et al.[6] published a series of five patients diagnosed within 25 years of age, which included two adolescents, 12 and 15 years-old.

The most frequently breast cancer encountered in children is the SBC, which is a very rare type of breast carcinoma with frequency of less than 1% of all breast malignancies[7]. Diallo et al.[8] reported 13 cases of SBC; Lamovec and Bracko[9] reported four cases of SBC in a retrospective series of 7,038 breast carcinoma cases, and Botta et al.[10] found one case of SBC among 3,000 breast carcinoma cases.

SBC was first described in 1966 by Mcdivitt and Stewart[1]. This is a rare breast neoplasia first identified in female children and adolescents. Tumors with similar features were subsequently observed in male children and young boys, in adult men and in women of all ages, with the result that at a certain point this type of tumor was no longer defined as a "juvenile carcinoma". It is not particularly an aggressive tumor and it presents an excellent prognosis. The age at presentation varies from 3 to 87 years-old with a median age of 25[1,11]. The male-female ratio is approximately 1:6[12].

Heterogeneity is an important feature that is reflected in genetic analysis of breast cancers at the molecular level. Gene expression profiling can stratify breast cancer into five subtypes: luminal A (estrogen receptor positive), luminal B (estrogen receptor and HER2/NEU positive), HER2/NEU overexpressing (estrogen receptor negative), basal-like (estrogen receptor and HER2/NEU negative), and normal breast like.

The correlation between known risk factors for breast carcinoma and SBC is not yet fully understood. Since the presence of estrogen and progesterone receptors is extremely variable in patients with SBC, the etiopathogenesis of such tumors is probably not linked to female sex hormones. In the SBC related for Vieni et al.[13], the E-cadherin expression was found positive, which would support the hypothesis that this type of tumor is a variant of the infiltrating ductal carcinoma. Immunohistochemically the negative stain for oestrogen and progesterone receptors in our case are in agreement with previous reports[14,15].

Management of the present case consisted of simple mastectomy and low axillary dissection. Longo et al.[16] related local recurrence near the surgical scar eight months later in a four-year-old girl, and a wide elliptical excision of the scar and underlying tissue was performed with subsequent radiotherapy of the surgical bed.

In our case, we found that the tumor showed a low risk factor, once it is smaller than 2.0 cm, it has low histological grade, absence of vascular invasion, low proliferation rate assessed by Ki-67 and HER2/NEU negative immunostain.

Although loco-regional and distant metastases from SBC are extremely rare, Viene et al.[13] reported a rare case of SBC with axillary lymph node metastases in a 33-year-old woman. It is necessary to verify the possible presence of systemic and/or axillary lymph node metastases, for the correct staging of the disease.

In order to avoid the complete dissection of the axillary fossae and its post-operative complications (pain, parasthesia, seroma, lymphedema of the upper arm), in our case the sentinel lymph node was intra-operatively accessed. Sentinel lymph node is a minimally invasive alternative to routine axillary lymph node dissection with few long-term side effects[17].

Primary breast carcinoma is exceedingly rare in the pediatric age group. In girls, diagnostic interventions may injure the developing breast and cause subsequent disfigurement. Given this risk and the low prevalence of malignant disease in this population, a prudent course should be followed in the diagnosis of breast lesion. Although malignancy is rare, lesions with suspicious imaging findings or progressive growth should be subjected to cytologic or histologic examination[18].

For differentiation of SBC *versus* abnormal thelarche, we used the FNA biopsy, but the results were inconclusive. While it is undeniable the interest of FNA biopsy for the preoperative diagnosis and a more rational treatment of these lesions of the breast with aspects recently characterized by some authors[19], the diagnosis of SBC has been published in most cases supported by histological examination of the final product of excision of the tumor[20].

The cytological features of SBC have been reported primarily in adults. FNA biopsy is a very important diagnostic tool in the pediatric population, since it provides a fast, minimally invasive, low risk, and well-tolerated procedure. The cytologic smears were rather cellular with cell groups arranged in three-dimensional sheets. A characteristic feature is the presence of secretory vacuoles and occasional intranuclear pseudoinclusions. The cells with eosinophilic cytoplasm vacuolated or finely granular nuclear show mild atypia that is not recoverable, as observed in this case[20]. The diagnostic difficulty in aspiration of breast lesions in children is due to the rarity of carcinoma in this age group and the possibility of epithelial or fibroepithelial proliferation with lush as papilloma and juvenile fibroadenoma.

Conclusions

Although breast cancer is extremely rare in children, history of a painless, enlarging, firm breast mass should raise concern about possible neoplastic disease.

