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Case Report

Successful Management of Late-Stage HER2-Positive Breast Cancer with Trastuzumab-Based Therapy

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ABSTRACT

Background:
Breast cancer is a disease where malignant cells form in the breast tissue causing symptoms like a new lump, swelling, or skin changes. HER family refers to a group of related cell-surface receptors that belong to the Human Epidermal growth factor Receptor (HER / ERBB) family. These receptors play a central role in cell growth, division, and repair, and abnormalities in this family are involved in many cancers-especially breast cancer.

Objectives:
A 41-year-old female, a mother of 4 children, last child age 4 months. suffering from pain in the breast area for three month she attributed it to symptoms of the pregnancy and childbirth. This patient was diagnosed with metastatic breast cancer HER2, specifically stage IV, and a treatment protocol was proposed for pertuzumab and Herceptin.

Results:
The protocol followed has led to success in halting the disease.

Conclusion:
In summary, first-line dual HER2 blockade with pertuzumab and trastuzumab can achieve meaningful disease control in advanced HER2-positive breast cancer and is well tolerated. The outcome in our patient mirrors the efficacy observed in many studies, reinforcing current guideline recommendations while highlighting the potential for early intervention to optimize patient outcomes. Although single-case observations cannot be generalized, this report provides valuable insight into the real-world application of dual HER-targeted therapy.

KEYWORDS: cancer, Trastuzumab therapy, HER2-targeted therapy, Anti-HER2 therapy, Treatment response.

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INTRODUCTION

Advanced breast cancer, Late-stage breast cancer, Metastatic breast Breast cancer is a disease where malignant cells form in the breast tissue causing symptoms like a new lump , swelling , or skin changes .
It is the most commonly diagnosed cancer globally, especially in women and the leading cause of cancer deaths in women worldwide, with an estimated 2.3 million women new cases and over 500,000 deaths worldwide annually according to the World Health Organization statistics (WHO) (1).
-The relationship between HER2 (a member of the HER / ERBB family) and breast cancer was established in the mid-1980s, with a key landmark discovery in 1987.
-HER family refers to a group of related cell-surface receptors that belong to the Human Epidermal growth factor Receptor (HER / ERBB) family.
-These receptors play a central role in cell growth, division, and repair , and abnormalities in this family are involved in many cancers-especially breast cancer.
-Members of HER (ERBB) Family
There are four main receptors(2)

1.ErbB1 (EGFR or HER1)
– Binds epidermal growth factor (EGF) and other growth factors.

2.ErbB2 (HER2 or Neu)
– Has no known direct ligand; it is the preferred partner for dimerization with other ErbB receptors.
– Overexpressed in some breast cancers.
3.ErbB3 (HER3)
– Has impaired kinase activity (weak catalytic ability), so it must pair with another ErbB receptor to signal.

4.ErbB4 (HER4)
– Has multiple ligands and plays roles in development (heart, nervous system) and normal tissue

) - How the HER (ErbB) Family Works
-They act like antennas on the cell surface that receive signals from growth factors. (3)

1. Ligand Binding (Signal Arrival)
Certain molecules—called growth factors—float around outside the cell.
Examples: EGF, neuregulin.

A growth factor binds to the extracellular part of a HER receptor (like a key fitting a lock).
- HER1, HER3, HER4 have known ligands.
- HER2 has no ligand; it stays "ready to pair" with others.

2. Dimerization (Receptors Pair Up)
When a ligand binds, the receptor changes shape and pairs (dimerizes) with another HER receptor:
- Homodimer = pairs with itself
- Heterodimer = pairs with a different HER member

Examples:
- HER2 + HER3 → one of the strongest signaling pairs
- HER1 + HER1
- HER1 + HER2

Dimerization is essential—because the pair activates the next step.

3. Activation of the Kinase Domain
Inside the cell, HER receptors have a tyrosine kinase domain.

When two receptors form a dimer:
- They activate each other.
- They add phosphate groups to themselves (autophosphorylation).

This works like flipping multiple "ON switches."(4)

4. Intracellular Signaling Pathways Turn On
The phosphorylated receptors recruit signaling proteins inside the cell.
Major pathways activated include:
MAPK pathway → cell proliferation
PI3K/AKT pathway → cell survival
JAK/STAT pathway → growth and differentiation

These pathways control:
- Cell division
- Survival
- Movement
- Tissue repair
- Development

