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Efficacy of Anti-HER2 Targeted Therapies on Peritoneal Metastasis of Lobular Mammary Carcinoma: A Case Report

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Metastatic breast cancer; Invasive lobular carcinoma; HER2 overexpressed

Abbreviations:

CT: Computerized Tomography; FISH in Situ Hybridization; ILC: Invasive Lobular Carcinoma; ER: Estrogen Receptor; PR: Progesterone Receptor

1. Introduction

Invasive lobular breast cancer (ILC) is the second most common histological subtype of breast cancer after invasive ductal cancer, comprising up to 15% of all cases. These tumors are generally of a good prognostic phenotype, being low histological grade and low mitotic index, hormone receptor positive and HER2 negative. HER2 amplification is effectively described in less than 5% of cases [1, 2]. Clinically, patients with ILC differ from those with invasive ductal cancer. They seem to have a significant worse late prognosis independent of Estrogen Receptor (ER) status and present a different metastatic pattern, more frequently involving unusual sites such as the gastrointestinal tract and the meninges [3]. Thus, clinicians face countless challenges in the diagnosis andlong-term management of patients, as they encounter a cancer that can be difficult to detect through screening, demonstrates a very invasivenature and a propensity for widespread metastatic colonisation. These distinguishing features sometimes make the response to the different antineoplastic therapeutic strategies that are mainly tested for patients with ductal breast cancer, uncertain. Here we report, for the first time to our knowledge, the case of a patient with peritoneal metastatic HER2 overexpressed invasive lobular breast cancer with an excellent response to anti-HER2 blockade.

2. Case Presentation

A 69-year-old patient presented, in April 2006, an ILC of the left breast, SBR II, ER positive 95%, PR (progesteron receptor) negative, Her2 not overexpressed. She underwent a mastectomy associated with axillary and left internal mammary curage. Histologically the tumor was an ICL, pT3 (15 cm) pN3b (12/12) SBR II. The patient underwent adjuvant chemotherapy (3 cycles of fluorouracil epirubicin cyclophosphamid then 3 cycles of Docetaxel) and 50 Gy of radiotherapy of the chest wall and axillary lymph node areas and left internal mammary chain, completed in January 2007. Hormone therapy with letrozole was continued until June 2012, for a total of 5 years. In July 2013, one year after the end of adjuvant hormone therapy, the patient presented an occlusive syndrome revealing extensive peritoneal carcinosis over the entire colonic framework and mesentery (Figure 1). There were also two liver lesions and bilateral pleural effusion. Histological samples collected during exploratory laparotomy confirmed peritoneal and hepatic metastases of known ILC. Hormone receptors were negative, the Her2 oncogene was amplified (in situ Hybridization (FISH) technique). Because of the occlusive syndrome, the patient was fitted with a discharge gastrostomy and fed parenterally artificially. Treatment with trastuzumab in combination with paclitaxel was

started in August 2013. Rapidly the patient showed clear clinical improvement, with resumption of diarrhea-like bowel movements one week after the first injection, followed by gradual resumption of oral nutrition within one month. The patient was stopped parenteral nutrition and returned to normal oral nutrition 7 weeks after starting paclitaxel-trastuzumab. The gastrostomy tube was removed later. CT (computerized tomography) scan confirmed the response to treatment with a single residual nodule of peritoneal carcinosis in front of the lower tip of the liver (Figure 2). Treatment was discontinued in May 2014 due to grade 3 toxicity (acute renal failure secondary to diarrhea and Staphylococcus Epidermidis septicemia, with removal of the central venous line). The patient had a second-line combination of capecitabine with lapatinib between June 2014 and June 2016. She again presented an occlusive syndrome, confirmed on CT scan and a third line of therapy with trastuzumab-emtansine was initiated in June 2016. The patient responded for 2 years to treatment with trastuzumab-emtansine with a clinical (World Health Organization status=1), biological and CT response. In June 2018, the patient progressed and began a fourth line of treatment with Navelbine Trastuzumab before developing a new occlusive syndrome and digestive hemorrhage, which led to her death in July 2018.

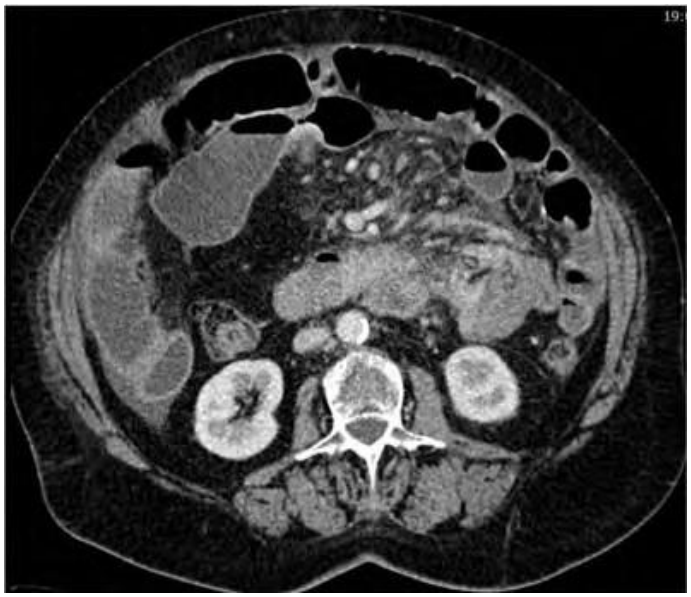

Figure 1:

