



Advancement of secretory breast carcinoma: a narrative review

Ningning Min^{1,2}, Jingjin Zhu^{1,2}, Mei Liu³, Xiru Li²

¹School of Medicine, Nankai University, Tianjin, China; ²Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing, China; ³Department of Pathology, The First Medical Center of Chinese PLA General Hospital, Beijing, China

Contributions: (I) Conception and design: N Min; (II) Administrative support: X Li, M Liu; (III) Provision of study materials or patients: N Min; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mei Liu. Department of Pathology, The First Medical Center of Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China. Email: liumei301@126.com; Xiru Li. Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China. Email: 2468li@sina.com.

Background and Objective: Secretory breast carcinoma (SBC) is a rare breast malignancy. Most available studies on SBC are case reports or small case series, and the few large-sample studies available lack critical information due to database limitations. To improve the understanding of SBC and provide a reference for clinical practice, we systematically reviewed the demographic, clinical, pathologic, and genetic characteristics of SBC, as well as its treatment and prognosis.

Methods: We conducted a PubMed search with the keywords “secretory breast carcinoma” or “juvenile breast carcinoma”. Relevant English-language publications published from January 1966 to February 2022 were screened manually at 3 levels—title, abstract, and full text—to identify the articles that presented the demographic, clinical, pathologic, and genetic characteristics of SBC, as well as its treatment and prognosis.

Key Content and Findings: SBC lacks specific clinical manifestations and has typical pathological and molecular characteristics, including intracellular and extracellular eosinophilic secretions, immune spectrum similar to hormone receptor-positive tumors, and the *ETV6-NTRK3* fusion gene. Surgery remains the primary treatment for SBC. Postoperative radiotherapy is recommended by most researchers for adult SBC but not for pediatric patients. The evidence of chemotherapy and endocrine therapy is insufficient, and targeted therapy of the *ETV6-NTRK3* fusion gene shows a good response. Most patients with SBC have a good prognosis except for a few patients who experience distant metastases. Future studies will be focused on the molecular characteristics of those patients with SBC who have a poor prognosis.

Conclusions: The development of histopathology and molecular genetics has promoted the progress of the clinical diagnosis of SBC. The purpose of this review is to serve as a guide for the better clinical treatment of SBC, particularly in the areas of disease identification and prognosis classification for patients.

Keywords: Secretory breast carcinoma (SBC); demography; clinical manifestation; histopathology and genetics; treatment and prognosis

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Introduction

Secretory breast carcinoma (SBC) is a rare malignant neoplasm of the breast, accounting for less than 0.15% of all infiltrating breast carcinomas (1). It has characteristic histopathological and molecular features, a distinctive

genetic translocation, and a favorable prognosis. Reports have shown that SBC is the main subtype of breast cancer in children and young people under 20 years old (2,3). It was named juvenile breast carcinoma originally because the first reported cases occurred in children and adolescents (4). Subsequent studies found that this unique subtype of

Table 1 Search strategies of this study

Items	Specification
Date of search	February 20, 2022
Databases searched	PubMed
Search terms used	“Secretory breast carcinoma”, “Juvenile breast carcinoma”
Timeframe	From 1966 to 2022
Inclusion and exclusion criteria	Inclusion criteria: papers mentioning or reporting demographic, clinical, pathologic, or genetic characteristics of SBC, and/or the treatment and prognosis of SBC Exclusion criteria: non-English language papers
Selection process	The selection was conducted by 2 authors independently and was discussed with the other 2 authors in the case of any disagreements

SBC, secretory breast carcinoma.

breast cancer also occurred in adults and has characteristic histomorphologic features such as intracellular and extracellular, eosinophilic, and periodic acid-Schiff (PAS) staining-positive secretion. As a result, it was renamed SBC (5). It was classified as an exceptionally rare tumor type and variant according to the World Health Organization (WHO) classification of breast tumors, fourth edition (6). The majority of the literature indicates that SBC is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), but positive for basal-cell markers; therefore, it has been classified as a specific subtype of triple-negative breast cancer (TNBC). However, recent large-sample studies have concluded that SBC mimics the immune characteristics of hormone receptor-positive cancer rather than TNBC. In 2002, SBC was first reported to harbor the following recurrent balanced chromosomal translocation: t(12;15)(p13; q25); this translocation leads to the formation of the *ETV6-NTRK3* fusion gene (7). Targeting the *ETV6-NTRK3* fusion gene and the downstream signaling pathway has become a major focus of current studies. At present, surgery is considered the mainstay of treatment for SBC and can include wide local excision, simple mastectomy, and modified radical mastectomy. There is no reliable evidence concerning the efficacy of chemotherapy or endocrine therapy for SBC. Most available studies on SBC are case reports or small case series, and a few large-sample studies lack genomics data. This review focuses on the demographic characteristics, clinical manifestations, histopathological and genetic characteristics, treatment, and prognosis of SBC to provide a reference for clinical practice and contribute to

greater accuracy in diagnosis and treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2491/rc>).

Methods

A PubMed search using the search terms “secretory breast carcinoma” OR “juvenile breast carcinoma” was conducted with no restriction on the article type. To identify the articles that presented the demographic, clinical, pathologic, and genetic characteristics, and/or the treatment and prognosis of SBC, relevant English-language publications published from January 1966 to February 2022 were screened manually at 3 levels: titles, abstracts, and full texts. References from the searched articles and other supplementary articles were also studied. The final database search was conducted on June 14, 2022 (Table 1).

Demographic characteristics

It is possible for SBC to occur at any age, regardless of gender. According to the retrospective analyses from Gong *et al.* (8) and Jacob *et al.* (9) [incorporating 190 patients with SBC in the Survival, Epidemiology, and End Results (SEER) database and 246 patients with SBC in the National Cancer Database (NCDB), respectively], the median age at diagnosis is 56 years (range, 2 to 96 years), the average age at diagnosis is 56 years (range, 18 to 89 years), and the male to female ratio is 1:30 to 1:31. However, previous literature reported a median age at diagnosis of 25 years

(range, 3 to 83 years), and a male to female ratio of 1:6 (10). The discrepancy between different studies was considered to result from the scattered sample sources in the literature review. Due to the particularity of male breast cancer, Ghilli *et al.* (11) performed a pooled analysis of 32 male patients with SBC reported in the literature, in which the average age at diagnosis was 19 years (range, 3 to 79 years), with 34.4% diagnosed under the age of 14 years and 12.5% between the age of 15 and 18. Moreover, only 13.16% of all patients with SBC were diagnosed below the age of 30 years in the SEER database and 37.0% were diagnosed under the age of 50 years in the NCDB. Therefore, we can speculate that male SBC is more likely to occur at a younger age than is female SBC. Notably, in the small series composed exclusively of pediatric and adolescent patients, males also were the majority among pediatric patients with predominantly low-grade and early-stage tumors (12).

Interestingly, the incidence of SBC has been declining in recent decades, which may be related to the reduction of the misdiagnosis rate resulting from the enhanced understanding of SBC and the improvement of diagnostic technology (8).

