Case Report

Targeting the Warburg Effect with the Glucose Mutation Theory: A Case Study of 36-Year-Old Female Treated for Stage IV Metastatic TPBCUsing Glucosodiene Over a 15-Day Period

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Triple-positive breast cancer, characterized by the concurrent overexpression of estrogen receptors (ER+), progesterone receptors (PR+), and human epidermal growth factor receptor 2 (HER2+), presents a significant clinical challenge in oncology. This particular subtype, distinguished by its aggressive behavior and propensity for metastasis, necessitates a comprehensive therapeutic approach. Current treatment modalities, primarily centered around targeted therapies, encounter obstacles, underscoring the imperative to explore alternative interventions. The emergence of Glucosodiene, grounded in Maher Akl's hypothesis regarding glucose mutation, introduces a promising avenue for therapeutic intervention. This innovative pharmacological agent exhibits efficacy in targeting the Warburg effect, a characteristic feature of tumors reliant on anaerobic glucose metabolism. A positron emission tomography (PET) scan conducted on a 36-year-old female patient following oral administration of Glucosodiene at a daily dosage of 100 ml over 15 consecutive days revealed encouraging findings, including regression of lesions in the left breast and a favorable response in axillary lymph nodes. Additionally, improvement was evident in the abdomino-pelvic region and musculoskeletal system, indicative of a partial metabolic response compared to prior imaging studies. Noteworthy reductions were observed in the number, size, and metabolic activity of osseous lesions, indicative of favorable disease progression. The mechanistic underpinnings of Glucosodiene position it as a versatile and impactful therapeutic option in the

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landscape of cancer management, offering promise for enhanced patient outcomes. The trial is registered under clinicaltrials.gov number NCT05957939.

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1. *Background*

Triple-positive breast cancer, characterized by the overexpression of estrogen receptors (ER+), progesterone receptors (PR+), and human epidermal growth factor receptor 2 (HER2+), represents a formidable challenge in oncology. The positive HER2 status in this subtype accentuates the aggressive nature of the disease, elevating its potential for rapid progression and metastasis. The amplification of HER2, a proto-oncogene, intensifies the signal transduction pathways, fostering uncontrolled cell growth and proliferation. One pivotal aspect of concern is the propensity of triple-positive breast cancer to invade the lymph nodes, significantly amplifying the risk of distant metastasis. The intricate interplay between HER2 overexpression and lymph node involvement underscores the intricate pathophysiology of this malignancy, necessitating comprehensive diagnostic and therapeutic strategies.[1][2][3] Addressing the therapeutic landscape, current modalities predominantly focus on targeted therapies, such as anti-HER2 agents like trastuzumab and pertuzumab. These drugs aim to impede HER2-mediated signaling cascades, hindering tumor progression. Despite the remarkable advancements, challenges persist, with treatment limitations and the emergence of resistance posing formidable hurdles.[4] The complexity of triple-positive breast cancer demands a multifaceted approach, integrating chemotherapy, endocrine therapy for ER and PR components, and HER2-targeted agents.[5]

Moreover, the limitations of existing treatments become evident in the face of resistance mechanisms, necessitating ongoing research into novel therapeutic avenues. The quest for more effective interventions against triple-positive breast cancer remains an imperative in the relentless pursuit of improving patient outcomes and mitigating the morbidity associated with this intricate malignancy.[6] Maher Akl's theory on glucose mutation has laid the foundation for the development of Glucosodiene, offering a ray of hope amidst the formidable challenges. This innovative drug exhibits great promise in targeting the Warburg effect prevalent in tumors dependent on anaerobic glucose metabolism.[7] Notably, positive outcomes have been documented, exemplified by a case study

