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ORIGINAL ARTICLE

Case series of inflammatory breast cancer in two Greek hospitals: our experience and critical appraisal

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'*S u m m a r y.* Inflammatory breast cancer (IBC) represents a very aggressive type of locally advanced cancer. Because of its rarity, management of IBC appears heterogeneous; thus, reporting experiences from different clinics can be helpful. Fourteen female patients with IBC in two clinics of Greek hospitals were included in this case series study. The type of surgery performed in the eight patients that underwent surgery was modified radical mastectomy after neoadjuvant chemotherapy. Moreover, lymph node excision (level one and two) was performed in all (n=14) patients; all but one patients had positive lymph nodes. Sentinel biopsy technique was avoided in the above female patients with IBC. Radiotherapy was applied to all patients, except one elderly patient. Second-line chemotherapy was applied in three patients with aggressive, recurrent tumors. Two patients out of 14

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(~14.3%) died within 3 years after initial treatment, 2 patients are alive (~14.3%) with recurrence after 5 years, and 10 patients are still alive (~71.4%) with no clinically apparent recurrence. Four patients (~28.6%) had local recurrence; among them, two (~14.3% out of total) were treated with lumpectomy, and two (~14.3%) were diagnosed with distant metastasis. Second line chemotherapy was applied to 4 (~28.6%) patients. In addition, IBC cases represented around 2% of the total number of female patients with breast cancer in our centers. Patients with IBC who were treated with multimodal management (i.e., chemotherapy and surgical treatment) did not have higher disease-free survival rates compared to those treated with chemotherapy alone. According to our experience, and in contrast to the typical low prognosis of IBC, the aggressive management of patients with IBC leads to relatively high prognosis rates and high level of disease-free survival in our case series. This approach needs to be assessed in larger clinical settings within the broader aim of exploring potential new approaches in management of patients with IBC.

1. INTRODUCTION.

Inflammatory breast cancer (IBC) is a distinct, aggressive type of locally advanced cancer, comprising ~1-10% of breast cancer in western societies, with variations in these rates possibly due to varying case definitions [1]. Predisposing factors include parameters, such as duration of breast feeding that exceeds 24 months, rural origin, educational level less than 5 years, and body mass index higher than 30kg/m^2 compared to patients with other types of breast cancer [2]. On the one hand, the term *inflammatory* was historically introduced by Lee and Tannebaum in 1924 [3]. IBC might have represented in the past even up to 30-55% of diagnosed breast cancer in some countries, i.e., North Africa: Tunisia [2]. Of note, according to some authors, the term *inflammatory* is a misnomer, since the breast's inflammation is because the dermal lymphatics are blocked by the tumor infiltrate, and not because of inflammatory cells' infiltration [4] [5]. However, alternative names including *carcinomatous mastitis*, *mastitis carcinoma*, *acute mammary carcinoma*, *acute brawny cancer*, *lactation cancer*, *lymphocytoma of the breast*, and *breast cancer of pregnant and lactating women* have not been widely cited [6]. On the other hand, according to the American Joint Committee on Cancer, IBC is a *clinicopathological entity characterized by diffuse erythema and edema of the breast, often without an underlying palpable mass* [7].

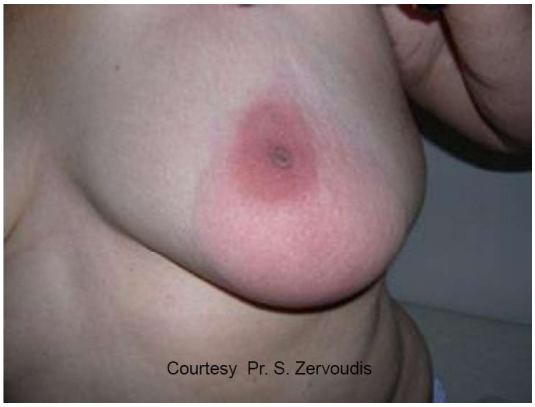

Figure 1. *Breast Erythema in Inflammatory Breast Cancer (Courtesy of Prof. S. Zervoudis)*