Clinical manifestations

The typical clinical presentation of SBC is a slow-growing, painless, well-circumscribed, mobile palpable mass. The tumor size of female SBC ranges from 0.5 to 16 cm but is usually between 1.5 to 3.0 cm and tends to be larger in adults (10,13). Most of the cases are solitary, but multicentric cases have been reported (13). In adults, the tumor is more common in the outer upper quadrants (8,14), and in pediatric patients, case reports have usually described the location as subareolar (11,15). This may be related to the relatively small size of the breast mound deep in the nipple-areola complex (NAC) in younger patients. Nipple discharge may occur in some subareolar tumors (16). Several patients with *in situ* SBC have primarily shown nipple or areola mass and bloody nipple discharge (17). Consistently, SBC shows indolent biological behavior. The percentage of regional lymph node metastasis among female SBC has been reported to be 29.29% (8) or 32.0% (9), and can reach 45.8% in male SBC (18). Patients with more than 4 metastatic lymph nodes are rare (19). It is also uncommon for lymph node metaplasia to occur in children and adolescents and patients with tumors smaller than 2 cm (5,8,20). However, there has been 1 report of anterior lymph node metastasis in a 6-year-old patient with SBC (13).

The imaging features of SBC are similar to those of other well-defined benign breast tumors (2,21-23). In contrast to invasive ductal carcinoma (IDC), on mammography, SBC has a variety of nonspecific features, ranging from discontinuous, lobulated, isolated, benign-looking masses with smooth or irregular edges to suspicious asymmetric densities with speculated margins, but rarely microcalcifications (11). Since young female breast glands are dense, mammography examination has limited diagnostic value, with an overall misdiagnosis rate of 29.6% (24). Compared with mammography examination, ultrasonography plays a more important role in the diagnosis of SBC, showing a confined, well-defined isoechoic or hypoechoic mass with occasional internal heterogeneous echogenicity and lobulated margins. However, it is still difficult to distinguish SBC from other benign lesions using ultrasonography, with the misdiagnosis rate being as high as 22.2% (24).

In pediatric patients with SBC, it is difficult to obtain reliable images of breast masses because the diagnostic methods routinely used in adults are not as effective in children. Since other breast examinations used in adults may expose children to radiation or yield poor quality images, ultrasonography remains the main examination for pediatric evaluation (25).

Gohara *et al.* (26) first reported a case of pediatric SBC using ultrasonic tissue elastography to evaluate breast mass. The researchers measured the tumor tissue elasticity using tissue elasticity imaging equipment with no manual compression and obtained the color-coded scoring according to the Tsukuba scoring system. The stiff lesion confirmed as SBC by histological examination had a preoperative elasticity score of 4, and conventional ultrasound was classified as Breast Imaging-Reporting and Data System (BI-RADS) category 4. This finding suggests that parameters such as stiffness score on elastography are practical, noninvasive, and objective diagnostic tools for the accurate preoperative diagnosis of breast tumors in children. Breast masses in children with elastography stiffness scores of more than 4 should be referred for invasive diagnostic procedures, such as excisional biopsy or fine-needle aspiration. Ultrasound elastography, called E-mode ultrasound after A, B, D, and M mode, provides tissue stiffness information with gray-scale or color-coding images to display, locate the lesion, and identify the nature more vividly. According to the Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer Screening and Diagnosis, 2018 Edition (27), adding elastography to

B-mode ultrasound may increase the negative predictive value of diagnostic breast ultrasound in women and reduce the number of false-positive results without missing cancers. Breast elastography is expected to improve the accuracy of diagnostic breast ultrasound and reduce the number of unnecessary biopsies. More clinical data are still needed to support the positive role of elastography in the diagnosis of breast cancer in children.

Histopathological and genetic characteristics

The diagnosis of SBC mainly depends on the pathological examination of masses, including preoperative puncture biopsy and surgical resection biopsy. Preoperative biopsy of adult breast tumors includes fine-needle aspiration cytology and biopsy gun histology, and the latter is more common and plays an important role in the diagnosis of adult SBC. From the pathologists' perspective, preoperative puncture biopsy is also an important diagnostic tool for pediatric patients, especially fine-needle aspiration cytology. However, pediatric patients require general anesthesia or deep sedation to ensure the precise location of the lesion through a fine-needle biopsy. Additionally, fine-needle aspiration for cytological diagnosis is limited by the possibilities that inadequate samples might be obtained or that sampling may damage breast buds and lead to postoperative breast development deformity (25). The application of mass puncture biopsy in the diagnosis of children's tumors is quite limited, and pediatric patients usually receive mass excisional biopsy for definitive histopathological diagnosis (13).

Histopathological characteristics

SBC has typical histopathological features. The tumor mainly presents with multinodular or infiltrative growth with a clear boundary and no peritumoral envelope (9). Several SBCs have been reported as a noninvasive component and were subsequently referred to as SBC *in situ* (28-30). The normal lobular structure and the myoepithelium of invasive SBC are lost in invasive SBC, yet the intact myoepithelial cells can be seen around the cancer nest of SBC *in situ*. In SBC, 3 morphologic patterns can be seen in a variety of combinations with different proportions, including tubular, solid, and microcystic (19). The microcystic pattern consists of small cysts that mimic thyroid follicles, which contain rich eosinophilic secretions. The solid pattern is presented as dense flakes or lumpy

structure, in which the cytoplasm of tumor cells contains eosinophilic particles and secretory vesicles, and a few adenoid cavities containing secretions can also be seen in tumor cell masses. The tubular pattern consists of small tubes with many secretions in the lumen. Moreover, SBC also manifests with papillary morphological characteristics, in which tumor cells are arranged in a papillary pattern with multiple layers of tumor cells and a delicate fibrovascular core within the dilated duct (13,31). Hoda *et al.* (30) and Yang *et al.* (17) found that SBC *in situ* tended to grow in a papillary manner. In addition, similar to other subtypes of ductal carcinoma, SBC often has an associated intraductal component (32).

Tumor cells show minimal atypia and rare mitotic activity and have a round nucleus, clear nucleolus, large volume, and round or polygonal shape. They can be divided into secretory cells with eosinophilic granules in the cytoplasm (type A cells) and secretory cells with transparent vacuoles like cytoplasm (type B cells) and can coexist with different proportions. The strongly eosinophilic mucus secreted by tumor cells can be found in the cytoplasm of individual cells, the lumen of glandular ducts, the solid nest, or the interstitial tissue. The secretions show positive for PAS staining, PAS staining after amylase digestion, and Alcian blue staining, indicating the existence of acidic mucopolysaccharide and mucin components (11), which are similar to milk. Researchers have found that whether the tumor is dominated by type A cells or type B cells has no significance for prognosis (5). According to the NCDB database, SBC is more likely to be well differentiated (SBC: 32%; IDC: 18%; $P < 0.001$) and less likely to be poorly differentiated (SBC: 11%; IDC: 36%; $P < 0.001$) compared with infiltrating ductal carcinoma (IDC) (9).

Ultra-structurally (5), with type A cells as an example, the tumor cells are arranged in well-defined clusters and connected by the interdigitation of cytoplasmic processes and desmosomes. A large number of intracellular and extracellular lumens filled with diffusely dispersed granular material have been observed within neoplastic cell clusters. The size of extracellular lumens is usually several times that of the largest intracellular lumens and communicates with the intercellular spaces. Compared with intracellular secretions, the majority of extracellular secretions show different electron densities. There are obvious electron-dense spherical bodies in the extracellular lumens, but only rarely can dense spherical central components be observed in the intracellular secretions. This may be related to the different concentration ratios of protein and

carbohydrate in the intracellular and extracellular secretory material. A number of microvilli can be seen projecting into the extracellular and intracellular lumens. There are also microvillous cytoplasmic processes around the cell membrane, which are interdigitated with similar processes of adjacent cells and pass through the distinct intercellular space filled with secretions. The clusters of tumor cells are partially surrounded by a clear and continuous basal layer, with no myoepithelial cells being present. Tumor cells often have an empty dilated cistern, and the Golgi apparatus and rough endoplasmic reticulum are prominent in many cells. Lipid droplets can be observed in a few cells, and the nuclei are mainly oval, with occasional distinct nucleoli and indentation.

