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Breast Cancer: Basic and Clinical Research

Diagnosis of a Nonpalpable Intraductal Papilloma without Radiological Abnormality by Nipple Discharge Smear Examination: A Case Report

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ABSTRACT: Nipple discharge is the third most common breast complaint after breast pain and breast mass, most commonly associated with endocrine alterations and/or medications, pregnancy, lactation, post lactation, fibrocystic disease, intraductal papilloma, duct ectasia, nipple adenoma, infection, chronic mastitis, subareolar abscess, and least frequently, breast carcinoma. Cytological examination of nipple discharge (ND) is a noninvasive method of diagnosing the underlying breast pathology. We report a 46 year old female, who presented with pain and blood-mixed ND from the right breast with an impalpable mass. Cytological examination of the discharge was done and diagnosis of papillary neoplasm with degeneration, metaplasia, and atypia was given, which was further confirmed on histology and positive IHC for HMWCK and p63. Final diagnosis was intraductal papilloma of the lactiferous duct with squamous metaplasia and infarction. Differentiating benign papilloma from a carcinoma is challenging to the cytopathologist and requires clinico-pathological correlation and a good knowledge of cytology.

KEYWORDS: nipple discharge, papillary neoplasms, infarction, HMWCK, p63

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Introduction

Diagnosing the underlying breast pathology from the cytological examination of nipple discharge (ND) is challenging to a cytopathologist.[1] Nipple discharge, which is the third most common breast complaint after breast pain and breast mass, can be of several types, including milky, multicolored and sticky, purulent, clear and watery, yellow or serous, pink or serosanguinous, and bloody or sanguinous. Most ND are the result of a clinically insignificant benign process; therefore, less invasive, nonsurgical diagnostic modalities have been explored to reduce the need for surgical intervention.[1] The ability to detect malignancy by cytologic examination of ND ranges from 45 to 82% with 0.9–2.6% false positive rate.[2] Particularly, intraductal papilloma pose a real diagnostic problem to a cytopathologist because of its overlapping clinical as well as cytological features with that of lesions like ductal carcinoma in situ of micropapillary type, intracystic papillary carcinoma, and low grade invasive papillary carcinoma.[3] In the present case, a diagnosis of intraductal papilloma was made on the smears prepared from the ND in spite of overlapping clinical as well as cytological features with malignancy that was further confirmed on immunohistochemical investigation.

Case Report

A 46 year old female presented with complaints of pain and blood-mixed ND from the right breast for the past six months. There was no history of medication or significant family history. On examination there was a fine granular feeling on the breast, no definite lump was palpable. The other breast was normal on examination and there was no axillary lymphadenopathy. No abnormality was detected on mammography.

