

## A xanthogranulomatous process resembling residual disease on end-of-treatment 18f-FDG-PET/CT and Whole Body Magnetic Resonance performed on a primary breast lymphoma treated by ibrutinib plus rituximab-chop

D. ALBANO<sup>1</sup>, C. PATTI<sup>2</sup>, P. ALONGI<sup>3</sup>, A. BRUNO<sup>1</sup>, G. DI BUONO<sup>4</sup>, A. MULÈ<sup>2</sup>,  
E. GULOTTA<sup>4</sup>, A. AGRUSA<sup>4</sup>, R. IENZI<sup>1</sup>, R. LAGALLA<sup>1</sup>, M. GALIA<sup>1</sup>

**SUMMARY: A xanthogranulomatous process resembling residual disease on end-of-treatment 18f-FDG-PET/CT and Whole Body Magnetic Resonance performed on a primary breast lymphoma treated by ibrutinib plus rituximab-chop.**

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*We report the case of a woman, affected by breast diffuse large B-Cell lymphoma, who developed a xanthogranulomatous process*

*wrongly interpreted as residual disease on 18F-FDG-PET/CT and Whole Body Magnetic Resonance after treatment with ibrutinib plus standard immunochemotherapy. Newer drugs, such as immunomodulatory agents and checkpoint inhibitors, have demonstrated high effectiveness on lymphoma, but are associated with unclear imaging features such as tumor flare or pseudo-progression, related to inflammatory reactions. Wide imaging techniques availability improves diagnostic possibilities. However, the awareness of the adopted treatment strategy and its possible implications on imaging features is crucial to make a correct response assessment.*

KEY WORDS: Breast lymphoma - FDG-PET/CT - Whole Body Magnetic Resonance - Xanthogranulomatous process - Ibrutinib - Rituximab.

### Introduction

Primary breast lymphoma is very rare with a prevalence ranging from 0.04 to 0.5% of breast neoplasms (1). The most frequent histologic type is Diffuse Large B-Cell Lymphoma (DLBCL), usually occurring as unilateral mass, indistinguishable from a breast carcinoma (1, 2). The diagnosis of lymphoma is obtained by pathologist through the evaluation of morphology and immunohistochemistry of bioptic specimen of locations of disease. Combined 18F-fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) is applied in several oncologic fields (3-7), especially in lymphoproliferative

disorders (3); indeed, it is recommended both for staging after diagnosis and for end-of-treatment assessment of DLBCL (8). Whole Body Magnetic Resonance (WB-MR) with diffusion-weighted imaging (DWI) is a technique more and more applied in general, urgent (9-12) and oncologic fields, especially in lymphoma and myeloma patients (13-17). Regarding the role of WB-MR in the evaluation of response to therapy there are promising preliminary results but larger studies are necessary to validate its reliability (18). We report the case of a 40-year-old woman, affected by primary breast DLBCL, who developed a xanthogranulomatous process wrongly interpreted as residual disease on FDG-PET/CT and WB-MR after treatment with ibrutinib plus standard immunochemotherapy.

### Case presentation

A 40-year-old female patient on May 2015 developed a right breast mass without skin changes, nipple retraction or systemic symptoms. A mammography was performed displaying a large mass, oval in shape, with no evidence of calcifications, greater than 4 cm in diameter. It was confirmed by ultrasound, which showed

<sup>1</sup> Department of Radiology, DIBIMED, University of Palermo, Palermo, Italy  
<sup>2</sup> Department of Hematology I, "Azienda Ospedali Riuniti Villa Sofia-Cervello", Palermo, Italy  
<sup>3</sup> Department of Radiological Sciences, Nuclear Medicine Unit, San Raffaele G. Giglio Institute, Cefalù, Italy  
<sup>4</sup> Department of General Surgery and Emergency, University of Palermo, Palermo, Italy

Corresponding authors: Giuseppe Di Buono, e-mail: gju.dibuono@gmail.com; Domenico Albano, e-mail: albanodomenico@me.com

