Triple-negative breast cancer in children: a case report

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Case Report

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Abstract

Background

Triple-negative breast cancer (TNBC) is often considered a breast tumor with a poor prognosis that lacks or decreases the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). It tends to occur in middle-aged and older women, and cases of TNBC in children are rarely reported.

Methods

We report a case of basal-like TNBC in a child at our hospital and review the related literature.

Results

Based on the patient's condition we performed a local mass excision, and despite the postoperative pathological diagnosis of TNBC, this case of basic TNBC had a good prognosis and was very different from conventional basic TNBC in many ways.

Conclusions

Although secretory breast cancer is a subtype of basal-like TNBC, it has its peculiarities and is completely different from basal-like TNBC. There is a need to raise awareness of the disease, select individualized treatment options, and prevent medical errors.

Background

Breast carcinoma is one of the common malignant tumors in humans. Its incidence has jumped to the top of the list of malignant tumors and is the main cause of death from malignant tumors in women[1]. Triple-negative breast cancer (TNBC)is a subtype of breast cancer that represents about 15-25% of breast cancer cases and is characterised by the absence or reduction of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) [2]. Compared to other breast cancer subtypes, TNBC is characterised by a higher recurrence rate, greater metastatic potential, and shorter overall survival time. TNBC is more common in middle-aged women compared with young people[3, 4]. TNBC in children is extremely rare and the pathogenesis is closely linked to genomic instability and mutations [5]. According to reports, the survival rate after metastatic TNBC surgery is very low [6].

Case Presentation
An 8-year-old girl was presented to HongQi hospital with a right breast lump for 4 months. There was a hard mass under the right nipple, about 1.5 cm in diameter, with clear borders and good mobility. Her preoperative ultrasonic findings showed a hypoechoic lesion next to the right nipple, measuring approximately 1.4 x 0.8 cm with clear borders, regular morphology, and a significant blood flow signal. She had no family history of the tumor. The tumor was resected after the completion of relevant examinations. The tumor was white to gray-red tissue with a volume of 1.6 x 1.4 x 0.7 cm and a solid gray-white cut surface. Histological findings showed that the main structure was papillary and also tubular with pink or pale pink cells, and secretory vacuoles and interstitial powdery secretions were seen (Figure 3). Immunohistochemical results showed ER few cells (+), PR (-), HER-2 (-), Ki-67 less than 10% (+), CEA lesions (+), and P53 wild type. A diagnosis of TNBC (secretory breast carcinoma) was made. The child underwent a second resection. No tumor cells were found in the residual tumor cavity around the resection margin and biopsies of the anterior lymph nodes. Genetic testing showed an ETV6-NTRK3 gene fusion. After surgery, no herbal, radiotherapy, chemotherapy, or immunotherapy was administered. The child was followed up for 1-year and was in good health.

Discussion

In recent years, the incidence of TNBC has been increasing, becoming younger, and becoming a hot spot in clinical research\cite{1}. Regardless of the fact that TNBC is generally considered to be highly malignant and has a very poor prognosis, a large number of documents display that TNBC is heterogeneous, showing significant differences in pathological features, biological behaviour and gene expression profiles\cite{8, 9, 10, 11, 12}. Therefore, understanding the TNBC classification has great clinical significance. At present, TNBC has a variety of typing methods and a variety of subtypes with different biological characteristics. By summarising the relevant literature on TNBC classification from 2009 to 2019, Chen Lin\cite{13} found that the intraluminal androgen receptor (LAR), basal-like (BL), mesenchymal (MES) and immunomodulatory/basal-like immune activation (IM/BLIA) classifications were repeatedly mentioned in several TNBC classifications and are the more accepted ones currently. Joensuu H\cite{14} et al. divided TNBC into BL and non-BL types, of which BL type accounts for 80% and has a high degree of malignancy and poor prognosis compared to non-BL type. BI-TNBC is divided into BL1 and BL2 types, which are characterized by overexpression of cell cycle-related genes and DNA damage response genes\cite{15} and have a strong proliferative capacity through these features. The top gene ontologies for the BL1 subtype are heavily enriched in cell-cycle and cell division components and pathways (cell-cycle, DNA replication reactome, G2 cell-cycle pathway, RNA polymerase, and G1 to S cell cycle). Elevated DNA damage response (ATR/BRCA) pathways accompany the proliferation pathways in the BL1 subtype. Increased proliferation and cell-cycle checkpoint loss are consistent with the elevated expression of the DNA damage response genes observed. The BL2 type displays a unique gene ontology involving growth factor signalling (EGF pathway, NGF pathway, MET pathway, Wnt/β-catenin and IGF1R pathway), as well as glycolysis and gluconeogenesis. It has features suggestive of a basal/myoepithelial origin and exhibits higher levels of expression of TP63 and MME (CD10).
Recent studies have shown that programmed death ligand 1 (PD-L1) and apurine/pyrimidine endonuclease 1 (APE1) play a role in the development of TNBC, and it is hypothesized that APE1 may be involved in regulating PD-L1 expression, promoting greater metastatic and invasive capacity of tumour cells and further participating in immune escape of tumours\cite{16}. Accordingly, the emergence of immune checkpoint therapy may be a future research direction. If the process of homologous recombination (HR) is unavailable or impaired, this is referred to as ‘homologous recombination deficiency’ (HRD)\cite{17,18}. In this situation, DNA repair is more error-prone, which leads to genomic instability. Breast cancer susceptibility genes 1/2 (BRCA1/2) are oncogenes that maintain genomic stability by playing a key role in DNA repair, cell-cycle arrest and transcriptional control. BRCA1 and BRCA2 play a role in the repair of DNA double-strand breaks (DSBs) through the HR process, with BRCA1 guiding the repair towards error-free HR\cite{19}. Loss of BRCA1/2 function leads to HRD\cite{20}, and deletion or mutation of BRCA is closely associated with the development of TNBC. Ki67 significantly correlates with the proliferation level of tumour cells and is predictive of the prognosis of TNBC\cite{21}. Compared to other subtypes of TNBC, BL-1 type has a high value-added rate\cite{22}, indicating active tumour cell proliferation and a poor prognosis.