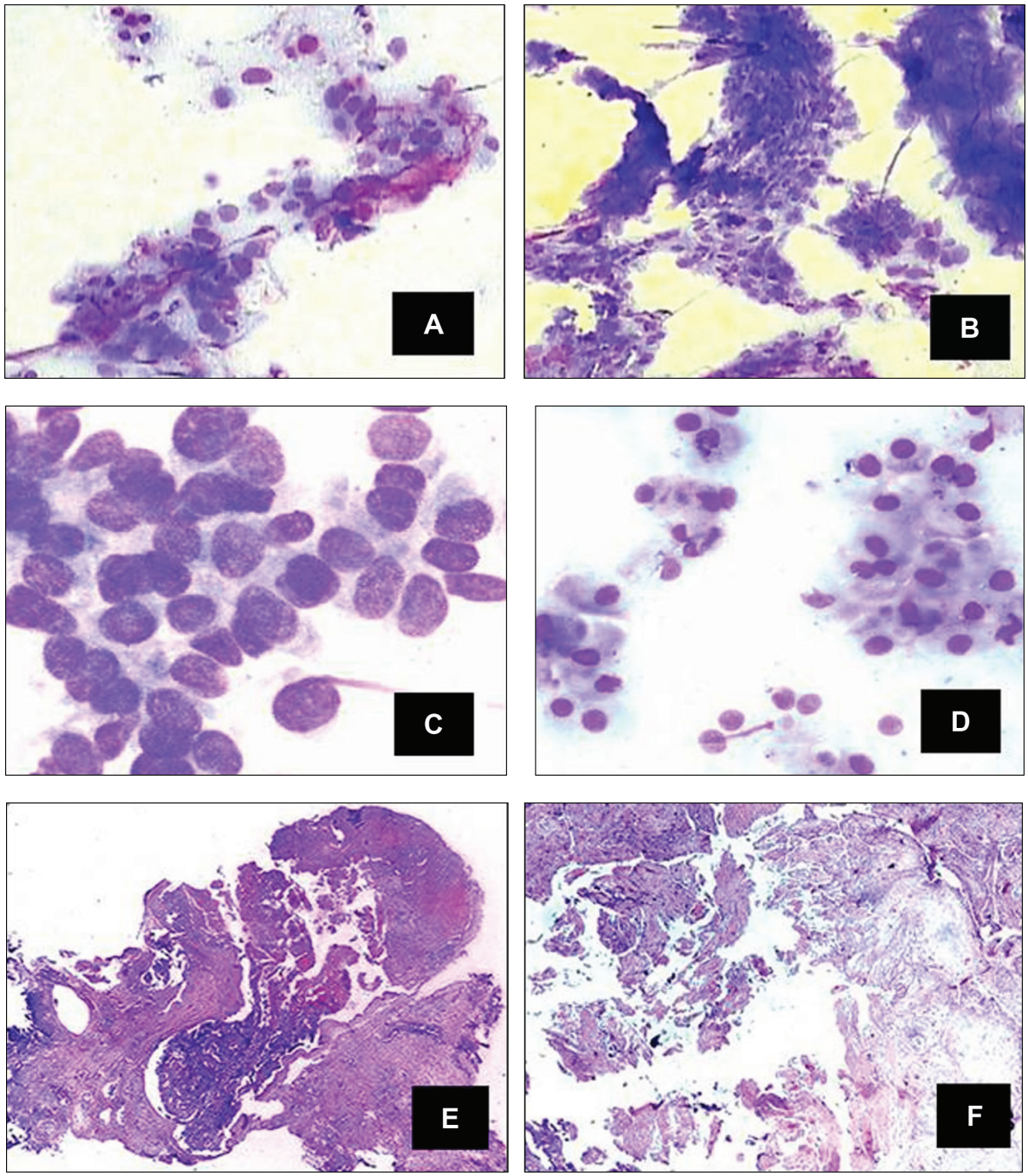

Figure 1. (**A**) A delicate papillary fragment showing mainly epithelial cells with mild loss of cohesion and occasional myoepithelial cells (Giemsa × 160); (**B**) papillary fragments with cohesive cells showing squamous metaplasia (center) (Giemsa × 80); (**C**) a group of epithelial cells showing poorly formed acini with loss of cohesion and mild nuclear pleomorphism (Giemsa × 320); (**D**) a group of cells showing apocrine metaplasia (Giemsa × 160); (**E**) whole mount of the section showing a papillomatous lesion in large duct with necrosis and degeneration on the surface (H&E × 20); (**F**) higher magnification of surface showing squamous metaplasia with necrosis and degeneration (H&E × 40).

The patient could not afford more sensitive tests like ductography. Routine hematological investigations were within the normal range. For cytological examination, smears prepared from ND were blood mixed with a few white flakes. Smears were stained with Giemsa and Papanicolaou stains. Microscopically, the smears were highly cellular showing finger like projections with scant fibrovascular core, ductal epithelial cells in branching sheets, and cohesive clusters (Fig. 1A). The ductal epithelial cells showed mild overcrowding and atypia with mild pleomorphism and prominent nucleoli (Fig. 1B). At places, cells were showing foamy changes and squamous metaplasia (Figs. 1C and 1D). Myoepithelial cells were scant. On the basis of cytological findings, the case was diagnosed as papillary neoplasm with degeneration, metaplasia, and atypia. Based on cytological diagnosis, the patient underwent local excision. A small piece of tissue, 1.0 × 0.8 × 0.7 cm in size,

