

Clinical presentation, imaging, pathological profile and management of benign breast conditions based on aberrations of normal development and involution classification: A prospective cohort study

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Abstract

Aim: To map the spectrum of benign breast disorders in patients with reference to ANDI, attempt a clinicopathological and imaging correlation, and evaluate the impact of this concept on the choice of treatments and their outcome.

Material and Methods: This prospective study was carried out in the Department of Surgery at tertiary care hospital in central India. A total of 176 consecutive female patients who have attended menarche and presenting with benign breast conditions classified under ANDI classification attending the surgery department From November 2012 to November 2014 for benign breast conditions were enrolled in the study. Patient parameters were recorded on a predesigned case record form. After clinical assessment, imaging and pathologic evaluation was done as indicated.

Results: The mean age of presentation was 26.70±8.86 years. Most of patients presented with a commonest complaint of lump in the breast (89.2%). History of painless lump & lumpiness/nodularity was found in 99 cases. The maximum number of patients i.e. 114 (64.8%) presented within first 12 months of appearance of lump. Right breast was commonly involved i.e. in 72cases (40.90%). Mastalgia was not a predominant symptom in patients with benign breast conditions. Consistency in majority of cases was firm i.e. in 162 (92%) cases. Maximum number of breast lumps was located in the upper outer quadrant of breast i.e. 60(34.1%). Nodularity was not seen in 78% cases. Maximum no. of cases had discrete lump on presentation i.e.72%. There was no tenderness in 74% cases. 68% of patient had fibroadenoma. Most common age group was 21-30 yrs. Right upper quadrant was most commonly involved. Out of 121 cases, 84 underwent surgery, 29 conservative treatment & 8 both conservative with surgery. 57(32.38%) patients were diagnosed with mastalgia with or without nodularity. Diagnostic accuracy of Sono mammography in detection of fibroadenoma is 98.68. Diagnostic accuracy of FNAC and Histopathology in detection of fibrocystic changes is 98.8. Out of total 176 cases, 94 underwent surgery, 73 conservative treatment and 9 underwent conservative with surgery.

Conclusion: The ANDI classification, a comprehensive system, can resolve most of the issues that face a clinician when dealing with benign breast diseases.

Keywords: Benign breast disorders, ANDI

1.Introduction

Benign breast disorders (BBD) constitute the most prevalent group of conditions treated at breast clinic but there is a great deal of confusion in their nomenclature, classification, and treatment protocols. An important reason is discordance between the

clinical, radiologic, and, pathologic features of these conditions. Formerly, the term fibrocystic disease was used to describe all benign conditions. This term, however, caused confusion when distinguishing between normal physiologic changes and pathologic

ones[1]. Subsequently, attempts were made to achieve uniformity in the classification of benign lesions of the breast, two of which are noteworthy.

In 1985, Dupont and Page reviewed 10,366 biopsies of benign lesions and classified benign breast conditions into three groups based on their potential for malignant change: nonproliferative lesions, proliferative lesions without atypia, proliferative lesions with atypia[2]. The second landmark was the development of the Aberrations of Normal Development and Involution (ANDI) concept by Hughes *et al*[3]. This framework was designed to correlate clinical presentation with pathogenesis of BBDs. It was suggested that breast conditions are a continuum, ranging from normal to aberrations of physiology to frank disease.

The ANDI classification for benign breast disorders provides an overall framework for categorizing benign conditions of the breast, encompassing both pathogenesis and the degree of abnormality. It is a bidirectional framework based on the fact that most BBDs arise from normal physiologic processes. The horizontal component defines BBD along a spectrum from normal to mild abnormality (disorder) to severe abnormality (disease). The vertical component defines the pathogenesis of condition. Together, these components provide a comprehensive framework into which most BBDs can be fitted. Despite these two concepts gaining widespread theoretical acceptance over the past two decades, it is surprising that most epidemiologic studies or clinical series have not used

these two classifications. Older terms, such as fibrocystic disease and fibroadenosis, are used frequently in the literature even today. Because these terms denote a lack of clear understanding of the underlying pathophysiology, many patients with normal physiologic changes undergo unnecessary investigations, including biopsy, and suffer from avoidable anxiety and morbidity.

2. Material and Methods

This prospective study was carried out in the Department of Surgery at tertiary care hospital in central India. A total of 176 consecutive female patients who have attended menarche and presenting with benign breast conditions classified under ANDI classification attending the surgery department From November 2012 to November 2014 for benign breast conditions were enrolled in the study. Patient parameters were recorded on a predesigned case record form.