Immunohistochemical features

There is no consensus concerning the status of ER, PR, and HER2 in relation to SBC. The vast majority of the literature reported SBC to be negative for ER, PR, and HER2, and positive for basal-cell markers, and, therefore, classified SBC as a particular subtype of TNBC (32,33). However, recent large-sample studies have concluded that SBC mimics the immune spectrum of hormone receptor-positive cancer rather than TNBC. According to the SEER database, 58% and 40% of 99 patients with SBC stained positive for ER and PR, respectively (8). Similarly, 64% and 44% of 246 patients with SBC were ER and PR positive in the NCDB database, respectively (9). Li *et al.* (24) also found that 48% and 52% of 44 patients with pure SBC showed positive staining for ER and PR, respectively. Furthermore, 4% to 36.4% of SBC patients were HER2 positive according to these large-sample studies (9,24). Diallo *et al.* (34) also reported a case of SBC with HER2 overexpression. Moreover, multiomics studies indicate that SBC has substantially different genomic and proteomic profiles compared with the landscape of basal-like TNBC (BL-TNBC), which may support distinguishing SBC from BL-TNBC (35). For example, several significantly upregulated metabolic pathways in SBC are one of the significant features of hormone receptor-positive breast cancer, not BL-TNBC. Meanwhile, Garlick *et al.* (15) found that ER status was not significantly correlated with the age and tumor size of SBC patients, but Hoda *et al.* (30) found that ER positivity was more common in adult SBC. Further studies are needed to clarify the status of the hormone receptor and the true expression of HER2 in SBC.

Studies show that SBC exhibits strong positive reactions

to E-cadherin, vimentin, epidermal growth factor receptor (EGFR), c-Kit (CD117), CK5/6, and CK14, indicating that tumor cells may originate from basal cells of the duct, similar to TNBC. However, SBC patients have demonstrated a lower Ki-67 index with an average value of about 10% (range, 1% to 50%) (24), a lower cyclinD1 proliferation rate, and a lower P53 mutation rate, which is consistent with the inert biological behavior of the tumor. Multiple studies have revealed that tumor cells of SBC are strongly positive for S-100 protein, epithelial membrane antigen, and α -lactalbumin. Moreover, myoepithelial markers including α -smooth muscle actin (α -SMA) and calponin have been found to be mostly negative or focally weakly positive in invasive SBC and positive in SBC *in situ* (17). Generally, P63 nuclear staining is used as an effective marker of myoepithelial cells to determine the invasive status of breast cancer (36). Interestingly, Bratthauer *et al.* (37) found that cells with secretory changes or secretory cancer showed strong cytoplasmic reactivity to the P63 antibody and that the concentration of the P63 antibody could also be observed in the extracellular lumen. No similar positive reaction was detected in breast epithelial cells differentiated from parietal plasma cells and breast mucinous carcinoma. Therefore, the deletion of myoepithelial markers such as α -SMA and calponin and the cytoplasmic-positive reaction of the P63 antibody is of great value for the determining the presence of SBC. Additionally, in the research of Krings *et al.* (38), all patients with SBC expressed *MUC4* and *SOX10*, previously described in mammary analogue secretory carcinomas (MASCs) (39,40), suggesting that these 2 markers may provide an additional diagnostic tool valuable for the differential diagnosis of SBC. The validity of *MUC4* and *SOX10* as diagnostic markers of SBC needs to be further verified by large sample studies.

Studies have confirmed that signal transducer and activator of transcription (*STAT*) 5a, known as the mammary growth factor, remains actively expressed in SBC and causes secretory changes in tumors (41). In physiological conditions, *STAT5a* can be activated through a variety of mechanisms, most notably by binding to prolactin receptors in the breast to promote the normal proliferation and differentiation of the breast. It was found that the expression of *STAT5a* decreased in atypical and malignant breast ductal epithelial cells and was negative in ductal carcinoma *in situ* and invasive ductal carcinoma without secretory changes, other cytoplasmic secretory gland metaplasia, and special types of breast cancer, such

as breast mucinous carcinoma and clear cell carcinoma. Consequently, the immunohistochemical (IHC) staining of *STAT5a* may be helpful in distinguishing SBC from other histological types of breast cancer.

Genetic characteristics

SBC is associated with a characteristic chromosomal translocation: t(12;15)(p13;q25). It causes the rearrangement of genes of the E26 transformation-specific translocation variant 6 (*ETV6*) on chromosome 12 and neurotrophic tyrosine receptor kinase 3 (*NTRK3*) on chromosome 15 rearrangement, resulting in an *ETV6-NTRK3* fusion gene, in which the N-terminal helix-loop-helix (HLH) domain of the highly expressed transcription factor *ETV6* is linked to the tyrosine kinase (TRK) domain of the gene *NTRK3* (7). An in-frame fusion between *ETV6* exon 5 and *NTRK3* exon 15 is observed most frequently. Chimeric proteins are affected by ligand-dependent HLH-mediated dimerization and subsequently activate the TRK domain. Activated TRK, then, through the Ras/MAPK and PI3K/Akt signaling pathways, induces the transformation and mitotic activity of fibroblasts and ductal epithelial cells and promotes the proliferation of tumor cells (7,42). Considering that kinase-active *ETV6-JAK2* fusion protein in leukemia subgroup can phosphorylate *STAT5a*, Strauss *et al.* (41) suggested that *ETV6-NTRK3* fusion protein in SBC may also promote *STAT5a* phosphorylation, resulting in the tumor cells having the same secretory phenotype as the breast epithelium during pregnancy.

The *ETV6-NTRK3* fusion gene can also be found in the secretory carcinoma of the parotid gland, salivary gland, sweat gland, lacrimal gland, thyroid, and other organs (43-48). These histologic mimics of secretory carcinoma, also called *MASC*, exhibit histopathological and immunophenotypic features similar to those of SBC. In addition to the typical *ETV6-NTRK3* gene fusion, *MASC* may also harbor several alternative gene fusions involving other kinase-coding genes, such as *ALK*, *MET*, or *RET* (49-53). Previous reports have suggested that *NTRK* fusions are limited to the secretory subtype of breast cancer. However, Maund *et al.* (54) found there to be secretory versus nonsecretory statuses in the *NTRK* fusion-positive cases with breast cancer: the nonsecretory subtype had *NTRK1* fusions in 7 of 11 cases, each with a different fusion partner.

The *ETV6-NTRK3* fusion gene has been observed in 92% of SBCs (11) and has not been observed in other types

of breast cancer (55,56). Consequently, *ETV6-NTRK3* fusion gene tests have become important tools in SBC diagnosis, including fluorescence in situ hybridization (FISH) using an *ETV6* break-apart probe and next-generation sequencing (NGS) technology of DNA or RNA. Nevertheless, molecular testing is limited by a long turnaround time, high expense, and lack of availability in many laboratories. Researchers have attempted to identify the *NTRK* fusion gene by IHC staining. IHC using a pan-TRK antibody, which recognizes a conserved sequence near the C-terminus of TRK proteins, is valuable in identifying *NTRK* rearrangements in various tumor types (57-60). To evaluate the diagnostic value of pan-TRK IHC for SBC, Harrison *et al.* (61) compared the pan-TRK staining results of SBC with those seen in other types of breast carcinoma and histologic mimics of secretory carcinoma. The results confirmed that pan-TRK IHC is a specific and sensitive marker for SBC in the setting of diffuse and at least local strong nuclear staining. It serves as a more cost-effective and rapid test than do *ETV6* FISH or NGS-based assays. Similarly, Carretero-Barrio *et al.* (62) also reported a case with recurrent SBC diagnosed by fine-needle aspiration based on the cytomorphological features and pan-TRK IHC on the cell block, and identified TRK overexpression, as a fusion surrogate, on the cytological sample. Furthermore, Remoué *et al.* (56) found that only 1 of 339 invasive breast carcinomas was positive according to pan-TRK IHC staining and that other nonsecretory carcinomas do not harbor any TRK protein expression, showing negative for pan-TRK IHC. Therefore, a definitive diagnosis can be rendered for most cases based on the pan-TRK staining pattern in combination with the distinctive morphology. Notably, in the research of Zaborowski *et al.* (63), the addition of screening IHC for *NTRK* in patients with TNBC failed to identify any more patients harboring *NTRK* fusion gene rearrangements. *ETV6* FISH is still recommended for cases with no straightforward histomorphology or negative IHC for pan-TRK.