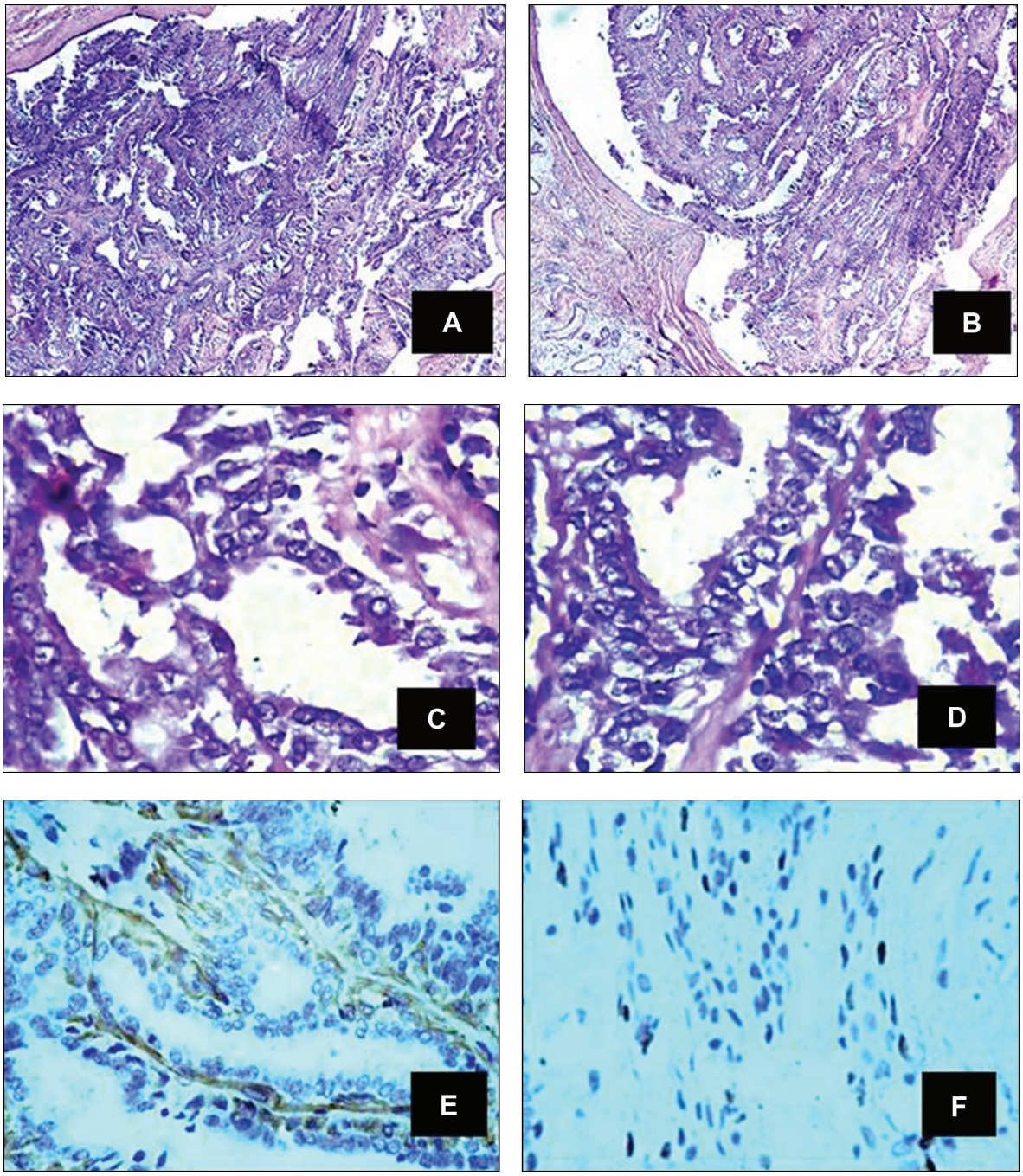

Figure 2. (**A**) Middle area showing densely packed papillary structures lying back to back and lined by epithelial cells (H&E × 40); (**B**) basal area showing intact ductal lining with papillary structures (H&E × 40); (**C**) and (**D**) higher magnification showing mildly pleomorphic epithelial cells with prominent nucleoli, mild loss of polarity, and multilayering. Myoepithelial cells are not clearly visible (H&E × 320); (**E**) Myoepithelial cells showing positive cytoplasmic staining for HMWCK (IHC × 160); (**F**) myoepithelial cells showing positive nuclear staining for p63 (IHC × 160).

was received. Histological examination showed papillary folds with scant fibrovascular stroma lined by normochromic round to oval ductal epithelial cells with vacuolated or flattened myoepithelial cells. At places, squamous metaplasia, multilayering, overcrowding, and mild pleomorphism were seen (Figs. 1E, 1F, and 2A–D). Immunohistochemistry showed cytoplasmic positivity for HMWCK and nuclear positivity for p63 confirming the presence of myoepithelial layer (Figs. 2E and 2F). Final diagnosis was confirmed as intraductal papilloma of lactiferous duct with squamous metaplasia and infarction (subareolar duct papilloma).

