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Breast cancer patients with hormone neoadjuvant bridging therapy due to asymptomatic Corona virus infection. Case report, clinical and histopathologic findings

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ABSTRACT

INTRODUCTION: Breast cancer management during COVID-19 pandemic has changed and in case of COVID-19 patients with simultaneous neoplasia, it has been strongly recommended to treat Sars-CoV-2 infection firstly.

PRESENTATION OF CASE: We reported a case of a 53-years-old women with early breast cancer and simultaneous asymptomatic SARS-CoV-2 infection. According to COVID-19 breast cancer recommendations she underwent hormone neoadjuvant treatment as a bridging therapy for surgery. Six months from the diagnosis, after virus eradication, patient underwent breast surgery. No SARS-CoV-2 RNA was found both in the surgical specimen and sentinel lymph node but micrometastasis were reported. During the last follow-up, the patient was in good clinical condition and started the adjuvant chemotherapy.

DISCUSSION: COVID-19 outbreak determined the publication of temporary recommendation leading to an extensive use of neoadjuvant chemotherapy in breast cancer patients. Although endocrine therapy is a mainstay in the adjuvant treatment, its role in the neoadjuvant schedule is unclear.

CONCLUSION: Upfront awake surgery should be preferred especially in asymptomatic COVID-19 patient with early breast cancer when monitoring of tumor response is not feasible.

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1. Introduction

COVID-19 is a respiratory disease that spreads from human to human. Due to its dramatical worldwide spread, WHO (World Health Organization) declared the pandemic on March 11, 2020 [1]. This Pandemic poses a challenge to health care system which had to face simultaneously the infectious emergency and other pathologies [2]. Due to this emergency, oncological diagnostic procedures and treatments suffered a significant slowdown in order to save resources towards COVID-19 [3]. Several scientific societies have released consensus recommendations for management of cancer patients [4,5]. Proposal are driven by the common aim to prioritize cancer treatments and preserve resources for COVID-19 emergency [3]. Multidisciplinary treatment of these patients

has changed. The risk associated with surgery (e.g. staff and patient's exposure to virus and the need of resources) were balanced against the risk of cancer progression while the patient was receiving alternative therapy (e.g. systemic therapy, radiotherapy) [6]. In case of COVID-19 patients with simultaneous neoplasia it was strongly recommended to treat Sars-CoV-2 infection firstly due to its mortality, morbidity and contagiousness [5–7]. This implied a delay on the diagnosis and treatment of cancer; Vanni et al. [2]. In addition, COVID-19 patients' anxiety and refusal of health facilities admission could contribute to a further the delay [8].

We report a case of woman with COVID-19 and simultaneous early breast cancer treated with neoadjuvant endocrine therapy in lieu of upfront surgery and with lymph node micrometastases at pathological examination. This work is reported by following the surgical case report (SCARE) guidelines [9].

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2. Presentation of case

A 53-years-old G5P3 post-menopausal women, in good clinical condition, visited our surgical outpatient clinic on February, 14 2020, with a new-onset breast lesion noted with self-examination. Family history was negative for cardiovascular and oncological disease. Her past medical history included moderate psoriasis treated with Tofacinib [10]. Physical examination revealed a palpable lesion, with a diameter of about 1 cm in the lower inner quadrant of the right breast without any clinically suspicious axillary lymph nodes. She underwent mammography and breast ultrasonography that revealed a suspicious malignant breast nodule BIRAD-V, with a maximum diameter of 1.4 cm. At ultrasonography, lymph nodes appear increased in volume (about 1.1 cm) but with predominant hilar vessel architecture without any radiological suspicion of malignancy. Biopsy of the nodule was planned and the malignant nature of the lesion was confirmed. The pathological examination of the biopsy revealed invasive ductal carcinoma: ER positive 90%, PR positive 45%, Ki67 25% and c-Erb-B2 negative score 0. The case was discussed at the breast cancer multidisciplinary meeting and up-front surgery was planned (right breast quadrantectomy and sentinel lymph node biopsy). On March 7, 2020 her husband was admitted to hospital due to COVID-19. Despite she was asymptomatic she underwent SARS-CoV-2 test and resulted positive (Molecular test on nasal and throat swab). According to oncological recommendations during COVID-19 pandemic, the case was re-discussed at the multidisciplinary meeting and neoadjuvant endocrine therapy was planned (bridging therapy) in lieu of upfront surgery. Patient accepted the scheduled treatment and reported anxiety and fear regarding Coronavirus diagnosis during follow-up telehealth reevaluation. Patient remained asymptomatic, blood tests (lymphocyte count and subpopulation, D-dimer, coagulation indices, and blood inflammatory indices) were regular with positive Sars-CoV-2 tests (totally four swabs) for two months. She did not receive any treatment for COVID-19. Eighty-seven days after SARS-CoV-2 positive tests, nasal and throat swab resulted negative. Two other swab were performed respectively fifteen and thirty days from the negative one, and both confirmed the negative result. After infectious disease resolution, the surgical procedure was planned. Totally she was treated with 20 mg/day of Tamoxifene for 90 days with no noteworthy side effects and good adherence to treatments. On July 1, 2020 the patient underwent, by breast surgeon with twenty-years of experience, right breast quadrantectomy and sentinel lymph nodes biopsy (resulted negative at frozen section). Histological examination revealed invasive ductal carcinoma grade 2 spanning at least 1.2 cm in the greatest dimension associated with an in situ component less than 20%. Immunohistochemical staining revealed strongly and diffusely ER and PR positive in tumor cells: <95% and 40% respectively (Fig. 1B–D) HER2 was negative and Ki67 was 30% (Fig. 1E and F). Sentinel lymph node presented a micrometastasis of 0.3 mm and showed germinal centers in reactive exhaustion and mild expansion of T-dependent paracortical zone, consistent with benign reactive lymphadenitis as a result of the viral infection (Hematoxylin-Eosin staining, 2x; 10x in the insert) (Fig. 1A). No viral RNA of SARS-CoV-2 was found in lymph node or in the breast. On 1 month's follow-up patient was in good clinical condition with adjuvant chemotherapy on going. In the same visit, written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