involving a patient with metastatic triple-negative breast cancer affecting the bones. Within a concise 15-day treatment period, Glucosodiene demonstrated remarkable efficacy, leading to significant improvements. [8] This case pertains to a, 36-year-old lady patient of Caucasian and Arab descent, with a notable family medical history, including pancreatic cancer in an aunt, stomach cancer in an uncle, uterine cancer in another aunt, and colon cancer in her grandfather. After approximately three years of treatment without significant improvement, the patient's condition remained refractory to therapeutic interventions. Despite the implementation of sequential regimens, including PACLITAXEL/PERJETA/HERCEPTIN, KADCYLA, and ENHERTU, the disease demonstrated relentless progression, as evidenced by the persistence of severe cervical pain and paresthesia in the left upper limb, alongside the PET-CT scan revealing ongoing involvement of the breast, lymph nodes, and bones. The affirmative response observed in this triple-positive breast cancer case, juxtaposed against a comparable timeframe to the previous case of TNBC, accentuates Glucosodiene's capacity to effectively target all recognized breast cancer receptors. This compound presents itself as a multifaceted therapeutic modality, poised to serve as a primary, secondary, adjunctive, or salvage therapy, particularly in instances where conventional treatment modalities falter. Anchored in its mechanism of action, which selectively targets the Warburg effect within the tumor microenvironment, Glucosodiene emerges as a versatile and impactful contender in the landscape of cancer therapeutics, offering renewed hope for patients with refractory breast cancer.

2. *Patient information*

This case pertains to a, 36-year-old lady patient of Caucasian and Arab descent, with a notable family medical history, including pancreatic cancer in an aunt, stomach cancer in an uncle, uterine cancer in another aunt, and colon cancer in her grandfather.

2.1. Clinical findings timeline

The patient has been under medical surveillance since **March 2021** for left-sided breast carcinoma, characterized by positivity for estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2, (ER+, PR+, HER2+), The tumor exhibited a high proliferation index (Ki-67 at 50%) and demonstrated axillary lymph node involvement. Additionally, an lytic lesion at the T11 vertebra was noted upon diagnosis. Treatment initiation involved a regimen comprising PACLITAXEL/PERJETA/HERCEPTIN, administered for 5 cycles, followed by maintenance therapy with

PERJETA/HERCEPTIN. In January 2022, due to osseous progression, the regimen was switched to KADCYLA, with the patient receiving 15 cycles until **October 2022**. Subsequently, ENHERTU was commenced. However, treatment was prematurely halted after the 4th cycle of ENHERTU due to the patient's travel plans.Upon her return, the patient presented with severe cervical pain and paresthesia in the left upper limb in September. A PET-CT scan conducted **on September 8, 2023** revealed progression of disease involving the breast, lymph nodes, and bones. [Figure 1]