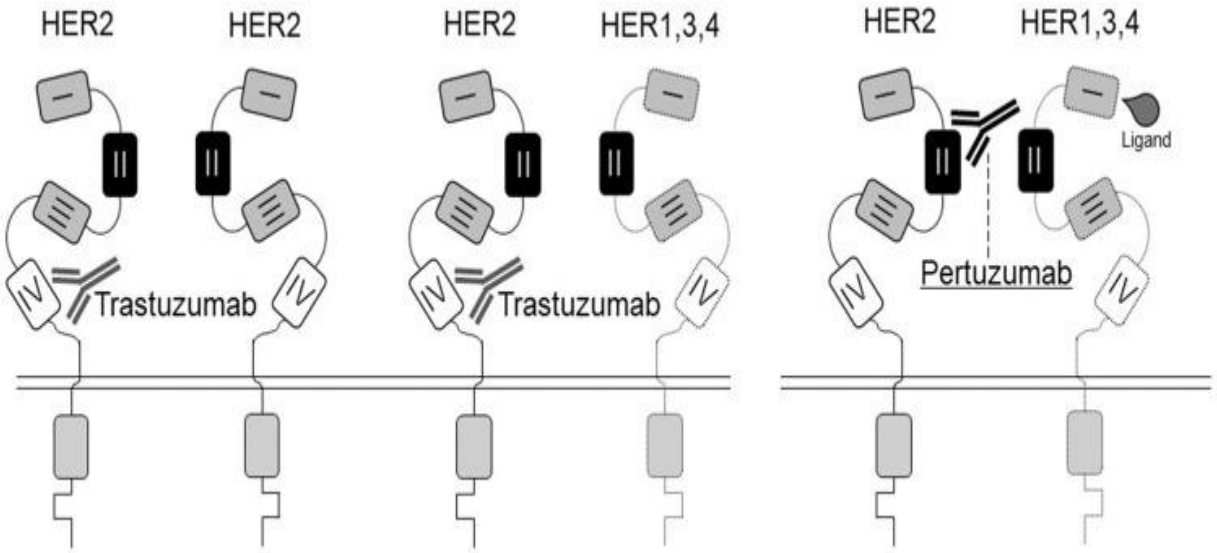
5. Cellular Response
Depending on which receptors pair and which ligands bind, the cell can respond by:
- Growing or dividing
- Surviving stress
- Differentiating
- Developing specialized functions

-Overexpression or gene amplification of HER2 occurs in (15-20%) of breast cancers. HER 2-positive tumors are often more aggressive and have poor prognosis, without targeted therapy.
-The development of HER2- targeted drugs evolved through four waves:
1-Monoclonal antibody → Herceptin
2-Dual HER2 inhibition → Pertuzumab
3-Antibody-drug conjugates→ T-DM1, T-DXd
4-TKIS→Lapatinib, Neratinib, Tucatinib
-Each was improved and transformed HER2- positive breast cancer from one of the most aggressive subtype to one of the most treatable(5).

-Trastuzumab is a monoclonal antibody act by:

- Inhibits HER2 signaling
- revents HER2 dimerazation
- Activates ADCC (immune-mediated killing)(6).

Figure 1(7).



CASE PRESENTATION

A 41-year-old female, a mother of 4 children, last child age 4 months. suffering from pain in the breast area for three month she attributed it to symptoms of the pregnancy and childbirth. (no medical history) (no family history. She consulted a doctor for an ultrasound. Clinical finding by physical examination show a mass in the left breast with signs suggestive of a cancerous tumor.

-Assessment by ultrasound (Imaging studies) reveals a mass suspicious of neoplasm.
-CT scan confirmed the presence of cancerous masses in the breast area, lymph nodes, lung, liver, and lumbar vertebrae. She was diagnosed with stage IV cancer.
-Biopsy Findings
Sections showed invasive mammary carcinoma of combined lobular and ductal component (stage IV)
-Left axillary lymph node fine needle aspiration (FNA) cytology obtained which showed scattering aggregates of malignant epithelial cells consistent with metastatic mammary carcinoma.
-IMMUNOHISTOCHEMISTRY was done 6/11/2021, and the result as follow:
-Estrogen receptor (negative)
-Progesterone receptor (negative)
-HER2… 3+(often graded from 0-3+), A 3+ indicates positive result.
-A PET (Positive Emission Tomography) scan was performed on 30/10/2021, and the result was recorded as follow:
(Hyper metabolic multiple soft tissue mass lesions in all quadrants of the left breast, multicentric primary malignancy),
(Hyper metabolic multiple left axillary level 1-111 lymph nodes & mediastinal lymph node metastases),
(Hyper metabolic multiple hypodense metastatic lesions in both lobes of the liver),
(Hyper metabolic few portal and portocaval metastases lymph node),
(Hyper metabolic multiple lytic -metastatic lesions in the sternum, right scapula & head of the right humerus, few bilateral ribs with pathological fracture of the right 4thrib, C1 multiple dorsal, lumbar vertebra , sacrum ,bilateral iliac bones and left acetabulum

Treatment

Treatment was started after diagnosis on30\10\2021 with:
1-TRASTUZUMBUM 150 mg (Herceptin), Doses are given every 21 days.
2-PERTUZUMAB (420) mg -14ml (Perjeta), Doses are given every 21 days.
3-Taxol (paclitaxel) 14 ×cycles
4- Reciveol AC × 1cycle
5- Zoeta (Zolidronic acid) every 3 month

-After about 4 months, the PET scan was repeated on 10/03/2022, the findings as compared to previous PET scan dated on 30/10/2021 was as follows:
-Interval resolution of multiple hyper metabolic mass lesion in the left breast.
-Interval resolution of left axillary and subpectoral lymph node metastases.

