

## A Case of Secretory Carcinoma in a Patient With a History of Contralateral Medullary Carcinoma

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**Abstract.** *Background: Secretory and medullary carcinomas of the breast are rare subtypes of infiltrating ductal carcinoma. The different histological behavior of medullary and secretory carcinomas is correlated with different imaging features on mammography, ultrasound, and magnetic resonance imaging. Case Report: We report the case of a Caucasian woman in which both subtypes of tumors were diagnosed in an 8-year time interval and evaluate, in antithesis, histopathological and imaging aspects of medullary and secretory carcinoma. Conclusion: To our knowledge, this is the first case reported in literature of secretory carcinoma with a complete imaging tumor evaluation in a patient with a previous contralateral medullary cancer.*

Breast cancer represents the most common tumor, except for skin cancers, and the first cause of death in women worldwide (1). Among invasive cancer, medullary and secretory carcinomas are rare subtypes, accounting for less than 5% and 0.15% of invasive breast cancer cases, respectively (1, 2).

Rindolfi *et al.* described medullary carcinoma for the first time in 1977 as a tumor characterized by specific histological

malignant features (3). However, it has a favorable prognosis compared with invasive ductal carcinoma, with 5-year overall survival rate of 98.1% (4). For its clinical and radiological behavior, medullary carcinoma may be underestimated and confused with a benign lesion.

Secretory carcinoma was initially called juvenile breast carcinoma by McDivitt and Stewart in 1966 (5), as they reported only seven cases in young children, but in a more recent review, Tavassoli and Norris (6) also recognized this subtype in adults and decided to rename it secretory carcinoma on account of its histological characteristics. The fusion gene ETS variant transcription factor 6 (*ETV6*)–neurotrophic receptor tyrosine kinase 3 (*NTRK3*), resulting from a balanced translocation t (12;15) (p13; q25), is responsible for the origin of secretory carcinoma (2, 7). Three morphological histological patterns are seen in different combinations: Microcystic, solid, and tubular (2). Most patients present with early-stage disease and, even if nodal involvement is diagnosed in almost 30% of cases, it is associated with good long-term survival (2, 7). The breast imaging characteristics are non-specific and can mimic benign breast lesions (2, 8, 9).

Although both tumor types are rare entities, for medullary carcinoma, several works and some reviews exist in literature, while for secretory carcinoma, only some case reports are published. Our aim was to describe the case of a Caucasian woman in which both subtypes of tumors were diagnosed within an 8-year interval and evaluate, in antithesis, histopathology and imaging aspects of medullary and secretory carcinoma.

### Case Report

A 54-year-old Caucasian woman was referred to our Department for assessment of a palpable lump in her right

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breast. She had a significant family history for breast cancer: her grandmother, cousin and sister underwent surgery for breast cancer, the latter presenting breast cancer gene 1 (*BRCA1*) mutation.

In May 2013, the patient was diagnosed with left medullary breast cancer by core biopsy. At our Breast Unit, she underwent quadrantectomy and sentinel lymph node excision (negative for metastases), followed by adjuvant breast radiotherapy and chemotherapy. We show the details of local-staging magnetic resonance imaging (MRI) examination in Figure 1.

At definitive histopathological analysis, pleomorphic and nucleated cells were present, arranged in cord and sheets, there was a marked inflammatory lymphoplasmacytic infiltrate, numerous areas of necrosis and an elevated mitotic index ( $>20$  mitoses/mm<sup>2</sup>). There was no evidence of tumor infiltration, neither vascular nor capsular, and the tumor immunohistochemistry was negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) and Ki67 (60%).

In March 2021, the patient returned to our hospital for a first level evaluation of a new lump in the right breast. Mammography, with 3D acquisition, displayed a solid mass with no-circumscribed margins, localized in the superior outer quadrant of right breast, without associated atypical microcalcifications (Figure 2).

The breast sonogram showed a 24×3 mm solid irregularly-shaped hypoechoic mass, with poor intralesional vascularization on Doppler study and right axillary lymph node with focal cortical thickening (3 mm) (Figure 2).