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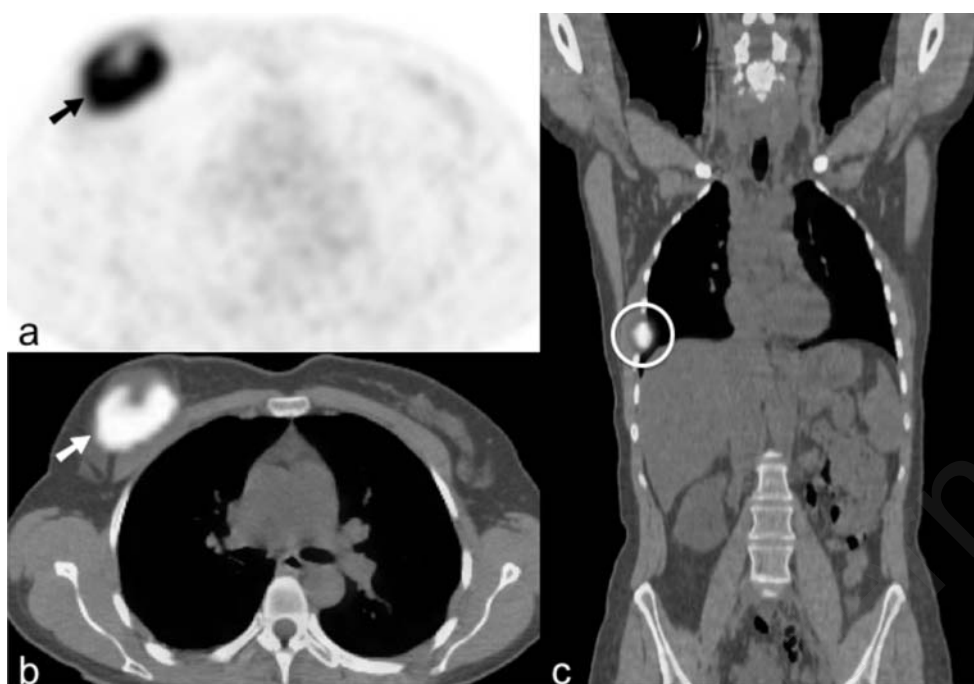


Figure 1 - FDG-PET/CT performed before treatment. Axial FDG-PET (a) and axial combined FDG-PET/CT (b) show a large right breast mass with high FDG uptake. Coronal combined FDG-PET/CT (c) shows pathological FDG uptake in the sixth right rib (arrow).

a solid hypoechoic mass, with lobulated margins and poor vascularity on power-Doppler. An ultrasound-guided breast core biopsy was performed and the histologic and immunohistochemical features led to the diagnosis of DLBCL non-germinal centre type (19) CD20+, BCL2+, BCL6 +, CD5-, MUM1+, CD10-, CD30-, Ki67 90%. Hence, she was admitted to the haematology department and underwent FDG-PET/CT (Figure 1), which revealed a large breast mass with high FDG uptake (maximum standard uptake value=SUVmax 28) and other pathological FDG uptakes in a right axillary lymph node (SUVmax 4.7) and in the sixth right rib (SUVmax 18.6). Then, the patient performed contrast enhanced CT and unenhanced WB-MR (Figure 2) that confirmed the locations of disease. On July of the same year the patient accepted to participate in a clinical trial for patients with DLBCL non-germinal centre type that combined ibrutinib with the standard immunochemotherapy with rituximab plus cyclophosphamide-doxorubicin-vincristine-prednisolone (CHOP). Thus, she started to receive ibrutinib plus 6 courses of rituximab plus 6 of CHOP. On November, FDG-PET/CT was performed six weeks after the end of therapy. It showed a pathological FDG uptake in a small nodule within the right mammary gland (SUVmax of about 5.4, Deauville score 4) suspicious for residual disease, without any other sites with pathological FDG uptake (Figure 3). The suspect was confirmed by WB-MR which demonstrated the disappearance of right axillary lymph node and rib lesion and the reduction in size of the right breast nodule that

showed a diameter of 1.3 cm and a restricted pattern of diffusion on apparent diffusion coefficient (ADC) map (Figure 4). On December, the patient performed an ultrasound displaying a residual inhomogeneously hypoechoic breast nodule that was biopsied (Figure 5). The diagnosis was xanthogranulomatous process mostly consisting of foamy macrophages, in absence of residual pathological lymphomatous cells. On January of the next year, the patient was also treated by radiotherapy with a breast irradiation consisting of a total dose of 30.6 Gy. FDG-PET/CT performed three months after the end of radiotherapy was negative and the patient is to date in complete remission.

