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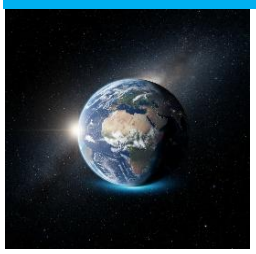

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Inflammatory Breast Cancer at Stage T4dN2aM0 – Efficacy of Neoadjuvant Therapy Based: A Case Report

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ABSTRAKT

A case of a 64-year-old female patient diagnosed with left-sided inflammatory breast cancer at stage T4dN2aM0 was described. Histopathological examination revealed grade 3 invasive ductal carcinoma, negative for hormonal receptor expression (ER−, PR−), with HER2 overexpression (3+) and a high Ki-67 proliferation index (85%). Metastatic involvement of the axillary lymph nodes was present.

Neoadjuvant therapy was administered, resulting in a partial clinical response. Subsequently, a modified radical mastectomy according to the Madden technique was performed. Postoperative histopathological assessment demonstrated no residual carcinoma within the breast (ypT0); however, metastatic involvement was confirmed in 5 lymph nodes (ypN2a). Adjuvant treatment included trastuzumab and radiotherapy.

During follow-up, no evidence of local recurrence or distant metastases was observed. Extended genetic testing did not identify mutations associated with hereditary cancer predisposition.

INTRODUCTION

Inflammatory breast cancer (IBC) is a rare (1–6%) but highly aggressive malignancy [1,2,3]. It is characterized by rapid disease progression and an increased risk of distant metastases [1]. According to the AJCC (American Joint Committee on Cancer) classification, inflammatory breast cancer is categorized as T4d. The diagnosis is based on the presence of erythema involving at least one-third of the breast surface, breast skin edema (peau d'orange sign), and increased breast warmth. The onset of symptoms is abrupt, and the clinical course is dynamic [1,4]. The majority of IBC cases (including the case described) represent invasive ductal carcinoma [1,5].

Treatment strategies that have significantly contributed to improved prognosis include neoadjuvant chemotherapy, surgical management, and radiotherapy [1,2]. Prior to the introduction of chemotherapy, treatment consisted solely of surgery and/or radiotherapy, which was associated with an approximately 5% five-year survival rate [1]. Currently, in patients with HER2 overexpression and no distant metastases, the addition of trastuzumab—a monoclonal antibody directed against the HER2 receptor—is recommended as part of chemotherapy [3,6]. An essential component during trastuzumab therapy is regular cardiological monitoring.

Although this agent demonstrates high therapeutic efficacy, it is associated with a risk of developing cardiotoxicity [7].

The HER2 receptor (human epidermal growth factor receptor 2) is expressed at low levels in many normal tissues. HER2 overexpression is observed in approximately 15–20% of breast cancer cases and constitutes a poor prognostic factor in untreated patients [8,9]. In breast cancer with high HER2 gene expression and concomitant absence of estrogen receptor (ER) and progesterone receptor (PR) expression, the tumor is classified as the intrinsic HER2-positive subtype. It has been proposed that intrinsic breast cancer subtypes may be determined on the basis of immunohistochemical evaluation of ER, PR, HER2, and Ki-67 [8]. Parameters such as the Ki-67 proliferation index are also useful factors in predicting response to treatment [8].

Keywords: Inflammatory breast cancer, Trastuzumab, Neoadjuvant therapy, BRCA1 gene, Post-mastectomy radiotherapy, HER2-positive breast cancer

CASE REPORT

A 64-year-old female patient presented for mammographic examination within a population-based screening program. The examination was performed on February 17, 2017. The technical quality of the acquired projections was assessed as adequate, allowing for reliable image interpretation. The mammographic imaging demonstrated a predominance of fatty glandular tissue composition. The examination was classified as BI-RADS 0 (Breast Imaging Reporting and Data System), indicating an inconclusive assessment and the need for urgent extension of imaging diagnostics.