Diallo *et al.* (64) performed array comparative genomic hybridization (aCGH) and observed an average of 2.0 genomic aberrations in each SBC case (range, 0 to 6), with a loss of 22q(2/8) or gain of 1q(2/8) or 8q(3/8), which is significantly lower than that of conventional ductal carcinoma of no specific type, which ranges from 5.4 to 13.8. Similarly, Krings *et al.* (38) conducted capture-based NGS of 510 cancer-related genes on 9 SBCs and 6 *MASCs*. Compared with most breast basal carcinomas, the mutational burden of SBC was very low, and no additional

pathogenic aberrations were identified in genes typically mutated in breast cancer. Even in the cases with axillary lymph node metastasis, SBC still presented simple genomes, low tumor mutation burden, stable microsatellite sites, and single-nucleotide polymorphism (SNP) heterozygous mutation (65). The lack of pathogenic mutations in common cancer-related genes suggests that the *ETV6-NTRK3* fusion gene alone may be sufficient to drive these tumors and likely helps explain their indolent behavior. Del Castillo *et al.* (66) used aCGH and observed that gains of 12p(2/9) and 16(2/9) and deletions of 22(4/9) were the most common genomic aberrations in patients with SBC.

Hoda *et al.* (30) explored the biological characteristics of aggressive clinical courses of SBC and found that aggressive tumors revealed a *TERT* promoter mutation, loss of the 9p21.3 locus, and amplification of the 16p13.3 locus. Mutations of *TERT* promoter have been identified in many organ systems and reported in association with aggressive tumor biology (67,68). The 9p21.3 locus includes *CDKN2A* (*p16INK4A*), *CDKN2A* (*p14ARF*), and *CDKN2B*. Cipriani *et al.* (69) recently reported on the loss of *CDKN2A/B* in a case of dedifferentiated salivary gland mammary analogue secretory carcinomas (MSAC). Shukla *et al.* (70) also observed *TERT* promoter mutation and *CDKN2A* loss in an SBC case with left chest wall recurrence and bilateral lung metastases through whole-genome sequencing (WGS). Amplification of the 16p13.3, which contains *TRAF7*, *TSC2*, *NTHL1*, and 3-phosphoinositide-dependent protein kinase 1 (*PDPK1*), has been shown to be among the most commonly seen in invasive breast cancers (71). Meanwhile, PDK1, the coding protein of *PDPK1*, is a critical component of the PI3K/Akt signaling pathway and plays its carcinogenic role by activating AKT to regulate the downstream pathway. Maurer *et al.* (72) found that the *PDPK1* copy number increase or PDK1 overexpression itself is not carcinogenic but can significantly enhance the ability of upstream lesions (*ERBB2* amplification, *PTEN* loss, or *PIK3CA* mutation) to signal AKT and stimulate cell growth and migration. However, Hoda *et al.* (30) did not observe HER2 overexpression in any SBC cases. In addition, Ghilli *et al.* (11) reported a case of SBC in a boy with 3q28 duplication, whose healthy father and grandfather with breast cancer had the same copy number variation detected. The 3q28 locus contains only 1 gene, *FGF12*, a member of FGF family with cell survival and mitogenic activities, indicating that it may be a potential oncogene. To date, *FGF12* has not been found to be associated with any neoplastic diseases. In a case of

distant metastasis reported by Del Castillo (66), aCGH showed the gains of 5p, 12p, 16whc, and 21whc and the losses of 3p, 5q, 9whc, 13whc, 15whc, 17p, 20p, and 22whc. The number of gene mutations was as high as 13.09, which was significantly higher than that of other patients with SBC with a good prognosis. Further molecular studies are needed to explore the genetic pattern of SBC and identify gene mutations associated with aggressive clinical behavior.

Special histopathological and genetic characteristics

In addition to the above typical changes, Xu *et al.* (73) presented a case of an *ETV6-NTRK3* fusion-positive SBC with sarcomatous dedifferentiation and aggressive clinical behavior. The tumor was composed of a traditional secretory carcinoma component and sarcoma component with predominantly monotonous tumor cells, both of which were positive for the *ETV6-NTRK3* fusion gene. In some areas of the sarcoma component, the tumor cells were arranged in herringbone bundles, with occasional mitotic figures and mild nuclear atypia; in other areas, the tumor cells were larger with plump cytoplasm, oval to round nuclei, brisk mitoses, and syncytial arrangement. In the whole sarcomatous component, a hemangiopericytic vascular pattern including large, gaping vascular spaces was a prominent feature. The sarcoma component lacked the IHC features of classic SBC, with negative S100, E-cadherin, and cytokeratin AE1/AE3 but did have a patchy positive expression of CD34 and a homozygous deletion of *CDKN2A*. The patient received chemotherapy and endocrine therapy after mastectomy and died of multiple metastases 14 months after the first diagnosis. Del Castillo *et al.* (66) also reported a case of distant metastasis with high-grade transformation. The tumor had a solid pattern, scant secretory features, necrotic changes, and vascular involvement. FISH *ETV6* balanced break-apart was observed in 24% of cells and unbalanced break-apart with a gain of oncogenic derivative in 40% of cells.

Differential diagnosis

Since SBC lacks unique clinical characteristics, the current gold standard for final diagnosis is based on histopathologic studies. Pathologists should carefully evaluate the morphological and molecular features of SBC to distinguish it from benign breast changes and other tumors that mimic the histopathologic characteristics of SBC. These characteristics are described in the following sections.

- (I) Active breast, lactating nodules, and secretory adenomas: these are highly proliferative secretory acinar structures and mainly occur during pregnancy or lactation. Microscopically, the lobule structure is complete and closely aggregated with complete myoepithelium and basement membrane, akin to SBC in situ. Different from SBC in situ, their diffuse changes involve the whole breast, with completely bland cell morphology and a lack of complex intraductal structure.
- (II) Lipid-rich carcinoma: tumor cells lack mucus and show a transparent vacuole-like appearance with abundant cytoplasm and obvious cell atypia. The intracellular and extracellular secretions are negative for PAS staining, yet positive for fat special staining.
- (III) Glycogen-rich cancer: tumor cells have clear boundaries, rich cytoplasm, and water-like transparent shape without the characteristics of internal and external secretions or the special staining of secretory cancer cells. The PAS staining can be positive but turn negative after amylase digestion.
- (IV) Mucinous adenocarcinoma: the section of the tumor is jelly-like and has fine intervals. An extracellular mucus lake can be observed alongside a lack of intracellular mucus accumulation, which can be distinguished from SBC in morphology.
- (V) Carcinomas with apocrine differentiation: tumor cells show large atypia and active mitotic activities, and form a gland cavity with small protrusions of spherical apical plasma secretion at the edge. Intracellular particles can be observed with strong PAS staining, but no positive extracellular secretion.
- (VI) Acinar cell carcinoma: the tumor is composed of microglandular, microcystic, and solid structures, with rich cellular components. Tumor cells are rich in granular, amphiphilic to eosinophilic cytoplasm, with high-grade differentiated nuclei. Amylase, lysozyme, α 1-antitrypsin, and S-100 positivity, along with GCDFP15 local positivity and PAS staining positivity, is of great value in diagnosis.
- (VII) Cystic hypersecretory carcinoma (CHC): tumor cells have obvious secretory activity. The milk-like secretory substances are distributed inside and outside the cells, forming dilated ducts and cysts similar to thyroid colloids. Vacuolar staining for adipophilin and positivity for α -lactalbumin, S-100, and lysozyme are diagnostic markers for CHC.