## Discussion

Breast lymphoma may mimic carcinoma because it has non-specific symptoms. Its most common clinical presentation is a painless mass without systemic symptoms such as fever, weight loss or sweating (20). The mammographic pattern is usually an oval high-density mass with well or partially defined margins, without calcifications (21). On ultrasound, breast lymphoma mass mostly appears oval or round in shape, homogeneous hypoechoic, commonly without apparent posterior attenuation (22). However, no specific mammographic or ultrasonographic imaging features may help to differentiate breast lymphoma from carcinoma or sarcoma. Thus, needle biopsy is necessary to achieve a correct diagnosis (1). FDG-PET/CT is recommended in

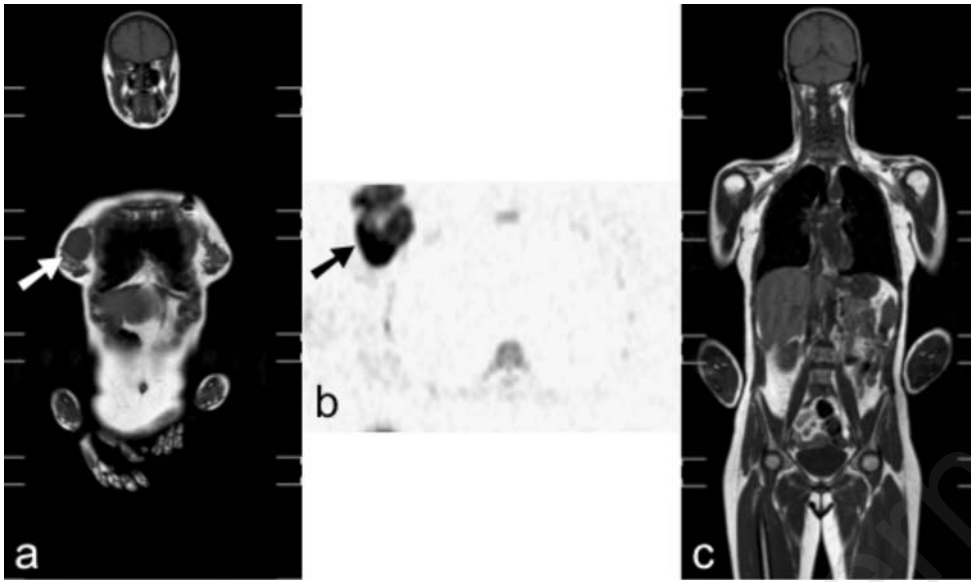


Figure 2 - WB-MR performed before treatment. Coronal WB-MR T1-weighted image (a) shows a large right breast mass (arrows) with restricted pattern of diffusion on axial grey-scale inverted DWI image (b). Coronal WB-MR T1-weighted image (c) shows also the pathologic enlargement of the sixth right rib (circle).