-Interval resolution of left internal mammary and mediastinal lymph nodes metastasis.
-Interval Significant decrease in size with resolution of metabolic activity in the liver lesions.
-Interval resolution of periportal and portocaval lymph nodes.
-Interval sclerotic changes with resolution of metabolic activity in multiple bone lesions.
-No other abnormal hypermetabolic lesion elsewhere in the rest of the whole-body survey.
-No interval new lesion noted.
-The patient continued with the same previous treatment protocol:
-TRASTUZUMBUM 150 mg (Herceptin)
-PERTUZUMAB (420) mg -14ml (Perjeta)
-Doses are given every 21 days
-Zometa every 3 month
-On 28/09/2022 PET scan was performed, the result show:
-No evidence of metabolically active residual recurrent lesions in the left breast parenchyma.
-Small stable speculated nodular lesion in the superior-lateral quadrant of the right breast, with minimal metabolic activity which in favor of benign pathological lesions.
-No significant regional lymphadenopathy
-No other remarkable metabolically active lesion in the reminder of whole-body survey.

-The patient continued with the same previous treatment protocol:
-TRASTUZUMBUM 150 mg (Herceptin)
- PERTUZUMAB (420) mg -14ml (Perjeta)
- Doses are given every 21 days
-On 30/ 0/\2022, PET scan was performed, the result in comparison to the previous one show:
-No metabolically active recurrent lesion in the left breast parenchyma, no abnormal Fluoro- Deoxy-Glucose FDG avid enlarged left axillary lymph node.
-Stable metabolically inactive small sclerotic lesions in D 8,D10andD12 vertebral bodies .
-Stable size mild degree FDG avid small speculated lesion in the upper outer quadrant of the right breast with no chest wall infiltration.
-No other hypermetabolic pathological lesion in the rest of the whole-body survey.

- The patient continued with the same previous treatment protocol:

-TRASTUZUMBUM 150 mg (Herceptin)
-PERTUZUMAB (420) mg -14ml (Perjeta)
-Doses are given every 21 days

-On 21/ 03/ 2024, PET scan was performed, the result in comparison to the previous one show:
-Physiological limit of FDG metabolic activity in the liver (AUV max =2.3) as well as the spleen and bowel with no evidence of active focal lesion.
-Physiological excreted FDG activity in both-calyceal system and urinary bladder.
-No hyper metabolic abdominal or pelvic lymph node.
-Physiological limit of FDG metabolic activity in the whole musculoskeletal system with no evidence of active focal lesion.
-No any convincing hypermetabolic lesion at the left breast to suggest local disease recurrence.
-No any convincing hypermetabolic suspicious lesions was seen in the study.

- The patient continued with the same previous treatment protocol:

-TRASTUZUMBUM 150 mg (Herceptin)
-PERTUZUMAB (420) mg -14ml (Perjeta)
-Doses are given every 21 days

- On 6/ 08/2025, PET scan was performed, the result in comparison to the previous one show:

-Interval no significant change in non FDG avid, small irregular soft tissue density in the upper outer quadrant of the left breast most likely inactive residual.
-Interval no significant change in non FDG avid sub centimeter irregular soft tissue density in the upper outer quadrant of the right breast (nonspecific) lesion currently considered benign, follow up is highly recommended.
-Non FDG avid sub centimeter bilateral axillary lymph nodes
(reactive lesion)
-No other abnormal hypermetabolic lesion elsewhere in the whole-body survey.

DISSCUSSION:

-Human epidermal growth factor receptor 2 (HER2) overexpression or gene amplification occurs in approximately 15–20% of breast cancers and is associated with aggressive tumor biology and poorer prognosis in the absence of targeted therapy. The introduction of HER2-directed monoclonal antibodies has dramatically improved outcomes in both early and advanced disease settings.
-The combination of trastuzumab and pertuzumab represents a dual HER2 blockade strategy that targets different extracellular domains of the HER2 receptor. Trastuzumab binds to subdomain IV of the HER2 extracellular domain, inhibiting ligand-

independent signaling and mediating antibody-dependent cellular cytotoxicity (ADCC). In contrast, pertuzumab binds to subdomain II, preventing HER2 heterodimerization with other HER family receptors (particularly HER3), which is a key driver of downstream PI3K/AKT signaling. The complementary mechanisms result in more comprehensive HER2 pathway inhibition and synergistic antitumor activity.

-Treatment with pertuzumab & trastuzumab is relatively new, but many studies indicate its effectiveness in treating breast cancer of the Human Epidermal Growth Factor Receptor 2 (HER2). Preclinical data shows that combining of pertuzumab with trastuzumab more completely inhibits downstream HER2 signaling pathways than either antibody alone, reducing tumor proliferation and survival in HER2+ models. Complementary actions blocking HER2 dimerization (pertuzumab) and signaling/internalization (trastuzumab)-underlie the enhanced therapy. In this patient's case, a 41-year-old woman, we observe the effectiveness of using this medication in treating the disease and controlling the symptoms even though the disease was classified as metastatic before initiation of treatment and the patient is considered as a hopless case. (PET SCAN 2.3.4)

-In the context of the present case, the observed clinical response is consistent with data from large clinical trials and real-world studies demonstrating high response rates and durable disease control with dual HER2 blockade (Franklin et al. (Cancer Cell, 2004) (رقم). Importantly, this regimen has shown efficacy across various subgroups, including patients with visceral metastases and those with de novo metastatic disease. This patient selected for a treatment plan that included pertuzumab and trastuzumab as two therapies within the framework of immunotherapy against cancerous tumors specific HER 2 in breast cancer, without the need for surgery or radiation therapy. This option is difficult because the patient is in the advanced stages of the disease.