The lesion was classified as Breast Imaging Reporting and Data System category (BI-RADS) 5 and was characterized by ultrasound guided biopsy using 14-gauge needle.

The histopathological analysis demonstrated a secretory breast carcinoma. Microscopically, the neoplasm presented as an intraductal neoplasm with tumor cells showing glands and microcystic spaces filled with abundant pale secretions. The cells presented small, round low-grade nuclei (grade 1-2) with poor inflammatory lymphoplasmacytic infiltrate. Immunohistochemistry was negative for ER, weakly positive for PR (5%) and Ki67 (15%), and negative for HER2 (Hercrptest). The tumor also stained positiveIy for SRY-box transcription factor 10 (SOX10) and epithelial membrane antigen, and weakly focally positive for CD117. There was no perineural or vascular invasion (Figure 2).

For a complete pre-surgery evaluation, a local-staging MRI was performed: On pre-contrast sequences, the lesion appeared hypointense on T1-weighted images and intermediately hyperintense on T2-weighted images, presented no restricted diffusion and, after contrast medium administration, displayed early and intense enhancement (Figure 3).

## Discussion

*Imaging findings. Mammography:* The most common pattern for both medullary and secretory subtype is represented by solid mass with round/oval shape and of equal or high density compared to the surrounding breast tissue (1, 8-10). They may present smooth or irregular borders and medullary carcinoma in particular may exhibit non-circumscribed margins (lobulated, obscured, spiculated or indistinct) due to lymphoplasmacytic reaction on the mass periphery which can obscure them. Focal architectural distortion is extremely rare and microcalcifications are not characteristic of these subtypes; sometimes a partial or complete halo sign is visible (1, 2, 8-10).

*Ultrasound:* The two carcinoma subtypes may present benign imaging features, appearing as oval or round lesions with well-defined margins, although both may likewise present an irregular shape and non-circumscribed margin (1, 2, 8-10). Mun *et al.* investigated the sonographic features of secretory carcinoma in their work, reviewing imaging studies of six patients with diagnosis of this uncommon carcinoma and reported that four cases presented microlobulated margins and two cases well-circumscribed margins (8).

Both subtypes exhibit hypoechoic appearance, especially medullary carcinoma due to the extremely packed cellularity (1, 8-10). The lesions are usually homogeneous but can also be heterogeneous, in particular, secretory carcinoma may have cystic portions (1, 2, 9).

Secretory carcinoma can also be associated with ductalectasia or radiological features which mimic intraductal papillary lesions (8, 9).

*MRI:* MRI is employed to determine the true extensions of a lesion and characterize peripheral tumor tissue, guiding surgical management. Medullary carcinoma presents low signal intensity on both T2-weighted and T2-weighted fat-saturated sequences and is sometimes associated with a hypointense rim, corresponding to a fibrous capsular component. Occasionally, on T2-weighted fat-saturated sequence, it can appear slightly hyperintense for hemorrhage or edematous stroma presence (1). It shows an increased signal on diffusion-weighted imaging and low apparent diffusion coefficient values (1).

To the best of our knowledge, in literature, MRI findings of only few cases of secretory carcinoma are reported. It appears as a relatively well-defined mass, sometimes heterogeneous for the coexistence of solid and necrotic/cystic components: the solid portion appears hypointense on T1- and T2-weighted sequences, in contrast, the necrotic/cystic portion is a hyperintense area on T2-weighted imaging and with intermediate signal on T1-weighted imaging due to associated hemorrhagic components (9). Secretory carcinoma behavior in diffusion-weighted sequences is not reported in literature.

