REVIEW PAPER

Analyzing Nipple Discharge: A Surgeon's Perspective

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Received on: 02 September 2022; *Accepted on:* 16 November 2022; *Published on:* 30 December 2022

Abstract

Aim: This review article aims to provide a bird's-eye view for a surgeon dealing with a patient with Nipple discharge (ND).

Background: Nipple discharge is the third most common complaint of a woman visiting a breast clinic. It can be physiological, due to benign disorders like duct ectasia or can be a presenting symptom of breast cancer. Hence, it is extremely important to evaluate every patient with ND thoroughly with robust history and clinical examination followed by necessary investigations like ultrasonography and mammography (MMG).

Review results: Ultrasonography and MMG are the mainstays in the evaluation of ND. The role of magnetic resonance imaging, ductography, ductoscopy, and nipple aspiration cytology is not very well-defined and is evolving. Nonbreast etiologies of ND also need to be considered and relevant investigations to manage such patients are needed, clues for which lie in the presenting complaints of the patients. Various drugs also interfere with the physiology of breast secretions and are an important cause of ND and need to be managed appropriately. Management of ND should be directed toward the inciting cause of the disease. Surgical options include microdochectomy or a more radical Hadfield's surgery.

Conclusion: Directed investigations to determine the etiology of ND guided by clues found during the clinical examination of a patient can help in the appropriate treatment of ND and also avoid unnecessary surgery.

Clinical significance: Nipple discharge is one of the most common complaints with which a woman attends a breast clinic and needs to be approached systematically to identify the cause and decide on appropriate management strategies.

Keywords: Benign breast disease, Breast lump, Diagnostic evaluation, Duct ectasia, Nipple discharge, Prolactinoma.

Indian Journal of Endocrine Surgery and Research (2022): 10.5005/jp-journals-10088-11199

Introduction

Nipple discharge is the fluid that extrudes spontaneously from the nipple.[1] If it occurs from the nipple of a nonpregnant, nonbreastfeeding woman, it is called pathological ND.[2] Up to 80% of women during their reproductive years have an episode of ND accounting for 2–5% of medical visits.[3,4] It is the third most common complaint prompting medical care after breast pain and lump.[5] Most ND is benign in origin (97%); however, it can be the presenting feature of breast cancer in 5–12% of women.[2,3,6]

Pathophysiology of ND

Terminal duct lobular unit is the functional unit of breast. Secretions originate in these lobules and empty into the lactiferous sinus *via* intralobular and extralobular ducts, finally emptying into the vestibule of the nipple. Fifteen to twenty such segments exist with unique drainage.[1] Various hormones like estrogen, progesterone, prolactin, insulin, thyrotropin-releasing hormone, etc., are involved in the production of milk and hence contribute to ND.[7,8]

During pregnancy, progesterone secreted from the placenta causes secretary initiation, and small amounts of milk secretion can happen by 16 weeks of gestation. Postpartum, a sudden drop of progesterone along with elevated prolactin, cortisol, thyroid hormones, and insulin causes secretory activation with copious milk production (Flowchart 1).[1,7]

It has been hypothesized that breast cancer development involves a cascade of sequential molecular and morphological changes in the ductal epithelium (Fig. 1). If this process can be detected before malignant transformation, it would be possible to develop preventive strategies. In this regard, the biochemical and cytological makeup of ND might prove to be useful.[1]

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How to cite this article: Bhat G, Sooraj R, Ramakant P. Analyzing Nipple Discharge: A Surgeon's Perspective. Indian J Endoc Surg Res 2022;17(2):53–60.