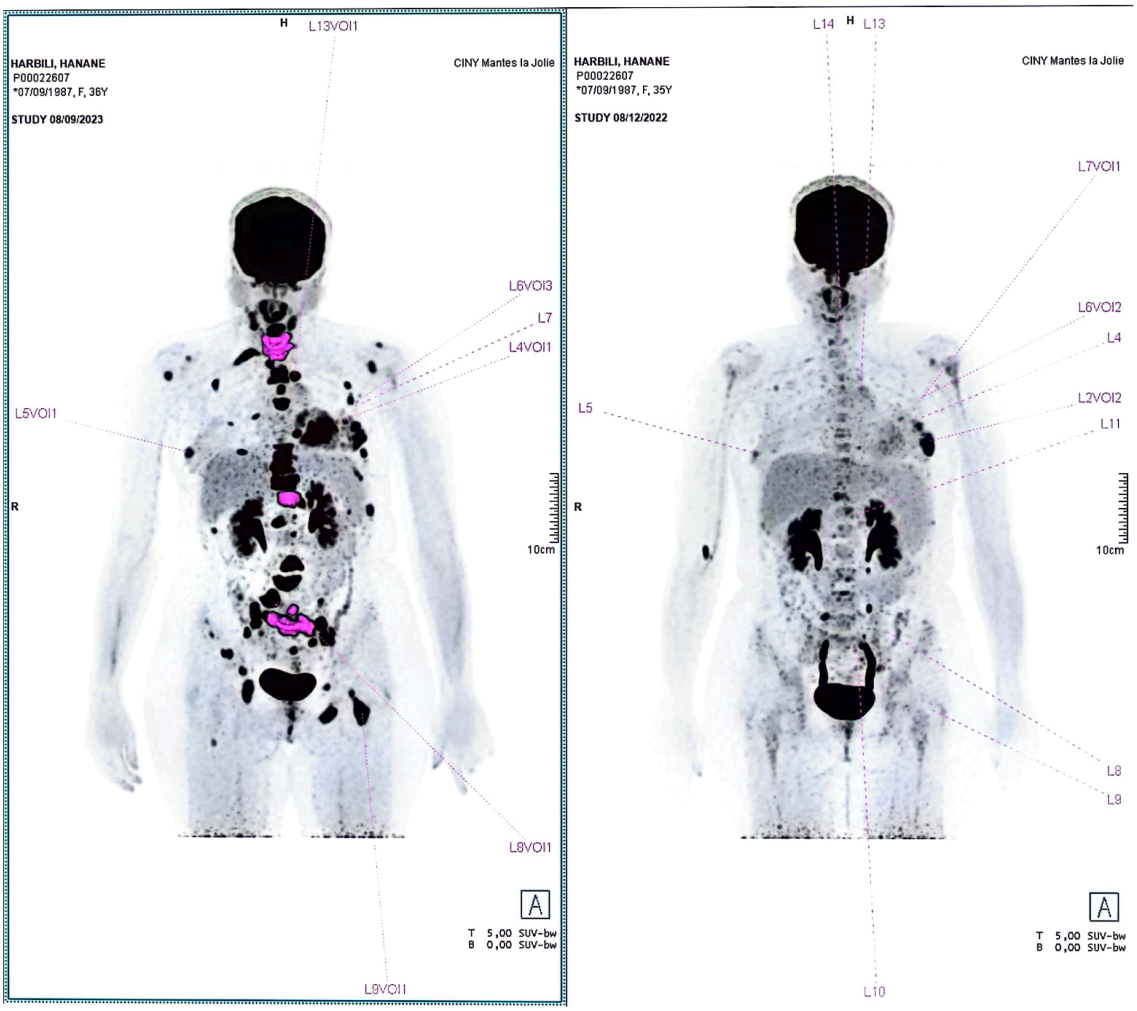

Figure 1. On September 8, 2023 In the cervico-encephalic region, no suspicious hypermetabolic focus was observed in the cerebral area, nor in the cervical lymph nodes or upper aerodigestive tract. Similarly, no abnormal hypermetabolic focus was detected in the thoracic pulmonary area. Regarding the evaluation of the breast mass, morpho-metabolic stability was noted in the left breast mass at the junction of the outer quadrants, while metabolic progression was observed in the mass of the upper outer quadrant of the left breast, contiguous to the previously described lesion. Additionally, metabolic progression was detected in the focus at the junction of the upper quadrants of the left breast. Morpho-metabolic progression was also noted in the previously described focus at the junction of the outer quadrants of the right breast. In the axillary lymph nodes, there was morpho-metabolic progression in the previously described left axillary lymph nodes, with additional involvement adjacent to the outer border of the pectoralis minor muscle. Moving to the abdomino-pelvic region, no suspicious hypermetabolic focus was identified in the liver, spleen, adrenal glands, or pancreas, nor in the para-aortic or pelvic lymph nodes. Stable increased uptake was observed in the left ovarian region, non-specific for age. In the musculoskeletal system, marked progression was noted in the number, extent, and intensity of known secondary osseous lesions, now

manifesting as lytic lesions. Notable targets included lytic lesions at various locations, with significant progression observed in the sacral lesion and the emergence of multiple intensely hypermetabolic lytic lesions.

