BREAST DISEASE: DIAGNOSIS AND
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NIPPLE DISCHARGE

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Nipple discharge is a common complaint in women of reproductive age but seldom is caused by serious pathology. Nipple discharge often raises concern for the possibility of two uncommon but serious conditions—breast cancer and a pituitary tumor. This concern may result in a battery of diagnostic tests, including endocrinologic studies, such as serum prolactin and thyroid function tests, and radiographic imaging, such as mammography, breast ultrasonography, and head CT or MRI imaging. When used indiscriminately, these tests not only have an extremely low yield but often result in false-positive findings, which lead to anxiety and further evaluation or intervention. The goal in evaluating nipple discharge should be to make an accurate diagnosis that results in appropriate treatment and reassurance. Clinical judgment should prevail rather than reflex diagnostic panels. In most cases, either the correct diagnosis can be made, or appropriate diagnostic studies can be selected based on the history and physical examination. Numerous confusing and complicated classification systems have been used to categorize nipple discharge based on color, consistency, and whether the discharge is spontaneous or provoked, unilateral or bilateral, and uniductal or multiductal. Although there are merits to all of these systems, none reliably differentiates among the various causes of nipple discharge. This article presents an overview of the etiologies and an algorithm for determining a specific diagnosis.

A detailed history is the most important element in the evaluation of nipple discharge and, when combined with a careful physical examination, usually results in an accurate differential diagnosis including endocrinologic or local pathology.

ENDOCRINOLOGIC CAUSES

Endocrinologic causes of nipple discharge result in an appropriate end-organ (breast) response to an inappropriate endocrine signal. All endocrinologic

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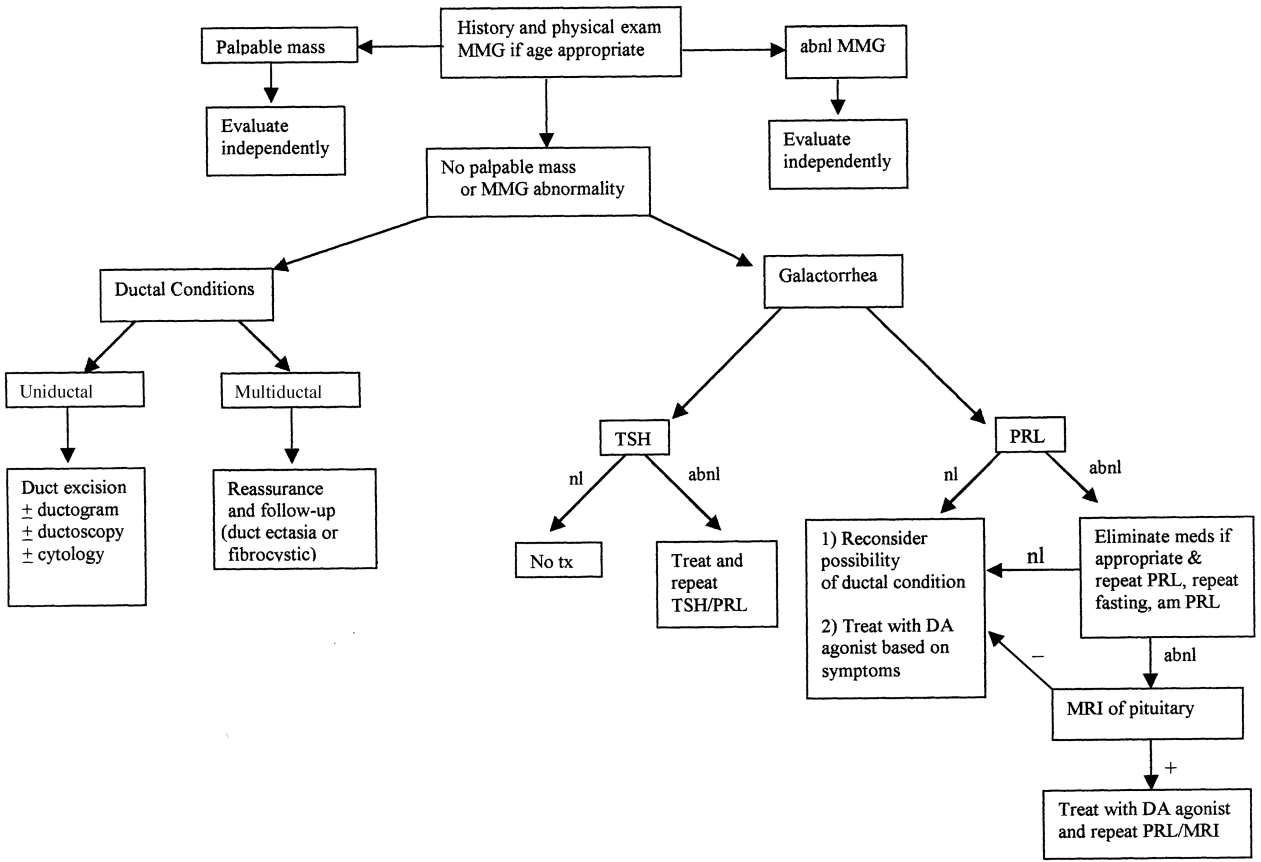