Source of support: Nil

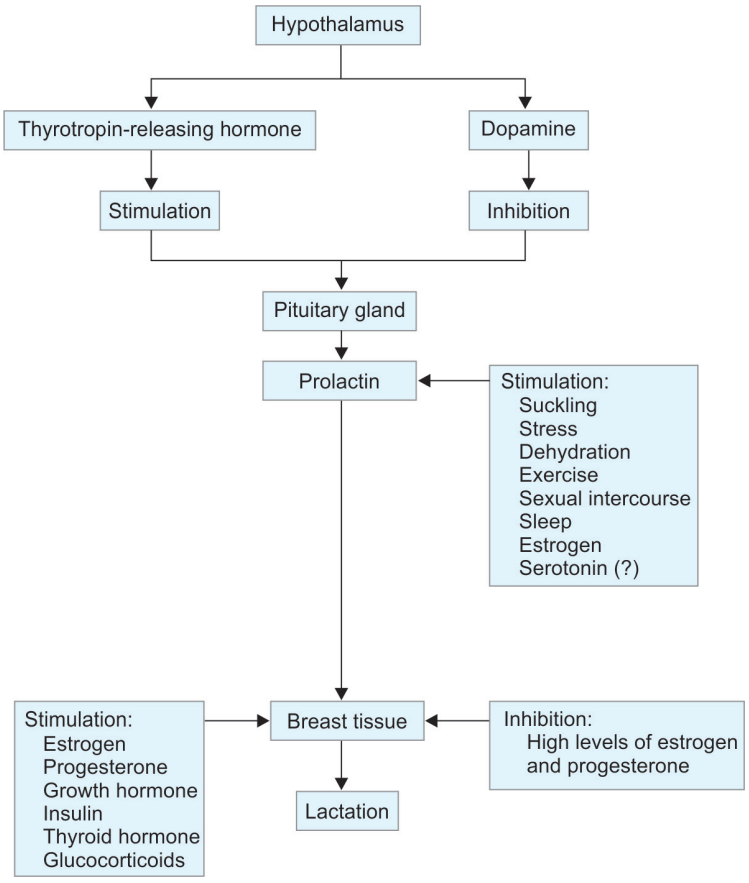
Conflict of interest: Dr. Pooja Ramakant is associated as Editor-in-Chief of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of the Editor-in-Chief and his research group.

Clinical Evaluation of ND

Nipple discharge must be approached in a systematic fashion owing to the high anxiety in the patients' minds (Table 1). It is important to take a detailed history to characterize the nature, origin, and duration of the discharge. An important factor in history is whether the ND is spontaneous or elicited. Spontaneous discharge raises the index of suspicion for pathological ND. The quantity of discharge, scanty, or copious is also important. Generally, ND that occurs only on breast manipulation doesn't need further evaluation; however, if it is profuse, clear, bloody, or serous seen on routine clinical examination or during a mammogram, further evaluation is warranted.

It must also be ascertained whether ND is unilateral or bilateral, single duct or from multiple ducts. The color and consistency of the observed ND must be enquired about. Any associated lump, pain,

Flowchart 1: Physiology of lactation



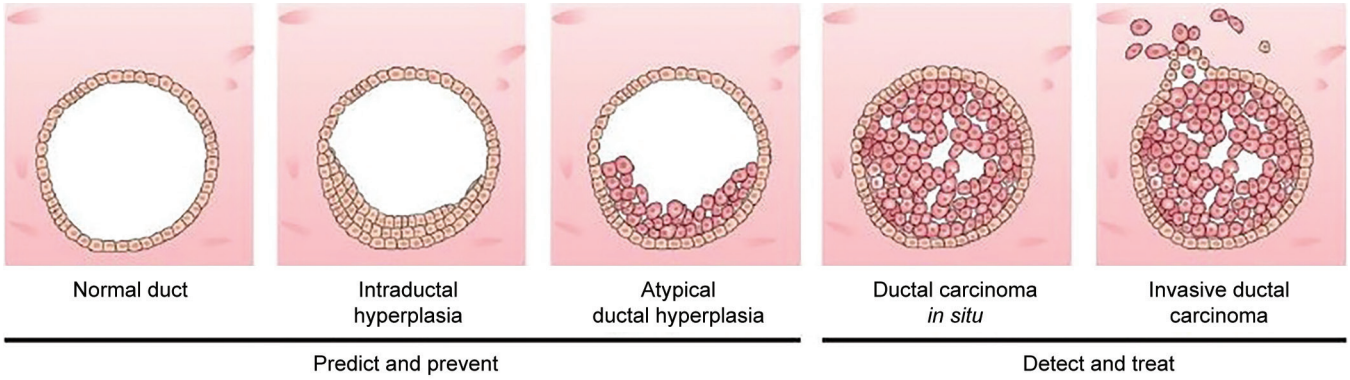


Fig. 1: Multistep pathogenesis of breast cancer

Table 1: Scheme of evaluation of ND

History	*Associated features*	*Rule out*	*Examination*	*Investigations*	*Treatment*
• Spontaneous/ elicited • Quantity • Laterality • Single/multiple ducts • Nature • Associated features	• Lump • Itching • Nipple retraction • Nipple excoriation	• Pregnancy/ lactation • Trauma • Medications • Endocrine disorders	• Trigger point • Number of ducts and laterality • Nature • Lump in breast • Nipple deformity • Axillary lymphadenopathy	• USG ± MMG of the breast • MRI • Ductography • Ductoscopy • Cytology	• Treat the cause • Microdochectomy • Hadfield's surgery

skin changes, or nipple deformities should also be ascertained. Unilateral nipple excoriation may point toward Paget's disease and if bilateral may point toward eczema.[1]

Recent history of pregnancy or lactation, trauma to breast/chest wall, detailed history of current medications, and history of endocrine problems are also important. The presence of fever (abscess/mastitis) and symptoms suggestive of hypothyroidism, prolactinoma (headache, visual disturbances, and infertility/menstrual irregularities), or liver disease (ascites and jaundice) may help narrow down the differential diagnosis.[2] History of any chronic abscess near the areola region or any slit or inverted nipple also needs to be taken.