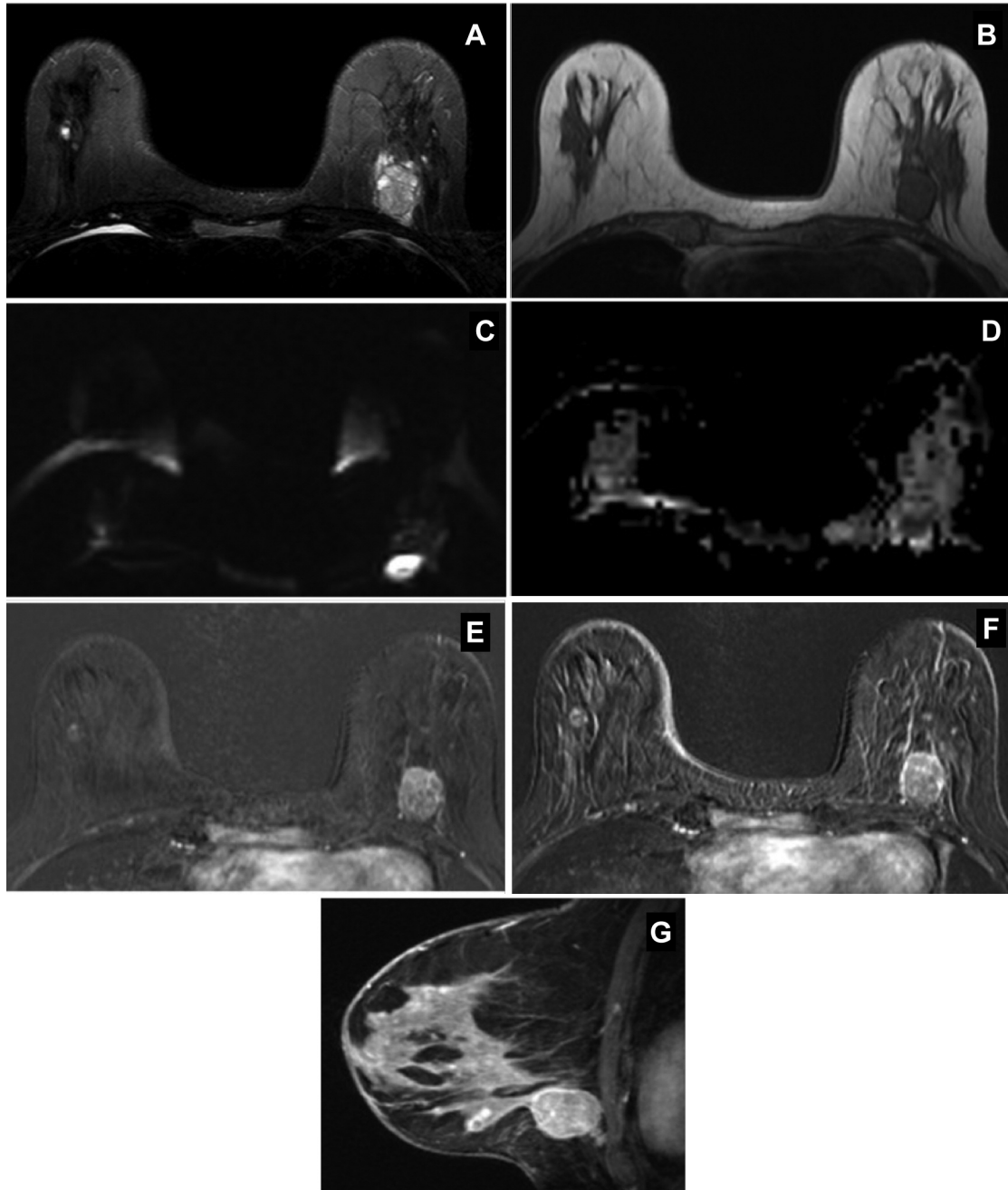


Figure 1. Magnetic resonance imaging findings. A, B: T2- And T1-weighted imaging sequences showing the left breast lesion: intermediate hyperintense on T2-weighted imaging and hypointense on T1-weighted. C, D: Diffusion-weighted imaging demonstrates increased signal and reduced apparent diffusion coefficient values (aliasing artifacts in C). E, F: Early and heterogeneous enhancement of the tumor after contrast medium administration. G: The sagittal image displays an uncertain cleavage plane between the lesion and the pectoral muscle.