Figure 1. Algorithm for evaluation of nipple discharge. abnl = abnormal; nl = normal.

causes of nipple discharge have in common a relative or absolute increase in serum prolactin resulting in galactorrhea. Prolactin is a polypeptide normally produced by lactotroph cells of the anterior pituitary. Daily production of prolactin fluctuates in response to numerous physiologic conditions and stimuli. Physiologic conditions resulting in increased prolactin release include the following:

- Physical and emotional stress
- Eating (especially midday, high-protein meal)
- Sleep
- Orgasm
- Exercise
- Late follicular and luteal phase of menstrual cycle
- Excessive breast stimulation
- Pregnancy/puerperium/nursing

Serum levels in the nonpregnant state are maintained within the normal range by the inhibitory effect of the prolactin-inhibiting factor (dopamine) produced by the hypothalamus and through a variety of autocrine and paracrine factors, peripheral hormones, and neurotransmitters.

Conditions that interfere with the normal regulatory mechanism, such as pituitary stalk or hypothalamic lesions or exogenous dopamine antagonists, result in elevation of serum prolactin levels. Excessive endogenous production of prolactin by pituitary adenomas (prolactinomas) or ectopic production of prolactin by other tumors also produces hyperprolactinemia. Conditions such as hypothyroidism, with increased levels of thyrotropin-releasing hormone (TRH), and oral contraceptives can result in pituitary lactotroph stimulation.[13, 24] Estrogen also has an antidopaminergic effect at the pituitary level, resulting in increased prolactin release.[21]

Although there are numerous endocrinologic pathways contributing to hyperprolactinemia, the final clinical manifestation is galactorrhea, the inappropriate production of milk in a nonlactating woman. As a result of the bioactive heterogeneity of prolactin, some women with normal prolactin levels may have galactorrhea, whereas only one third of women with hyperprolactinemia have galactorrhea. Galactorrhea usually is defined as milk production more than 1 year after weaning or in any nulligravid or menopausal woman. Distinguishing galactorrhea from other forms of nipple discharge usually is not difficult. The discharge has the appearance of milk, occurs from multiple ducts, and usually is spontaneous rather than provoked and most commonly bilateral. This presentation is consistent with a normal end-organ response to an inappropriate endocrine signal. Any palpable abnormalities on breast examination or lesions seen on mammography or ultrasonography should be evaluated as separate problems and not attributed to hyperprolactinemia. When nipple discharge is consistent with galactorrhea, the medical history often will reveal the specific etiology. Important components of the medical history include medications; the reproductive history (recent pregnancy, frequency of menstrual periods, and fertility status); constitutional, skin, gastrointestinal symptoms, which may suggest thyroid dysfunction; neurologic symptoms, such as headache and visual field defects (bitemporal hemianopia); and the medical/surgical history.