3. Discussion

SARS-CoV-2 has dramatically spread worldwide forcing the implementation of restrictive measures and changing our daily routine [3]. Health system experienced a total reorganization which also involved breast units and their guidelines [3–6].

Before COVID-19 pandemic, patient such as this, with clinical stage T1N0, hormone receptors positive HER2-negative breast cancer, would have been a candidate for upfront surgery [11]. Given the size of patient's breast and the small diameters of the lesion, conservative breast surgery would be recommended to preserve body image and reduce hospitalization especially in this emergency period [12–14].

According to modified management of breast cancer patients during COVID-19 pandemic, this patient was candidate to neoadjuvant endocrine therapy followed by conservative breast surgery and radiotherapy; Spring et al. [6–15]. Moreover, despite the patient was asymptomatic, she resulted SARS-CoV-2 positive. In order to reduce the risk of cross-infection among health workers and other patients, the avoidance of hospitalization and the availability of a bridging therapy could be considered feasible and safe.

Neoadjuvant hormone therapy was administered for 3 months and during this time the negativization of SARS-CoV-2 was achieved [6]. Although endocrine therapy is a mainstay in the adjuvant treatment, its role in the neoadjuvant schedule is unclear [6]. Moreover, despite the lack of image guided clinical response evaluation during primary therapy, neoadjuvant regimen allowed to perform surgery safely for patient, and to avoid cross infection in health care workers and other patients [3].

Pathological examination of sentinel lymph node showed germinal centers in reactive exhaustion and mild expansion of T-dependent paracortical zone, consistent with benign reactive lymphadenitis resulting from the viral infection. Unlike what reported in literature, no viral RNA was found in the lymph nodes [16–18]. The absence of RNA of SARS-CoV-2 in the lymph node could be probably correlated to the eradicated infection. However, the T-dependent response could be an indirect sign of SARS-CoV-2 infection. In literature was reported that SARS-CoV-2 RNA can be detected in routine histopathological samples even before COVID-19 disease development [19]. Differently, in our case viral RNA was not found neither in the surgical specimen probably correlating with the infection eradication.

Waiting time between diagnosis and surgery in our case was about 6 months. During the pandemic, oncological diagnostic procedures and treatments experienced a significant slowdown [2–20]. In our opinion waiting time can influence breast cancer staging [3]. Bridging neoadjuvant hormone therapy could be a valid option in order to achieve a partial or complete response [6]. Monitoring cancer response rates during the lockdown, especially in patients SARS-CoV-2 positive may not be easy to achieve. In our case, histological examination of sentinel lymph nodes revealed micrometastasis. Due to node involvement patients started adjuvant chemotherapy with a strong impact on her quality of life [9]. We cannot exclude that this lymph node involvement is correlated to the longer waiting time.

