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Review

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Luminal androgen receptor (LAR) subtype of triple-negative breast cancer: molecular, morphological, and clinical features

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Abstract: According to the classification presented by Lehmann BD (2016), triple-negative breast cancer (TNBC) is a heterogeneous group of malignant tumors with four specific subtypes: basal-like (subtype 1 and subtype 2), mesenchymal, and luminal androgen receptor (LAR) subtypes. The basal-like subtypes of carcinomas predominate in this group, accounting for up to 80% of all cases. Despite the significantly lower proportions of mesenchymal and LAR variants in the group of breast carcinomas with a TNBC profile, such tumors are characterized by aggressive biological behavior. To this end, the LAR subtype is of particular interest, since the literature on such tumors presents different and even contradictory data concerning the disease course and prognosis. This review is devoted to the analysis of the relevant literature, reflecting the main results of studies on the molecular properties and clinical features of the disease course of LAR-type TNBC carcinomas.

Key words: Luminal androgen receptor (LAR) subtype; Triple-negative breast cancer (TNBC); Androgen receptor (AR); Prognosis

1 Introduction

Triple-negative breast cancer (TNBC) comprises a group of malignant breast tumors with specific features that are characterized by the lack of estrogen receptor (ER) and progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER2) amplification (Perou et al., 2000). Despite the presence of clearly defined molecular criteria that allow the detection of such breast tumors by immunohistochemistry and their assignment to a specific group, it is known that breast carcinomas with the described molecular and genetic profile differ in their biological features, clinical course, resistance to therapy, as well as in the indicators of metastasis-free, disease-free, and overall survival (Guestini et al., 2016; Ali et al., 2017; Bhattacharya et al., 2017; Jia et al., 2017; Chalakur-Ramireddy and Pakala, 2018).

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On the one hand, the morphological, molecular, genetic, and clinical differences revealed in numerous studies for TNBCs, identified according to certain criteria, demonstrate the pronounced heterogeneity of such tumors, which in turn presents difficulties for both the disease course prognosis and the selection of treatment strategy. On the other hand, such diversity within the identified group of breast carcinomas provides opportunities for the stratification of prognostic parameters and, consequently, for a wide range of therapeutic interventions (Hennigs et al., 2016; Pareja et al., 2016).

In 2011, the gene expression analysis of TNBC cases prompted a group of researchers led by Lehmann BD to describe seven possible subtypes within this breast cancer type (Lehmann et al., 2011). Lehmann et al. (2016) revised this classification on account of newly revealed features of breast cancers detected by the histologic evaluation, laser microdissection, and gene expression analysis of TNBCs. In this proposed classification, four tumor-specific subtypes were identified within this breast cancer phenotype: basal-like (BL; BL1 and BL2), mesenchymal, and luminal androgen receptor (LAR) subtypes. The BL subtypes

prevail in the TNBC group (up to 80% of cases), while the mesenchymal and LAR subtypes occur in a significantly smaller number of cases (Nielsen et al., 2004; le Du et al., 2015). According to studies carried out by Jiang et al. (2019), the occurrence frequency of LAR subtype was up to 23% of all TNBC cases included in the study group (based on genome sequencing of 360 cases).

Despite the significantly lower incidence of mesenchymal and LAR subtypes among TNBCs, according to the data presented in the literature, such tumors are biologically more aggressive. Echavarria et al. (2018) reported a more pronounced potential for distant dissemination in cases of mesenchymal tumors; in this TNBC type, distant metastases were most commonly diagnosed in the lungs. Other studies indicated that tumor cells in the mesenchymal TNBC subtype have high plasticity and the ability to differentiate into endothelial-like cells with the formation of vascular structures that can increase blood supply and consequently stimulate the processes of metastasis (Wagenblast et al., 2015; Camorani et al., 2017; Hill et al., 2019). The LAR subtype was characterized by the most frequent metastases in regional lymph nodes, and in cases of distant metastases, a tendency or tropism toward bone lesion was observed. It is worth noting that, when compared with BL1 TNBC, the LAR subtype was characterized by the lowest rate of pathologic complete response to chemotherapy (65.6% vs. 21.4%) (Echavarria et al., 2018). Therefore, it remains unclear which TNBC patients have a worse disease prognosis and a higher risk of distant tumor dissemination. This prompts the search for new biological markers that could be effective and possess personalized features for determining the likelihood of relapse and metastasis in TNBC (Balkenhol et al., 2020).