Breast Cancer gene (BRCA) 1/2 mutation carriers, history of ipsilateral breast cancer, and age over 50 years are predictive for malignancy in the presence of pathological ND. Previous breast biopsy with a diagnosis of atypia is also considered a predictor of malignancy. Hence, a history of these high-risk features also needs to be taken.[5]

Nipple discharge in male patients is uncommon but needs thorough evaluation as the incidence of malignancy is 23–57%.[4]

Examination

Examination in a patient with ND aims to identify the trigger point of origin, the duct/s producing it, its color, and its nature. The patient is also carefully examined for the presence of breast lumps, changes in NAC, and nipple inversion/retraction. If spontaneous ND is not visible, the examiner should attempt to elicit ND by applying pressure evenly from the periphery toward the nipple (pressure point exam).[2]

A single duct ND is more suspicious of malignancy than multiple duct ND (relative risk: 4.07).[9] It is paramount to examine the bilateral breast and also the axilla to look for lumps or lymphadenopathy.

Leis and colleagues described four types of ND in ascending frequency of likelihood of association with cancer (Table 2).[10]

A watery ND on manipulation becoming pink stained is commonly found during examination. This is often indicative of duct papillomas, which are friable and hence bleed easily on manipulation.[4]

Imaging Evaluation

Imaging should be performed in all patients to seek a focal occult lesion or to characterize a lump identified on examination (Table 3).

Ductography/galactography can be performed to define intraductal abnormality. Water-soluble contrast (0.2–1.0 mL of 60% iothalamate meglumine) is injected into the suspect duct and mammograms are performed immediately. Findings include a cutoff sign or ductal obstruction, ductal dilatation, filling defects, irregularity of duct wall, ductal narrowing, and distortion of ductal arborization. It is a challenging procedure to perform and also inconvenient for the patient hence, not routinely performed at all centers.[1]

Table 2: Types of ND (Leis et al.)

Type of ND	*Frequency of association with cancer*
Serous	6.3%
Serosanguineous	11.9%
Sanguineous	24%
Watery	45.5%

Ductoscopy allows direct visualization of the interior of the discharging duct. Introduced in the 1990s, it is a safer alternative to ductography.[4] Intraductal mass, irregularity of duct wall, obstruction, and scarring are the usual findings. Multiple papillomas may also be identified, which is usually missed by other investigations. Ductoscopy can also be combined with cytological and therapeutic procedures. Despite good results with ductoscopy, it remains unpopular due to the lack of availability and supply of disposables.[5]

Nipple aspiration fluid is performed by gently squeezing the nipple and spreading the secretion on to a glass slide. After smearing, the slides are immediately fixed with immersion in 95% ethyl alcohol and stained as per the pathology department.[11]

A classification system developed by Sartorius et al. found that a minimum of 50–100 cells are required for diagnosis.[12] They classified cytological findings in ND as (Table 4 and Fig. 2).

Nipple aspiration fluids have also been evaluated biochemically for:

- Prostate-specific antigen
- Human Kallikrein
- Basic fibroblast growth factor
- Cellular markers such as S-phase fraction, DNA index, and cytology[1]

Occult blood testing of the discharge is not necessary because both serous and blood-tinged discharge may be associated with malignancy.[6,13]

Nipple aspiration fluid, although an attractive approach to evaluating ND, has several pitfalls owing to the inadequacy of samples. It has an overall pooled sensitivity is only 38% but a high pooled specificity of 90%. Hence, though it is easy to perform, low cost, and virtually painless, discharge cytology is possibly only an adjunctive study and is inappropriate and not routinely recommended as the only modality of evaluation.[4,5]

Other investigations that might be useful are an MRI of the brain for suspected prolactinoma and serological tests such as Thyroid stimulating hormone (TSH), prolactin, etc.[4]

Etiologies of ND

Physiological: Physiologic discharge may be yellow, green, or white. It is typically bilateral, and nonspontaneous, and occurs in multiple ducts (Table 5).[6]

Nipple discharge is normal during the last few weeks of pregnancy, after childbirth, and during lactation and may persist for up to 1 year postpartum or after cessation of breastfeeding.[2,5] It can also be seen in women who are not pregnant and not breastfeeding during their reproductive years. Stress has also been shown to cause ND. However, all post-menopausal ND is significant and needs evaluation.[2]

