Benign Breast Diseases: Classification, Diagnosis, and Management

FERDINANDO MANNELLO, GAETANA A.M. TONTI
Institute of Histology and Laboratory Analysis, University Carlo Bo, Urbino, Italy

We read with concern the review by Guray and Sahin [1] that adds to the body of evidence on clinical features and practical management of benign breast diseases (BBDs) [2]. We believe that the aspects regarding fibrocystic changes contained in the article deserve some comments (in particular for cystic lesions), and furthermore, several caveats are implicit (the data tend to be correlative rather than mechanistic in nature).

Although the most common presenting symptoms of fibrocystic changes (FCCs) are breast pain and tender nodularities in the breast, most breast cysts (especially microcysts) are not painful, not progressive, and spontaneously regress. It is therefore possible for women to live their lives in blissful ignorance of the fact that they have a cyst: these women would be those who do not examine their breasts and do not have a heightened awareness of breast cancer (BC). By contrast, the women who discover palpable macrocysts in the breast are those who may practice self-examination and are BC aware [3]. These two groups of women are likely to be very different in terms of other risk factors, and potential epidemiological differences (e.g., a family history of BC, postponement of the first pregnancy, use of the pill, and use of hormone-replacement therapy). These determinants lead to the pathogenesis of BC in women with a history of gross cystic breast disease (GCBD) [4].

Moreover, an overview of GCBD studies carried out during the last 30 years sheds light on the different biochemical, molecular, and morphological differences of the two breast gross cyst types [5], providing evidence that the peculiar electrolyte, protein, sex hormone, growth factor, and proteolytic enzyme accumulation reflects both the biochemical environment and the morphological aspect of the epithelium lining the gross cysts, developing into the terminal duct-lobular unit. The different biocompound profiles found in the flattened low-risk and apocrine high-risk gross cysts may aid in the classification of gross cyst subtypes [6] and the identification of a biomolecular/morphological pattern [4, 5, 7, 8] in women with a history of GCBD who go on to develop subsequent breast cancer [9–11]. These gross cyst types also differ in their natural history, particularly in terms of multiplicity and recurrence [11, 12]. Although care should be taken in translating the potential biological activity of several constituents (e.g., mitogenic growth factors, steroid hormones, proteolytic enzymes) into trophic effects within the breast and subsequent BC risk, gross cysts lined by apocrine epithelium show the ability to actively synthesize and secrete bioactive molecules [5], strengthening the epidemiological evidence of the increased risk for BC in GCBD-affected women [12].

The best evaluation of FCCs should take into account the natural history of some BBDs [4, 10], and cytomorphology may be helpful to discern between nonproliferative and proliferative lesions, with and without atypia, through an accurate cytology index [13]. In this respect, several morphological studies on GCBD have revealed that apocrine gross cysts result from an active process [7, 14], and the increased metabolic activity of the apocrine cells lining these cysts is associated with the presence of steroids, mitogenic growth factors, and proteinases, explaining at least in part their higher susceptibility to malignant transformation, especially in younger women [15–17].

The relation between GCBD and carcinoma of the breast is much debated [4], and is a subject worthy of thorough epidemiological and clinical discussions. Although the GCBD does not represent a preneoplastic condition per se [18], it has a peculiar place among BBDs and many stud-
ies point out that the different gross cyst subtypes differ in epidemiological, biomolecular, and clinical behavior [5, 9, 11, 12, 16, 19]. Most clinicians favor a policy of cautious/ close observation [20, 21], even though there is no certain evidence that the risk for BC in GCBD will fall as a result. We are far from the certainty that biomolecular and morphological analyses of fluid that is needle aspirated from gross cysts will ever be an accurate predictor of BC risk [5], and more studies are needed to answer the question of whether GCBD (and/or associated hyperplastic lesions) increase the risk for BC and to stratify women with GCBD into high-risk groups for BC [9].

Female BC is the most common malignancy in women in Western countries [22], and the use of noninvasive methods may greatly improve the possibility of recognizing, categorizing, and managing BBDs [4, 23]. In this respect, Guray and Sahin [1] did not report (probably for reasons of brevity) the usefulness of nipple aspirate fluid (NAF) collection, which provides a rich source of biomarkers (Mannello et al., submitted) to both aid in the assessment of the short-term risk for developing BC and predict/assess responses to prevention interventions [24]. Both NAF biochemical analysis and morphological evaluation of epithelial cells in NAF specimens attempt to improve the identification of high-proliferative epithelium with atypia, recognizing the high metabolic activity through proteomic, degradomic, and genomic approaches [25–27], and an accurate cytological grading system [28]. NAF collection may represent a promising noninvasive method for BC risk assessment, especially in asymptomatic women without suspicious lesions on physical exam or mammography [4], and may help to distinguish the most frequent benign lesions of the breast (e.g., inflammatory lesions, fibrocystic changes, stromal lesions, with and/or without atypia and/or hyperplasia) from BC (both in situ and invasive carcinoma), in order to also assess the most appropriate treatment management [29].

Finally, the high-quality overview of the clinicopathological features of benign breast lesions by Guray and Sahin [1] should not prescind careful consideration of the possibility of stratifying the risks of BBD in relation to developing subsequent BC through NAF collection and analysis, which provide direct evidence of the early changes in carcinogenesis (at a translational rather than a transcriptional level) [30], useful in identifying women with nonproliferative or proliferative changes at high risk of developing more-advanced precancerous lesions and eventually cancer [24]. The promise of intraductal research is based on the understanding of how the breast works, helping us to determine how to predict and to reverse early cancerous changes. Because neoplastic biomarkers and cellular markers from NAF are also used in ongoing trial studies, in order to identify women with BBD at higher-risk for BC and to evaluate chemoprevention to reverse atypia or to prevent the progression from hyperplasia to atypia [29], correct information to pathologists, radiologists, oncologists, and researchers should be more comprehensive, critically evaluating the diagnosis/management limitations in conjunction with cautious emphasis of future promising perspectives, for the fight against female BC [4].

ACKNOWLEDGMENTS

This work was supported by a Research Grant Award 2005 from the Dr. Susan Love Research Foundation (Pacific Palisades, CA; http://www.susanlovemdfoundation.org).

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

REFERENCES

In Reply

Merih Guray, Aysegul Sahin

University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

We would like to thank Drs. Mannello and Tonti for their kind comments on our review “Benign Breast Diseases: Classification, Diagnosis, and Management.” We completely agree with their comments that fibrocystic changes of the breast constitute the most frequently seen disorder in women. As the authors have mentioned, the most important aspect of these changes is the breast cancer risk associated with them. Breast cysts, which are considered as nonproliferative lesions of fibrocystic changes, are very frequently seen in the female breast. Although there seem to be two distinct subtypes of breast cysts, namely, type 1 and type 2, as Mannello et al. [1] have clearly pointed out in their review, to date there is no definitive study demonstrating which type of cyst is more prone to develop breast cancer. Nevertheless, different molecular, hormonal, and morphologic characteristics of these cysts, which are nicely summarized in the same manuscript, encourage the classification of these lesions as such. We agree that both morphologic evaluation of cysts and biochemical analysis of cyst contents are important in the classification of these lesions.

In our review, because of publication restrictions, this topic may not have been covered completely. Furthermore, the main aim of our manuscript was to cover most of the benign lesions of the breast in order to aid the practicing physician. Again, we would like to thank Drs. Mannello and Tonti for their invaluable comments and contributions to our review.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

Reference