In this respect, the LAR subtype of TNBC is of particular interest. It is known that androgen receptor (AR) expression is detected in about 60%–80% of all breast carcinomas, with the highest frequency in ER-positive tumors. In TNBC, AR-positive tumors are considerably less common (Asano et al., 2016; Pietri et al., 2016; Bozovic-Spasojevic et al., 2017; Kensler et al., 2019; Vidula et al., 2019). In a study by Hon et al. (2016), the frequency of AR-positive expression in TNBC breast tumors ranged from 10% to 43%. However, in other studies, AR-positive TNBCs were detected in 55% (67/122) of cases, and this parameter was significantly higher in the group of elderly women (over 75 years) than in the group of younger women (55–64 years) (65% vs. 38%, P=0.004) (Honma et al., 2021). The high interest in thorough detailed studies on morphological and molecular features of LAR subtype tumors is fueled by the fact that currently available data on the prognostic value of AR expression in TNBC remain contradictory and unclear (Bozovic-Spasojevic et al., 2017; Kono et al., 2017; Gerratana et al., 2018; Anestis et al., 2020; Bhattarai et al., 2020; Honma et al., 2021).

2 Molecular, morphological, and genetic features

The review of literature data on the above-mentioned problem initially dictates the need to define concepts such as “AR-positive TNBC” and “LAR subtype of TNBC,” as there are differences in their criteria. AR-positive TNBCs are breast carcinomas with an appropriately confirmed molecular genetic profile, and they are characterized by the presence of positive AR immunohistochemistry expression in the tumor. In some cases, the indicator of AR-positive status in such carcinomas is determined in the presence of marker expression (AR>0%), whereas in other cases, TNBC is considered as AR-positive when the marker is expressed in the tumor of ⩾10%. In most studies presented in the literature, the LAR subtype is defined as a variant of TNBC, which includes not only the presence of an indicator of AR-positive expression, but also many other morphological, molecular, and genetic characteristics. Accordingly, these concepts cannot be considered identical. In this regard, in our review, we decided to conduct in-depth investigation and tried to organize the information available in the literature regarding the AR-positive TNBC and the LAR subtype.

The LAR subtype features high levels of AR expression, which is its specific hallmark. The level of this marker in LAR tumors is over 10 times higher compared to other variants of TNBC tumors described in Lehmann’s classification. The tumors whose molecular genetic profile corresponds to the LAR type of TNBC predominate in the group of older women (Kim et al., 2018; Ding et al., 2019).

Morphologically, the LAR subtype is characterized by the presence of apocrine differentiation features (apocrine carcinoma or carcinoma with apocrine features) (Choi et al., 2015; Kim et al., 2018; Borri and Granaglia, 2021). Among these TNBC tumors, non-ductal histology prevails and carcinomas have lower histological grades, low levels of Ki-67 expression, and the lowest levels of tumor infiltrating lymphocytes (TILs) (Wang et al., 2016; Kim et al., 2018; Dieci et al., 2019). Santonja et al. (2018) showed that, for a significant percentage of LAR tumors in the TNBC group (more than 71%), the proliferative index Ki-67 is 50% or less. In a study by Liu et al. (2016), 100% of LAR tumors (n=29) had a Ki-67 value of ⩾14%. At the same time, such carcinomas are described in the literature as breast cancers characterized by cellular immobility (Asghar et al., 2017).

The analysis of the transcriptome profile of 165 TNBC samples showed that LAR carcinomas can be characterized by a significant increase in the activity of signaling pathways crucial in the metabolism of androgens, estrogens, and porphyrins, and in the biosynthesis of steroid hormones, as well as by the elevated activity of peroxisome proliferator-activated receptor (PPAR) signaling pathway receptors that activate peroxisome proliferation. A specific feature of such tumors is that their gene expression profile is defined by the increased activity of the estrogen signaling pathway (Liu et al., 2016).

Breast tumors that belong to the LAR subtype are characterized by high/positive expression of luminal cytokeratins (CK7/8, CK18, and CK19) and the absence of expression of basal cytokeratins (CK5/6, CK14, and CK17) that are typical for the BL (BL1 and BL2) subtypes and mesenchymal subtypes of TNBC (Borri and Granaglia, 2021). It is important to note that there is long-standing evidence in the literature on that breast cancers positive for CK7/8, CK18, and CK19 are associated with a more favorable prognosis than carcinomas positive for basal phenotype markers (Abd El-Rehim et al., 2004).