The diagnosis of breast cancer\cite{23} is made by clinical examination, radiological/imaging examination (including mammography, magnetic resonance imaging (MRI) ultrasonography, etc. and immunohistopathological examination. Early diagnosis of TNBC is difficult and relies on intraoperative rapid frozen section pathological examination and postoperative pathological findings. Surgery combined with neoadjuvant chemotherapy is the main treatment for TNBC\cite{24}. The different histological subtypes of TNBC differ significantly in terms of clinical presentation, treatment and prognosis, and histological classification can help scientists develop the best individualised treatment approach. Platinum drugs and PARP inhibitors\cite{25} have a helpful effect on BL-1 type of TNBC. Platinum-based drugs affect the replication of double-stranded DNA in tumour cells by cross-linking with their DNA, leading to the death of tumour cells. They are very effective against TNBC caused by impaired repair of genetic damage due to BRCA gene mutations. Mutated BRCA cannot repair DSBs and will result in defects in homologous recombination and cause disease. PARP is a single-strand break (SSB) damage recognition and repair protein that plays an important role in starting SSB repair in DNA through base excision repair. PARP inhibitors can cause accumulation of SSBs, leading to the formation of DSBs for therapeutic purpose.

According to the worldwide classification of intrinsic subtypes, secretory breast carcinoma (SBC) is classified as basal-like TNBC\cite{26}, but the clinical course of SBC is highly indolent. To date, there are no standard treatment guidelines for SBC. It in children is usually solitary, firm, well-defined, less than 20mm in diameter, with good mobility, slow growth, and mostly without lymph node metastasis. In this case, the lesion was simply excised with no tumor cells at the margin, and no incisional enlargement or lymph node dissection was given. Our initial surgical decision was correct in terms of the results of the secondary surgical resection and lymph node dissection. Multiple surgeries caused physical, psychological and financial stress to the child and family to some extent. Our shortcomings were that our anticipatory judgment of the disease and preoperative examination were inadequately prepared, and
rapid frozen sections were not performed intraoperatively. At the 1-year postoperative follow-up, the prognosis was good.

SBC belonging to BL-1 type of TNBC has a characteristic t(12:15) equilibrium shift, resulting in the ETV6-NTRK3 gene fusion\(^{[27]}\). Its fusion gene product activates a certain pathway and eventually leads to the production of SBC. The clinical presentation of SBC is mostly benign, and surgical excision is the main option. Depending on the condition, local mass excision or breast-conserving surgical treatment combined with an anterior lymph node biopsy is desirable. However, when local excision is not extensive enough, SBC is at risk of recurrence and metastasis\(^{[28]}\). For SBC patients with infiltration and metastasis, a modified radical mastectomy or radical mastectomy combined with tyrosinase and Ras inhibitor therapy\(^{[29]}\) is available.

**Conclusions**

Although SBC is classified as BL-1 type of TNBC, it differs dramatically from BL-TNBC in terms of pathogenesis, clinical presentation, treatment and prognosis. Therefore, it is extremely important to choose the best individualized treatment plan. Some scholars\(^{[26,30]}\) believe that it is necessary to distinguish SBC from BL-TNBC in order to prevent misdiagnosis and mistreatment, and our view is consistent with theirs. Although these differences objectively exist, SBC has so far been classified as the BL-1 subtype of TNBC, whether this is due to the heterogeneity of TNBC and other factors remains to be further studied and proven.

**Abbreviations**

TNBC
Triple-negative breast cancer
ER
estrogen receptor
PR
progesterone receptor
HER-2
human epidermal growth factor receptor2
CEA
carcinoembryonic antigen
PD-L1
programmed death ligand 1
APE1
apurine/pyrimidine endonuclease 1
BRCA
Breast cancer susceptibility genes
BL
basal-like
DSBs
DNA double-strand breaks
SSB
single-strand break.

Declarations

Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary information files.

Competing interests

Not applicable.

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Not applicable.

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Authors’ contributions

SLX, ZYN, SZW and ZYC: Pictures collection and all cowrite the manuscript. ZWL and SLX: reviewing and editing of the manuscript. All authors read and approved the final manuscript.

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Consent for publication

Consent for publication of images and information was obtained from the patient’s parents.

Ethical approval and consent to participate

The Institutional Review Board of Hongqi Hospital, Mudanjiang Medical University, approved this study.
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Figures

Figure 1

Postoperative pathological results of the tumour under the microscope; secretory vacuoles can be seen.

Supplementary Files

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