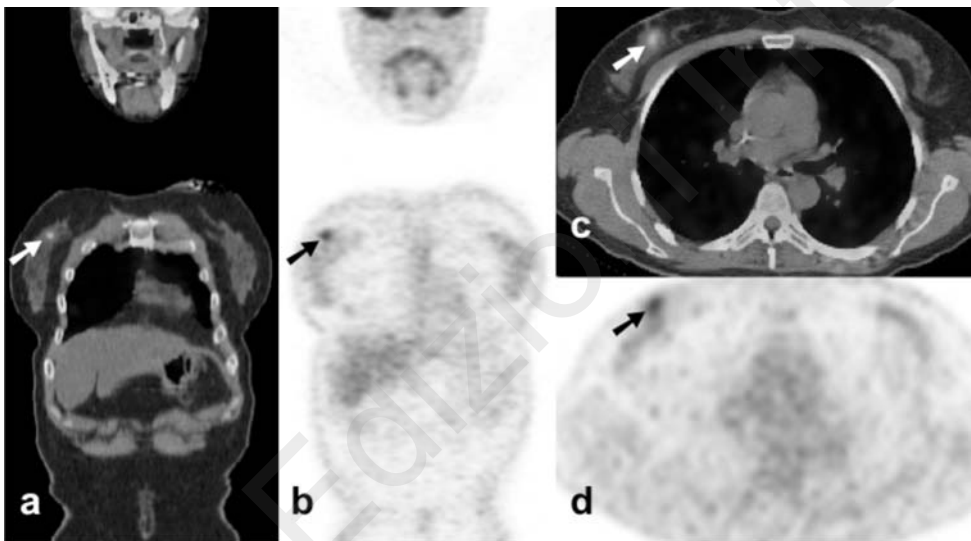
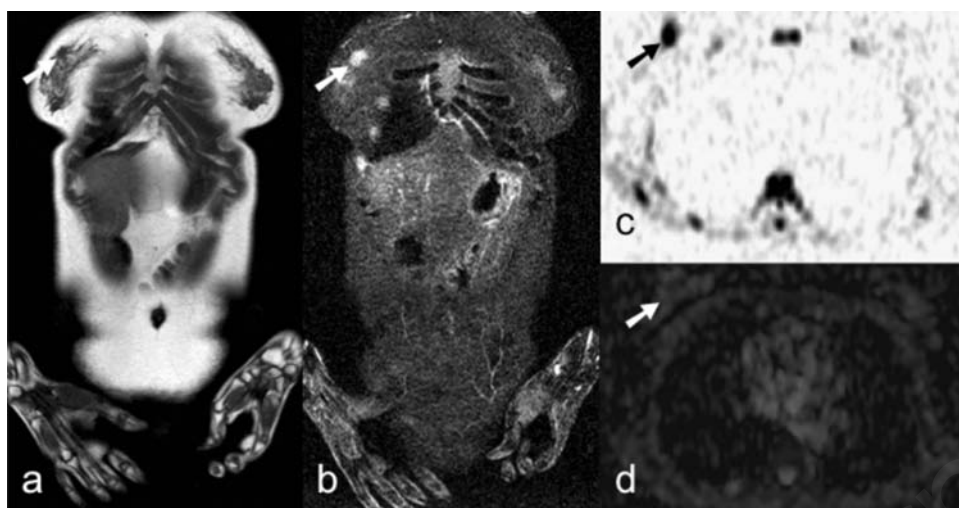


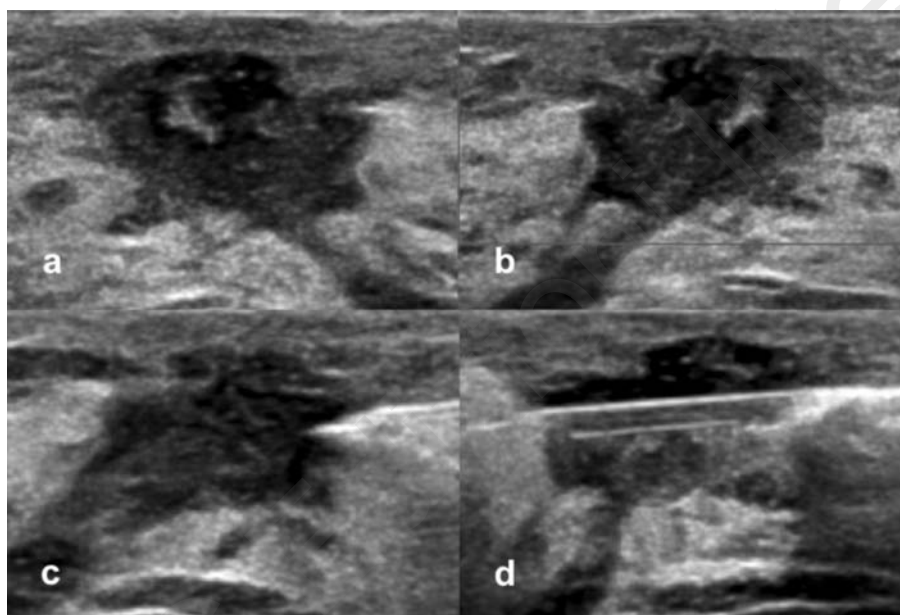
Figure 3 - FDG-PET/CT performed after treatment with ibrutinib plus rituximab-CHOP. Coronal combined FDG-PET/CT (a), coronal FDG-PET (b), axial combined FDG-PET/CT (c) and axial FDG-PET (d), demonstrate FDG uptake in a small nodule within the right mammary gland suspicious for residual disease (arrows).

