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Case Report

ETV6-NTRK3 gene fusion positive secretory carcinoma breast in a two year seven-month-old child with metastatic axillary lymph node: a case report and review of literature

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ABSTRACT

Secretory breast carcinoma (SBC) is an exceptionally rare type of breast carcinoma, accounting for less than 0.15% of all breast cancers. Only few cases have been reported in literature and even less with axillary lymph node metastasis and there is emerging application of use of Sentinel Lymph node biopsy (SLNB) or Low axillary sampling to assess the nodal status. There is a lack of consensus regarding the exact management and the role of targeted therapy is evolving. We report a case of SBC in a 2 year 7-month-old child. The child presented with a painless mobile peri areolar lump with blood-stained nipple discharge. She underwent excision biopsy outside followed by wide excision of residual lump with Low axillary sampling of the axilla showing axillary lymph node metastasis in our Centre and was subjected to level III axillary clearance. The tumor showed positivity for Estrogen receptor (ER) and the characteristic translocation, t (12; 15) (p13; q25) that results in the expression of the ETV6-NTRK3 fusion gene. After careful analysis of the case in Multidisciplinary team meeting, the child was started on Tamoxifen due to ER positivity and was decided to avoid use of chemoradiotherapy considering the age and doubtful benefit. Later when the tumour turned out to be positive for the fusion gene, she was started on targeted therapy with Entrectinib. To our knowledge, this is the youngest case reported in literature. The increasing use of targeted agents has been an evolving trend in the management of SBC with successful treatment outcomes. After careful analysis of our case and available literature, we have come to a conclusion that the treatment of choice for SBC should be conservation surgery with SLNB or Low axillary sampling followed by hormonal treatment if hormone responsive and the use of targeted agents. There is no reliable data regarding the role of adjuvant chemotherapy in SBC. Regarding adjuvant Radiotherapy, though it has been used in adults, its use in children should be limited.

Keywords: Breast, Secretory carcinoma, ETV6-NTRK3, Entrectinib

INTRODUCTION

This uncommon variety of mammary carcinoma in children was first described by Mc Divitt et al and was designated as "juvenile carcinoma" which is characterized by intracellular and extracellular secretions and the granular eosinophilic cytoplasm of the cells.[1] It was later renamed as secretory carcinoma due to the varied age of presentation from 9 to 69 years (median age 25 years) by Norris et al.[2] Only very few cases have been reported in literature till date. It has got a favorable prognosis in children compared to adults where it is potentially aggressive.[3] However slow growth and delayed recurrence are a characteristic feature of these tumors. Also published literature has only reported few cases with axillary lymph node metastasis and only four cases with distant metastasis.[4] Local recurrences have been reported as late as 16 years after definitive management.[5] Hence data accumulation is required to further characterize the disease and to formulate a treatment plan.

Here, we describe the case report of a girl child who was diagnosed with SBC at the age of 2 years 7 months, which is the youngest described in literature. The tumor size was less than 2 cm; and demonstrated axillary lymph node metastasis, detected by low axillary sampling and showed positivity for ER and fusion gene ETV6-NTRK3.

CASE REPORT

A 2-year 7-month-old girl with Asian Ethnicity with no significant medical or family history of cancer, presented to another Centre with spontaneous non profuse blood-stained discharge from the right nipple at the age of 2 years 7 months which was managed conservatively and the same persisted intermittently and stopped after three months. During the same period, the mother noticed a swelling in the peri areolar region of right breast which was gradually increasing in size. On examination, it was a well circumscribed painless mobile peri areolar lump of size 0.5×0.5 cm. Fine needle aspiration of the lump was indicative of a benign pathology with no atypical cells or abnormal mitosis. She underwent excision biopsy of the lump preserving the nipple and part of areola without addressing the axilla and was referred to our center.

Histopathological examination of the biopsy specimen and the slide block review at our institution revealed grade II Secretory carcinoma with closest margin 0.4mm. Tumor was composed of polygonal to round cells with eosinophilic granular and vacuolated cytoplasm. Individual tumor cells showed round nuclei arranged in microcystic, macrocystic, solid and focal papillaroid pattern, PAS positive, diastase resistant; mild to moderate nuclear pleomorphism, 0-1/10 HPF mitotic figures.

Immunohistochemical (IHC) evaluation showed positivity for MUC-4, S-100, SOX 1, GATA 3, CK5/6 focal, ER positive (Allred score 4/8), PR and Her2/neu negative, MIB Index 10% and positive for mammaglobin (Figure 1).