After contrast medium administration, medullary carcinoma often presents mass-like enhancement, it may demonstrate homogeneous or heterogeneous enhancement depending on the presence of necrosis or cystic degeneration (1). All

medullary tumors exhibit rim enhancement during the delayed phase due to marginal lymphoplasmacytic reaction, inflammatory changes or peripheral breast tissue compression (1). While heterogeneous enhancement is typical of secretory

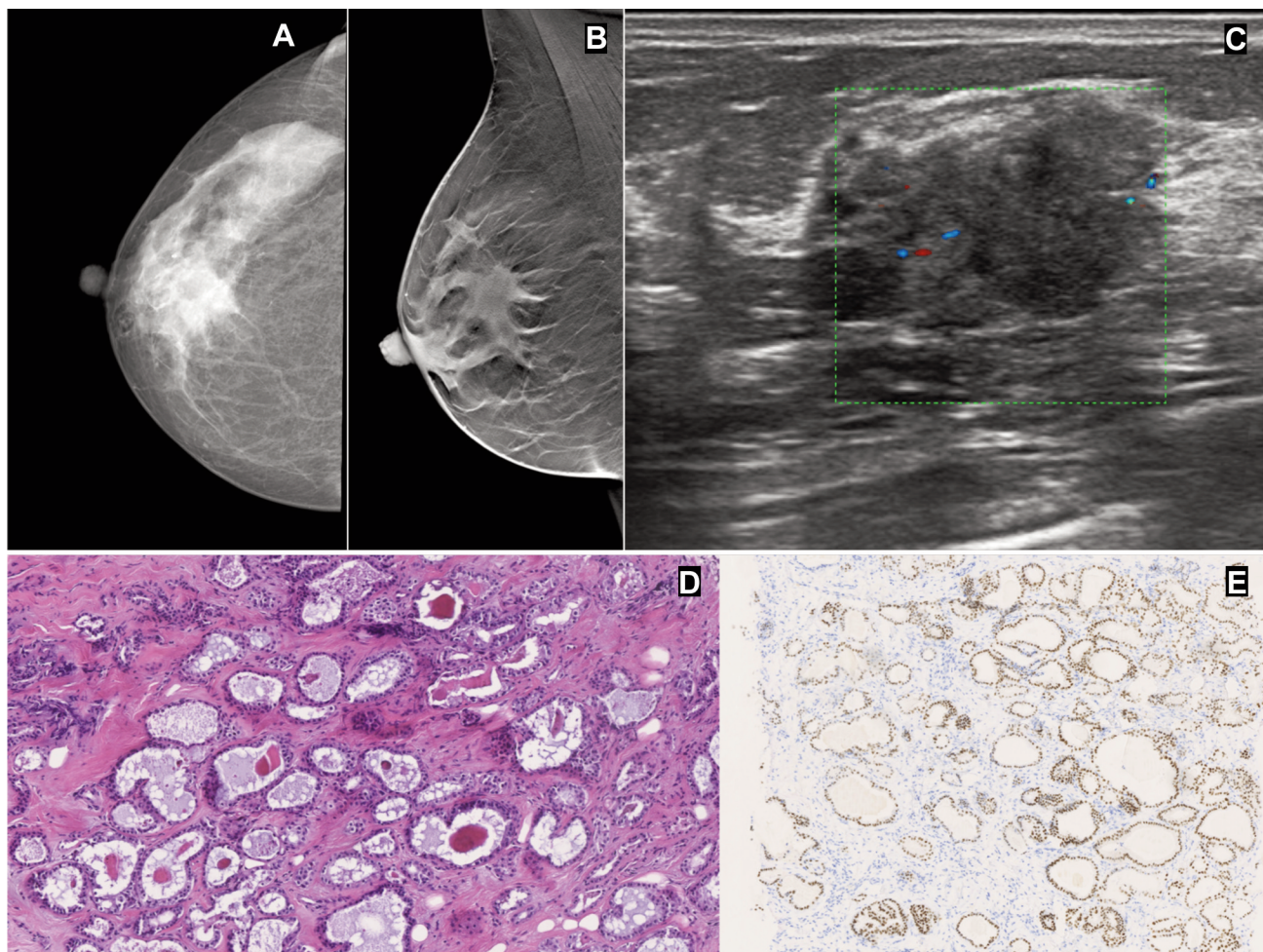


Figure 2. A: Craniocaudal mammographic views of the right breast showing hyperdense not-circumscribed mass without suspicious microcalcifications. B: 3D oblique acquisition highlighting the presence of the lesion. C: Ultrasound image showing a 24×3 mm irregularly-shaped hypoechoic solid mass with poor intralesional vascularization. D: Microscopic histological features: The tumor cells were arranged in cystic and microcystic pattern (hematoxylin and eosin, ×10). E: Immunohistochemistry showing positivity for SRY-Box transcription factor 10 (×6).

subtype, as a result of its mixed conformation, sometimes a rim enhancement may be noted (9).

Both tumor types may show similar MRI contrast medium kinetics, with a rapid uptake and reduction in enhancement in the delay phase of the study (type III curve), but medullary tumor may also present a type II intensity–time curve (1, 9).

**Pathological findings.** Medullary carcinoma is well circumscribed and moderately firm. The cut surface is fleshy and gray-tan and may appear lobular or nodular (4). Foci of hemorrhage, necrosis and even cystic degeneration are not unusual. These tumors tend to be smaller than 3 cm, with a median size ranging from 2 to 3 cm (4).

It has well-defined pushing borders, high-grade cytology with pleomorphic and vesicular nuclei, numerous mitoses

and a syncytial growth pattern (at least 75%) (11). Tubule formation and *in situ* components are not seen. A prominent tumoral lymphocytic infiltrate is often present (11).

At the molecular level, these tumors are grouped with basal tumors, showing lack of expression of ER and PR expression and HER2/neu genes and they variably express basal markers such as cytokeratin 5/6 (CK5/6), CK14 and p53 (8). However, weak hormone receptor expression also occurs (11).

Medullary carcinoma should meet all of the following five morphological criteria as defined by the World Health Organization 2012 classification (12): Syncytial growth pattern in more than 75% of the tumor; no glandular or tubular structures; moderate to marked diffuse lymphoplasmacytic infiltrate in the stroma moderate to marked nuclear pleomorphism; complete histological circumscription.