-From a therapeutic sequencing perspective, the trastuzumab–pertuzumab combination remains the preferred first-line regimen for advanced HER2-positive breast cancer according to international guidelines (Ishii et al. (Core Evidence, 2019)

-The integration of subsequent lines of HER2-directed therapies has further transformed the disease into a more chronic, manageable condition for many patients.

-The clinical response observed in our patients is consistent with the findings of the CLEOPATRA trial, which demonstrated a significant improvement in progression-free and overall survival with the addition of pertuzumab to trastuzumab in the first-line HER2-positiv

-Cleopatra phase III Randomized Trial conducted in 2008-2010 published in 2012 , selecting 808 patients with previously untreated HER2-positive metastatic breast cancer find the use of trastuzumab and pertuzumab significantly improved progression -free survival (PFS) , the overall survival was significantly longer, the trial changed clinical practice, establishing the combination as first -line standard of care in metastatic HER2-positive disease.

-Although dual HER2 blockade has demonstrated significant survival benefit in first-line metastatic disease, certain studies such as the PHEREXA, a randomized multicenter , phase III trial in patients with HER2-positive metastatic breast cancer did not show statically significant overall survival advantage in previously treated patients. Additionally, subgroup analyses suggest reduced benefit in heavily pretreated populations and those with central nervous metastases. These findings highlight the importance of patients selection and individualized therapeutic decision-making.

-In summary, first-line dual HER2 blockade with pertuzumab and trastuzumab can achieve meaningful disease control in advanced HER2-positive breast cancer and well tolerated. The outcome in our patient mirrors the efficacy observed in many trials reinforcing current guideline recommendations while highlighting the potential for early intervention to optimize patient outcomes. Although single-case observations cannot be generalized, this report provides valuable insight into the real-world application of dual HER2-targeted therapy.

-Chi Pan a,1, Lan Ge a,1, Huifeng Zhang As a recombinant monoclonal antibody that targets HER2, Trastuzumab (Herceptin®) has demonstrated significant efficacy in reducing recurrence and mortality rates among HER2-positive. (8) Pertuzumab is a humanized monoclonal antibody, which acts in complementary fashion with trastuzumab by binding to different domains of the tumor. Chinese Society of Clinical Oncology guidelines for BC version 2022 have highlighted that, for patients with HER2-positive status, the recommended approach for new adjuvant treatment consists of either anthracycline plus paclitaxel or non-anthracycline plus trastuzumab ± pertuzumab as the first-line treatment. The addition of pertuzumab is expected to improve the rate of complete pCR, particularly in patients with HR negative and lymph node positive conditions, thereby offering additional benefits. The combination of pertuzumab trastuzumab and chemotherapy has demonstrated enhanced disease-free survival rates in HER2-positive (9)

Pertuzumab + trastuzumab combination therapy is a well-validated, evidence-based approach in HER2 positive breast cancer across clinical scinarios. Stadared of care in first line metastatic disease. Improves response and outcomes in neoadjuvant and adjuvant settings. Acceptable safety profile with manageable side effects. Ongoing advancements in targeted therapies, including antibodu-drug conjugates (e.g Enhertu), may further refine treatment stratigies. But dual HER2 blockade remains a cornerstone therapy.

Denise Drittone, Claudia Lucci, Luisa Esposito, Found the evolution of anti-HER2 therapies has dramatically transformed the treatment landscape for HER2-positive breast cancer, with successive generations of treatments demonstrating increasingly impressive survival benefits (11). This progression highlights both the remarkable advances in targeted therapy and areas requiring further investigation. The introduction of trastuzumab marked the first significant improvement in overall survival (OS), extending median OS from 20.3 to 25.1 months compared to chemotherapy alone (12).

CONCLUSION

In summary, first-line dual HER2 blockade with pertuzumab and trastuzumab can achieve meaningful disease control in advanced HER2-positive breast cancer and is well tolerated. The outcome in our patient mirrors the efficacy observed in many studies, reinforcing current guideline recommendations while highlighting the potential for early intervention to optimize patient outcomes. Although single-case observations cannot be generalized, this report provides valuable insight into the real-world application of dual HER-targeted therapy.