Pathological: Pathological ND is defined as clear, serous or bloody secretion, spontaneous, and discharging from a single duct and unilateral.[5] Most pathological ND is due to benign etiologies like papillomas (35–56%) and duct ectasias (6–59%), and the risk of malignancy is 5–23%.[4,11,14]

Papillomas are the most frequent causes of pathological ND. They are usually solitary, benign epithelial lesions growing within the ducts. Histologically, they are arborizing lesions with papillary fronds and a fibrovascular core, lined by epithelial and

Table 3: Imaging evaluation of ND

Imaging	*Usual findings*	*Utility*	*Comments*
USG			
• Of central breast to identify dilated ducts and intraductal lesions • Maneuvers like 2 hand compression, peripheral compression, and rolled-nipple techniques can be helpful[4]	• Duct ectasia: dilated retroareolar ducts with anechoic fluid or hypoechoic debris • Papillomas: hypoechoic nodule with a central vascular pedicle on color doppler[5]	For malignant lesions: • Sensitivity: 63% • Specificity: 84%[5]	• USG elastography: disputable role, needs further studies
MMG			
• Spot compression and magnification views: improve spatial resolution[5]	• Masses • Asymmetrically dilated retroareolar ducts • Focal density asymmetry • Architectural distortion • Calcifications[5]	Normal MMG: 80–93% For detecting malignancy: • Sensitivity: 22% • Specificity: 93% • Positive predictive value (PPV): 46% • Negative predictive value (NPV): 80%[4]	• All women above 40 years of age should get an MMG done with USG • If MMG in the past 6 months, USG should be the first examination • Men >25 yrs[4]
MRI			
• Not routinely warranted • Exceptions: other imaging modalities have failed to identify an underlying cause[4]	• Normal-caliber ducts are not apparent • Dilated ducts: high-intensity branching tubular structures • Intraductal papillomas: homogeneously enhancing, well-circumscribed • Malignant lesions: segmental, linear, enhancing intraductal masses/"nonmass enhancement"[5,6]	Detection of any kind of lesion: • Sensitivity: 92% • Specificity: 76% • Specificity for breast cancer: 97%[6,11]	

Table 4: Cytological findings in ND (Sartorius et al.)

Normal	*Ductal lining cells are uniform in size and staining*
Hyperplasia	An excessive number of ductal groups with multilayering and slight anisocytosis, with normal nuclear characteristics
Atypical hyperplasia	Greater variation in nuclear size and shape
Suspected carcinoma	Marked nuclear abnormality, chromatin clearing, and nuclear membrane irregularity

myoepithelial cells (Fig. 3). The friability of these papillary fronds leads to bloody ND.[1,6]

Nipple adenoma or florid papillomatosis of the terminal portion of lactiferous ducts is also associated with bloody ND. Occasionally, intraductal papillary carcinoma and invasive ductal carcinoma may arise in nipple adenoma.[1]