MEDICATIONS

Several medications may cause hyperprolactinemia through their dopamine antagonism or by stimulating pituitary lactotrophs. Medications known to cause

galactorrhea include opiates, oral contraceptives, tricyclic antidepressants, methyldopa, metoclopramide, phenothiazines, cimetidine, calcium channel blockers, prochlorperazine, butyrophenones, and amphetamines.

REPRODUCTIVE HISTORY

Milk production may continue for up to 1 year following weaning; therefore, it should not be considered galactorrhea (inappropriate milk production) within this period. In addition to galactorrhea, hyperprolactinemia can result in oligomenorrhea or anovulation owing to prolactin-induced gonadotropin-releasing hormone (GnRH) suppression. A history of galactorrhea and oligomenorrhea or amenorrhea usually is indicative of hyperprolactinemia and increases the likelihood of a pituitary prolactinoma. Most prolactinomas are histologically benign microadenomas (<1 cm), and some remain stable or regress without treatment. The coexistence of headaches and demonstrable bitemporal hemianopia increases the likelihood of larger lesions (macroadenomas).

HYPOTHYROIDISM

Hypothyroidism results in increased TRH production and lactotroph stimulation and decreased metabolic clearance of prolactin.[5, 13] Because hypothryoidism is a relatively common problem, women with galactorrhea should have a thyroid-stimulating hormone (TSH) assay performed and, if necessary, a full thyroid function panel. Recognition and treatment of hypothyroidism with thyroid supplementation (levothyroxin) results in normalization of TSH levels and resolution of hyperprolactinemia and the associated galactorrhea.

MEDICAL AND SURGICAL CONDITIONS

Several medical and surgical conditions can cause increased prolactin levels and galactorrhea. Medical and surgical conditions associated with hyperprolactinemia include the following:

- Chronic renal failure
- Hypothyroidism
- Hypothalamic lesions
- Growth hormone–producing pituitary lesions
- Previous thoracotomy
- Thoracic neoplasms
- Herpes zoster (shingles)
- Hypernephroma
- Bronchogenic carcinoma

DIAGNOSTIC EVALUATION OF GALACTORRHEA

When the medical history and physical examination suggest galactorrhea, an evaluation should be undertaken to define the specific etiology. Rather than proceeding immediately to a battery of diagnostic studies, many of which are of low yield or expensive, the evaluation should proceed in a stepwise fashion.

Following the history and physical examination, a random serum prolactin and TSH measurements are appropriate. A normal prolactin level rules out pituitary adenoma and obviates the need for further prolactin measurement and CT or MR imaging of the pituitary.

In some women, galactorrhea will develop that is associated with serum levels in the normal range, either owing to relative hyperprolactinemia or increased production of biologically active prolactin undetectable by the standard assay. Although a normal prolactin level does not preclude a diagnosis of endocrinologic-related discharge (galactorrhea) it suggests a careful reevaluation of the history and physical examination to exclude the possibility of a ductal etiology of the discharge.

When hyperprolactinemia is confirmed on random serum prolactin measurement, medications that may result in elevated levels at serum prolactin should be withheld if medically appropriate, and the test repeated. If withholding medication is inappropriate or if no medication is identified, a fasting morning prolactin level should be obtained for confirmation or to distinguish persistent hyperprolactinemia from normal physiologic fluctuations.

If true hyperprolactinemia is not considered to be caused by medications or hypothyroidism, the possibility of a pituitary adenoma must be considered. Although the findings of a pituitary macroadenoma is uncommon in women with mild (<100 ng/mL) hyperprolactinemia in the absence of neurologic findings, a smaller lesion (microadenoma) must be ruled out by performing pituitary imaging. Although coned-down views of the sella and CT scanning of the pituitary may reveal the presence of an adenoma, MR imaging is the most sensitive technique to identify small lesions.

TREATMENT OF GALACTORRHEA

The treatment of galactorrhea is directed toward reducing the relative or absolute prolactin level. The appropriate treatment should be based on specific clinical manifestations, the presence or absence of a pituitary adenoma, the level of prolactin, and the specific goals of therapy.