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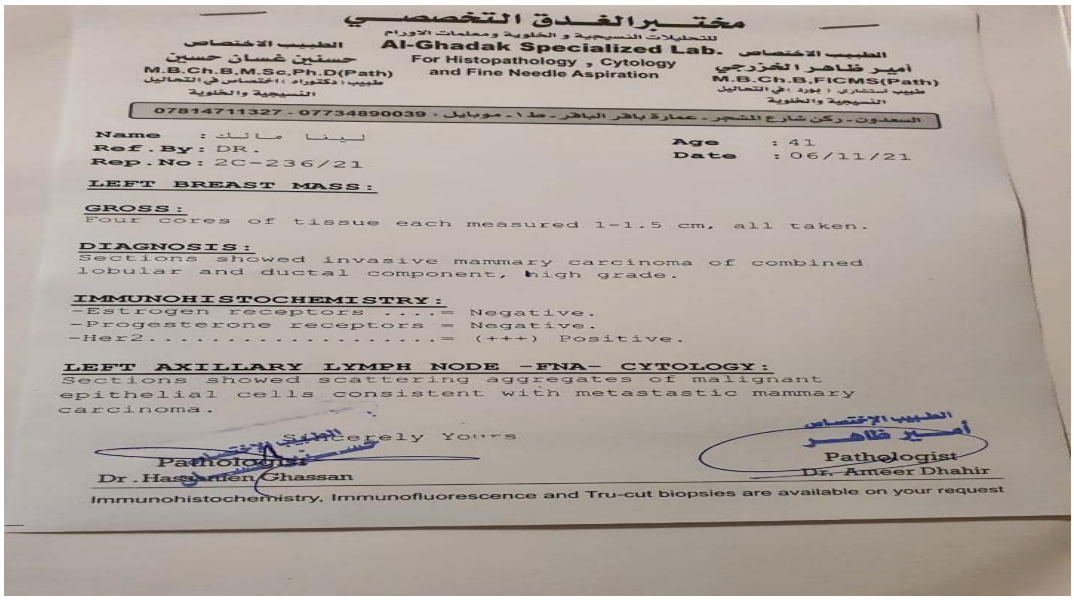

مختبر الغدق التخصصي
للتحليلات النسيجية و الخلوية ومعلمات الأورام
Al-Ghadak Specialized Lab.
For Histopathology , Cytology and Fine Needle Aspiration

الطبيب الاختصاص
حسنين غسان حسين
M.B.Ch.B.M.Sc.Ph.D(Path)
طبيب / دكتوراه / اختصاص في التحاليل النسيجية والخلوية

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07814711327 - 07734890039 : السعدون - ركن شارع الشجر - عمارة باقر الباقر - ط١ - موبايل

Name : لينا مالك
Ref.By: DR.
Rep.No: 2C-236/21

Age : 41
Date : 06/11/21

LEFT BREAST MASS:

GROSS:
Four cores of tissue each measured 1-1.5 cm, all taken.

DIAGNOSIS:
Sections showed invasive mammary carcinoma of combined lobular and ductal component, high grade.

IMMUNOHISTOCHEMISTRY:
-Estrogen receptors ....= Negative.
-Progesterone receptors = Negative.
-Her2.....= (+++) Positive.

LEFT AXILLARY LYMPH NODE -FNA- CYTOLOGY:
Sections showed scattering aggregates of malignant epithelial cells consistent with metastastic mammary carcinoma.

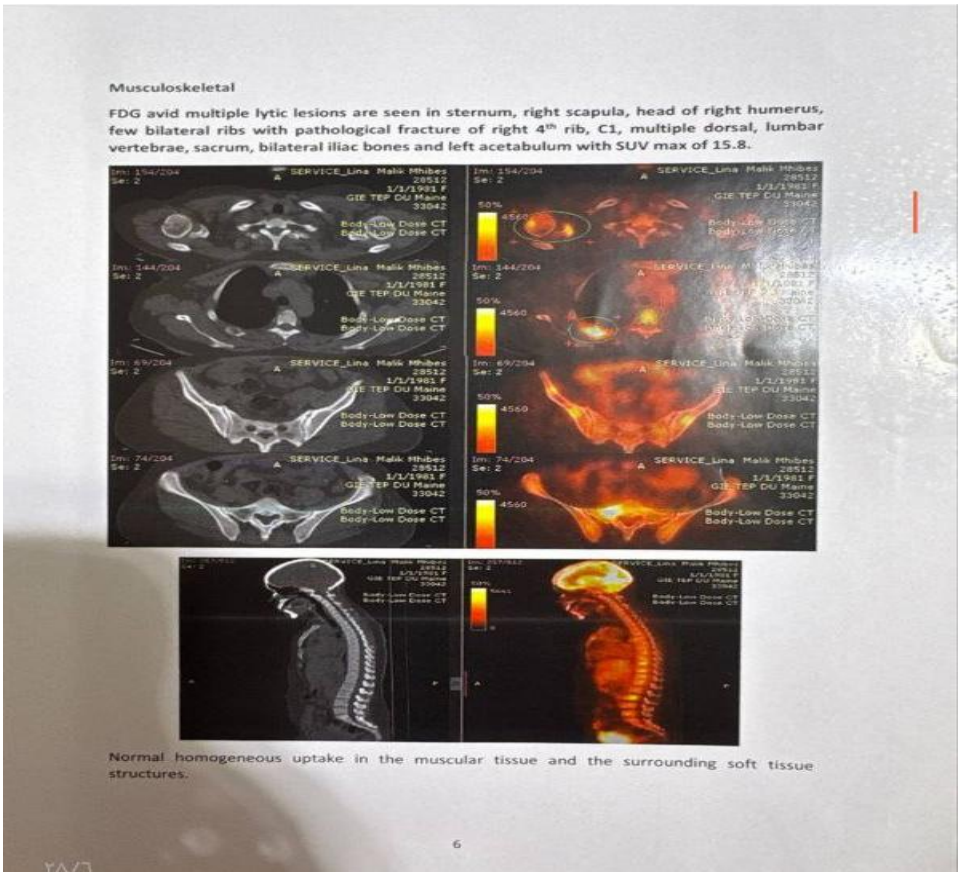
Sincerely Yours

Pathologist
Dr .Hassanien Ghassan

الطبيب الاختصاص
أمير ظاهر
Pathologist
Dr. Ameer Dhahir

Immunohistochemistry, Immunofluorescence and Tru-cut biopsies are available on your request