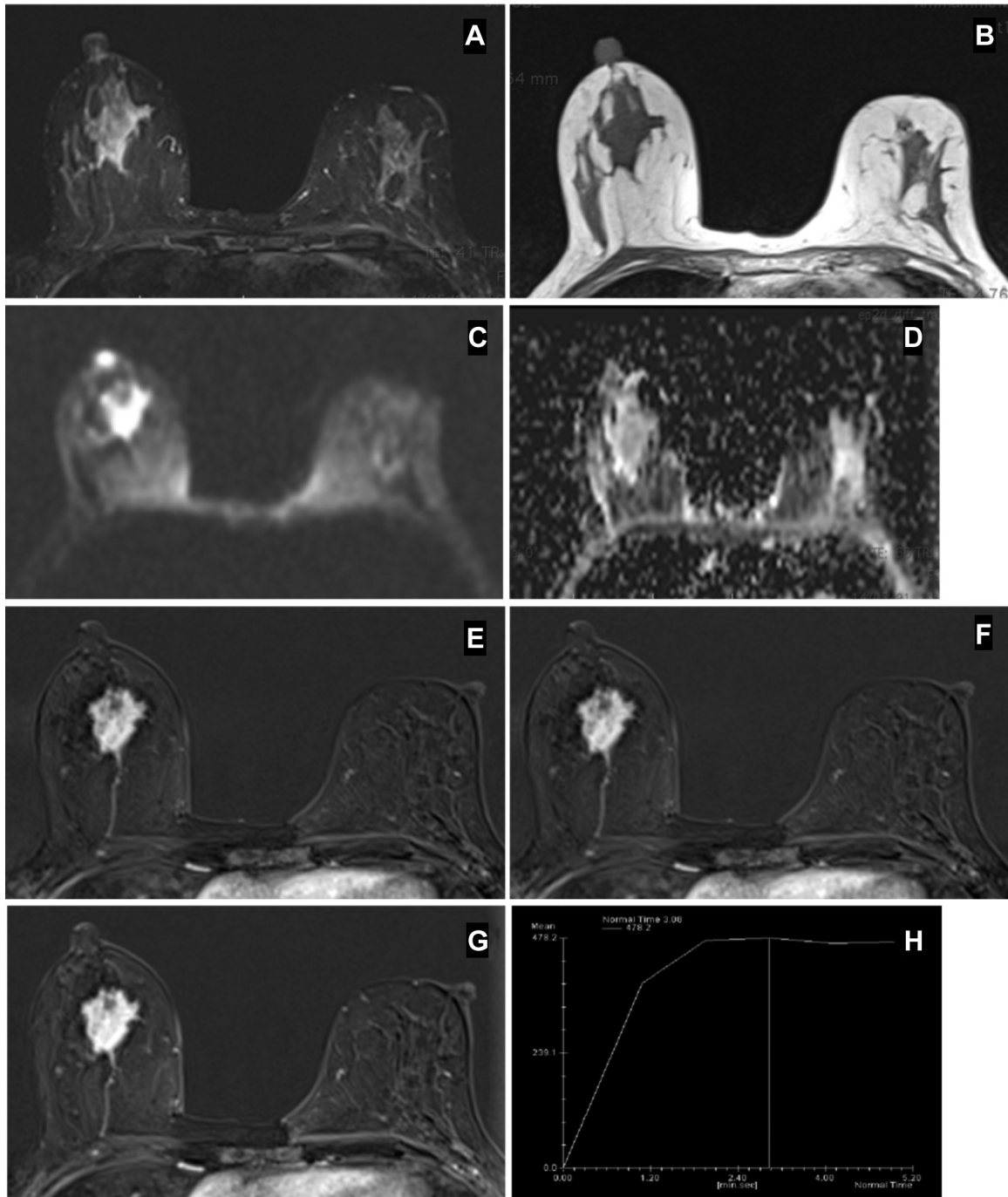


Figure 3. Magnetic resonance imaging findings. A, B: Short tau inversion recovery and T1-weighted imaging sequences revealing the right breast lesion: Intermediate hyperintense on T2-weighted imaging and hypointense on T1-weighted. Left quadrantectomy outcomes are shown. C, D: The lesion did not restrict diffusion. E-G: After administration of contrast medium, the lesion presented early and intense enhancement. H: The lesion showed a type II signal intensity/time curve.

Secretary carcinoma is generally a well-circumscribed and non-capsulated lesion, and tends to be smaller than 2 cm (13). This tumor type is composed of polygonal tumor cells with eosinophilic granular or vacuolated cytoplasm and round to

oval nuclei arranged in microcystic/honeycomb, solid, tubular, or papillary growth patterns (13). Intracytoplasmic and extracellular eosinophilic or amphophilic secretions are consistently present and stain positively with periodic acid–

Schiff, mucicarmine and Alcian blue, and are diastase-resistant (13).

Immunohistochemically, the tumor usually shows strong reactivity for S-100 and SOX10, and is negative for ER, PR and HER2 (14).

In conclusion, breast secretory carcinoma is a very rare entity characterized by pathognomonic histological findings. To our knowledge this is the first case reported in literature of secretory carcinoma with a complete imaging tumor evaluation in a patient with a previous contralateral medullary cancer, another rare but prognostically favorable tumor.

### Conflicts of Interest

All Authors declare no conflicts of interest.

### Authors' Contributions

Rita Stefanucci: Study concepts and design, article preparation. Domiziana Santucci: guarantor of integrity of the entire study, study concepts and design. Silvia Maria Rossi: Article preparation. Matteo Sammarra: Literature research. Eliodoro Faiella: article editing. Ermanno Cordelli: Statistical analysis. Vittorio Altomare: Supervision. Rosario Francesco Grasso: Supervision. Bruno Beomonte Zobel: Supervision.