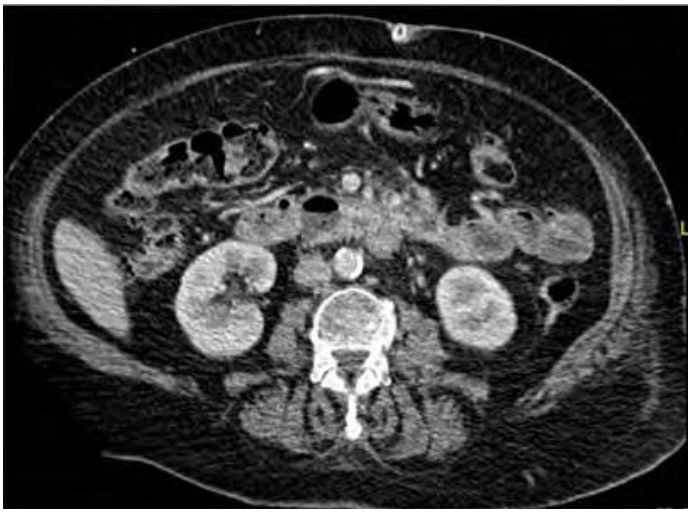

Figure 2:

3. Discussion

ILC is the second most common histological type of invasive breast cancer, accounting for 5-15% of cases. Hormone receptors are more frequently expressed, but HER2 gene amplification is most often absent (less than 5%) [1, 2]. The discrepancy in HER2 amplification between primary tumor and metastatic relapse is described in many studies with rates ranging from 10 to 15%, reason why, as recommended, patients should be re-biopsied at metastatic setting, to reassess hormone receptor and HER2 status. The appearance of HER2 amplification, rather than its disappearance, during metastatic progression is more frequent [4-6]. This phenomenon may be, in part, correlated with increased aggressiveness of the metastatic disease [5, 6]. Gastrointestinal organs, internal genitalia, pleural serosa and peritoneal serosa represent the preferential tropism of ILC metastasis [1, 7]. Several explanations for this specific tropism have been suggested, such as the loss of expression of a cell adhesion molecule, E-Cadherin, which is a calcium dependent transmembrane protein, or the richness of tumors in mucipar cells known as "signet-ring". The loss of E-cadherin expression confers resistance to tumor cells, making them able to survive independently of the adhesion to neighbouring epithelial cell [8]. The deregulation of E-Cadherin seems to occur at the early stage of ILC tumorigenesis due to frequent and irreversible genomic alterations targeting the CDH1 gene (30 to 80% depending on the studies). Mutations in the CDH1 gene have also been identified in other types of epithelial cancers such as gastric carcinomas of diffuse type, associated with the presence of independent cells known as “signet-ring” cells, with a tumor diffusion pattern similar to ILC. However, to date, neither CDH1 gene mutations nor loss of cadherin E expression represent therapeutic targets. In contrast, more HER2 gene alterations (mutations, amplification) have been identified in mutated CDH1 ILC [8-10]. CDH1-altered ILC with an ERBB2 mutation may be correlated with a significantly worse prognosis [11]. Some of these HER2 gene mutations are

responsible for the activation of the HER2 pathway and therefore potential targets for current anti-HER2 therapies. The latter have represented a major advance in the management of patients with progression-free survival and improved overall survival with the addition of the different anti-HER2 therapies: trastuzumab, pertuzumab and trastuzumab emtansine. In the case reported here, the patient responded remarkably well to anti-HER2 therapies. Progression-free survival of the first metastatic line was 10 months with the combination of paclitaxel and trastuzumab (stopped for toxicity, not ineffectiveness) consistent with the literature [12]. In addition, the two-year progression-free survival achieved with capecitabine plus lapatinib significantly exceeded that reported in the EMILIA trial (6.4 months). Progression-free survival with trastuzumab emtansine was greater than 15 months (patient still responding). In the EMILIA trial, trastuzumab emtansine achieved a median progression-free survival of nearly 10 months, 3 months longer than capecitabine-lapatinib [13].

In conclusion, this is the first time, to our knowledge, that a prolonged response has been described following an anti-HER2 blockade in a patient with metastatic invasive lobular breast cancer. The association of CDH1 mutations and HER2 gene alterations in invasive lobular breast cancer, as well as its involvement in disease aggressiveness and cell invasion, require further exploration to better identify patients who may benefit from anti-HER2 blockade and to identify potential new therapeutic targets.

4. Acknowledgements

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