Discussion

Duct papilloma is a benign, wart-like tumor with or without a stalk that has grown inside a breast duct. Papillomas frequently involve the major duct in the subareolar region and usually (80%) cause bloody or sticky discharge from a single breast duct. Approximately 90% of the cases are solitary.[4] Multiple

papillomas are seen in younger patients, arise in the smaller ducts, are usually not associated with ND, and are bilateral in one-fourth of cases.[5] As lumpectomy is the treatment of choice for papilloma and there is no indication that patients so treated have a higher incidence of carcinoma at a later date, a definitive presurgical diagnosis is of utmost importance to avoid unnecessary blind mastectomy for a ND lesion with impalpable breast lump. Unfortunately, there are no specific criteria for distinguishing between benign and malignant papillary lesions on cytology, with considerable overlap, particularly cases with atypia and features of degeneration (infarcting papilloma). In general, papillomas present with hypercellular smears, large cohesive epithelial fragments, with or without three dimensional papillary architecture, and fibrovascular cores with anatomic edges. Cells are of short or tall columnar epithelium, often palisading at the edges of the papilla with nuclear stratification. Background shows blood and hemosiderin-laden macrophages. Myoepithelial cells are usually present. Significant epithelial atypia may be present.[6] Lee had reviewed the cytology of 174 specimens of abnormal ND with cyto-histological correlation with the aim of evaluating the sensitivity and specificity of ND cytology in palpable and nonpalpable breast lesions and concluded that ND cytology is very helpful in detecting an underlying breast lesion even if the case has no palpable mass in the breast though slightly less sensitive in detecting papillomas or malignant lesions.[7] Gupta et al reviewed 1948 ND samples to determine whether cytological findings from ND smears could provide useful diagnostic information regarding various breast lesions and concluded it to be a reliable method.[8]

Dawson et al concluded that the markedly increased cellularity, numerous single cells, nuclear hyperchromasia, stratification, and absence of benign background cells, such as apocrine metaplasia favor papillary cancers. Two cases of papillomas in their study had marked nuclear atypia with background necrosis and inflammation, which represented infarcted papillomas, a potential pitfall in the diagnosis of cancer.[9] In the present case, the clinical presentation (bloody discharge from unilateral breast in a middle-aged female) mimicked malignancy. On cytology, features that raised suspicion of carcinoma were high cellularity, scant stroma, nuclear crowding, cellular atypia, presence of squamous metaplasia, and presence of occasional myoepithelial cells. However the absence of loss of cohesiveness and high mitotic activity and the presence of foamy cells in background was favoring its benign nature. Diagnosis was made as papillary neoplasm with degeneration, metaplasia, and atypia. Histology confirmed the benign nature of the neoplasm, which was further confirmed on immunohistochemistry showing positivity for HMWCK and p63.

Conclusion

Differentiating benign papilloma from a carcinoma is challenging to the cytopathologist and if it is an infracting one, then it is all the more tricky and requires clinicopathological correlation and a good knowledge of cytology. Immunocytochemistry and histology (core biopsy) provide further help. A definitive pre-intervention diagnosis is beneficial for both the patient and clinician so as to avoid speculative blind radical mastectomy for a ND lesion with unpalpable breast lump.

Author Contributions

Conceived and designed the experiments: AS, VM, PAS. Analyzed the data: AS, JSN. Wrote the first draft of the manuscript: JSN. Contributed to the writing of the manuscript: AS, VM. Agree with manuscript results and conclusions: JSN, AS, VM, PAS. Jointly developed the structure and arguments for the paper: VM, PAS. Made critical revisions and approved final version: VM, PAS. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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