Compared to the previous PET scan **On December 8, 2022**, there was evidence of progression in the breast lesions, axillary lymph nodes, and osseous lesions, highlighting the aggressive nature of the disease and the need for further investigation and management. An urgent MRI performed **on September 15, 2023** confirmed multiple secondary spinal lesions extending from the cervical to sacral spine, complicated by pathological fractures, notably at C4, C6, C7, T1, T4, T11, T12, L4, and S1 levels. Neurosurgical consultation was sought from Hospital Foch, with additional imaging requested before therapeutic decision-making. Immediate immobilization with cervical collar and brace was implemented, alongside urgent radiotherapy.

During the initial preparation phase, 24 to 48 hours before Glucosodiene treatment, the patient strictly adhered to a specialized diet, eliminating all sources of glucose, sugars, and carbohydrates. **On 7 February 2024**, the patient commenced treatment with Glucosodiene at a dosage of 100 milliliters orally daily, starting on the fifth day. Notable improvement was reported by the patient, particularly in bone pain intensity, along with regained mobility and functionality without experiencing fatigue. The patient completed a total of 15 doses of Glucosodiene, administered orally every 24 hours. Subsequently, **on February 22, 2024**, a PET scan was conducted to assess treatment response. [Figure 2]

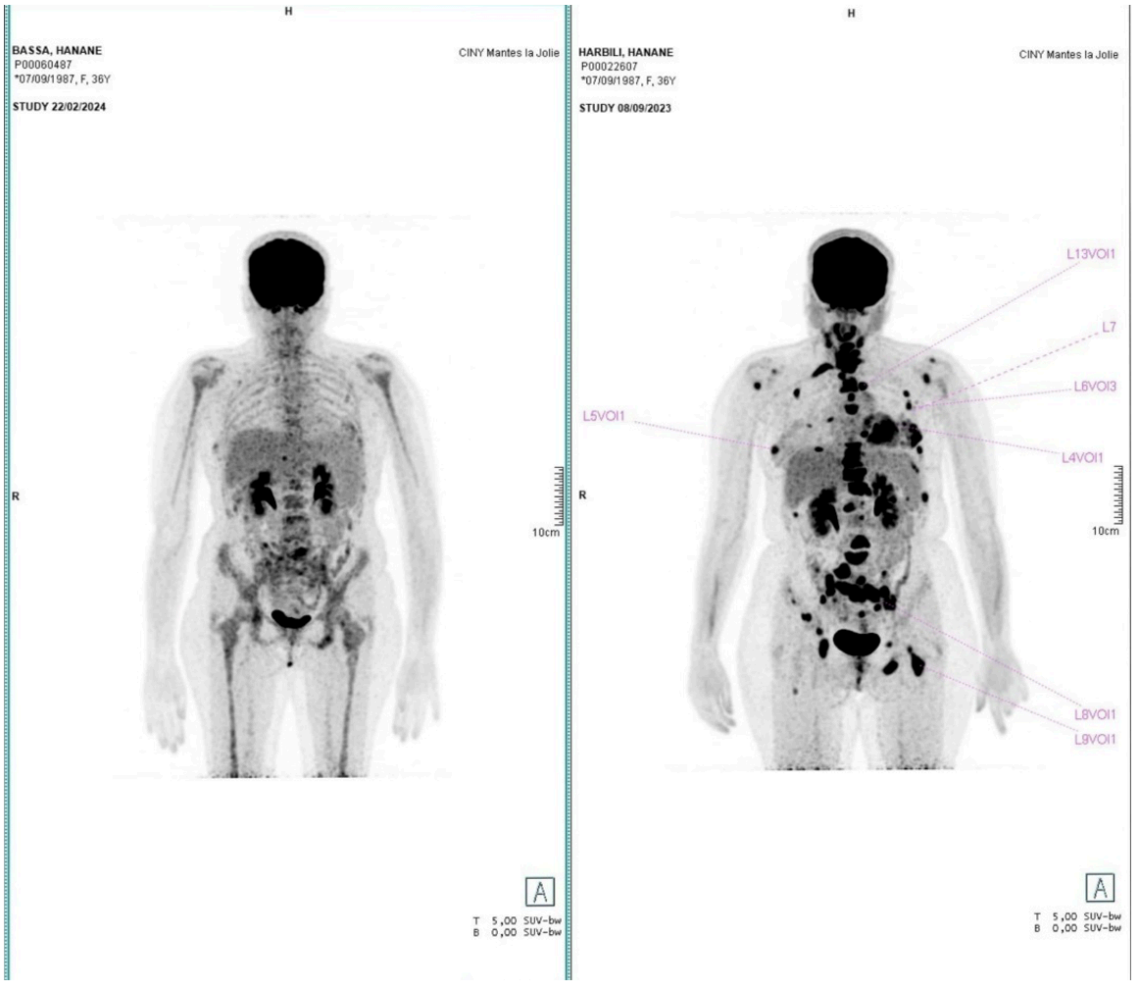

Figure 2. The PET scan conducted **on February 22, 2024**, showed promising results for the patient. No abnormal metabolic activity was detected in the cervico-encephalic or thoracic regions. Partial regression was noted in left breast lesions, with a positive response in axillary lymph nodes.

No abnormal metabolic activity was found in the abdomino-pelvic region, with improvement seen in the musculoskeletal system. Overall, compared to the previous scan, there was a partial metabolic response to treatment, indicating positive progress in the patient's condition.In the cervico-encephalic region, no suspicious hypermetabolic focus was observed in the cervical or cerebral regions. Similarly, no abnormal hypermetabolic focus was detected in the pulmonary parenchyma. Regarding breast lesions, a partial morpho-metabolic regression was noted in the left multifocal breast lesions, while a partial morpho-metabolic response was observed in the right breast lesion. Additionally, a near-complete to complete metabolic response was observed in the left axillary lymph nodes.In the abdomino-pelvic region, no suspicious hypermetabolic focus was identified in the hepatic, adrenal, splenic, or pancreatic regions, nor in the coeliac-mesenteric, para-aortic, or pelvic lymph nodes. A partial metabolic response was observed in the left ovarian region, with no evidence of peritoneal effusion or peritoneal nodules.