The LAR subtype differs not only by AR-positive expression, but also by the presence of mutations in the phosphatidylinositol-3-kinases (PI3K) catalytic subunit α (PIK3CA) signaling pathway and the sensitivity to therapy with the dual PI3K inhibitor NVP-BEZ235 (Lehmann et al., 2011; Borri and Granaglia, 2021). Lehmann et al. (2011) presented their findings on the presence of mutations in the *PIK3CA* (55%), lysine methyltransferase 2C (*KMT2C*, 19%), and cadherin 1 (*CDH1*, 13%) genes in the LAR TNBC subtype. Bareche et al. (2018) also showed the presence of higher mutation load in similar breast tumors with the highest frequency of mutations in the *PI3KCA* (55%), protein kinase B (*AKT*, 13%) and *CDH1* (13%) genes. Kumar et al. (2021) analyzed cases of TNBC and detected *PIK3CA* mutations in 16.0% (13/80) of patients, of which 33.3% (4/12) were carcinomas of the LAR subtype.

The study of molecular features of the MDA-MB-231 cell line of TNBC by Li SP et al. (2021) indicated that exosomes can act as essential mediators of cancer progression. In particular, exosomes enriched with the CD151 protein were isolated in the studied cells, which, based on the obtained results, contributed to the processes of cell migration and tumor invasion (Li SP et al., 2021). Similar results were obtained by Li D et al. (2021), who devoted their study to the molecular mechanisms that determine the features of cancer progression in the LAR subtype of TNBC using the MDA-MB-453 cell line as an example. Their results indicated that the invasive potential of malignant tumor cells may be due to the activation of exosomes enriched with CD151. This assumption was made following the finding that CD151 knockdown in MDA-MB-453 cells in the LAR subtype was accompanied by a decrease in the invasive properties of these cells. This conclusion prompted the consideration of the exosomal CD151 protein as a potential target for the treatment of LAR subtype TNBC tumors (Li D et al., 2021).

3 Features of metastasis and disease prognosis

3.1 AR-positive TNBC

In the literature, AR-positive TNBCs are described as tumors with contradictory data on the course and prognosis of the disease. Bozovic-Spasojevic et al. (2017) used AR-positive expression as a prognostic hallmark in breast cancers at early stages, including TNBC, which was found to correlate with better overall and disease-free survival rates. A meta-analysis of TNBC focused on the study of AR expression characteristics in such tumors suggested that AR-positive status pointed to a low risk of disease recurrence

(Wang et al., 2016). The literature also included the results of a comprehensive analysis of 122 cases of TNBC with the comparison of data for AR-positive and AR-negative tumors. Based on the findings, Honma et al. (2021) concluded that AR-positive expression is an independent predictor of a favorable course and outcome of the disease with a low recurrence rate in patients over 75 years of age.

On the contrary, Dieci et al. (2019) studied the TNBC characteristics and found that the presence of AR-positive expression in the tumor is associated with low rates of metastasis-free survival in patients after chemotherapy and surgical treatment. Similar data were obtained by Choi et al. (2015), which indicated that AR-positive expression in TNBC is associated with worse overall survival.

Xu et al. (2020) published interesting findings regarding the prognosis of AR-positive TNBC in the *Journal of Clinical Breast Cancer*. Conducting searches for the necessary information in the PubMed, Embase, and Cochrane Library databases allowed the authors to include the results of 27 studies conducted between 1946 and 2019. The positive expression of ARs was determined in 1315 out of 4703 cases (27.96%). Regardless of the presence of various factors and the heterogeneity of cases included in their study, the findings suggested that the presence of AR-positive expression in TNBC carcinomas did not determine the rates of metastasis-free, relapse-free, or overall survival. Therefore, it was concluded that AR expression in TNBC was not associated with disease prognosis (Xu et al., 2020).

In the work by Choi et al. (2015), AR-positive expression in the group of TNBC patients with no lymph node metastases was identified as a significant predictor of poor overall and metastasis-free survival. In AR-positive TNBC carcinoma cases, a greater number of metastases in the regional lymph nodes were recorded than those in AR-negative tumors (Wang et al., 2016).