After clinical assessment, imaging and pathologic evaluation was done as indicated. Ultrasonography (USG) of the breasts and fine-needle aspiration cytology (FNAC) was advised to patients presenting with nodularity/discrete lump in the breast. Mammography was advised for women considered to be at a high risk for breast cancer and for suspicious lesion. Bloody or serous nipple discharge was sent for cytologic examination for malignant cells.

Table 1: ANDI (aberration of normal development and involution) classification

Stage	Main clinical presentation		
	Normal Process	Aberration	Diseases
Early reproductive (15-25years)	Lobular Development	Fibroadenoma	Giant Fibroadenoma
	Stromal development	Adolescent hypertrophy	Gigantomastia
	Nipple eversion	Nipple inversion	Subareolar Abscess/ mammary duct fistula
Mature reproductive (25-40years)	Cyclical changes of menstruation	Cyclical mastalgia Nodularity	Incapacitating mastalgia
	Epithelial hyperplasia of pregnancy	Bloody nipple discharge	
Involution (35-55 years)	Lobular involution	Macrocysts Sclerosing lesions	
	Duct involution -dilation -sclerosis	-Duct ectasia -Nipple retraction	Periductal mastitis
	Epithelial turnover	Simple epithelial hyperplasia	With atypia

2.1 Exclusion Criteria

Exclusion Criteria includes Cases of malignancy of breast and patients not willing to participate.

2.3 Statistical analysis

The data was analysed by using SPSS version 16 & EPI info software.

3. Results

3.1 Age distribution

The mean age of presentation was 26.70±8.86 years. The youngest patient was of the age 15 years and the oldest was of 48 years.

3.2. Clinical presentation

Most of patients presented with a commonest complaint of lump in the breast (89.2% n =157) followed by pain (42.6% n=75) and discharge from nipple(6.8% n=12).

3.3. Presentation of Lump in relation to pain

History of painless lump or lumpiness/nodularity was found in 99 cases, painful lump & lumpiness/nodularity in 58 cases

3.4. Duration of lump

The maximum number of patients i.e. 114 (64.8%) presented within first 12 months of appearance of lump, followed by 21 cases (11.9%) between 13>24months. The mean duration of symptoms was 13.69 ± 16.92 months.

3.5. Distribution of study subjects in relation to laterality (side) of lump

Right breast was involved in 72cases (40.90%), followed by left which was involved in 50 cases and bilateral in35 cases.

3.6. Mastalgia

Mastalgia was not a predominant symptom in patients with benign breast conditions accounting for 49 patients (27.8%) of that cyclical mastalgia was present in 36(20.4%) patients while the rest had non-cyclical mastalgia (7.3%).

3.7. Nipple discharge

A total of 12(6.81%) patients presented with complaints of nipple discharge. Discharge was serous in 6 patients, milky in 3 patients, greenish 2, and blood-stained in 1patient.

3.8. Distribution of nipple discharge in relation to laterality

Discharge was bilateral in 6(50%) cases and unilateral in 6(50%) cases.

3.9. Consistency of lump

Consistency in majority of cases was firm i.e in 162 (92%) cases out of 176 cases

3.10. Quadrant wise location of lumps

Of the total 176 cases, maximum number of breast lumps was located in the upper outer quadrant of breast i.e. 60(34.1%).

Table No 2: showing distribution of Nodularity

Nodularity	Number of Patients	%
Present	46	26.1
No nodularity	130	73.8
Total	176	100

Table no.3: Showing Spectrum of clinical presentation:

Patients' Symptoms	No. of Patients	%
Discrete lump	127	72.1.
Mastalgia with nodularity	38	21.5
Nipple discharge	12	6.8
Mastalgia alone	11	6.25
Nodularity alone	8	4.5

Table No 4: Showing distribution of Tenderness:

Tenderness	No. of Patients	%s
Tender	45	25.6
Non- tender	131	74.4

Table No.5 a: Spectrum of benign breast conditions as per the ANDI classification

Benign breast conditions	No. of patients	%
Fibroadenoma	121	68.75
Cyclical mastalgia with nodularity	27	15.34
Mastalgia with nodularity	10	5.68
Cyclical pronounced mastalgia	9	5.11
Nodularity	8	4.55
Duct Ectasia	4	2.27
Mastalgia	2	1.14
Incapacitating mastalgia with nodularity	1	0.57
Sclerosing adenosis	1	0.57
Atypical ductal hyperplasia	1	0.57
Breast cyst	1	0.57
Bloody nipple discharge	1	0.57