Within the left breast, in the central region, a pathological shadow measuring approximately 60 × 50 mm was visualized, requiring further diagnostic verification. Extended diagnostic workup was recommended, including additional imaging studies and oncological consultation in order to differentiate the lesion and determine further therapeutic management. The patient was immediately referred to an oncology center, where comprehensive diagnostic evaluation was initiated. On March 9, 2017, breast ultrasonography and core needle biopsy (CNB) of the focal lesion were performed. Ultrasonographic examination revealed breasts with predominantly

fatty architecture. In the left breast, at the junction of the upper quadrants, a lesion measuring approximately 60 × 65 × 55 mm was identified, accompanied by overlying skin edema with a thickness of up to 10 mm. No focal lesions were detected in the right breast. In the left axilla, suspicious enlarged lymph nodes measuring up to 21 mm in diameter were visualized, whereas the right axilla was free of pathological findings. Fine-needle aspiration biopsy, and oncological consultation were recommended.

In the specimen obtained from the left breast tumor (at the junction of the upper quadrants), histopathological examination revealed carcinoma ductale invasivum mammae (invasive ductal carcinoma of the breast), histological grade G3 according to the Elston–Ellis classification (Nottingham Grading System). In the specimen collected from the left axillary lymph node, the presence of malignant cells (cellulae carcinomatosae) was confirmed. Subsequently, on March 11, 2017, an ultrasound-guided fine-needle aspiration biopsy (FNAB) of the left breast lesion was performed. The procedure was completed without complications. Immunohistochemical analysis demonstrated: absence of estrogen receptor expression (ER−) and progesterone receptor expression (PR−), overexpression of the HER2 receptor (3+), positive E-cadherin expression (E-cadherin +), and a high Ki-67 proliferation index of 85%.

Based on the clinical presentation, imaging findings, and immunohistochemical profile, the patient was diagnosed with left breast cancer at clinical stage T4dN2aM0 (T4d – inflammatory breast cancer; N2a – metastases to 4–9 axillary lymph nodes; M0 – no distant metastases), with clinical features consistent with inflammatory carcinoma.

The biological characteristics of the tumor — absence of hormonal receptor expression (ER−, PR−), HER2 receptor overexpression (3+), and a high Ki-67 proliferation index — corresponded to the non-luminal HER2-positive subtype, associated with high biological aggressiveness.

On March 28, 2017, the patient's case was presented at a meeting of the multidisciplinary oncological tumor board. Based on the overall clinical presentation, imaging findings, and histopathological results, a decision was made to initiate systemic therapy consisting of targeted treatment with trastuzumab combined with chemotherapy using carboplatin and docetaxel. A total of 18 cycles of trastuzumab were planned, including 6 cycles administered in combination with carboplatin and docetaxel prior to the planned surgical intervention, followed by

continuation of targeted therapy in the form of 12 additional administrations of trastuzumab as adjuvant treatment after surgery.

On March 29, 2017, the patient was qualified for the first cycle of systemic therapy. Prior to treatment initiation, routine laboratory investigations and electrocardiography (ECG) were performed. The ECG demonstrated left axis deviation, regular sinus rhythm at a rate of 84 beats per minute, and features consistent with left ventricular hypertrophy. Laboratory investigations revealed mildly decreased erythrocyte count, hemoglobin concentration, and hematocrit values, consistent with mild anemia. Additionally, a slight decrease in the percentage of eosinophils and a minor increase in the percentage of monocytes and basophils were observed. These abnormalities were minimal in nature and of no significant clinical relevance, and therefore did not constitute a contraindication to the initiation of systemic therapy (TABLE 1). The patient received the first cycle of therapy consisting of trastuzumab, carboplatin, and docetaxel. The treatment was well tolerated, without significant adverse events. The patient was discharged from the hospital the following day in good general condition.

TABLE 1: Blood Tests – 29.03.2017

Parameter	**Result**	**Reference Range**
Alanine aminotransferase (ALT)	20.8 U/L	0.0 – 33.0 U/L
Aspartate aminotransferase (AST)	17.4 U/L	0.0 – 31.0 U/L
Total bilirubin	5.70 µmol/L	0.00 – 17.10 µmol/L
Sodium	140 mmol/L	136 – 145 mmol/L
Potassium	4.05 mmol/L	3.50 – 5.10 mmol/L
Creatinine	66.00 µmol/L	45.00 – 84.00 µmol/L
Estimated glomerular filtration rate (eGFR)	78.5 mL/min/1.73 m²	———————————
Urea	6.20 mmol/L	0.00 – 8.30 mmol/L
Leukocytes	5.34 G/L	4.00 – 10.00 G/L
Erythrocytes	3.76 T/L	4.00 – 5.00 T/L
Hemoglobin	11.0 g/dL	12.0 – 16.0 g/dL
Hematocrit	34.3%	37.0 – 47.0 %
Mean corpuscular volume (MCV)	91.2 fl	84.0 – 94.0 fl