Treatment and prognosis

Treatment

There is no guideline or consensus on the treatment of SBC. At present, surgery is considered the primary treatment, supplemented by radiotherapy, chemotherapy, and targeted drug therapy (74). Treatment regimens are determined by the age of the patient, tumor size, lymph node status, and molecular biology status. For pediatric SBC, most researchers pay special attention to the future development of the breast and recommend local excision of the breast mass, with preservation of the breast buds in prepubertal girls (11,26,75). However, in young children, it is technically difficult to preserve the breast mound at the time of surgery given the small amount of breast tissue and the proximity to the NAC. Furthermore, breast-conserving surgery (BCS) in children with local excision is considered to be associated with a higher chance of local recurrence (76). Therefore, several researchers recommend simple mastectomy over local excision as the first-choice treatment for children (13). For adult SBC, extensive local excision or mastectomy should be chosen depending on the tumor size, location, and lymph node status. Since the size of an SBC tumor can assist in the assessment of axillary lymph node metastasis and axillary lymph node metastasis is less common in tumors <2 cm, some researchers have recommended that BCS should be preferred for tumors <2 cm with clear borders to ensure adequate margins and no suspicion of axillary lymph node metastasis (24). However, the majority of researchers support at least a simple mastectomy for adult SBC (77), and modified radical mastectomy should be performed in patients with tumors >2 cm and positive for sentinel lymph nodes (SLNs) (75). There is still considerable debate about the use of routine axillary lymph node dissection (ALND) in SBC. Distant metastases from SBC are extremely rare, and ALND may carry the risk of postoperative complications, such as pain, seroma, paresthesia, difficulty with shoulder movements, and lymphedema of the upper extremity. Total ALND during mastectomy has been considered overtreatment for SBC (16). However, the involvement of more than 3 lymph nodes may be associated with the risk of distant metastasis and poor prognosis. It is considered necessary to examine lymph node status using SLN biopsy or ALND (15,20,78). For patients positive for SLNs, total ALND should be performed; for patients with more than 3 positive axillary lymph nodes, positron emission tomography, computed tomography, and other examinations should be performed

to evaluate the systemic metastasis (15).

In general, adjuvant radiotherapy after BCS improves locoregional control and disease-specific survival. With the improvement of radiotherapy equipment and technology, adjuvant radiotherapy after BCS is recommended by more doctors. Horowitz *et al.* (20) reviewed 83 patients with SBC from the 2012 SEER database and found that 80% (4/5) of the young cohort (<30 years old) received a simple mastectomy and only 1 patient received adjuvant radiotherapy; meanwhile, 48.7% of the older adult patients (>30 years old) received local excision of the mass and 56% received radiotherapy. Additionally, the use of radiotherapy increased over time. Gong *et al.* (8) reviewed the 190 SBC patients from the 2021 SEER database and found that the breast cancer-specific survival (BCSS) of patients receiving BCS and radiotherapy was significantly better than that of those receiving simple mastectomy ($P=0.014$), yet the overall survival (OS) was comparable in both ($P=0.185$). The difference was considered to relate to the fact that radiotherapy improves the local control but also leads to increased radiation damage to the heart and lungs. Gold *et al.* (79) reported that radiation exposure is most harmful when treating pediatric tumors at the peak of breast development in girls, usually 10–16 years old, among whom about 40% develop breast cancer 20 years later. Radiation in children and adolescents has been associated with lung fibrosis, thoracic asymmetry, impairment of costal growth, and long-term effects on surrounding skin and breast tissue (13,75,80). Therefore, postoperative adjuvant radiotherapy is not recommended for pediatric SBC. Moreover, SBC is not sensitive to multiple chemotherapy regimens. Lombardi *et al.* (81) suggested that this chemoresistance may be associated with mutations acquired during the slow growth of tumor cells. Some researchers have recommended that adjuvant chemotherapy may be suitable for patients with lymph node-positive tumors (82,83). There is a lack of effective evidence to support that adjuvant chemotherapy is beneficial to the long-term survival of patients with SBC, especially in children (83,84). In the retrospective analysis of the NCDB, the results of hormone treatment in patients with SBC and IDC were similar (9). Reliable evidence for hormone therapy for SBC is also not available.

As a novel therapeutic strategy, TRK inhibitor (TKI)-targeted therapy for patients with *NTRK* fusion-positive tumor, including MASCs, congenital mesoblastic nephroma, infantile fibrosarcoma, and many other tumors in different organs, has been shown to be associated with high response rates (85). Larotrectinib and entrectinib are

the first generation of TKIs with nanoscale activity for all 3 TRK protein isomers (TRKA, TRKB, TRKC). Drilon *et al.* (86) reviewed 55 patients with *NTRK* fusion-positive tumors treated with larotrectinib, including MASC of the salivary gland (in 12 patients), infantile fibrosarcoma (in 7), thyroid tumor (in 5), colon tumor (in 4), lung tumor (in 4), melanoma (in 4), gastrointestinal stromal tumor (in 3), and other cancers (in 16). The overall response rate was 80%, and the partial response rate and complete response rate were 62% and 13%, respectively. Shukla *et al.* (70) reported an *ETV6-NTRK3* fusion-positive SBC case successfully treated with larotrectinib. The patient showed a strong clinical response to larotrectinib with sufficient tolerance and no significant adverse drug reactions. Another 2 *ETV6-NTRK3* fusion-positive SBC cases showed a good response to pan-TKI (30). There is currently no report of entrectinib for *ETV6-NTRK3* fusion-positive SBC (23). The first-generation TKIs have so far been known to have two kinds of drug resistance: targeted resistance and off-target resistance, while the second-generation TKIs can overcome the drug resistance of the first generation TKIs (85,86). In addition, Ras inhibitors have also been found to be useful in the clinical treatment of locally advanced SBC patients with the *ETV6-NTRK3* fusion gene (87).

Prognosis

Even if it metastasizes to axillary lymph nodes, SBC is generally considered to be associated with a good prognosis. Horowitz *et al.* (20) and Gong *et al.* (8) retrospectively analyzed the SEER database in 2012 and 2021 and showed that the 5-year BCSS of 83 and 190 patients with SBC was 94.4% and 95.79%, respectively, while the 10-year BCSS was 91.4% and 93.16%, respectively. Both the differences in BCSS ($P=0.018$) and OS ($P<0.001$) among SBC patients were statistically significant between the different age groups, and the prognosis was less favorable with increasing age. However, there was no significant difference in BCSS ($P=0.365$) or OS ($P=0.603$) between the groups with different hormone receptor status (8). Garlick *et al.* (15) and Li *et al.* (24) found no significant association between ER or PR status and distant metastasis or clinical outcome, and there were also no significant differences in OS, axillary lymph node status, or distant metastasis between 44 patients with SBC and 88 patients with IDC. Tavassoli *et al.* (5) reported that a good prognosis for patients with SBC was associated with age at diagnosis <20 years, mass diameter <2 cm, and clear borders, and that in adult

patients, progressive enlargement of the mass with poorly defined borders indicated a risk of disease progression (19). Multicentricity and involvement of more than 3 lymph nodes are also important indicators of poor prognosis (10,74). Male patients seem to have a worse prognosis than do female patients (18,84). Furthermore, Del Castillo *et al.* (66) pointed out that even in accurately diagnosed SBC, tumor-node-metastasis (TNM) stage and histological grade have an important impact on prognosis and treatment management. Except for those with histologically high-grade tumor, patients with SBC usually have a good prognosis.