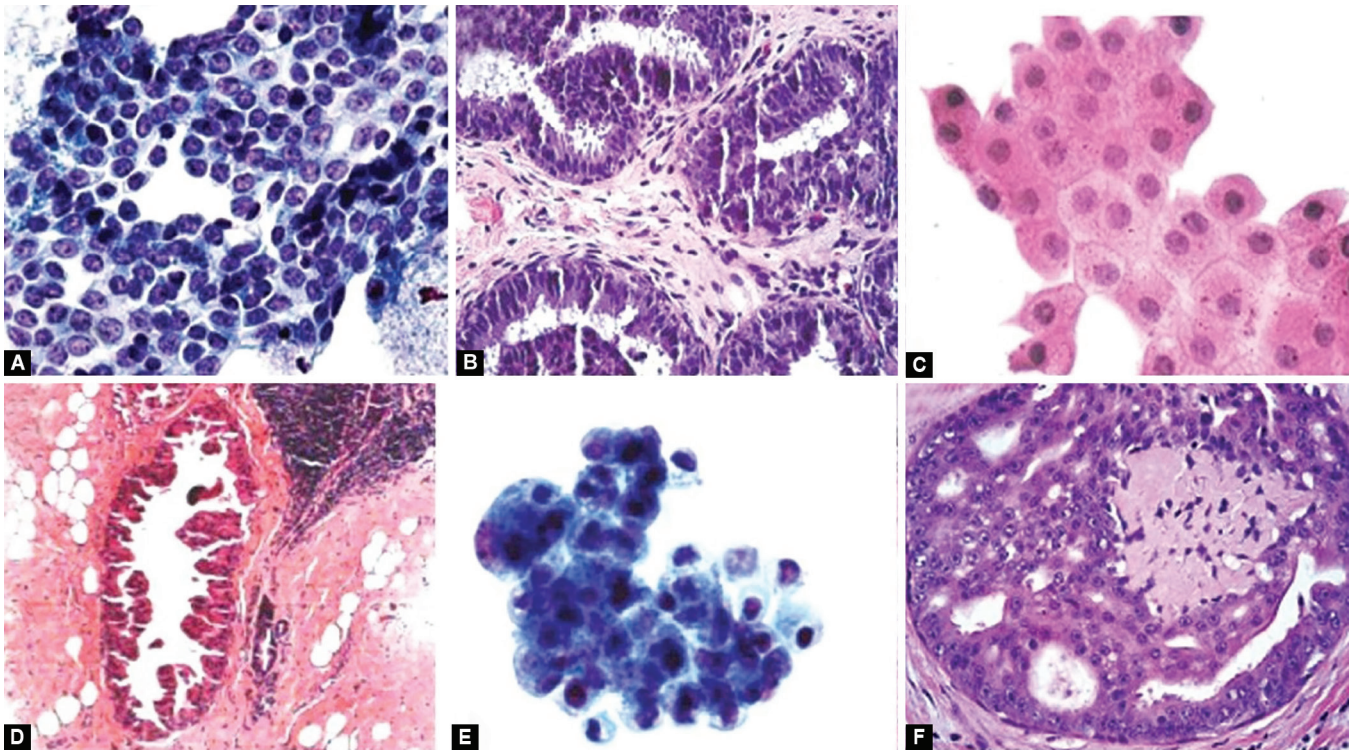
Duct ectasia: Ectasia refers to the dilation of ducts, greater than 3 mm in diameter, with loss of elastin and presence of chronic inflammatory cells around the duct walls (Fig. 4). Normal involution of the breast that occurs with aging manifests as mild duct ectasia.[15] Other etiologies include transudation of secretions sequestered in dilated ducts from a previous pregnancy and primary periductal inflammation. When these secretions accumulate, the result may be a thick, creamy discharge of off-white, gray, green, or brown color.[6] Histologically, the ductal epithelium is not hyperplastic and may be thinned out or absent. Sloughed epithelium, lipid-laden foamy histiocytes, cholesterol crystal, and calcification may be seen. ND from duct ectasia has been shown to have bacteria (Enterococcus, Streptococcus, Staphylococcus aureus, and Bacteroides); however, whether infection is the primary cause or secondary colonization is debatable. Duct ectasia does not predispose to cancer.[1]

Lactational bloody discharge (Rust pipe syndrome): It is usually spontaneous, occurs after the first trimester, involves multiple ducts, and resolves within 2 months. Numerous epithelial cell clusters sometimes in a papillary configuration are seen; delicate capillary networks within these tufts of cells get traumatized easily leading to bloody ND. Hence, it is reasonable to observe bloody ND during pregnancy and lactation after confirmation of the absence of suspicious clinical or radiological findings. Evaluation is done with ultrasound (USG) followed by MMG. Magnetic resonance imaging has no role in pregnancy as Intravenous (IV) gadolinium crosses the placenta and increased vascularity during lactation may limit its sensitivity.[4,11]

Iatrogenic ND: Postoperative fluid collection post breast conservative surgery may result in serous or serosanguineous discharge. Bloody ND after a needle biopsy of the retroareolar region is also observed.[6]

Drug-induced ND

Several drugs can cause galactorrhea due to their antidopaminergic effects. The most common drugs are listed in Table 6.



Figs 2A to F: NAF cytology and corresponding histology showing: (A and B) Epithelial hyperplasia, (C and D) Apocrine metaplasia, and (E and F) High-grade DCIS

Table 5: Characteristic features of ND

Characteristic features	*Normal ND*	*Physiological*	*Pathological*
Presentation mode	Bilateral milky white color	Yellow, green, and brown multi-colored ND	Serous, Blood stained
Pertinent history	History of lactation	Any medicines intake, history of hypothyroidism	Associated breast lump, nipple excoriation or axillary lymphadenopathy. Headache, visual disturbances in Prolactinomas
Ducts involved	Bilateral multiple ducts	Bilateral multiple ducts	Usually unilateral single duct
Amount of ND	Copious	Scanty or copious	Copious