The evaluation of clinical and pathological parameters in AR-positive and AR-negative TNBC tumors provided evidence that the presence of positive AR expression in these breast carcinomas was associated with a higher incidence of metastases in the axillary lymph nodes (Astvatsaturyan et al., 2018).

Collina et al. (2019) analyzed tumor tissue samples from 163 cases of carcinomas with TNBC profile for the expression of long non-coding RNA (lncRNA) *HOTAIR* and identified certain regularities. The presence of a high expression of the marker was associated with the detection of metastases in the lymph nodes (P=0.039), as well as increased levels of AR expression (Collina et al., 2019).

3.2 LAR subtype of TNBC

Bareche et al. (2018) evaluated the genomic changes in TNBC tumors to determine the differences in patient survival rates, and found that the LAR subtype is associated with the worst prognosis in the course of the disease.

Studies on the features of tumor dissemination in LAR TNBC carcinomas are insufficiently represented in the literature. In a study by Liu et al. (2016) on the LAR subtype of TNBC, metastases were found in one to three lymph nodes in 17.2% of cases and more than three lymph nodes in 37.9% of cases. A retrospective study of 114 TNBC cases made it possible to identify 18 tumors of the LAR subtype profile, of which 33.3% were characterized by the presence of metastases in the lymph nodes, while no lymph node metastases were found in 67.7% of cases (Li et al., 2020). The highest percentage of lymph node involvement with metastases in the LAR subtype was also found by Elfgen et al. (2019). In a study by Echavarria et al. (2018) on TNBC, the highest incidence of regional lymph node involvement was observed in the LAR variant of TNBC, while such carcinomas also showed a clear tendency to distant metastases in the bones.

4 Clinical effect of therapy

Studies on the various molecular and genetic features of TNBC tumors with AR-positive expression and carcinomas of the LAR subtype are aimed at searching for possible targets in the framework of creating new therapeutic approaches for the treatment of such patients. Barton et al. (2017) suggested that AR activation had an effect on maintaining the population of malignant tumor stem cells that initiate a tumor, and served as a kind of anti-apoptotic factor, since the in vitro inhibition of ARs led to the inverse effect. Thus, these results demonstrated that treatment targeting AR can lead to an increase in the effectiveness of chemotherapy in cases of TNBC, even in cases

with a low expression of this marker (Barton et al., 2017).

The history of scientific research on TNBC is reflected in numerous studies, which represent continuous attempts to search for biological markers that can reveal the role of tumor molecular mechanisms in the drug resistance formation, predict the disease prognosis, and consequently differentiate patients within this molecular genetic type when choosing a therapy strategy. ARs in such breast tumors are considered as an attractive target in determining the most effective form of treatment (Marra et al., 2020).

4.1 AR-positive TNBC

The literature mostly included studies in which TNBC carcinomas were considered AR-positive, and where the positive expression of marker in the tumor was of ⩾10% (AR cutoff⩾10%). In a study by Gucalp et al. (2013) on bicalutamide in a phase II trial including metastatic TNBC carcinomas with AR-positive expression, no advantage in the clinical benefit rate (CBR) or median progression-free survival (mPFS) was found. The values of these indicators were 19% and 12 weeks, respectively. The criterion for AR-positive status for TNBCs in this study was the positive expression of the marker in the tumor at over 10% (Gucalp et al., 2013).

Given the presence of a nuclear AR pathway, Traina et al. (2018) studied the non-steroidal antiandrogen enzalutamide in a group of TNBC patients in a phase II trial, in order to analyze the possible overcoming of acquired resistance to androgens through the cytoplasmic AR pathway. Therein, two comparison groups were presented: AR-positive tumors with an AR-positive expression index of more than 0% (AR>0%) and AR-positive breast carcinomas with an AR-positive expression index of ⩾10% (AR⩾10%). The differences in the indicated groups in CBR and mPFS values were 25% and 2.9 months versus 33% and 3.3 months, respectively (Traina et al., 2018). In an earlier study, Traina et al. (2015) showed that in TNBC carcinomas with AR-positive expression in the tumor (AR⩾10%; n=56), the CBR with enzalutamide was 39%. This indicator in AR-negative TNBCs (n=62) corresponded to the value of 11% (Traina et al., 2015).