Local recurrence is relatively common in patients with SBC and has been reported in 33–44% of cases receiving local control such as BCS, usually occurring in the same area of the breast (15,19). Due to the indolent and slow-growing nature of the tumor and the fact that most recurrences arise between 10 and 20 years after the initial appearance, all patients are recommended to have a long-term follow-up of at least 20 years or for life regardless of age (42,88). The risk of SBC spreading to other parts of the body is considered very low. Tumors >2 cm and more than 3 involved axillary lymph nodes can be used as predictors of distant metastasis (15). According to the review of Lian *et al.* (89), 20 cases of SBC with distant metastases have been described over the last 50 years (15,24,30,66,70,83,89–94), with a male to female ratio of 4:11 and an average age of 26 years (range, 8 to 73 years) except for 6 cases with unknown clinical information. Additionally, Tang *et al.* (77) were first to report an SBC case complicated with multiple brain metastases, and the patient eventually died of systemic multiple metastases. More generally, for patients with SBC and distant metastases, the median time between diagnosis and metastasis was 25 months (range, 2.5 to 240 months), with most metastases seen in lung (9 cases), liver (5 cases), and bone (4 cases) (89), and the mean survival time after the initial diagnosis was 74.6 months (range, 6 to 240 months) (77).

Summary

As a rare breast malignancy, SBC is the predominant type of pediatric breast cancer and is characterized by certain histopathological and IHC features. The large-sample studies based on SEER and NCDB databases have challenged the previous view that SBC belongs to a special subtype of TNBC and have demonstrated that the immune spectrum of SBC is closer to that of hormone receptor-positive tumors. Multiomics studies have also identified

genomic and proteomic features of SBC that distinguish it from BL-TNBC. *ETV6-NTRK3* fusion-positive status is a unique molecular feature of SBC. Low mutational burden and a lack of chromosome locus mutations common in other breast cancers indicate the possibility of the *ETV6-NTRK3* fusion gene as a driver of oncogenic programs of SBC. The newly reported pan-TRK IHC staining brings new hope for the economical detection and convenient clinical diagnosis of SBC. Surgery is still the primary treatment option for SBC. Adults can choose BCS or mastectomy according to tumor size and lymph node status. Considering the future breast development of children, extensive mass resection is recognized by most authors, but children are exposed to the risk of postoperative recurrence. Either SLN biopsy or ALND is considered necessary. Patients who receive BCS following postoperative radiotherapy show higher BCSS than do those who undergo total mastectomy. At present, there is still a lack of convincing evidence for chemotherapy and endocrine therapy. Targeted therapy for the *ETV6-NTRK3* fusion gene and its activated signal pathway has become a research hotspot. Overall, the overwhelming majority of SBC patients have a good prognosis, except for several patients with multiple distant metastases. Future research will focus on finding the molecular characteristics of poor-prognosis SBC to provide theoretical support for individualized clinical treatment.

In conclusion, this review provides a comprehensive introduction to SBC, a rare breast malignancy, by integrating the previously published literature on PubMed. The development of histopathology and molecular genetics has advanced the clinical diagnosis of SBC. It is hoped this review will provide better guidance for the clinical practice of SBC treatment, especially in the disease identification and prognosis classification of those with SBC.

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Footnote

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References

- Sharma V, Anuragi G, Singh S, et al. Secretory Carcinoma of the Breast: Report of Two Cases and Review of the Literature. *Case Rep Oncol Med* 2015;2015:581892.
- Wu IK, Lai YC, Chiou HJ, et al. Secretory Carcinoma of the Breast: A Case Report and Literature Review. *J Med Ultrasound* 2021;29:57-9.
- Misra M, Sagar P, Friedmann AM, et al. CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL. Case 12-2016. An 8-Year-Old Boy with an Enlarging Mass in the Right Breast. *N Engl J Med* 2016;374:1565-74.
- McDivitt RW, Stewart FW. Breast carcinoma in children. *JAMA* 1966;195:388-90.
- Tavassoli FA, Norris HJ. Secretory carcinoma of the breast. *Cancer* 1980;45:2404-13.
- Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. *Breast Care (Basel)* 2013;8:149-54.
- Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell* 2002;2:367-76.
- Gong P, Xia C, Yang Y, et al. Clinicopathologic profiling and oncologic outcomes of secretory carcinoma of the breast. *Sci Rep* 2021;11:14738.
- Jacob JD, Hodge C, Franko J, et al. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base. *J Surg Oncol* 2016;113:721-5.
- Vasudev P, Onuma K. Secretory breast carcinoma: unique, triple-negative carcinoma with a favorable prognosis and characteristic molecular expression. *Arch Pathol Lab Med* 2011;135:1606-10.
- Ghilli M, Mariniello MD, Scatena C, et al. Male secretory breast cancer: case in a 6-year-old boy with a peculiar gene duplication and review of the literature. *Breast Cancer Res Treat* 2018;170:445-54.
- Simon CT, McHugh JB, Rabah R, et al. Secretory Carcinoma in Children and Young Adults: A Case Series. *Pediatr Dev Pathol* 2022;25:155-61.
- Soyer T, Yaman Bajin İ, Orhan D, et al. Secretory breast carcinoma in a 6-year-old girl: mastectomy with sentinel lymph node dissection. *Pediatr Surg Int* 2015;31:677-81.
- Aktepe F, Sarsenov D, Özmen V. Secretory Carcinoma of the Breast. *J Breast Health* 2016;12:174-6.
- Garlick JW, Olson KA, Downs-Kelly E, et al. Secretory breast carcinoma in an 8-year-old girl: A case report and literature review. *Breast J* 2018;24:1055-61.
- Benabu JC, Stoll F, Koch A, et al. De-escalating systemic therapy in triple negative breast cancer: The example of secretory carcinoma. *J Gynecol Obstet Hum Reprod* 2018;47:163-5.
- Yang Y, Wang Z, Pan G, et al. Pure secretory carcinoma in situ: a case report and literature review. *Diagn Pathol* 2019;14:95.
- Li G, Zhong X, Yao J, et al. Secretory breast carcinoma in a 41-year-old man with long-term follow-up: a special report. *Future Oncol* 2015;11:1767-73.
- Richard G, Hawk JC 3rd, Baker AS Jr, et al. Multicentric adult secretory breast carcinoma: DNA flow cytometric findings, prognostic features, and review of the world literature. *J Surg Oncol* 1990;44:238-44.
- Horowitz DP, Sharma CS, Connolly E, et al. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. *Breast* 2012;21:350-3.
- Paeng MH, Choi HY, Sung SH, et al. Secretory carcinoma of the breast. *J Clin Ultrasound* 2003;31:425-9.
- Novochadlo Klüppel E, Rodrigues da Costa L, Marquetto Tognolo C, et al. Secretory breast carcinoma in a male child: Case report and literature review. *Int J Surg Case Rep* 2020;73:310-4.
- Banerjee N, Banerjee D, Choudhary N. Secretory carcinoma of the breast, commonly exhibits the features of low grade, triple negative breast carcinoma- A Case