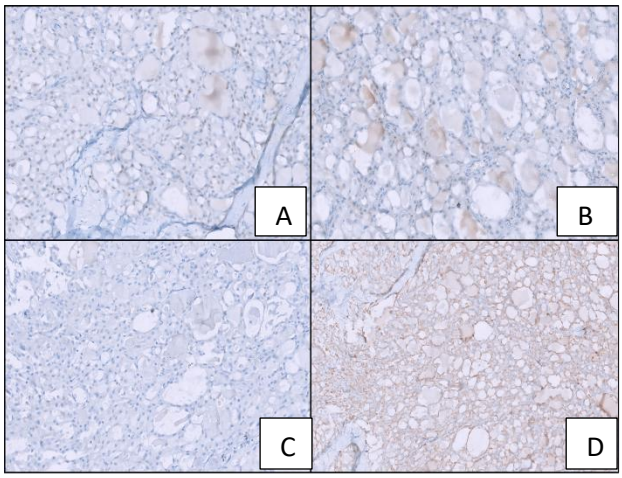

Figure 1: Immunohistochemical (IHC) staining showing: (A) estrogen receptor(er) weak positivity, all red 4/8; 10% tumor cells show nuclear staining with moderate intensity, (B) progesterone receptor staining negative, (C) her 2/neu staining: negative, (D) tumor cells positive for muc4 staining which is specific for secretory carcinoma.

On examination, child had a residual palpable nodule in right breast at the scar site close to nipple and a palpable right axillary lymph node of size 0.5×0.5 cm. Left breast and axilla was normal on examination. Ultrasound examination of right axilla revealed a prominent right axillary node with preserved fatty hilum corresponding to the clinical findings. It was sonolocalised and marked prior to surgery.

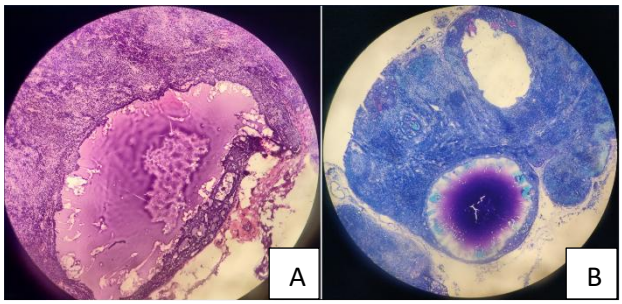

Figure 2: Frozen section image of low axillary sampling lymph node showing: (A) characteristic extracellular secretory material in H and E stain and (B) toluidine blue staining.

Based on the above clinical picture and the pathology report review at our Institution, Multidisciplinary team involving the Pediatric Surgical Oncology and Adult Breast Oncology team decided to proceed with definitive local treatment. The child underwent wide local excision of the right breast residual nodule and sentinel node biopsy. The suspicious node along with low axillary sampling was done. Frozen section analysis using

toluidine blue and hematoxylin eosin stain revealed the same secretory pattern with microcystic and macrocystic appearance in the prominent node (1/4) (Figure 2). Hence a combined decision was made to proceed with level III axillary clearance. Post-operative period was uneventful (Figure 3).

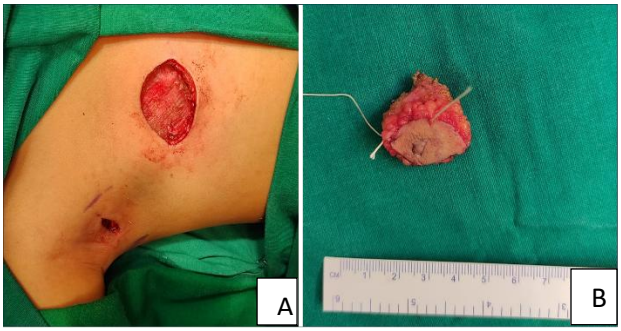

Figure 3: Intraoperative photograph showing: (A) wide excision of the primary up to pectoralis fascia and low axillary sampling and (B) specimen removed and oriented –short superior margin and long lateral margin.

Final histopathology revealed 0.5×0.4×0.4 cm gross lesion with firm to solid areas identified suggestive of scanty residual secretory carcinoma with free margins (Figure 4). Axillary clearance showed 1 out of 11 nodal metastases.