SBC is a rare slow-growing tumor best treated surgically. There are insufficient data to support the use of adjuvant radiation or chemotherapy. Its association with the ETV6-NTRK3 fusion gene gives some clues for the better understanding of this neoplasm and specific therapies.

References

1. McDivitt RW, Stewart FW. Breast carcinoma in children. JAMA. 1966;195(5):1446. DOI: 10.1001/jama.195.5.388.
2. Tavassoli FA, Norris HJ. Secretory carcinoma of the breast. Cancer. 1980;45(9):2404-13.
3. Tognon C, Knezevich SR, Huntsman D, Roskelley CD, Melnyk N, Mathers JA, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell. 2002;2(5):367-76. DOI: 10.1016/S1535-6108(02)00180-0.
4. Arce C, Cortes-Padilla D, Huntsman DG, Miller MA, Dueñnas-Gonzalez A, Alvarado A, et al. Secretory carcinoma of the breast containing the ETV6-NTRK3 fusion gene in a male: case report and review of the literature. World J Surg Oncol. 2005;3:35. DOI: 10.1186/1477-7819-3-35.
5. Rivera-Hueto F, Hevia-Vazquez A, Utrilla-Alcolea JC, Galera-Davidson H. Long-term prognosis of teenagers with breast câncer. Int J Surg Pathol. 2002;10(4):273-8.
6. Aceto GM, Solano AE, Neuman MI, Veschi S, Morgano A, Malatesta S. High-risk human papilloma infection, tumor pathophenotypes, and BRCA 1/2 and TP53 status in juvenile breast cancer. Breast Cancer Res Treat. 2009;122(3):671-83. DOI: 10.1007s10549-0596-6.
7. Page DL, Anderson TJ. Uncommon types of invasive carcinoma. In: Diagnostic histopathology of the breast. New York: Churchill Livingstone; 1987. p. 236-9.
8. Diallo R, Schaefer KL, Bankfalvi A, Decker T, Ruhnke M, Wulfing P. Secretory carcinoma of the breast: a distinct variant of invasive ductal carcinoma assessed by comparative genomic hybridization and immunohistochemistry. Hum Pathol. 2003;34(12):1299-305. DOI: 10.1016/S0046-8177(03)00423-4.
9. Lamovec J, Bracko M. Secretory carcinoma of the breast: light microscopical, immunohistochemical and flow cytometric study. Mod Pathol. 1994;7(4):475-9.
10. Botta G, Fessia L, Ghiringello B. Juvenile milk protein secreting carcinoma. Virchows Arch A. Pathol Anat Histopathol. 1982;395(2):145-52. DOI: 10.1007/BF00429608.
11. Karl SR, Ballantine TVN, Zaino R. Juvenile secretory carcinoma of the breast. J Pediatr Surg. 1985;20(4):368-71.
12. Herz H, Goldstein D. Metastasis secretory breast cancer. Non-responsiveness to chemotherapy: case report and review of the literature. Ann Oncol. 2000;11(10):1343-7. DOI: 10.1023/A:1008387800525.
13. Vieni S, Cabibi D, Cipolla C, Fricano S, Graceffa G, Latteri MA. Secretory breast carcinoma with metastatic sentinel lymph node. World J Surg Oncol. 2006;4:88.
14. Akhtar M, Robinson C, Ashraf M, Godwin JT. Secretory carcinoma of the breast in adults: light and electron microscopic study of three cases with review of literature. Cancer. 1983;51(12):2245-54.
15. Euhus DM, Timmons CF, Tomlinson GE. ETV6-NTRK3 – Trking the primary event in human secretory breast cancer. Cancer Cell. 2002;2(5):347-8. DOI: 10.1016/S1535-6108(02)00184-8.
16. Longo OA, Mosto A, Moran JC, Mosto J, Rives LE, Sobral F. Breast Carcinoma in childhood and adolescence: case report and review of the literature. Breast J. 1999;5(1):65-9.
17. Bond SJ, Buchino JJ, Nagaraj HS, McMasters KM. Sentinel lymph node biopsy in juvenile secretory carcinoma. J Pediatr Surg. 2004;39(1):120-1.
18. Chung EM, Cube R, Hall GJ, Gonzalez C, Stocker JT, Glassman LM. Breast masses in children and adolescent: radiologic pathologic correlation. Radiographics. 2009;29(3):907-31.
19. Buchino JJ, Moore GD, Bond SJ. Secretory carcinoma in a 9-year-old girl. Cytopathol. 2004;31(6):430-1.
20. Gouveia AMF, Lopes JM, Pimenta APA. Carcinoma secretor da mama no adulto: existem parâmetros bem definidos para decisão terapêutica? Acta Cir Bras. 2002;17(2):135-42.