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In the musculoskeletal system, there was a marked regression in the number, size, and intensity of hypermetabolic osseous lesions, presenting as secondary lesions with a denser appearance. Various bones showed improvement, including the iliac wings, sacrum, pelvic branches, coccyx, ribs, sternum, clavicles, femurs, and humeri, comparative to the PET scan conducted **on September 8, 2023**, there was evidence of a partial metabolic response, with improvements observed in breast lesions, axillary lymph nodes, and disseminated secondary osseous lesions. No new suspicious foci were detected. In the clinical assessment of This patient with metastatic TPBC, monitoring biomarkers such as Alkaline Phosphatase (ALP), Carcino-Embryonic Antigen (CEA), and Antigen CA 15-3 plays a pivotal role in gauging disease progression and response to treatment. Prior to initiating Glucosodiene therapy, the ALP level was markedly elevated at 700 units/L, well above the normal range of 40 to 150 units/L. ALP is an enzyme predominantly found in bones and the liver, and its elevation in cases of metastatic cancer typically signifies bone involvement or liver metastasis. The significant decrease in ALP levels post-treatment to 280 units/L indicates a favorable response to Glucosodiene therapy, suggesting a reduction in tumor burden and a potential halt in disease progression. Similarly, the reduction in CEA levels from 70.3 ng/mL to 36.9 ng/mL following treatment reflects a positive response to therapy. CEA, a glycoprotein produced during fetal development, is often elevated in the presence of certain cancers, including colorectal, lung, and breast cancers. A decrease in CEA levels post-treatment suggests a regression of tumor activity and a favorable therapeutic outcome. Furthermore, the decline in Antigen CA 15-3 levels from 146.6 KU/L to 78.1 KU/L post-treatment signifies a positive treatment response. Antigen CA 15-3 is a tumor marker primarily associated with breast cancer, and its elevation is indicative of disease progression or recurrence. The observed reduction in Antigen CA 15-3 levels following Glucosodiene therapy suggests a favorable treatment response and potential suppression of tumor activity. The rapid decline in these biomarkers within a short duration of 15 days post-initiation of Glucosodiene therapy underscores the efficacy of the treatment regimen in controlling cancer progression.