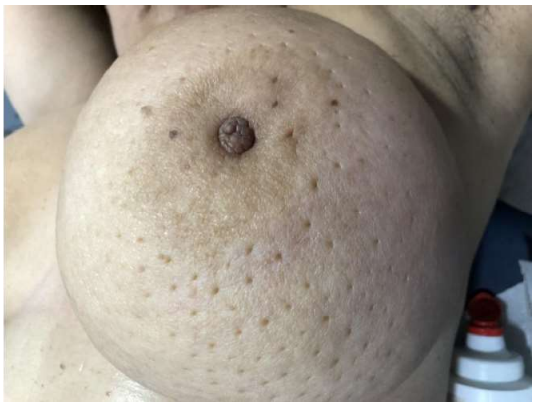

Figure 2. *Breast "peau d' orange" in Inflammatory Breast Cancer (Courtesy of Prof. S. Zervoudis).*

Importantly, the recent international expert panels on IBC –an area with many controversies yet to be resolved [8]– suggested the following criteria that are minimum ones required for diagnosing IBC, i.e., *a) Rapid onset of breast erythema, edema* **(Figure 1)** *and/or peau d'orange* **(Figure 2)** *and/or warm breast, with or without an underlying palpable mass*; *b) Duration of history of no more than 6 months*; *c) Erythema occupying at least one-third of the breast*, and *d) Pathological confirmation of invasive carcinoma* [9]. Also, IBC can be primary or develop after non-IBC type of non-bilateral breast cancer, and, in many cases, IBC represents a situation whose clinical picture may develop overnight and, as such, a medical emergency. From an anatomical pathology perspective, tumor emboli's detection in lymphatic vessels of the skin is not obligatory for diagnosis being only present in 50-75% of the cases; however, it is still considered a hallmark of the IBC phenotype. Moreover, IBC type is highly

lymphogenic and angiogenic. Also, from a molecular pathology viewpoint, overexpression of epidermal growth factor receptor, of E-cadherin and of NF-kB along with consecutive down-regulation of estrogen receptors is reported [10]. Moreover, RhoC guanine triphosphatase has been found to be over-expressed in 90% of IBC tumors in comparison to 38% of non-IBC tumors also showing an association with poorer prognosis [11].

Despite improvements in overall survival of female patients breast cancer over the last two decades, patients with IBC tend to have a poorer prognosis with 5- and 10-year survival rates of 40% and ~30% in white populations and black women, respectively. To this fact, a potential contributor could be than more than 30% of patients present with metastases at diagnosis [12]. Thus, the survival rate for patients with IBC falls back that of patients with non-IBC breast cancer by approximately 50% [6]. Nevertheless, it should be noted that the overall survival of patients with IBC has improved from 32 to 42% from 1975-79 to 1988-92 [13].

While studies on IBC have been performed across the globe, to our best knowledge no study focusing on IBC has been conducted in Greece. Therefore, in alignment with our established publication practice [14-17] on breast cancer that ultimately aims to provide compact, clinically useful to practicing breast cancer specialists of the Balkan and Mediterranean region, we here-in aimed to present our experience on IBC as part of two breast surgery centers in Greece.

2. METHODS

We applied a retrospective analysis of our case series data from our breast cancer centers, which records information on all incident cases of female patients with breast cancer that are diagnosed, treated and/or seek second medical advice and/or counselling at our centers. During medical examination and hospitalization, physicians were asked to register relevant clinical and epidemiological data.

This study aimed to includes all IBC cases diagnosed in our breast clinics located in two regions of Greece (i.e., Athens, and Alexandroupolis) during the period January 1st, 2016, and January 1st, 201. The medical record files of all patients with IBC were accessed to obtain additional information on presence of clinical inflammatory breast cancer symptoms (redness, swelling, peau d' orange), histological symptoms (dermal lymphatic invasion), clinical, and microscopic response to neoadjuvant and margin status after surgery. All patients had previously provided informed consent for their medical record to be retrieved for epidemiological studies upon anonymization. Statistical analysis was performed using the free-access R language (https://cran.r-project.org/), and a value of p=0.05 was considered statistically significant.