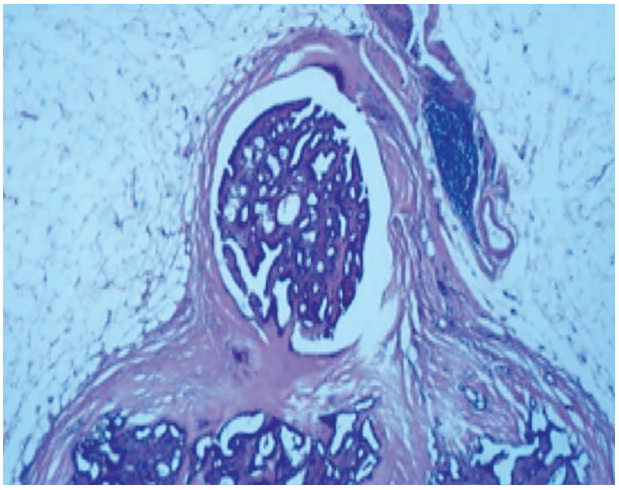


Fig. 3: Duct papilloma showing arborizing fronds

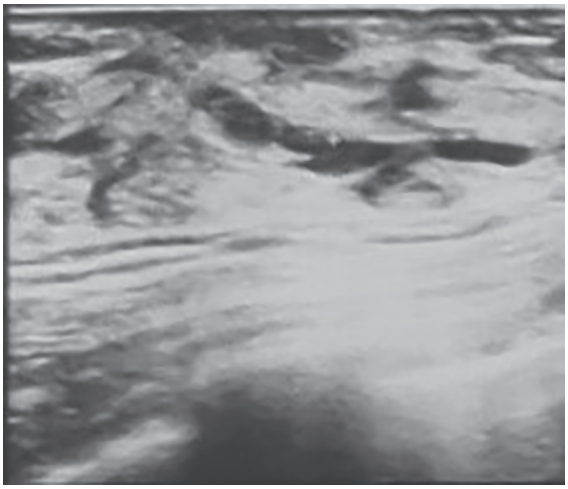


Fig. 4: USG showing dilated duct

Table 6: Drug-induced ND

Class of drugs	*Drugs*
Antidepressants	Alprazolam, Buspirone
Monoamine oxidase (MAO) inhibitors	Moclobemide
Selective serotonin reuptake Inhibitor (SSRI)	Citalopram, Fluoxetine, Paroxetine, Sertraline
TCAs	Clomipramine
Atypical antipsychotics	Risperidone, Clozapine, Olanzapine, Aripiprazole
Phenothiazines	Chlorpromazine, Prochlorperazine
Dopaminergic blockers	Metoclopramide, Domperidone
Antihypertensives	Atenolol, Reserpine, Methyldopa, Verapamil
H2 receptor blockers	Cimetidine, Famotidine, Ranitidine
Opiates	Codeine, Heroin, Methadone, Morphine
Hormones	Estrogens, Progesterones, Danazol
Others	Valproic acid, Sumatriptan, Cisapride, Octreotide

Atypical antipsychotics act on D2 receptors to cause hyperprolactinemia. Risperidone with a combined dopamine serotonin antagonism can significantly raise prolactin levels whereas clozapine, olanzapine, and aripiprazole with both agonist and antagonist properties on D2 receptors cause only transient hyperprolactinemia. Verapamil, which is a calcium channel blocker, also reduces hypothalamic dopamine. Opioids acting through μ-receptors also decreases dopamine. The mechanism of action of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) is not currently known.[1,7,16]

Estrogens and progesterones found in oral contraceptive pills (OCPs) may cause lactation possibly by direct action on the breast tissue. However, galactorrhea usually occurs on discontinuation of these drugs rather than during their use similar to the physiological postpartum hormone withdrawal.[8] D2 blockers like metoclopramide, fenugreek, and domperidone have been used by adoptive mothers to achieve "induced lactation."

Nonbreast Etiology

Hypothalamo-pituitary disorders: Around 50% of patients with prolactinoma have ND. If prolactin values are persistently elevated (>20 ng/mL) or the patient has a headache, the loss of visual fields or a history of infertility, an MRI of the head with pituitary images should be obtained. Prolactinomas <1 cm in size are called microprolactinomas, whereas those >1 cm are called macroprolactinomas. Prolactin levels correlate well with the size of the tumor with microprolactinomas having prolactin levels >200 ng/mL and macroprolactinomas having prolactin levels >1000 ng/mL.[7,17]

Nonprolactin-secreting tumors and infiltrative disorders of the pituitary stalk/hypothalamus: These tumors cause hyperprolactinemia by disrupting the flow of dopamine from the hypothalamus to the anterior pituitary by compressing the pituitary stalk. Prolactin levels are usually <200 ng/mL.[17]

Rarely, the "hook effect" needs to be considered in large pituitary adenomas but only mildly elevated prolactin levels. Due to extremely high prolactin levels in these conditions, the number of prolactin molecules binding to both the detection and capture antibody of the sandwich enzyme linked immunosorbent assay (ELISA) is low and diluting the sample shows a paradoxical increase in prolactin levels.[18]

Non-hypothalamo-pituitary Causes

Hypothyroidism: Elevated levels of thyrotropin releasing hormone (TRH) stimulate lactotrophs resulting in hyperprolactinemia.