- report with updated review of literature. *Autops Case Rep* 2021;11:e2020227.
24. Li L, Wu N, Li F, et al. Clinicopathologic and molecular characteristics of 44 patients with pure secretory breast carcinoma. *Cancer Biol Med* 2019;16:139-46.
 25. Murphy JJ, Morzaria S, Gow KW, et al. Breast cancer in a 6-year-old child. *J Pediatr Surg* 2000;35:765-7.
 26. Gohara T, Komura M, Asano A, et al. A case of secretory breast cancer in a 6 year-old girl: is it possible to make a correct preoperative diagnosis? *Breast Cancer* 2020;27:785-90.
 27. Uematsu T, Nakashima K, Kikuchi M, et al. The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer Screening and Diagnosis, 2018 Edition. *Breast Cancer* 2020;27:17-24.
 28. Sato T, Iwasaki A, Iwama T, et al. A rare case of extensive ductal carcinoma in situ of the breast with secretory features. *Rare Tumors* 2012;4:e52.
 29. Kameyama K, Mukai M, Iri H, et al. Secretory carcinoma of the breast in a 51-year-old male. *Pathol Int* 1998;48:994-7.
 30. Hoda RS, Brogi E, Pareja F, et al. Secretory carcinoma of the breast: clinicopathologic profile of 14 cases emphasising distant metastatic potential. *Histopathology* 2019;75:213-24.
 31. Shui R, Cheng Y, Bai Q, et al. Secretory breast carcinoma with a papillary-predominant pattern: an unusual morphological variant. *Histopathology* 2017;71:488-93.
 32. Laé M, Fréneaux P, Sastre-Garau X, et al. Secretory breast carcinomas with ETV6-NTRK3 fusion gene belong to the basal-like carcinoma spectrum. *Mod Pathol* 2009;22:291-8.
 33. Lambros MB, Tan DS, Jones RL, et al. Genomic profile of a secretory breast cancer with an ETV6-NTRK3 duplication. *J Clin Pathol* 2009;62:604-12.
 34. Diallo R, Schaefer KL, Bankfalvi A, et al. Secretory carcinoma of the breast: a distinct variant of invasive ductal carcinoma assessed by comparative genomic hybridization and immunohistochemistry. *Hum Pathol* 2003;34:1299-305.
 35. Jin MS, Lee H, Woo J, et al. Integrated Multi-Omic Analyses Support Distinguishing Secretory Carcinoma of the Breast from Basal-Like Triple-Negative Breast Cancer. *Proteomics Clin Appl* 2018;12:e1700125.
 36. Werling RW, Hwang H, Yaziji H, et al. Immunohistochemical distinction of invasive from noninvasive breast lesions: a comparative study of p63 versus calponin and smooth muscle myosin heavy chain. *Am J Surg Pathol* 2003;27:82-90.
 37. Bratthauer GL, Saenger JS, Strauss BL. Antibodies targeting p63 react specifically in the cytoplasm of breast epithelial cells exhibiting secretory differentiation. *Histopathology* 2005;47:611-6.
 38. Krings G, Joseph NM, Bean GR, et al. Genomic profiling of breast secretory carcinomas reveals distinct genetics from other breast cancers and similarity to mammary analog secretory carcinomas. *Mod Pathol* 2017;30:1086-99.
 39. Luk PP, Selinger CI, Eviston TJ, et al. Mammary analogue secretory carcinoma: an evaluation of its clinicopathological and genetic characteristics. *Pathology* 2015;47:659-66.
 40. Hsieh MS, Lee YH, Chang YL. SOX10-positive salivary gland tumors: a growing list, including mammary analogue secretory carcinoma of the salivary gland, sialoblastoma, low-grade salivary duct carcinoma, basal cell adenoma/adenocarcinoma, and a subgroup of mucoepidermoid carcinoma. *Hum Pathol* 2016;56:134-42.
 41. Strauss BL, Bratthauer GL, Tavassoli FA. STAT 5a expression in the breast is maintained in secretory carcinoma, in contrast to other histologic types. *Hum Pathol* 2006;37:586-92.
 42. Osako T, Takeuchi K, Horii R, et al. Secretory carcinoma of the breast and its histopathological mimics: value of markers for differential diagnosis. *Histopathology* 2013;63:509-19.
 43. Terada T, Kawata R, Noro K, et al. Clinical characteristics of acinic cell carcinoma and secretory carcinoma of the parotid gland. *Eur Arch Otorhinolaryngol* 2019;276:3461-6.
 44. Majewska H, Skálová A, Stodulski D, et al. Mammary analogue secretory carcinoma of salivary glands: a new entity associated with ETV6 gene rearrangement. *Virchows Arch* 2015;466:245-54.
 45. Ahn CS, Sangüeza OP. Malignant Sweat Gland Tumors. *Hematol Oncol Clin North Am* 2019;33:53-71.
 46. Tsutsui K, Takahashi A, Mori T, et al. Secretory carcinoma of the skin arising on the eyelid, distinguished by immunohistochemical markers and fluorescence in situ hybridization. *J Dermatol* 2020;47:e99-e100.
 47. Bortz JG, Zhang PJJ, Eagle RC Jr, et al. Secretory Carcinoma of the Lacrimal Gland: A Rare Case Report. *Ophthalmic Plast Reconstr Surg* 2018;34:e154-7.
 48. Chu YH, Dias-Santagata D, Farahani AA, et al. Clinicopathologic and molecular characterization of NTRK-rearranged thyroid carcinoma (NRTC). *Mod*