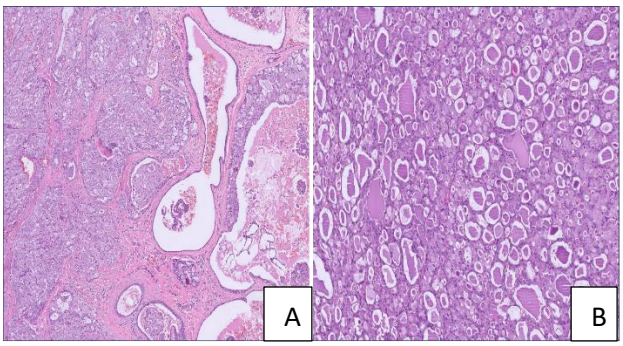

Figure 4: (A) Hematoxylin eosin (H and E) staining 4x magnification showing tumor with microcystic and tubular growth pattern, predominantly microcystic pattern and (B) H and E staining 10x magnification showing intracellular and extracellular secretory material.

Molecular testing showed pathogenic ETV6-NTRK3 fusion gene by NGS method and also indel mutation in exon 25 of DICER1 gene and exon 1 of FOXL2 gene.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DISCUSSION

McDivitt et al first reported this uncommon variant of breast cancer which was initially thought to occur only in children and was named juvenile carcinoma.[1] Tavassoli et al reported a series of 19 patients including adults with a median age of 25 years and renamed it as 'secretory carcinoma' which was established thereafter.[2]

SBC is an exceptionally rare type of breast carcinoma, accounting for less than 0.15% of all breast cancers.[6] It has been found to occur both in males and females with a reported ratio of 1:6. The median age of occurrence is 25 years[2] with reported cases ranging from 3 to 87 years.[7,8]

The most common clinical presentation is that of a painless mobile well circumscribed lump usually peri areolar or subareolar, especially in males.[1] Sub areolar lump will usually be associated with blood-stained nipple discharge. Most cases are solitary; multicentric have also been reported.[9] Axillary lymph node metastases have been found in about 15 to 30% of the cases where it rarely involves more than 3 nodes.[9]

The definitive diagnosis of tumor is made by the typical microscopic appearance which is characterized by the presence of tumor cells with vacuolated cytoplasm and abundant intra-and extracellular secretory material. The secretory material is usually positive for PAS, mucicarmine and alcian blue staining. Histologically, SBC presents as a solid, tubular, microcystic and rarely papillary pattern.[10] Tumor cells typically stain positive for alpha-lactalbumin, CEA and S100.

Secretory carcinoma is associated with a characteristic translocation, t (12; 15) (p13; q25) that results in the expression of the ETV6-NTRK3 fusion gene, the incidence of which has been reported at 75 to 92%.[11,12] Expression of this ETV6-NTRK3 gene leads to the formation of a chimeric tyrosine kinase that activates the Ras-MAPK and inositol-3'-kinase Akt pathways, which are noted to be the first event in the oncogenesis of SBC.[13,14]

SBC is typically negative for estrogen receptors, progesterone receptors, and does not over-express Her2/ Neu. Secretory carcinomas have also been noted to belong to the basal like spectrum of breast cancers. It was described by Lae, et al who found that SBC expressed CK5/6 and/or CK14 and 17, c-kit (CD-117), epidermal growth factor receptor and vimentin.[15] SBC also has been found to show strong membranous immunostain positivity for E-cadherin which supports the hypothesis that this might originate from the ductal component of the mammary gland and hence could therefore be considered as a variant of ductal carcinoma.

In our case, the tumor cells was weakly positive for estrogen receptors, and negative for progesterone and Her2/neu receptor. The tumor cells showed strong

positivity for S-100 and focal CK5/6 positivity. The presence of intracellular and extracellular eosinophilic PAS-positive material was the most remarkable feature.

Molecular testing using NGS based targeted panel study revealed the presence of ETV6-NTRK3 fusion and also indel mutation in exon 25 of DICER1 gene and exon 1 of FOXL2 gene. NTRK1,2 and 3 encode for the TrkA, TrkB, and TrkC receptor tyrosine kinases. Gene fusions involving NTRK family gene are reported in various tumors, including infantile fibrosarcoma, secretory carcinoma of breast, mammary analogue secretory carcinoma etc. These fusions are oncogenic and result in constitutive activation of Trk kinase activity. US-FDA has approved the use of Larotrectinib in NTRK fusion positive metastatic solid tumors.