4. Conclusion

Therefore, the use of bridging therapy in patients with early breast cancer, during pandemic, that could benefit from upfront surgery should be evaluated in large sample studies. If it is not feasi-

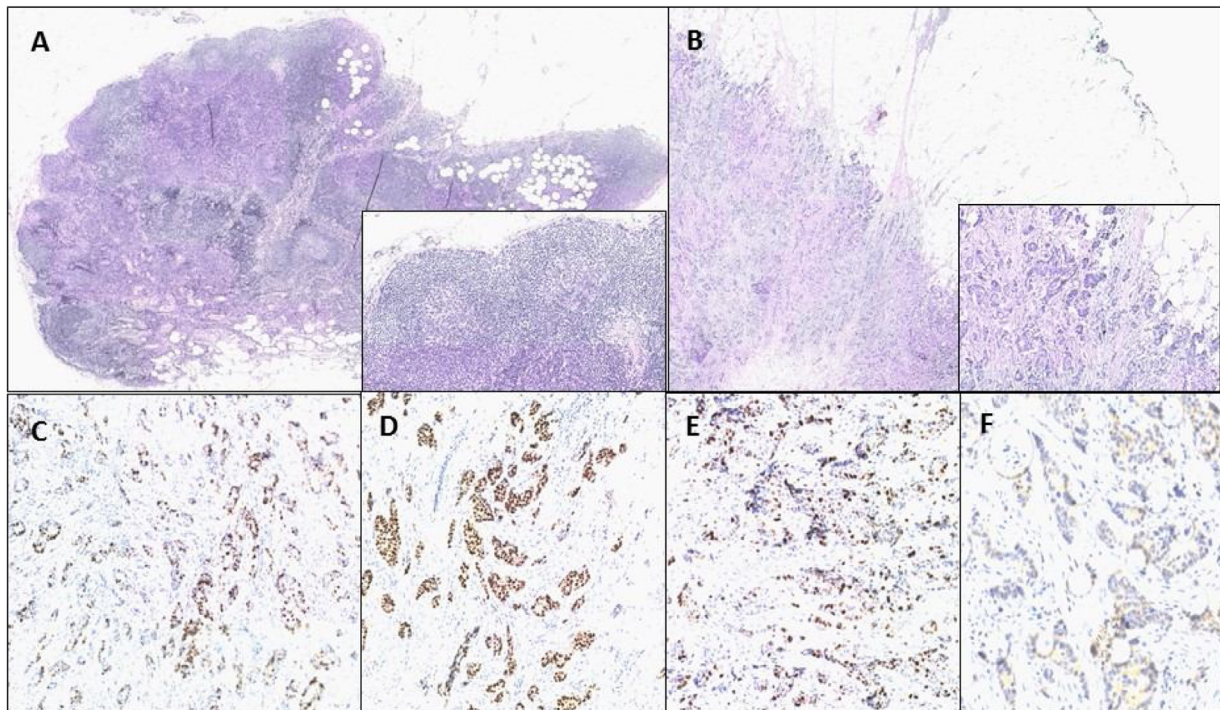


Fig. 1. Pathological examination of lymph node and breast surgical specimen.
 A) Section of axillary lymph node showing germinal centers in reactive exhaustion and mild expansion of T-dependent paracortical zone, consistent with benign reactive lymphadenitis post viral infection (Hematoxylin-Eosin staining, 2x; 10x in the insert).
 B) Section of breast tumor morphologically consistent with invasive ductal carcinoma, NST according to WHO Classification, grade 2 according to the Elston-Ellis modification of the Scarff-Bloom-Richardson (SBR) grading system (Hematoxylin-Eosin staining, 2x; 10x in the insert).
 C) Immunostaining showing Estrogen Receptor expression in neoplastic cells (clone SP1, Ventana Roche, 10x).
 D) Immunostaining showing Progesterone Receptor expression in neoplastic cells (clone 16, Leica, 10x).
 E) Proliferative index evaluated by Ki-67 immunostaining (clone MM1, Leica, 10x).
 F) Immunostaining for evaluation of Her2 expression, showing mild cytoplasmic reactivity and absence of membranous staining in neoplastic cells, classified as score 0 (clone CB11, Leica, 10x).

ble to monitor the tumor response during the neoadjuvant therapy, different strategy should be preferred. Awake breast surgery, with personal protective equipment especially in asymptomatic COVID-19 patient could be an option in order to reduce waiting time and possible cancer progression.

Declaration of Competing Interest

All the authors declare no conflict of interest.

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Ethical approval

For this study, ethical and ethnical approval are not required.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Marco Pellicciaro: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Gianluca Vanni: Conceptualization, Data curation, Formal analysis, Writing - review & editing. Alessandra Vittoria Granai: Conceptualization, Data curation, Formal analysis, Writing - review & editing. Francesca Servadei: Data curation, Formal analysis, Writing - review & editing. Erica Giacobbi: Data curation, Formal analysis, Writing - review & editing. Gloria Marchese: Data curation, Formal analysis, Writing - review & editing. Tommaso Perretta: Data curation, Formal analysis, Writing - review & editing. Rosaria Meucci: Data curation, Formal analysis, Writing - review & editing. Maria Cotesta: Data curation, Formal analysis, Writing - review & editing. Francesca Santori: Data curation, Formal analysis, Writing - review & editing. Chiara Adriana Pistolese: Data curation, Formal analysis, Writing - review & editing. Sandro Grelli: Data curation, Formal analysis, Writing - review & editing.

Registration of research studies

Not applicable.

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