Table No 5b: Spectrum of benign breast conditions as per the ANDI classification

Reproductive Period and normal process	Benign breast disorder		Benign breast disease	
Development	Diagnosis	No. of patients	Diagnosis	No. of Patients
Nipple eversion	Nipple inversion	-	Mammary duct fistula	-
	Single duct obstruction	-	Subareolar abscess	-
Lobular	Fibroadenoma	100	Giant/multiple fibroadenoma	21
Stromal	Juvenile hypertrophy	-	Gigantomastia	-
Cyclic change Hormonal activity				
	Mastalgia	11	Incapacitating mastalgia with nodularity	1
	Nodularity	8		
	Mastalgia with nodularity	37		
Epithelial activity				
Epithelia hyperplasia Of Pregnancy	Bloody Nipple discharge	1		
Involution				
Lobular involution	Cysts	1		
	Sclerosing adenosis	1		
Ductal involution	Nipple retraction	-	Periductal mastitis with suppuration	-
Dilatation	Duct ectasia	4		
Involutional epithelial hyperplasia	Simple epithelial hyperplasia	-	Lobular hyperplasia with atypia	-
			Duct hyperplasia with atypia	1

Table No 6: showing distribution of Correlation of benign breast conditions with the Age of the patients. (%)

Final Diagnosis	Number	Age in years			
		11-20	21-30	31-40	41-50
Fibroadenoma	121	48 (39.67)	50 (41.32)	20 (16.53)	3 (2.48)
Cyclical mastalgia with nodularity	27	5 (17.86)	12 (42.86)	9 (32.14)	2 (7.14)
Mastalgia with nodularity	10	-	3 (30)	3(30)	4(40)
Cyclical pronounced mastalgia	9	-	5(62.50)	3(37.50)	-
Nodularity	8	3(37.50)	1(12.50)	2(25)	4(50)
Duct ectasia	4	-	-	2(50)	2(50)
Mastalgia	2	-	2(100)	-	-
Incapacitating mastalgia with nodularity	1	-	-	-	1(100)
Sclerosing adenosis	1	-	-	1(100)	-
Atypical ductal hyperplasia	1	-	-	-	1(100)
Breast cyst	1	-	-	1(100)	-
Bloody nipple discharge	1	-	1(100)	-	-

3.11. Fibroadenoma

Right upper outer quadrant was involved most commonly out of 121 cases of fibroadenoma. Altogether 29 patients (23.97%) were managed conservatively. Among the rest excision was performed in those more than 25 years of age, patients with persistent symptoms, apprehensive patients and those whose fibroadenoma were more than 3cm.

Total 8 patients were both modality of management was used, one patient had bilateral multiple Fibroadenoma, where excision of largest lesion was done as patient was apprehensive and insisted for removal, other lesions managed conservatively, other 3 patients had bilateral Fibroadenoma where excision of largest lesion was done as patient was apprehensive and insisted for removal. one patient with bilateral Fibroadenoma had giant fibroadenoma which was removed other lesion

managed conservatively, 2 patients managed conservatively but after 6 months follow up they insisted for removal of Fibroadenoma, 2 patients apart from fibroadenoma also had mastalgia with or without nodularity. 29 patients (23.97%) after confirming their diagnosis were managed conservatively out of which 20 patients received antiestrogen (ormeloxifene) rest 9 patients managed conservatively without any medication.

29 patients (23.97%) after confirming their diagnosis were managed conservatively out of which 20 patients received SERM (ormeloxifene) rest 9 patients managed conservatively without any medication. During the follow up period, 19 patients on conservative management noted a reduction in the lump size, and 3 had complete disappearance, 7 patients noted an increase in size of lump. (Table 7)

Table No 7: showing distribution of Fibroadenoma based on management:

Treatment	No. o Patients	%
Surgery	84	69.42
Conservative	29	23.97
Conservative + Surgery	8	6.61
Total	121	100

3.12. Mastalgia and cyclic nodularity

A total of 57 (32.38%) patients were diagnosed with mastalgia with or without nodularity. Cyclic mastalgia was the complaint of 36 patients; 27 of these patients had associated nodularity, and 9 had only pain, this 9 patients had cyclical pronounced mastalgia. Noncyclical mastalgia was found in 13 patients 11 of these had associated nodularity, and 2 had only pain. Most patients were between 25 -40 years of age. Among 46 patients with nodularity (38 with mastalgia, 8 with only nodularity), 35 had diffuse nodularity and 11 had focal nodularity/lumpiness. Sono mammography was done in all patients with focal nodularity to exclude the