3. *Discussion*

The emergence of Glucosodiene as an independent drug agent in the treatment of metastatic Triple-Negative Breast Cancer (TNBC) to the bones has been substantiated in a case report, where it was employed within a 15-day therapeutic cycle. [8] The confirmation from the PET scan examination in this case unequivocally supports Glucosodiene's role as a primary therapeutic agent, demonstrating

its remarkable ability to cause the complete disappearance of all active foci in the bones within the specified treatment period. Positive outcomes have been observed after only 15 days of treatment with Glucosodiene at a daily oral dose of 100 milliliters, calculated based on the initial dosage administered to the first patient who received the treatment and demonstrated its success. Following the established treatment protocol demonstrated in a case of triple-negative breast cancer remission, and after rigorous safety evaluations within the physiological context, Glucosodiene is synthesized through a chemical reaction involving 3.5 grams of dextrose and 2.5 grams of sodium bicarbonate in a carefully filtered aqueous solution of 100 milliliters. The recommended therapeutic dose of Glucosodiene is administered orally once daily, every 24 hours, in a volumetric dose of 100 milliliters. Within each 100 milliliters of the Glucosodiene solution, there is an indicative dose of **Glucosodiene equivalent to 85.71 milligrams per kilogram of body weight**. [7] This synthesis approach was validated after safety experiments on the substance biologically. The patient's case results revealed a metabolic response to treatment, indicating positive progress in the patient's condition. Notably, there was a marked regression in the number, size, and intensity of hypermetabolic osseous lesions, indicating improvements in various bones compared to previous scans. Monitoring biomarkers such as Alkaline Phosphatase (ALP), Carcino-Embryonic Antigen (CEA), and Antigen CA 15-3 played a pivotal role in assessing disease progression and response to treatment. Significant decreases in ALP, CEA, and Antigen CA 15-3 levels post-treatment signify a favorable response to Glucosodiene therapy, suggesting a reduction in tumor burden and potential suppression of tumor activity. The rapid decline in these biomarkers within a short duration underscores the efficacy of Glucosodiene in controlling cancer progression.

4. Conclusion

In conclusion, the utilization of Glucosodiene as a therapeutic agent in metastatic Triple-Positive Breast Cancer (TPBC) has shown promising results in this case study. The comprehensive evaluation of its efficacy, supported by PET scan examinations and biomarker monitoring, highlights its potential as a primary therapeutic agent in treating aggressive forms of breast cancer. The observed partial metabolic response, along with significant improvements in osseous lesions and biomarker levels, underscores the importance of further research and clinical trials to validate Glucosodiene's effectiveness and establish its role in standard treatment protocols for TPBC. With continued investigation and refinement of its synthesis and administration protocols, Glucosodiene holds

promise as a valuable addition to the armamentarium against metastatic breast cancer, offering hope for improved outcomes and enhanced quality of life for patients facing this challenging disease.

Statements and Declarations

Informed consent: Before taking this case, information was given to the patient, and informed consent was obtained from the patient for follow-up and consent to share the investigations, figures, and any required data.

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Competing interest declaration: The authors declare that there are no conflicts of interest.

Ethical approval statement or statement of informed consent for case studies: This case was conducted in accordance with the Declaration of Helsinki and meets the CARE guidelines. Informed consent was obtained from the patient for follow-up, including permission for publication of all photographs, lab, and images herein. **Trial registration details: NCT05957939**

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Declarations

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