3. RESULTS

Overall, 23 patients diagnosed with IBC in our two breast clinics located in different regions of Greece (in Athens, and in Alexandroupolis) could have formed this study's population. However, 8 out of the 23 patients were lost during follow-up after the initial diagnosis with core biopsy, and they were most likely treated in other hospitals (where we have no access and/or consent to retrieve relevant information). Therefore, due to the limited number of patients with IBC, and an important number of patients that were lost during follow-up after the initial diagnosis of IBC (8 patients), we were able to ultimately assess fourteen patients with IBC for further analysis.

The mean age of the fourteen patients was 53.38 years (range: 32–79 years old). The tumor's mean size was 54.57 mm (range: 16-110mm). The diagnosis of IBC was based on the combination of clinical, ultrasound, mammography, and pathology findings. The following surgical procedures were performed, i.e., modified radical mastectomy was performed alongside excision of lymph nodes (level 1 and 2) in all (n=14; 100%) patients whereas lumpectomy with complete excision of the tumor with margins > 10 mm was performed in none of the patients (0%).

Moreover, all (n=14; 100%) patients were followed-up with physician examination, mammography on a per year basis, breast ultrasound every six months, whereas 12 out of 14 patients underwent breast MRI on an annual basis. Moreover, the follow-up was accompanied with computer tomography (CT) of the thorax and abdomen, bone scan, and dosage of tumor markers (CEA, CA15-3, and CA27-29 in some cases). Four patients (~28.6%) had local recurrence; among them, two (~14.3% out of total) were treated with lumpectomy, and two (~14.3%) were diagnosed with distant metastasis. Second line chemotherapy was applied to 4 (~28.6%) patients. In addition, IBC cases represented around 2% of the total number of female patients with breast cancer in our centers, with breast cancer-related deaths and or metastasis having been observed in 4 of 14 (28.6%) of patients with IBC in our centers.

Information on grade was available for 12 out of 14 patients; among them, there were 10 patients with grade 3 (~83.3% out of 12 patients), and the other two (~16.7%) with grade 2. Regarding ER/PR status, 50% of the patients corresponded to tumors that are PR-positive, and 57.1% corresponds to tumors that are ER-positive.

Moreover, 8 out of 14 patients (~57.1%) of women received chemotherapy and underwent surgical operation, whereas 6 out of 14 patients (~42.9%) only received chemotherapy. Unfortunately, one and one patient died within 2 years (at the age of 70 years old) and 3 years (at the age of 49 years old) after the prior therapy, respectively; therefore, the mean five-year breast cancer-specific survival rates was ~85.7%. In addition, two patients are alive (~14.3% out of 14 patients, in total) with recurrence after 5 years, and 10 patients (~71.4% out of 14 patients, in total) are still alive (~71.4%) with no clinically apparent recurrence.

To address whether (or not) the aggressive management of patients with IBC leads to relatively high prognosis rates and high level of disease-free survival in our case series, and given that our sample size is small, we performed Fisher's exact test. Because the result is not significant at $p < 0.05$ (Fisher's exact test statistic value is 1), we cannot reject the null hypothesis; therefore, the proportions of survival rates do not appear to be different between the combined chemotherapy-surgery *vs.* chemotherapy alone approach.

4. DISCUSSION

Robust epidemiological evidence suggests that albeit increasing over the last decades the survival rates of patients with IBC are consistently significantly lower than those other types of breast cancer at the same stage [1]. Based on IBC dedicated centers' experience, several risk factors can be identified, such as body mass index $\geq$ 25 kg/m^2 and family history of breast/ovarian cancer, both in >60% of women with diagnosis of IBC [18]. The role of classical epidemiological factors, such as history of pregnancy and related perinatal factors [19], area of residence [20], marital status [21], and maternal/ paternal age at birth [22] should always be kept in mind. In addition, IBC affects significantly more women of color (notably, black women and comparatively less Hispanic and South Asian) than white female patients, in terms of both its incidence (~45 *vs.* ~28cases per one million people) and survival (5-year survival rates of ~40 *vs.* ~30%) [1, 18]. This fact could explain why IBC may represent even one third of breast cancer diagnoses in certain countries of North Africa (e.g., Tunisia [2]). It is also an issue that should raise high clinical suspicion even to clinicians in other countries, in particular when it comes to refugees and migrant women of color visiting gynecology and breast cancer clinics.