Mean corpuscular hemoglobin (MCH)	29.3 pg	27.0 – 34.0 pg
Mean corpuscular hemoglobin concentration (MCHC)	32.1 g/dL	31.0 – 37.0 g/dL
Platelets	204 G/L	130 – 350 G/L
Nucleated red blood cells (NRBC)	0.000 G/L	0.000 – 0.015 G/L
NRBC %	0.000/100 WBC (White blood cells)	0.000 – 0.030 WBC (White blood cells)
Red cell distribution width – coefficient of variation (RDW-CV)	14.2%	11.5 – 14.5 %
Platelet large cell ratio (P-LCR)	35.5%	19.5 – 43.8 %
Neutrophils	3.52 G/L	1.80 – 7.50 G/L
Lymphocytes	1.21 G/L	1.00 – 4.00 G/L
Monocytes	0.46 G/L	0.10 – 0.80 G/L
Eosinophils	0.05 G/L	0.04 – 0.50 G/L
Basophils	0.08 G/L	0.00 – 0.10 G/L
Neutrophils %	65.9%	45.0 – 75.0 %
Lymphocytes %	22.7%	20.0 – 45.0 %
Monocytes %	8.6%	2.0 – 8.0 %
Eosinophils %	0.9%	1.0 – 5.0 %
Basophils %	1.5%	0.0 – 1.0 %
Immature granulocytes (IG)	0.02 G/L	0.01 – 0.04 G/L
IG %	0.4%	0.16 – 0.62 %

Subsequent cycles of systemic therapy consisting of trastuzumab + carboplatin + docetaxel were administered on April 19, 2017, and May 10, 2017. Prior to each administration, follow-up laboratory investigations and electrocardiographic (ECG) assessments were performed. The obtained results remained within normal limits, and the patient's general condition allowed for continuation of therapy. The treatment was well tolerated, without significant adverse effects. After each cycle, the patient was discharged home in good general condition. On May 10, 2017, concurrently with the administration of the subsequent chemotherapy cycle, a follow-up breast ultrasonography was performed to evaluate therapeutic response. The examination demonstrated a reduction in the dimensions of the previously described neoplastic lesion in the

left breast at the junction of the upper quadrants, currently measuring approximately 40 × 32 × 28 mm. A reduction in lymphatic edema was also noted, with associated decrease in skin thickening to 4 mm. Apart from the described lesion, no additional pathological foci were visualized in either breast. In the left axilla, multiple pathologically altered lymph nodes were still present; however, their dimensions had decreased, currently measuring up to 18 × 12 × 9 mm. The right axilla remained free of pathological findings. Subsequent cycles of therapy within the same regimen were administered on May 31, June 21, and July 13, 2017. The treatment course was uncomplicated, and the patient maintained good tolerance to therapy.

On June 29, 2017, the patient underwent a surgical consultation. Following evaluation of the therapeutic course to date and the achieved partial response to neoadjuvant treatment, a decision was made to qualify the patient for surgical management, scheduled for August 1, 2017. On July 31, 2017, the patient was admitted to the Clinical Department of Breast Cancer and Reconstructive Surgery for radical surgical treatment of the left breast malignancy after completion of 6 cycles of neoadjuvant chemotherapy (docetaxel + carboplatin + trastuzumab). On August 1, 2017, a left-sided mastectomy was performed using the Madden technique (modified radical mastectomy with axillary lymphadenectomy preserving the pectoral muscles). The postoperative course was uneventful. During hospitalization, comprehensive rehabilitation was implemented, including active free exercises, assisted exercises, isometric exercises, and individually tailored general conditioning exercises aimed at prevention of lymphedema and improvement of the range of motion of the ipsilateral upper limb. The patient was discharged home on August 10 in good general condition. During the surgical procedure, tissue specimens were obtained for histopathological examination. The results were communicated to the patient on August 11, 2017 (examination performed on August 7, 2017). The submitted material included the left breast with nipple–areolar complex and axillary contents; the specimen measured 29.0 × 19.0 × 8.5 cm. Histopathological evaluation revealed carcinoma invasivum post immunochemotherapiam, classified as ypT0N2a (yp – post-neoadjuvant assessment; T0 – no residual invasive carcinoma identified in the resected breast specimen; N2a – metastases present in 4–9 axillary lymph nodes). No viable residual carcinoma was identified within the breast parenchyma. At the junction of the upper quadrants, an area of necrosis measuring 3.5 cm in diameter was observed, accompanied by peripheral fibrosis and inflammatory reaction. The remaining breast tissue demonstrated adipose atrophy with focal fibrosis. A total of 33 lymph nodes were isolated from the left axillary dissection specimen. Metastatic carcinoma was identified in 5 lymph nodes (4 in the lower level and 1 in the middle level), without