FIRST PTC



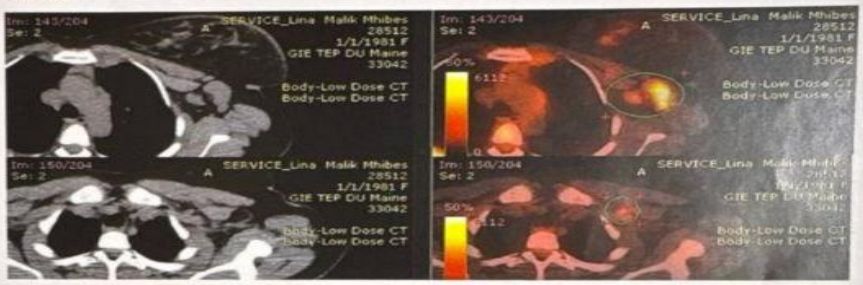
Musculoskeletal

FDG avid multiple lytic lesions are seen in sternum, right scapula, head of right humerus, few bilateral ribs with pathological fracture of right 4th rib, C1, multiple dorsal, lumbar vertebrae, sacrum, bilateral iliac bones and left acetabulum with SUV max of 15.8.

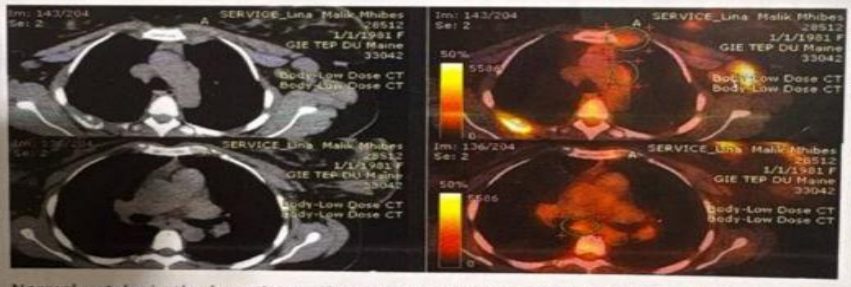
Normal homogeneous uptake in the muscular tissue and the surrounding soft tissue structures.

6

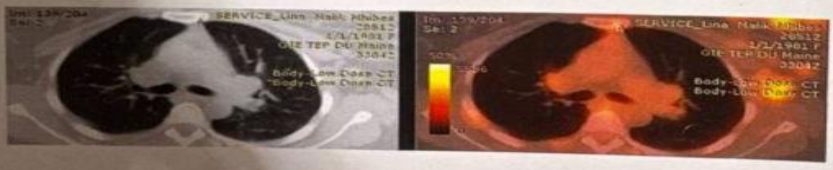
Diffuse left breast thickening is seen with maximum thickness of 12 mm. **FDG avid multiple left axillary level I –III lymph nodes are seen largest measuring 3.2 x 1.8 cm with SUV max of 16.6.**



FDG avid left internal mammary, paraaortic, right upper, lower paratracheal, A.P window, subcarinal and bilateral hilar lymph nodes largest measuring 1.7 x 0.9 cm with SUV max of 4.4.



Normal uptake in the lung tissue, showing no remarkable nodal or diffuse thickening in all lung segments. No pleural or pericardial effusion.