Renal failure: Hyperprolactinemia in renal failure is due to the failure of kidneys to clear prolactin. Prolactin levels of >1000 μg/L have been reported, which resolve rapidly post-kidney transplant.

Chest wall lesions like burns, surgeries, biopsies, breast and nipple stimulation, and herpes zoster have associations with hyperprolactinemia. The hypothesis is that the pain signals transmitted *via* the spinal cord to the hypothalamus results in decreased dopamine release leading to a transient rise in prolactin levels.

Management of ND

Treatment depends on the underlying cause of ND. Patients with physiological ND need only reassurance and six monthly follow-up. They are told not to keep pressing the nipple to check for any discharge. If ND is due to hormonal imbalances, they need to be evaluated and appropriately treated. Drug-induced ND needs either discontinuation of the offending drug or switching to alternative medicines. The mainstay in the treatment of hyperprolactinemia is bromocriptine and cabergoline. These are dopamine agonists and act on D2 receptors present on lactotrophs and inhibit prolactin production.[7]

Surgery

Surgery was once considered the primary treatment for ND; however, surgery can be deferred in patients with pathological ND with normal imaging as cancer was found post-surgery in only 1% of cases. Most of which are low-grade ductal carcinoma *in situ* (DCIS) with an excellent prognosis.[5]

However, if the ND is copious, causing discomfort to the patient or persists for more than 2 years despite negative imaging, surgery is indicated.[4,19]

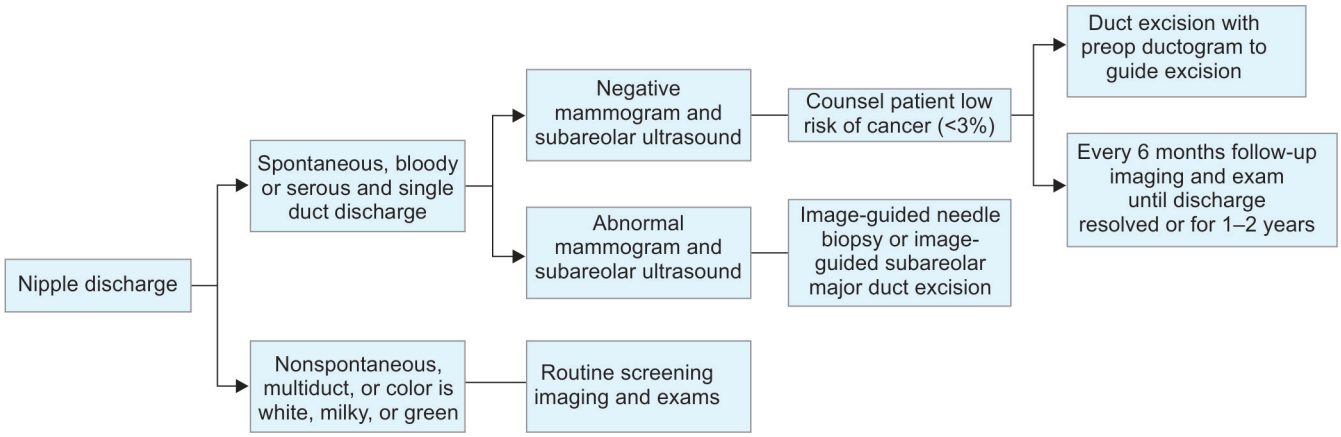
The surgical options include the following:

Hadfield's surgery: Complete excision of the major ductal system. A circumareolar incision is taken and a conical tissue resection of the affected ducts is done. It can cause difficulties with breastfeeding, loss of nipple sensation, nipple inversion, and areolar necrosis.[4]