presence of a discrete mass. The most common findings were increased echogenicity of fibroglandular tissue and/or cystic changes and/or prominent ducts, labeled as fibrocystic changes. Excision biopsy was done in the patients having FNAC report proliferative breast disease with atypia. Among the 57 patients with mastalgia, only 45 patients followed up on a regular basis for treatment. Among them, 15 patients experienced pain relief after being reassured. Another 21 patients had a complete or good response to evening primrose either alone or with vitamin E supplementation. 2 patients responded to danazol therapy, 4 patients responded to tamoxifen therapy. Tamoxifen preferred over danazol due to lower side effect profile. 1 patient did not get much relief even after trying all medications, finally she responded to bromocriptine. Whereas diffuse nodularity was mostly cyclic, focal nodularity was more persistent. Only 4 patients showed resolution of focal nodularity.

3.13. Mammography

Mammography was done selectively in only 11 patients, who had some risk factors and for diagnostic purpose in suspicious lesion. Mammography was done in two cases of duct ectasia to reach the diagnosis and in one case of atypical ductal hyperplasia and in two cases of focal nodularity and rest in suspicious cases of Mastalgia with nodularity. The Patient of atypical ductal hyperplasia on follow up developed carcinoma of breast.

Breast imaging-reporting and data system (BIRADS) 4 was present in one case of atypical ductal hyperplasia and in one case of suspicious Mastalgia with nodularity which was having Feature of neoplastic etiology clinically and also on other diagnostic investigation, patient underwent wide local excision and Histopathology report suggestive of fibrocystic changes.

Table No 8: Clinicopathological correlation of benign conditions of the breast

Cytopathological Category	Number (N=139)	%
Nonproliferative lesion	130	93.5
Proliferative lesion without atypia	5	3.59
Proliferative lesion with atypia	4	2.87

Table No 9: Comparative evaluation of diagnostic accuracy of Sono mammography in detection of benign conditions of breast

Findings	Sensitivity	Specificity	PPV	NPV	Accuracy
Fibroadenoma	98.86	98.44	98.86	98.44	98.68
Duct Ectasia	75	100	100	99.95	99.34
Mastalgia with and without Nodularity	82.61	100	100	92.98	94.73

Table No 10: Comparative evaluation of diagnostic accuracy of FNAC and Histopathology in detection of benign conditions of breast

Benign conditions of breast	sensitivity	specificity	PPV	NPV	accuracy
Fibroadenoma	84.30	70.59	76.42	80	80.12
Duct ectasia	75	100	100	98.29	98.3
Fibrocystic changes	68	100	100	98.84	98.8

PPV- Positive predictive value, NPV- Negative predictive value

3.14 Distribution of management of benign conditions of the breast in ANDI classification:

A diagnosis of benign breast disorder in 87.63 % of patients justified a conservative approach in their management .In this study in 73(41.48%) patients were managed conservatively and in 9(5.11%) patients were both modality of management was used as some patient was having more than one disorder . (Table No 11)

Table No 11. Showing distribution of management of benign conditions of the breast in ANDI classification

Treatment	No. of patients	%
Surgery	94	53.41
Conservative	73	41.48
Conservative + Surgery	9	5.11
Total	176	100

Total 9 patients were both modality of management was used as some patient was having more than one disorder, one patient had bilateral multiple Fibroadenoma with bilateral cyclical mastalgia with nodularity, where excision of largest lesion was done as patient was apprehensive and insisted for removal, other lesions managed conservatively, other 3 patients had bilateral Fibroadenoma where excision of largest lesion was done as patient was apprehensive and insisted for removal. one patient with bilateral Fibroadenoma had giant fibroadenoma which was removed other lesion managed conservatively, 2 patients of Fibroadenoma managed conservatively but after 6mth follow up they insisted for removal of Fibroadenoma,2 patients apart from fibroadenoma also had mastalgia with or without nodularity.

4. Discussion

The ANDI classification was recommended by an international multidisciplinary working group in 1992[8]. Despite having a sound pathophysiologic basis, however, it has not been utilized in many significant epidemiologic study or clinical series. Most clinicians prefer to use separate clinical and pathologic classifications[9], and there have been few attempts at clinicopathologic correlation. It may be partly because the term ANDI has been used variously as terminology, a concept, a framework,

and a classification system. This causes ambiguity and may be the reason why many authors prefer terms such as “benign breast condition” and “fibrocystic change” over benign breast disorder and ANDI[10].

However, using ANDI as a classification system in this study enabled us to map a large spectrum of clinical presentations in distinct categories, achieve pathologic correlation, and follow clearer guidelines of management. There are still some benign conditions that are not covered under this classification system (e.g., phyllodes tumor, adenoma, hamartoma, lipoma). If we keep rare tumors in the breast in a separate category of “benign neoplasms” of the breast distinct from “benign conditions” and “cancer” of the breast, it can resolve the remaining issues of nomenclature as well.