- Pathol 2020;33:2186-97.
49. Rooper LM, Karantanos T, Ning Y, et al. Salivary Secretory Carcinoma With a Novel ETV6-MET Fusion: Expanding the Molecular Spectrum of a Recently Described Entity. *Am J Surg Pathol* 2018;42:1121-6.
 50. Skálová A, Vanecek T, Simpson RH, et al. Mammary Analogue Secretory Carcinoma of Salivary Glands: Molecular Analysis of 25 ETV6 Gene Rearranged Tumors With Lack of Detection of Classical ETV6-NTRK3 Fusion Transcript by Standard RT-PCR: Report of 4 Cases Harboring ETV6-X Gene Fusion. *Am J Surg Pathol* 2016;40:3-13.
 51. Skalova A, Vanecek T, Martinek P, et al. Molecular Profiling of Mammary Analog Secretory Carcinoma Revealed a Subset of Tumors Harboring a Novel ETV6-RET Translocation: Report of 10 Cases. *Am J Surg Pathol* 2018;42:234-46.
 52. Sasaki E, Masago K, Fujita S, et al. Salivary Secretory Carcinoma Harboring a Novel ALK Fusion: Expanding the Molecular Characterization of Carcinomas Beyond the ETV6 Gene. *Am J Surg Pathol* 2020;44:962-9.
 53. Skálová A, Banečková M, Thompson LDR, et al. Expanding the Molecular Spectrum of Secretory Carcinoma of Salivary Glands With a Novel VIM-RET Fusion. *Am J Surg Pathol* 2020;44:1295-307.
 54. Maund SL, Sokol ES, Ang Houle A, et al. NTRK gene fusions are detected in both secretory and non-secretory breast cancers. *Pathol Int* 2022;72:187-92.
 55. Makretsov N, He M, Hayes M, et al. A fluorescence in situ hybridization study of ETV6-NTRK3 fusion gene in secretory breast carcinoma. *Genes Chromosomes Cancer* 2004;40:152-7.
 56. Remoué A, Conan-Charlet V, Bourhis A, et al. Non-secretory breast carcinomas lack NTRK rearrangements and TRK protein expression. *Pathol Int* 2019;69:94-6.
 57. Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of NTRK Fusions. *Am J Surg Pathol* 2017;41:1547-51.
 58. Hung YP, Fletcher CDM, Hornick JL. Evaluation of pan-TRK immunohistochemistry in infantile fibrosarcoma, lipofibromatosis-like neural tumour and histological mimics. *Histopathology* 2018;73:634-44.
 59. Rudzinski ER, Lockwood CM, Stohr BA, et al. Pan-Trk Immunohistochemistry Identifies NTRK Rearrangements in Pediatric Mesenchymal Tumors. *Am J Surg Pathol* 2018;42:927-35.
 60. Hung YP, Jo VY, Hornick JL. Immunohistochemistry with a pan-TRK antibody distinguishes secretory carcinoma of the salivary gland from acinic cell carcinoma. *Histopathology* 2019;75:54-62.
 61. Harrison BT, Fowler E, Krings G, et al. Pan-TRK Immunohistochemistry: A Useful Diagnostic Adjunct For Secretory Carcinoma of the Breast. *Am J Surg Pathol* 2019;43:1693-700.
 62. Carretero-Barrio I, Santón A, Caniego Casas T, et al. Cytological and molecular characterization of secretory breast carcinoma. *Diagn Cytopathol* 2022;50:E174-80.
 63. Zaborowski M, Gill AJ. Is secretory breast carcinoma underdiagnosed? In the era of targeted therapy should there be a low threshold to screen for NTRK immunohistochemistry in triple negative breast cancers? *Pathology* 2019;51:653-5.
 64. Diallo R, Tognon C, Knezevich SR, et al. Secretory carcinoma of the breast: a genetically defined carcinoma entity. *Verh Dtsch Ges Pathol* 2003;87:193-203.
 65. Chen M, Pu T, Wei B, et al. Genomic landscape of secretory carcinoma of the breast with axillary lymph node metastasis. *Pathol Res Pract* 2022;231:153790.
 66. Del Castillo M, Chibon F, Arnould L, et al. Secretory Breast Carcinoma: A Histopathologic and Genomic Spectrum Characterized by a Joint Specific ETV6-NTRK3 Gene Fusion. *Am J Surg Pathol* 2015;39:1458-67.
 67. Vinagre J, Pinto V, Celestino R, et al. Telomerase promoter mutations in cancer: an emerging molecular biomarker? *Virchows Arch* 2014;465:119-33.
 68. Shi X, Liu R, Qu S, et al. Association of TERT promoter mutation 1,295,228 C>T with BRAF V600E mutation, older patient age, and distant metastasis in anaplastic thyroid cancer. *J Clin Endocrinol Metab* 2015;100:E632-7.
 69. Cipriani NA, Blair EA, Finkle J, et al. Salivary Gland Secretory Carcinoma With High-Grade Transformation, CDKN2A/B Loss, Distant Metastasis, and Lack of Sustained Response to Crizotinib. *Int J Surg Pathol* 2017;25:613-8.
 70. Shukla N, Roberts SS, Baki MO, et al. Successful Targeted Therapy of Refractory Pediatric ETV6-NTRK3 Fusion-Positive Secretory Breast Carcinoma. *JCO Precis Oncol* 2017;2017:PO.17.00034.
 71. Naylor TL, Greshock J, Wang Y, et al. High resolution genomic analysis of sporadic breast cancer using array-based comparative genomic hybridization. *Breast Cancer Res* 2005;7:R1186-98.
 72. Maurer M, Su T, Saal LH, et al. 3-Phosphoinositide-dependent kinase 1 potentiates upstream lesions on the

- phosphatidylinositol 3-kinase pathway in breast carcinoma. *Cancer Res* 2009;69:6299-306.
73. Xu J, Weisman P. Dedifferentiated secretory breast carcinoma with fibrosarcomatous features harboring an ETV6-NTRK3 fusion in both components. *Genes Chromosomes Cancer* 2021;60:447-51.
 74. Kulkarni MM, Khandeparkar SG, Joshi AR, et al. A rare case of multicentric secretory carcinoma of breast in an adult female with review of literature. *Indian J Pathol Microbiol* 2016;59:209-11.
 75. Costa NM, Rodrigues H, Pereira H, et al. Secretory breast carcinoma--case report and review of the medical literature. *Breast* 2004;13:353-5.
 76. Tixier H, Picard A, Guiu S, et al. Long-term recurrence of secretory breast carcinoma with metastatic sentinel lymph nodes. *Arch Gynecol Obstet* 2011;283 Suppl 1:77-8.
 77. Tang H, Zhong L, Jiang H, et al. Secretory carcinoma of the breast with multiple distant metastases in the brain and unfavorable prognosis: a case report and literature review. *Diagn Pathol* 2021;16:56.
 78. Lee SG, Jung SP, Lee HY, et al. Secretory breast carcinoma: A report of three cases and a review of the literature. *Oncol Lett* 2014;8:683-6.
 79. Gold DG, Neglia JP, Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. *Cancer* 2003;97:2588-96.
 80. Mun SH, Ko EY, Han BK, et al. Secretory carcinoma of the breast: sonographic features. *J Ultrasound Med* 2008;27:947-54.
 81. Lombardi A, Maggi S, Bersigotti L, et al. Secretory breast cancer. Case report. *G Chir* 2013;34:125-7.
 82. Vieni S, Cabibi D, Cipolla C, et al. Secretory breast carcinoma with metastatic sentinel lymph node. *World J Surg Oncol* 2006;4:88.
 83. Herz H, Cooke B, Goldstein D. Metastatic secretory breast cancer. Non-responsiveness to chemotherapy: case report and review of the literature. *Ann Oncol* 2000;11:1343-7.
 84. de Bree E, Askoxylakis J, Giannikaki E, et al. Secretory carcinoma of the male breast. *Ann Surg Oncol* 2002;9:663-7.
 85. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol* 2018;15:731-47.
 86. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378:731-9.
 87. Cadoo KA, McArdle O, O'Shea AM, et al. Management of unusual histological types of breast cancer. *Oncologist* 2012;17:1135-45.
 88. Cabello C, Alvarenga M, Alvarenga CA, et al. Case report and review of the literature: secretory breast cancer in a 13-year-old boy--10 years of follow up. *Breast Cancer Res Treat* 2012;133:813-20.
 89. Lian J, Wang LX, Guo JH, et al. Secretory breast carcinoma in a female adult with liver metastasis: a case report and literature review. *Diagn Pathol* 2021;16:89.
 90. Woto-Gaye G, Kasse AA, Dieye Y, et al. Secretory breast carcinoma in a man. A case report with rapid evolution unfavorable. *Ann Pathol* 2004;24:432-5; quiz 393.
 91. Ozguroglu M, Tascilar K, Ilvan S, et al. Secretory carcinoma of the breast. Case report and review of the literature. *Oncology* 2005;68:263-8.
 92. Anderson P, Albarracin CT, Resetskova E. A large, fungating breast mass. Secretory carcinoma with apocrine differentiation. *Arch Pathol Lab Med* 2006;130:e50-2.
 93. Wong M, Jara-Lazaro AR, Hui Ng RC, et al. ETV6 disruption does not predict indolent clinical behavior in secretory breast carcinoma. *Breast J* 2012;18:604-6.
 94. Landman Y, Ilouze M, Wein S, et al. Rapid Response to Larotrectinib (LOXO-101) in an Adult Chemotherapy-Naive Patients With Advanced Triple-Negative Secretory Breast Cancer Expressing ETV6-NTRK3 Fusion. *Clin Breast Cancer* 2018;18:e267-70.

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