DLBCL patients for staging and assessment of response to therapy (3). The five-point visual scale known as the Deauville criteria has been incorporated into the updated standard response criteria for DLBCL (3). The Deauville criteria depend on a qualitative comparison of FDG uptake in the lesions to that of the liver. Specifically, Deauville  $> 3$  on end-of-treatment FDG-PET/CT is considered as positive with a residual disease and a demonstrated worse cumulative survival rate (23), even if FDG uptake reduces from baseline (3). Previous studies demonstrated that this qualitative assessment on end-of-treatment FDG-PET/CT is reliable to predict the outcome of lymphoma patients and that minimal residual FDG uptake is not associated with high risk of relapse (24). However, it has been postu-

lated that the use of rituximab, a monoclonal antibody against the protein CD20 used in B-cell lymphoma therapy, could lead to an increase of false positive end-of-treatment scans (25). Rituximab may lead to inflammatory changes with recruitment of immune cells, like the xanthogranulomatous process found in our patient, which might determine false positive FDG-PET/CT scans (25). Indeed, a xanthogranulomatous process is an inflammatory and reactive response with aspecific but characteristic findings such as the presence of granular, eosinophilic, PAS positive histiocytes, foamy macrophages, plasma cells, suppurative foci and hemorrhages (26). Post-therapy inflammatory changes may persist for up to 2 weeks after chemotherapy alone and for up to 2 or 3 months after radiotherapy (27). For



**Figure 4** - WB-MR performed after treatment with ibrutinib plus rituximab-CHOP. Coronal T1-weighted (a) and T2-weighted STIR (b) images show a small nodule (arrows) within the right mammary gland with restricted pattern of diffusion on axial grey-scale inverted DWI image (c) and axial ADC map (d) images.



**Figure 5** - Ultrasound-guided biopsy of the breast nodule after treatment. Ultrasound showed a solid inhomogeneously hypoechoic nodule (a), without intralésional vascular flow on power-Doppler (b), that was biopsied using ultrasound guidance (c-d).

this reason, end-of-treatment FDG-PET/CT is recommended 6 to 8 weeks after chemotherapy (27). Moreover, newer drugs, such as immunomodulatory agents and checkpoint inhibitors, have recently demonstrated high effectiveness on lymphoma, but are associated with unclear imaging features during and after treatment, such as tumor flare or pseudo-progression, which need to be subjects of future studies and they too are probably related to inflammatory reactions (28). One of these drugs is ibrutinib, an inhibitor of B-cell receptor signaling pathway whose target is Bruton tyrosine kinase. Cheson et al. have recently introduced the term “Indeterminate Response” in order to identify and correctly manage such lesions characteri-

zed by unclear clinical and imaging findings after treatment with drugs such as ibrutinib, suggesting to obtain a repeat imaging after an additional 12 weeks (29). WB-MR with DWI is a non-invasive imaging technique that avoids radiation exposure and contrast agent administration. The role of WB-MR, especially fused with PET in FDG-PET/MR, in breast cancer imaging is being investigated over the last few years, with promising preliminary results (29); instead, WB-MR has already a well-established role in lymphoma imaging. Its high contrast resolution enables an excellent evaluation of bone marrow, allowing a reliable evaluation marrow lymphomatous involvement (30) and the early identification of osteonecrotic lesions, which are

very common in the follow-up of patients who receive chemotherapies and high doses of corticosteroids (31-35). Furthermore, it provides functional information regarding tissue cellularity through DWI, which is a sequence probing the motion of water molecules in intra-cellular and inter-cellular spaces. Several studies have shown that it enables to differentiate benign lymph nodes from malignant ones (16, 36, 37). Nevertheless, there is no consensus on the reliability and reproducibility of quantitative measurements on ADC map, with no standardization of pathologic ADC cut-off values in the evaluation of response to therapy. Recently, Mayerhoefer et al. have demonstrated that DWI, especially the rates of changes of minimum and mean ADC values, may be useful to predict complete remission in lymphoma patients treated by rituximab (37). However, it is well known that inflammatory reactions, besides determining an increased uptake of FDG, may display hyperintensity on high b-value DWI with a restricted pattern of diffusion on ADC map, mimicking a malignant tissue (38, 39).

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## Conclusion

In conclusion, wide imaging techniques availability improves diagnostic possibilities. However, the awareness of the adopted treatment strategy and its possible implications on imaging features is crucial to make a correct imaging and clinical assessment of response to therapy. Furthermore, a correct timing when performing nuclear medicine and radiology scans is essential to avoid a misinterpretation of imaging features, even if it is possible to have false positive findings for a long time, especially after newer therapies, as it was in our case.

## Conflicts of interest

The Authors state that they have no conflict of interest.

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