extracapsular extension (no evidence of extranodal spread). Some lymph nodes demonstrated advanced fibrosis.

On August 24, 2017, the patient commenced continuation of therapy with subcutaneous trastuzumab, in accordance with the established adjuvant treatment protocol.

Between September 4 and September 29, 2017, the patient underwent adjuvant radiotherapy of a radical intent. The treatment was delivered on an outpatient basis, daily on working days, for a total of 20 fractions. A three-dimensional conformal radiotherapy technique (3D-CRT) was applied using photon (X-ray) beams with energies of 6 and 15 MV. The irradiation fields encompassed the left chest wall and regional lymphatic drainage areas, including the axillary fossa, supraclavicular, and infraclavicular regions, with an appropriate safety margin. A total dose of 45 Gy was administered, fractionated at 2.25 Gy per fraction over 20 fractions. Radiotherapy was well tolerated; the patient did not report significant adverse effects or symptoms of acute radiation toxicity. During the final visit in the course of radiotherapy, follow-up laboratory investigations (TABLE 2) and electrocardiography (ECG) were performed. The ECG demonstrated an intermediate electrical axis, regular sinus rhythm at a rate of 69 beats per minute, and persistent features of left ventricular hypertrophy. Laboratory findings revealed anemia with a mildly elevated mean corpuscular volume (MCV).

TABLE 2: Blood Tests – 29.09.2017

Parameter	**Result**	**Reference Range**
Alanine aminotransferase (ALT)	24.9 U/L	0.0 – 33.0 U/L
Aspartate aminotransferase (AST)	21.4 U/L	0.0 – 31.0 U/L
Total bilirubin	2.90 µmol/L	0.00 – 17.10 µmol/L
Sodium	144 mmol/L	136 – 145 mmol/L
Potassium	4.46 mmol/L	3.50 – 5.10 mmol/L
Creatinine	61.00 µmol/L	45.00 – 84.00 µmol/L
Estimated glomerular filtration rate (eGFR)	85.9 mL/min/1.73 m²	————————
Leukocytes	5.94 G/L	4.00 – 10.00 G/L
Erythrocytes	3.47 T/L	4.00 – 5.00 T/L
Hemoglobin	11.5 g/dL	12.0 – 16.0 g/dL

Hematocrit	35.7%	37.0 – 47.0 %
Mean corpuscular volume (MCV)	102.9 fl	84.0 – 94.0 fl
Mean corpuscular hemoglobin (MCH)	33.1 pg	27.0 – 34.0 pg
Mean corpuscular hemoglobin concentration (MCHC)	32.2 g/dL	31.0 – 37.0 g/dL
Platelets	183 G/L	130 – 350 G/L
Nucleated red blood cells (NRBC)	0.000 G/L	0.000 – 0.015 G/L
NRBC %	0.000/100 WBC (White blood cells)	0.000 – 0.030 WBC (White blood cells)
Red cell distribution width – coefficient of variation (RDW-CV)	13.9%	11.5 – 14.5 %
Platelet large cell ratio (P-LCR)	32.3%	19.5 – 43.8 %
Neutrophils	3.66 G/L	1.80 – 7.50 G/L
Lymphocytes	1.60 G/L	1.00 – 4.00 G/L
Monocytes	0.49 G/L	0.10 – 0.80 G/L
Eosinophils	0.13 G/L	0.04 – 0.50 G/L
Basophils	0.04 G/L	0.00 – 0.10 G/L
Neutrophils %	61.7%	45.0 – 75.0 %
Lymphocytes %	26.9%	20.0 – 45.0 %
Monocytes %	8.2%	2.0 – 8.0 %
Eosinophils %	2.2%	1.0 – 5.0 %
Basophils %	0.7%	0.0 – 1.0 %
Immature granulocytes (IG)	0.02 G/L	0.01 – 0.04 G/L
IG %	0.3%	0.16 – 0.62 %

Subsequent subcutaneous doses of trastuzumab were administered on the following dates: September 14, 2017; October 5 and 26, 2017; November 16, 2017; December 7, 2017; January 12, 2018; February 2 and 23, 2018; March 16, 2018; and April 6 and 27, 2018. Treatment was delivered in accordance with the established adjuvant therapeutic protocol.