The spectrum of BBDs as per the ANDI framework in this study showed that benign breast disorders accounted for 87.63% of these conditions, 12.36% were benign breast diseases,. The commonest presentation was a breast lump (72 %) followed by nodularity/lumpiness (26.1 %). Fibroadenoma (68.75%) was the commonest clinical diagnosis, as reported in previous Indian studies as well[4][7].

Use of the ANDI concept provides a rationale for the management of patients with BBD. A diagnosis of benign breast disorder in 87.63% of patients justified a conservative approach in their management.

In this study, 29.4% of fibroadenomas were managed conservatively, whereas excision was routine for fibroadenomas in previous series[5][7]. Most importantly, there was a paradigm shift in the management of patients presenting with mastalgia and diffuse or focal nodularity. These patients with painful nodularity were earlier labelled as having fibroadenosis or fibrocystic disease and were frequently subjected to a biopsy. Recognition of the fact that cyclical nodularity is an aberration of normal physiology of the breast, with no distinct radiologic or pathologic changes has favoured a conservative approach in its management. In this study, 36 patients presented with mastalgia and cyclic nodularity.

USG of the breast showed no distinct abnormalities in any of them, and none was subjected to biopsy. However, there was a group of 11 patients

who presented with persistent focal nodularity/lumpiness in whom mastalgia generally was not severe; most of them were 35–45 years of age. On USG, these women showed either normal appearance or brightly echogenic density of breast parenchyma, reported as prominent fibroglandular tissue. They underwent FNAC, the results of which were reported as nonproliferative or proliferative lesions without atypia in 8 and proliferative lesions with atypia in 3. All three patients with the report of a proliferative lesion with atypia underwent excisional biopsy.

“Proliferative lesion with atypia” on FNAC identifies a group of patients who may be at higher risk for developing breast cancer. A more recent study that evaluated the clinical utility of the subcategory “proliferative lesion with atypia” on breast FNAC samples reported that atypia was associated with significantly increased likelihood of malignancy compared with proliferative lesion without atypia[11].

The presence of a proliferative lesion with atypia in women clinically presenting with focal nodularity points to a group of patients who have histologic changes, which puts them at a higher risk for developing breast cancer and hence requires more detailed assessment. Probably these lesions account for the belief that fibrocystic disease places women at higher risk for breast cancer[12][13]. It also explains the reason behind thinking that a history of biopsy for benign breast disease is a risk factor for breast cancer. The challenge in managing these patients with focal nodularity/lumpiness thus lies in being able to identify those few patients who are at higher risk of developing breast cancer while avoiding unnecessary biopsies in the remaining population.

Hence a well-defined approach should be adopted when dealing with patients presenting with “breast nodularity”. A careful clinical assessment should be done; and if examination shows diffuse nodularity of the cyclic type, which is within normal limits, the patient may require simple reassurance and pain relief. If clinical examination shows focal nodularity/lumpiness, imaging and pathologic evaluation are in order so an early carcinoma is not missed. USG of the breast can be helpful for confirming or refuting a localized abnormality. It may pick up a deep-seated cyst or fibroadenoma in a vaguely palpable area. However, USG findings generally are either normal or show prominent fibroglandular tissue, as was seen in the patients [13].

Mammography, whenever added, is useful for detecting a preclinical lesion in the remaining breast tissue of a high-risk patient and sometimes as a

diagnostic tool. However neither of these imaging studies can detect lesions with atypical proliferative histology. Great reliance is thus placed on the pathologic assessment of focal nodularity/lumpiness. FNAC is a simple, quick method.

The efficacy of FNAC in detecting proliferative lesions with or without atypia has been reported to have high levels of concordance (85–90 %) with biopsy results[15][16]. However, there are cytologic features that overlap between proliferative breast disease without atypia, proliferative breast disease with atypia, and low-grade carcinoma of the breast[17][18]. In addition, the level of expertise required to keep the possibility of missing an atypical proliferative lesion on cytopathologic evaluation low may not be uniformly available. A core needle biopsy may be considered a more reliable investigation for evaluating these patients[19].

5. Conclusion

The ANDI classification, a comprehensive system, can resolve most of the issues that face a clinician when dealing with benign breast diseases. It delineates the borderline between normal and abnormal, achieves correlation of clinical signs and symptoms with histologic changes, and provides risk stratification and pragmatic definition of management protocols.

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