Perhaps due to small size of our case series, our study is not in complete alignment with previous knowledge exhibiting that the prognosis of IBC is extremely poor compared to other histological subtypes, i.e., a 5-year survival at 45% for IBC and more than 80% for ductal and lobular subtypes, respectively; of note, in contrast though to other histological types, the survival curve reached a plateau after five years and no women died from IBC afterwards [23]. However, this is far from suggesting that female patients who are alive after five years from diagnosis may be considered as cure. In fact, larger studies have shown a stable decline of survival of patients with IBC from five to ten years, even though a partial stability was shown after 80 months in one study [24] [25] [26]. Moreover, while, in general the prognosis of IBC has been shown not to differ according to histological subtype [27], whether the prognosis of patients with IBC presenting only histological characteristics of IBC is better than that of patients with additional clinical symptoms in our region (Balkan region) remains to be explored.

As far as therapeutic strategies are concerned, our results do not indicate a homogenous approach of IBC in our region. Of note, several different treatment combinations of neoadjuvant chemotherapy, surgery, and radiotherapy and have been observed in our case series. All women (n=14) were treated in a multimodality manner, i.e., with a therapy including surgery, chemotherapy (neoadjuvant), and radiotherapy (except one patient who did not undergo radiotherapy).

The results from this cases series do not allow us to interfere that aggressive management of patients with IBC (i.e., combination of chemotherapy and surgical treatment) have higher levels of disease-free survival compared to those who have been treated with chemotherapy alone; however, such results should only be seen as indicative and, thus, should be assessed in a much higher number of patients to allow adequate statistical power. Therefore, our results should be interpreted as a call-to-action (in conjunction with previous studies [28]) for more uniform and multimodal therapeutic approaches in our and, more broadly, the European region

since there is less than 15% of more than 5-year survival with either surgery or radiotherapy or both [29]. However, the 5-year overall survival of IBC female patients has improved to 40%, since the so-called *multimodality approach* that includes surgery, primary systemic chemotherapy that is based on anthracycline and taxanes, and radiation therapy were introduced [30, 31].

With regard to prognostic factors, lesions with no clinical IBC symptoms had … survival rates compared to lesions with clinical symptoms (alone or associated with histological symptoms). Previous studies have been conflicting in this topic over the last three decades ago, i.e., they study by Levine *et al.* reported the poorest prognosis among patients with IBC exhibiting only histological features of IBC [32], whereas others showed the opposite [33]. Relevant to these observations is a more recent study indicating that patients with IBC and with a palpable mass or with lower stage showed larger survival than patients without such a mass or higher stage, respectively [34]. Thus, certain critical questions are raised as to *a)* whether female patients without the clinical IBC symptoms but with only histological ones should be considered as patients with IBC, and *b)* whether these patients should be treated equally aggressively as women with clinical symptoms. In every case, nomograms predicting the 3- and 5-year survival rates in IBC appears to be useful [35, 36].

Present findings are also in accordance with previous studies showing that systematic or locoregional treatment or chemotherapy (either in its neoadjuvant or adjuvant form) had no effect on overall survival [34]. Interestingly, complete microscopic response to neoadjuvant chemotherapy was a considerable factor significantly linked to 5-year survival; this in line with findings reported from Ueno *et al.* [37], stating a markedly improved outcome in patients who showed a strong response to neoadjuvant chemotherapy.

Our study has certain limitations: *a)* The low sample size does not permit us to adjust for possible confounding factors; thus, we were obliged to present only observed survival rate; *b)* In the design of this study, the choice of treatment was determined individually according to the patient's health status and tumor characteristics. In only one case, radiotherapy was not selected as a therapeutic strategy because of the old age of the patient; *c)* This was a case series with a small number of cases and no control groups; however, we were still able to perform some basis multivariate analysis.