On November 16, 2017, a follow-up ultrasonographic examination was performed. The imaging described the status post left-sided mastectomy. Within the postoperative scar, edema with skin thickening up to 5 mm and fibrotic band-like changes were observed. Along the entire length of the scar, a partially condensed fluid collection was visualized; at the junction of the axillary fossa and the lateral margin of the scar, it measured 24 × 18 × 70 mm, whereas in the remaining portion it assumed a slit-like configuration up to 4 mm in thickness. In the right axilla, single elongated lymph nodes with a slightly widened peripheral cortex were identified, measuring up to 6 mm in the short axis, suggestive of reactive etiology; ultrasonographic follow-up was recommended. Apart from these findings, the scar region and axillary fossae showed no abnormalities. The right breast demonstrated predominantly fatty composition, without focal lesions suggestive of malignancy.

A subsequent follow-up ultrasonography was performed on January 12, 2018, during administration of the 12th dose of targeted therapy (FIGURE 1). The imaging findings were essentially stable: edema within the scar region with skin thickening up to 5 mm and fibrotic band-like changes persisted. Along the scar, a heterogeneous fluid collection was present; at the lateral margin of the scar and the border of the axillary fossa, a reservoir measuring 28 × 12 mm was described, transitioning into a slit-like area up to 5.5 mm, and more medially, an additional collection measuring 30 × 11 mm was identified. In the right axilla, normal-appearing lymph nodes measuring up to 6 mm in the short axis were observed. No features of local recurrence or new focal lesions were identified. The right breast remained predominantly fatty in composition, without focal lesions suggestive of neoplastic pathology.

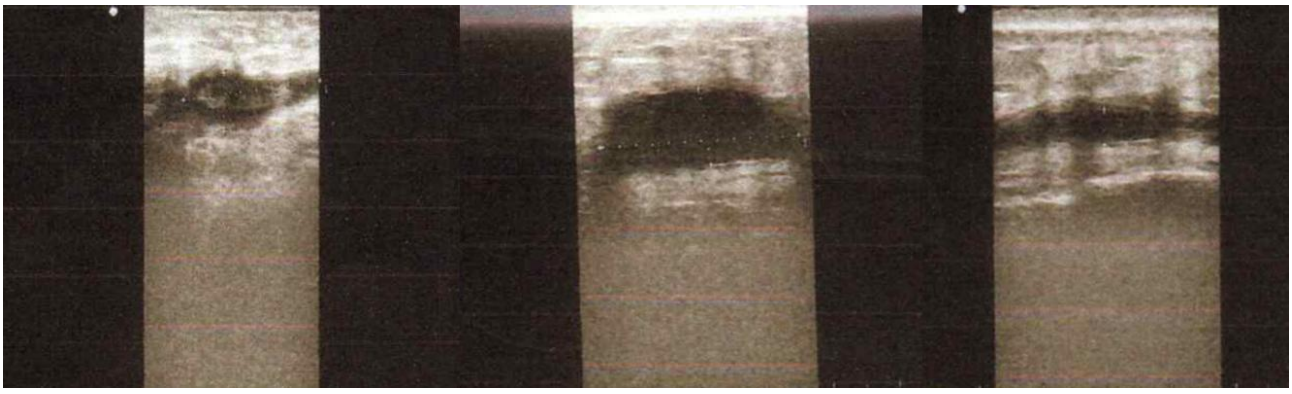

FIGURE 1: Breast Ultrasonography – 12.01.2018

On April 13 and May 25, 2018, follow-up echocardiographic examinations were performed. In both studies, no abnormalities of myocardial contractility or significant reduction in left ventricular ejection fraction were identified, indicating the absence of absolute contraindications to continuation of trastuzumab therapy, with ongoing cardiological surveillance. On June 8, 2018, the patient presented for a visit concluding systemic therapy. Continued oncological follow-up and periodic ultrasonographic examinations were recommended.