Differential diagnosis includes wide range of benign lesions like lactational change and adenoma, juvenile papillomatosis with apocrine metaplasia, collagenous spherulosis and cystic hypersecretory hyperplasia and malignant conditions like lipid and glycogen-rich carcinoma, mucinous carcinoma, acinic cell carcinoma, apocrine carcinoma and cystic hypersecretory carcinoma and even clear cell breast carcinoma and metastasis from a renal cell carcinoma.[16,17]

SBC is an indolent neoplasm with a favourable prognosis at least in children as is our case. As of now, there is no consensus regarding the management of SBC. The existing data supports surgery as the mainstay of management however there are no published guidelines for the extend of surgical resection. Furthermore, due to scarcity of the reported cases, the significance of neoadjuvant chemotherapy, adjuvant chemotherapy, and postoperative radiotherapy also remains unclear. The most frequently performed procedures in adults include Breast conservation surgery, modified radical mastectomy and radical mastectomy and in children, simple mastectomy, local excision with sentinel lymph node biopsy and complete axillary dissection are potentially adequate.[18]

According to Li et al, sentinel lymph node biopsy could effectively evaluate the axillary lymph node status in cases with SBC. Also, it has been reported that if tumor size is less than 2 cm, axillary lymph node metastasis is uncommon.[19,20] In our case, because the axillary sampling revealed a single node enriched with secretory material and tumor cells, it was decided to proceed with level III clearance however the metastasis was limited to the same node as evidenced by the final pathology report. This is in accordance with the findings by Veronesi et al who proposed sentinel node biopsy method, have demonstrated that in 40% of the cases, the other lymph nodes removed after sentinel lymph node positivity have not demonstrated metastatic colonisation.[25] Distant metastases are rare in SBC, however metastasis as late as 20 years have been reported.[21] Therefore, long term follow up of at least 20 years is recommended.[22]

Regarding chemotherapy, there remains paucity of data to support systemic treatment, but with metastatic disease being so rare, it is difficult to justify its use. Herz et al have reported non-responsiveness of the tumour to chemotherapy.[21]

Regarding post-operative radiotherapy, it should be proposed after BCS in adult patients, but is not advised for children because of the possible secondary side effects like fibrosis of the lung, damage to the ribs and the consequent asymmetry of the rib cage.[24]

In terms of hormonal blockade, most SBC is not hormone responsive. In the rare scenario of a hormone receptor positive SBC as is ours where ER is positive (Allred 4/8), hormonal blockade would be reasonable, but again there is no specific data to support its use in SBC.

Because the tumor demonstrates the fusion gene ETV6 NTRK3, attempts have been ongoing to demonstrate the use of targeted agents against SBC. Recently, a novel tyrosine kinase inhibitor that targets NTRK3, Entrectinib, was developed and is currently in phase II clinical trials (STARTRK-2) with promising preliminary results.[23] Another case reported by Shukla et al, there has been a case of successful targeted treatment of refractory pediatric ETV6-NTRK3 fusion-positive SBC with chest wall recurrences with oral pan-Trk inhibitor Larotrectinib.[26] They demonstrated successful reduction in the size of large fungating chest wall mass and near complete resolution of lung metastasis in the patient with this oral single agent.

Hence all these point out to the probable role of fusion gene as a driver mutation in SBC. Recently a multicentre phase I dose escalation study demonstrated objective response in adult patients with TRK fusion cancer and showed that it was well tolerated and provided consistent and durable antitumor activity.[27] Hence it offers a potential new standard of care for both pediatric and adult patients with NTRK fusion gene.

No deaths during childhood were reported. Reported deaths were late recurrences following diagnosis in adolescence. This emphasises the importance of long follow up and the importance of surgery in young patients despite locally advanced disease.[18]

CONCLUSION

SBC is an uncommon variant of breast carcinoma with a specific ETV6-NTRK3 fusion, which has got a slow growth rate and a good prognosis. There are no specific clinical or imaging findings characteristic of SBC and diagnosis should be based on microscopic findings with the characteristic secretory material. However, long term follow up is advised for the disease as there are chances of lymph node metastasis and local recurrence especially late onset and distant metastasis.

Once diagnosed, surgery should be the main stay of treatment and adjuvant therapy in the form of chemotherapy, radiotherapy and endocrine therapy should be individualised and used appropriately. Recent reports of successful targeted treatment with agents like Larotrectinib and Entrectinib have been published which could offer potential promising results.

Our patient is currently on tamoxifen and is being planned to start on Entrectinib.

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