### References

- Pintican R, Duma M, Chiorean A, Fetica B, Badan M, Bura V, Szep M, Feier D and Dudea S: Mucinous versus medullary breast carcinoma: mammography, ultrasound, and MRI findings. *Clin Radiol* 75(7): 483-496, 2020. PMID: 32057415. DOI: 10.1016/j.crad.2019.12.024
- Pohlodek K, Mečiarová I, Grossmann P, Martínek P and Kinkor Z: Secretory carcinoma of the breast: A case report. *Int J Surg Case Rep* 56: 74-77, 2019. PMID: 30852371. DOI: 10.1016/j.ijscr.2019.02.029
- Ridolfi RL, Rosen PP, Port A, Kinne D and Miké V: Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. *Cancer* 40(4): 1365-1385, 1977. PMID: 907958. DOI: 10.1002/1097-0142(197710)40:4<1365::aid-cnrcr2820400402>3.0.co;2-n
- Zangouri V MD, Akrami M MD, Tahmasebi S MD, Talei A MD and Ghaeini Hesarooeih A MD: Medullary Breast Carcinoma and Invasive Ductal Carcinoma: A Review Study. *Iran J Med Sci* 43(4): 365-371, 2018. PMID: 30046204.
- McDivitt RW and Stewart FW: Breast carcinoma in children. *JAMA* 195(5): 388-390, 1966. PMID: 4285563.
- Tavassoli FA and Norris HJ: Secretory carcinoma of the breast. *Cancer* 45(9): 2404-2413, 1980. PMID: 6445777. DOI: 10.1002/1097-0142(19800501)45:9<2404::aid-cnrcr2820450928>3.0.co;2-8
- Horowitz DP, Sharma CS, Connolly E, Gidea-Addeo D and Deutsch I: Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. *Breast* 21(3): 350-353, 2012. PMID: 22494666. DOI: 10.1016/j.breast.2012.02.013
- Mun SH, Ko EY, Han BK, Shin JH, Kim SJ and Cho EY: Secretory carcinoma of the breast: sonographic features. *J Ultrasound Med* 27(6): 947-954, 2008. PMID: 18499854. DOI: 10.7863/jum.2008.27.6.947
- Shin S, Kim H, Kim W, Lee H, Kim W, Park J and Kim D: Secretory breast carcinoma: A case report with MRI findings. *Journal of the Korean Society of Radiology* 80(4): 798, 2020. DOI: 10.3348/jksr.2019.80.4.798
- Meyer JE, Amin E, Lindfors KK, Lipman JC, Stomper PC and Genest D: Medullary carcinoma of the breast: mammographic and US appearance. *Radiology* 170(1 Pt 1): 79-82, 1989. PMID: 2642350. DOI: 10.1148/radiology.170.1.2642350
- Bandyopadhyay S, Bluth MH and Ali-Fehmi R: Breast carcinoma: Updates in molecular profiling 2018. *Clin Lab Med* 38(2): 401-420, 2018. PMID: 29776638. DOI: 10.1016/j.cl.2018.02.006
- WHO Classification of Tumors 5th Edition, Volume 2: Breast Tumors – IARC. Available at: <https://www.iarc.who.int/news-events/who-classification-of-tumors-5th-edition-volume-2-breast-tumors> [Last accessed June 4th, 2021]
- Arce C, Cortes-Padilla D, Huntsman DG, Miller MA, Dueñas-Gonzalez A, Alvarado A, Pérez V, Gallardo-Rincón D and Lara-Medina F: 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* 3: 35, 2005. PMID: 15963235. DOI: 10.1186/1477-7819-3-35
- Diallo R, Schaefer KL, Bankfalvi A, Decker T, Ruhnke M, Wülfing P, Jackisch C, Luttes J, Sorensen PH, Singh M and Poremba C: Secretory carcinoma of the breast: a distinct variant of invasive ductal carcinoma assessed by comparative genomic hybridization and immunohistochemistry. *Hum Pathol* 34(12): 1299-1305, 2003. PMID: 14691916. DOI: 10.1016/s0046-8177(03)00423-4

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