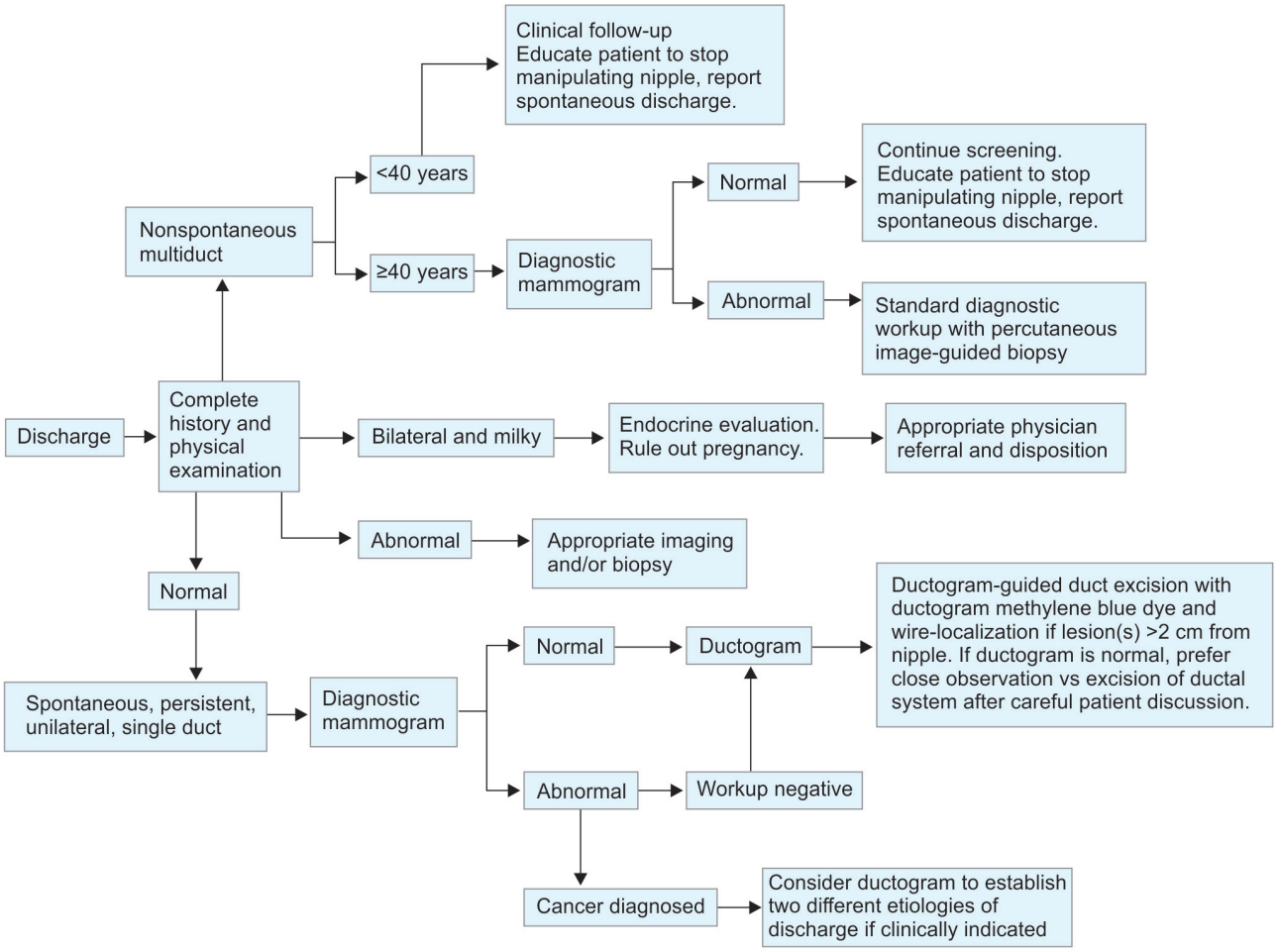
Microdochectomy involves excision of the discharging duct. The discharging duct is cannulated with a lacrimal probe or blunt tip needle, a periareolar incision epicentered over the trigger point is taken and a pyramidal-shaped specimen of surrounding tissue is dissected out, usually up to 5 cm in length. Methylene blue dye can also be injected to delineate the duct better. Another way of surgical approach is giving a radial incision over nipple-areola region and excising the cannulated duct.[1]

Microdochectomy can also be performed under the guidance of ductoscopy. After serial dilatation of the discharging duct, a 0.9 mm fiberoptic endoscope is introduced. The transillumination of the scope guides the margin of resection of tissue.[1]

Flowchart 2: Algorithm for evaluation of ND, Mayo Clinic



Flowchart 3: MD Anderson Cancer Centers' Algorithm for ND



Algorithms for the management of ND are shown in Flowcharts 2 and 3.

Conclusion

Clinical history and examination along with USG and MMG remain the initial steps in the evaluation of ND. MRI and ductoscopy when available and indicated can add useful information. Management of ND is primarily based on the etiology and unlike in the past, surgery must be considered only after thorough evaluation of the patient.

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