Despite these shortcomings, this study raises some key issues which might merit further investigation, i.e., *a)* the question whether the plateau observed correspond to an unknown biological mechanism, and *b)* the need for a uniform, standard, multimodality therapeutic quiver in order to improve the care of patients with this apparently rare type of breast cancer, which merits the characterization as an orphan disease. In light of this, novel approaches including omics-based markers, e.g., serum microRNAs and serum proteomic analysis, should be monitored in the sake of early preventive diagnosis [38].

Another future major research focus should relates to racial disparities in IBC, as both IBC-related incidence and mortality is higher in women of color, especially Black Women, than white women. We live in an era where racial disparities are, and should continue to be, factors to consider in clinical practice and, more broadly, health care. Therefore, in the quest to reduce inequalities and ultimately achieve equity in health care, deciphering such questions, –in particular, which is the parameter that modifies the effect between racial status and IBC–, is more imperative than ever [18]. Following similar studies in other cancer types , a major question to be answered refers to whether racial minority groups have less-than-optimal therapeutic results (also described as textbook outcomes) during treatment for IBC [39]. On the molecular level, following similar studies in triple-negative BC, it would be worth asking if specific differences in the gene expression profiling in patients with IBC *vs.* other types of breast cancer may be due to racial disparities [40, 41].

Moreover, there are several environmental (also called non-purely genetic factors) and genetic factors that may play a major role in IBC pathogenesis. On the one hand, there is the well-documented risk factor of *overweight* and *obesity,* which is more prevalent in women of color than White women [42, 43]. Whether obesity exercises direct effects on IBC or whether these IBC-related effects are mediated through obesity's actions on endocrine hormones (estrogen, progesterone, and even androgens [44]) is another question that needs to be addressed; of note, obesity has been quite prevalent in our case series. On the other hand, though, lie the genetic risk factors. Considering that IBC is a rare subtype of cancer, conducting genome-wide association studies, which –by their nature– require samples at the level of thousands only to retrospectively identify non-major DNA variants in most cases, is unlikely to reap rewards,

especially as such studies have been historically biased in favor of studying white people. Perhaps a more fruitful option, though one potentially already taking place, would be to analyze the genetic material (i.e., DNA, RNA) of IBC tissue samples (e.g., through next-generation nucleic acid sequencing methods), and compare the DNA variants and gene expression patterns in IBC of white patients *vs.* patients with color. Doing so could elucidate which genes and cellular pathways are different in IBC samples of the two racial groups. Moving forward, the much needed advancement in treating IBC could become part of precision medicine approaches that will consider the racial factor into the therapeutic algorithm [45]; however, as such approaches are quite expensive, their application could increase the so-called *financial toxicity* of the patient with IBC, an issue that should also be addressed in clinical practice [46].

5. CONCLUSION

Our case series study reveals a consistent pattern in the management of IBC in our settings, which is significantly based on the initial neoadjuvant chemotherapy combined with surgical procedures. Moving forward, considering the low incidence of IBC, breast physicians should be alarmingly prompted to discuss IBC diagnosis and treatment in senology boards and/or even grand rounds. Also, they should ultimately work towards creating IBC clinics which, —given the country's population and geography—, should not be more than two-three but yet appropriately distributed in the Northern and Southern parts of the country. Last, the emerging trends of immigration from North Africa where the incidence of IBC is high should raise suspicions of potential IBC diagnosis to breast physicians who treat patients with breast pathology issues, especially in health centers of refugee camps and breast cancer-specialized hospitals.

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Conflict of interests
The authors declare no financial or other conflict of interest.

Data availability
Descriptive raw data are available upon reasonable request.

Ethics statement
This study was conducted in accordance with the Declaration of Helsinki and its current amendments.

Informed consent
Informed consent was provided by the patient prior to inclusion in this case series study. Every action has been taken to achieve anonymization of the patients' data.

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