Ultrasonography performed on June 26, 2018, demonstrated the status post left-sided mastectomy, with persistent edema and skin thickening up to 5 mm, as well as band-like fibrosis within the postoperative scar. In the left axilla, a hypoechoic area measuring 27 × 17 mm was visualized, with a centrally located slit-like collection of condensed fluid, interpreted as a postoperative lesion. The right axilla and right breast remained unremarkable.

In subsequent follow-up ultrasonographic examinations, no evidence of local recurrence or metastases to regional lymph nodes was identified. The clinical and radiological status remained stable.

On August 31, 2021, the patient presented to a genetic counseling clinic due to a diagnosis of breast cancer in her daughter, constituting an indication for assessment of familial predisposition to malignant neoplasms. At the initial stage of genetic evaluation, testing for the five most common mutations in the BRCA1 gene was performed. No pathogenic variants were detected in the analyzed material.

On October 29, 2021, the patient was referred for fitting of an external breast prosthesis in order to improve physical comfort, aesthetic outcome, and overall quality of life following surgical treatment.

Subsequently, on February 15, 2022, molecular testing for mutations in the CHEK2 and PALB2 genes was conducted. No pathogenic variants were identified in these genes. To further extend the diagnostic workup, on April 27, 2022, a comprehensive oncological panel comprising 81 genes associated with increased cancer susceptibility was recommended. The analysis was performed using next-generation sequencing (NGS) methodology, followed by interpretation of detected variants in the context of their potential pathogenicity. Within the analyzed gene

panel, no known pathogenic variants associated with increased predisposition to malignancy were identified.

At this stage, genetic diagnostics were concluded, without confirmation of markers indicative of a hereditary cancer predisposition syndrome.

DISCUSSION

In the presented case, the patient was diagnosed with inflammatory breast cancer and the non-luminal HER2-positive subtype (ER−, PR−, HER2 3+, Ki-67 85%). Inflammatory breast cancer (IBC) is characterized by an aggressive clinical course and is classified as T4d [1,2,3]. HER2 overexpression is associated with a high proliferative activity of tumor cells; however, the introduction of anti-HER2 targeted therapy has significantly improved treatment outcomes in this patient population [8].

The therapeutic approach applied in this case, consistent with current clinical guidelines, included preoperative systemic therapy, surgical management using the Madden technique, adjuvant radiotherapy, and anti-HER2 therapy [1,3]. Neoadjuvant treatment resulted in tumor regression, which was confirmed by histopathological examination of the surgical specimen (ypT0). Nevertheless, the persistence of metastatic involvement in regional lymph nodes (ypN2a) indicates heterogeneity of treatment response and an increased risk of disease recurrence.

CONCLUSION

During long-term follow-up, no evidence of local recurrence or distant metastases was observed, confirming the effectiveness of the applied therapeutic strategy despite the initially advanced stage of disease (T4dN2aM0).

The implementation of a multidisciplinary combined treatment approach—including neoadjuvant chemotherapy with anti-HER2 therapy, radical surgical management, and radiotherapy—enables the achievement of a significant clinical and pathological response even in advanced cases.

Disclosure:

The authors declare that they have no financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the content of this manuscript. This work was conducted independently without any external funding or support.

Author's contribution:

Conceptualization: Sandra Czyż; methodology: Sandra Czyż; software: Wiktoria Marszał; check: Wiktoria Marszał; formal analysis: Wiktoria Marszał, Sandra Czyż; investigation: Sandra Czyż; resources: Sandra Czyż; data curation: Wiktoria Marszał; writing – rough preparation: Sandra Czyż,; writing – review and editing: Wiktoria Marszał, Sandra Czyż; visualization: Sandra Czyż; supervision: Sandra Czyż; project administration: Wiktoria Marszał; receiving funding: Not applicable All authors have read and agreed with the published version of the manuscript.

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Informed Consent Statement:

Our work did not involve direct human subject research or obtaining their consent for participation in the study.

Data Availability Statement:

Since this is a review paper, our work does not contain new data or analyses. Consequently, there are no particular databases or data accessibility to outline. The details and conclusions presented in this review are derived from previously published studies, which can be accessed through their respective sources as mentioned in the reference section

Conflicts of Interest Statement:

The authors assert that there are no notable conflicts of interest linked to this research endeavor.

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