Similar indicators were presented in a study by Bonnefoi et al. (2016). The study group consisted of cases with metastatic and inoperable locally advanced TNBC, in which the level of positive expression of AR in the tumor tissue according to immunohistochemistry also corresponded to a value of ⩾10% (AR⩾10%). The evaluation of the CBR index was carried out using a steroid inhibitor of androgen biosynthesis—abiraterone acetate and prednisone. After six months, the values of CBR and mPFS were defined as 20% and 2.8 months, respectively (Bonnefoi et al., 2016).

4.2 LAR subtype of TNBC

Lehmann et al. (2011) devoted their study to the identification of various subtypes and preclinical models within TNBC to select targeted therapies, and their findings demonstrated the presence of high sensitivity to the non-steroidal antiandrogen drug bicalutamide in tumors developing from LAR-specific cell lines in vivo. Santonja et al. (2018) showed that patients with the LAR TNBC subtype have the highest resistance to neoadjuvant anthracyclines and/or taxane-based chemotherapy with a complete tumor response rate of just over 14%. The results presented by Asghar et al. (2017) indicated that LAR cell lines, unlike other TNBC subtypes, are characterized by high sensitivity to cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. In subsequent research, the assessment of genomic alterations in primary tumor tissue cells in TNBCs with AR-positive expression also confirmed the high probability of developing sensitivity when using CDK4/6 inhibitors for the therapy (Jiang et al., 2019).

5 Conclusions

This review unveiled that the clinical, morphological, and molecular genetic features of the LAR subtype of TNBC presented in the literature clearly indicate the existing differences and tumor heterogeneity of similar breast carcinomas. Numerous studies devoted to the various biological markers as potential factors for assessing the course and prognosis of the disease demonstrate significant differences from each other, and sometimes even completely opposite results.

Firstly, one of the reasons for such discrepancies between studies in the group of TNBCs can be the use of different methods for tumor subtyping. As

already presented, Lehmann et al. (2011) identified the LAR subtype as one of the seven variants of TNBC based on the data of expression genetic analysis, which classification is currently considered the "gold standard" (Lehmann et al., 2011; Kim et al., 2018). Burstein et al. (2015) also identified and confirmed the LAR subtype of TNBC as a separate unique variant, while their analysis was based on messenger RNA (mRNA) expression data and DNA copy number profiling results. Later, Lehmann et al. (2016), when detailing the previously presented classification, supplemented the data of gene expression analysis with the results of histology and laser microdissection. Subsequently, this led to a change in the criteria for TNBC subtyping and detailing of possible TNBC types (Lehmann et al., 2016). In addition, some TNBC subtyping studies only used the method of immunohistochemistry (with tissue microarray) with a surrogate panel of markers (Kim et al., 2018). Accordingly, the populations of TNBC LAR tumors described in this review, selected based on the different subtyping methods, are not identical, and thus may be the basis for explaining the described differences in clinical course, prognosis, processes of tumor dissemination, and therapeutic efficacy.

Secondly, the differences in the results of studies on AR-positive TNBC tumors and LAR subtype TNBCs may be due to the absence of a clearly defined indicator of positive AR expression (AR cutoff) in the tumor. As previously noted, in most studies, TNBC carcinomas were considered AR-positive, provided that the tumor has an AR expression of ⩾10%. Meanwhile, the literature presented the results for assessing the prognosis of the disease in cases of TNBC with an AR expression level of >0%. Such differences in the criteria for determining AR-positive TNBC tumors and LAR subtype TNBCs can have a significant impact on the prognostic indicators.

Thus, the presented review demonstrates the need for a clear understanding of which tumors can be isolated as the LAR subtype of TNBC, what key criteria can be determined for their identification, which typing method can act as the main technique, and what additional components can be used for detailing the subtype of carcinoma in cases of TNBC. Only such clearly defined approach will allow us to accurately define the LAR subtype of TNBC group patients, in order to form possible options for therapeutic strategies.

We consider the LAR subtype of TNBC as one of the most important topics in oncology that has not lost its relevance for several decades. One field of particular interest relates to the questions of development and clinical implementation of new drugs to overcome the existing mechanisms of tumor resistance to therapy.

Author contributions

Sergey VTORUSHIN determined the topic of article, carried out the study design and article revision. Anastasia DULESOVA collected the literature. Nadezhda KRAKHMAL collected the literature, wrote the article, and guided the article. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Sergey VTORUSHIN, Anastasia DULESOVA, and Nadezhda KRAKHMAL declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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