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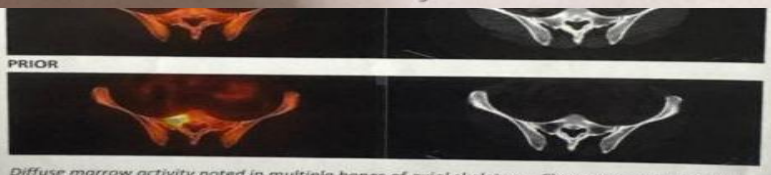
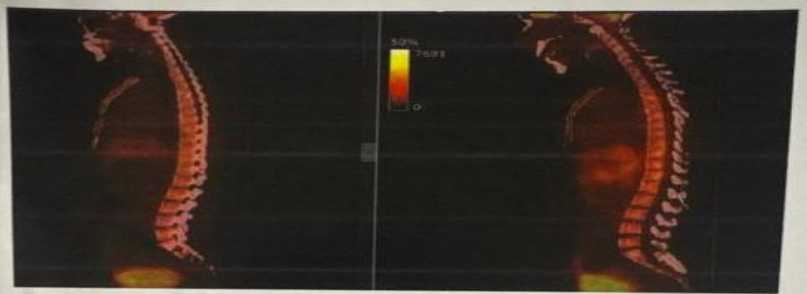
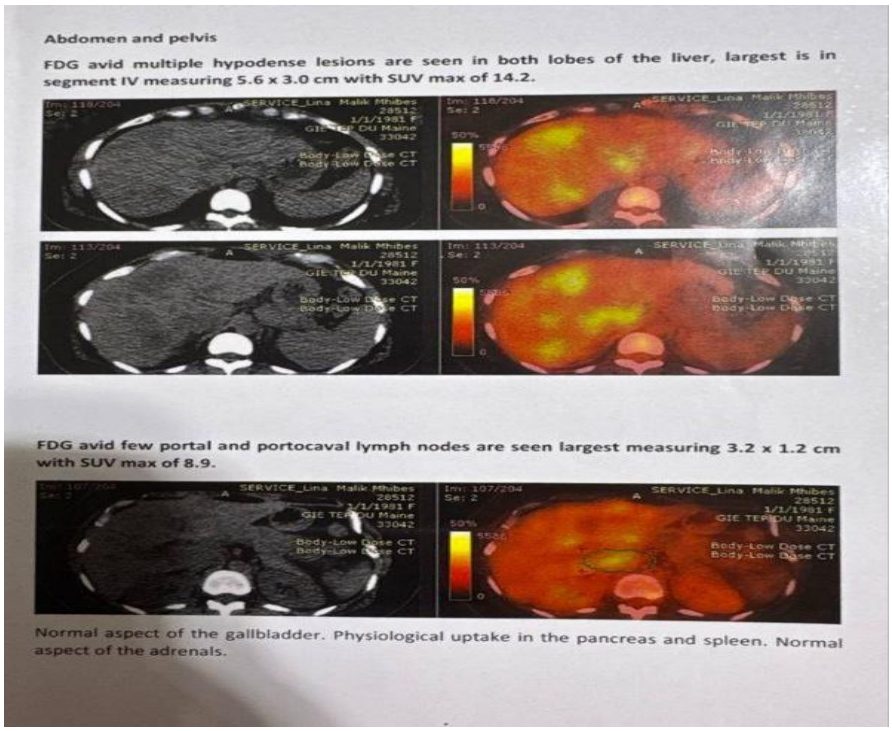


Diffuse marrow activity noted in multiple bones of axial skeleton – Chemotherapy induced.

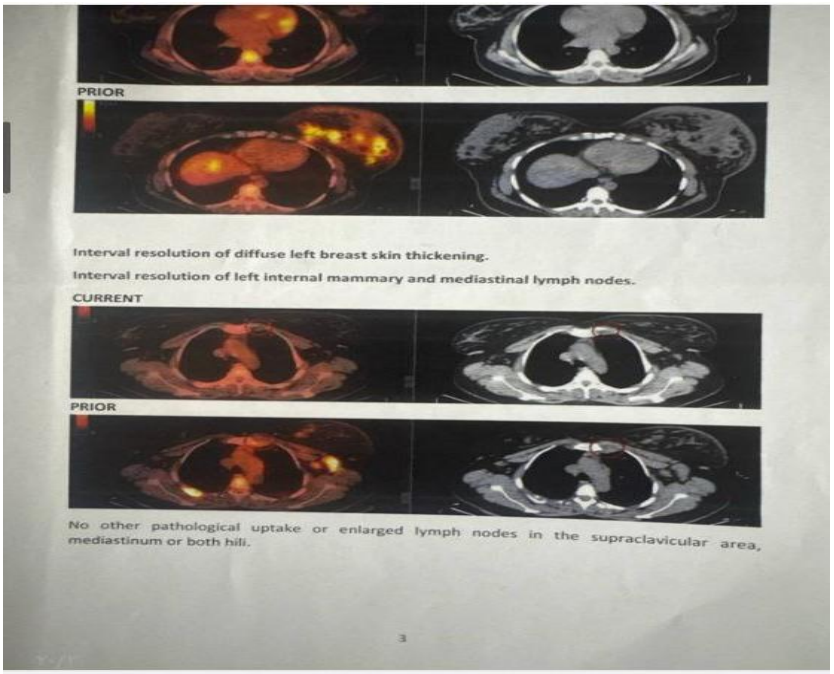
Normal aspect of the rest of the bony structures with no suspicious lesion or pathological uptake in the bony structures.

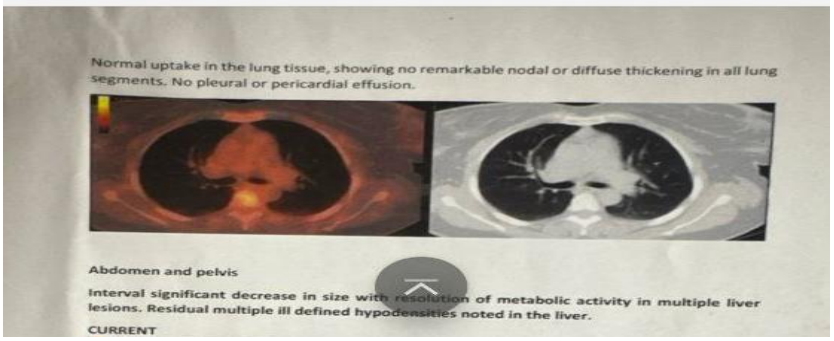


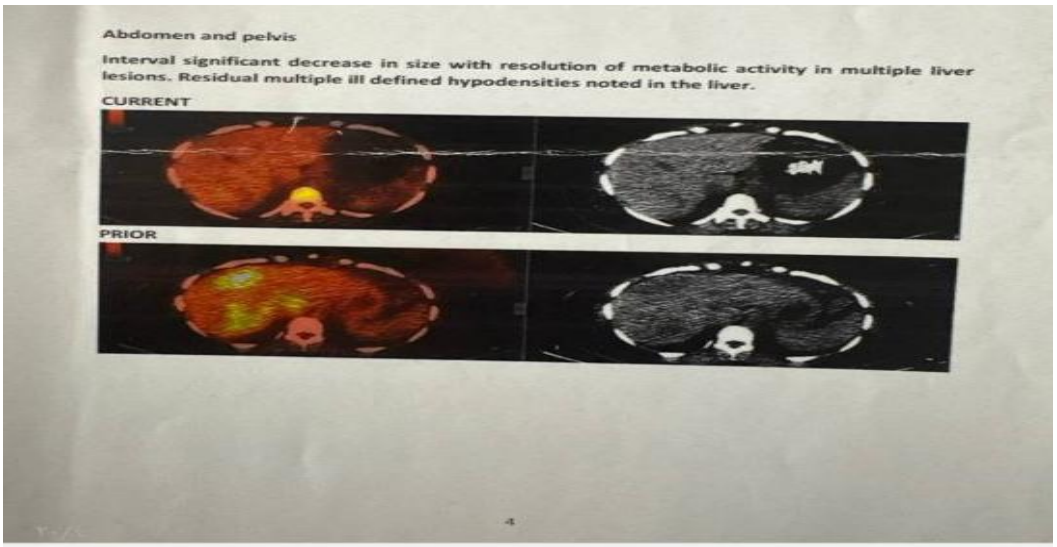
Normal homogeneous uptake in the muscular tissue and the surrounding soft tissue structures.

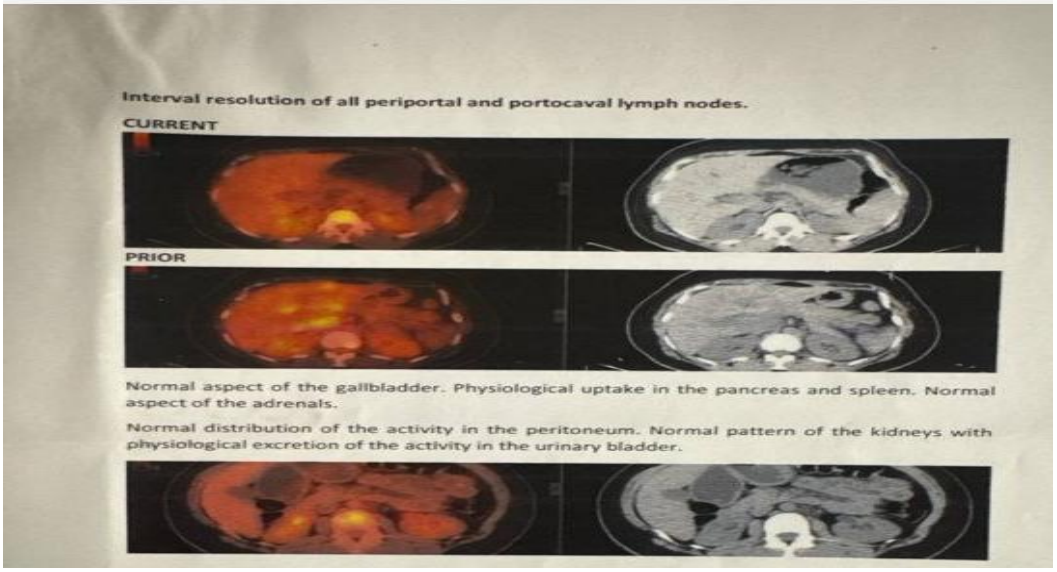

Abdomen and pelvis
FDG avid multiple hypodense lesions are seen in both lobes of the liver, largest is in segment IV measuring 5.6 x 3.0 cm with SUV max of 14.2.
FDG avid few portal and portocaval lymph nodes are seen largest measuring 3.2 x 1.2 cm with SUV max of 8.9.
Normal aspect of the gallbladder. Physiological uptake in the pancreas and spleen. Normal aspect of the adrenals.

SECOND PTC


PRIOR
Interval resolution of diffuse left breast skin thickening.
Interval resolution of left internal mammary and mediastinal lymph nodes.
CURRENT
PRIOR
No other pathological uptake or enlarged lymph nodes in the supraclavicular area, mediastinum or both hili.


Normal uptake in the lung tissue, showing no remarkable nodal or diffuse thickening in all lung segments. No pleural or pericardial effusion.
Abdomen and pelvis
Interval significant decrease in size with resolution of metabolic activity in multiple liver lesions. Residual multiple ill defined hypodensities noted in the liver.
CURRENT


Abdomen and pelvis
Interval significant decrease in size with resolution of metabolic activity in multiple liver lesions. Residual multiple ill defined hypodensities noted in the liver.
CURRENT
PRIOR


Interval resolution of all periportal and portocaval lymph nodes.
CURRENT
PRIOR
Normal aspect of the gallbladder. Physiological uptake in the pancreas and spleen. Normal aspect of the adrenals.
Normal distribution of the activity in the peritoneum. Normal pattern of the kidneys with physiological excretion of the activity in the urinary bladder.