Treatment of Relative or Absolute Hyperprolactinemia Without Evidence of Thyroid Disease or Pituitary Adenoma

In the absence of hypothyroidism or a pituitary adenoma, galactorrhea is an annoying but not serious condition. When accompanied by oligomenorrhea or anovulation, it may impair fertility. The decision to treat galactorrhea should be based on the serum prolactin level, the patient's desire to rid herself of symptoms, and fertility desires. Women with hyperprolactinemia are at risk for osteoporosis; therefore, a documented increase in prolactin levels should be treated.[15, 22] Women requesting treatment because of symptoms should be offered medical therapy with a dopamine agonist, either bromocriptine or cabergoline.[4, 25] The advantage of cabergoline over bromocriptine is its reportedly lower incidence of side effects and simpler dosing schedule. Bromocriptine is the drug of choice when treatment is for hyperprolactin-induced anovulatory infertility because of the lack of information regarding cabergoline in this setting.

Pituitary Adenoma

The primary therapy for a prolactin-producing pituitary adenoma is medical, with bromocriptine or carbergoline. Surgery is reserved for the rare tumor that progresses on medical therapy. Bromocriptine failures sometimes respond to quinagolide, a relatively new dopamine agonist.[18, 20]

DUCTAL CONDITIONS

The second category of nipple discharge is caused by ductal lesions, benign and malignant. All cases of nipple discharge not classified as galactorrhea fall into this category, and it is essential to determine the appropriate etiology based on history and physical examination. In the absence of a palpable mass or a mammographic abnormality, nipple discharge rarely is due to cancer.[16] The character of the discharge is not pathognomonic for any specific lesion. The discharge seen may be clear (serous), green, sticky (mucinous), bloody, or green-black. Most significant nipple discharges in this category are spontaneous, and, with the exception of fibrocystic changes and ductal ectasia, most discharges are unilateral, usually from a single duct orifice.

Ductal Conditions Causing Nipple Discharge

A variety of benign and malignant ductal conditions may cause nipple discharge, including ductal ectasia, fibrocystic breast changes, intraductal papilloma, intraductal carcinoma, and invasive (usually papillary) ductal carcinoma.

Ductal ectasia is a condition characterized by the dilatation of major ducts, usually in the subareolar region, and various degrees of inflammation and fibrosis around the ducts. It is seen at autopsy in approximately 25% of women.[10] The discharge may be serous, bloody, or purulent, but most often is dark green or black. This dark green or black discharge may appear to be blood, but a guaiac test is negative.

Although changes may be seen on mammogram or ultrasound evaluation, the diagnosis usually is made on histologic evaluation of surgically excised breast tissue removed for evaluation of uniductal discharge. Although surgery has been recommended for simple ductal ectasia, women with classic multiduct, nonbloody, green-black discharge should be reassured, and surgery avoided. When uniductal discharge is suspicious of a focal ductal lesion (frankly bloody, waters or post-menapausal), suggesting an intraductal papilloma or malignancy, duct excision is mandatory.

Fibrocystic breast changes, including proliferative and nonproliferative changes, may produce a serous or light green, often multiductal discharge that usually is provoked rather than spontaneous. A history of cyclic mastalgia with premenstrual ''lumpiness'' and a breast examination revealing diffuse fine nodularity are common. Mammography and ultrasonography demonstrate dense breast parenchyma, nodularity, and microcyst formation without other focal lesions. This history, a confirmatory breast examination, and imaging findings in a woman with nonbloody multiduct discharge should suggest fibrocystic changes as the cause of the discharge, and management with reassurance and supportive measures is appropriate. The discharge that occurs with fibrocystic changes may be the early manifestation of duct ectasia, which, not uncom-

monly, coexists with fibrocystic changes (discussed in detail elsewhere in this issue).

An intraductal papilloma is the most common cause of bloody, usually uniductal, nipple discharge. The discharge is most often spontaneous and easily reproducible on palpation from a single duct orifice. The discharge also may be serous. Most intraductal papillomas are located within 1 to 2 cm of the areolar edge within the major ducts. Although not considered true precursors of cancer, women with papillomas may be at slightly higher lifetime risk for carcinoma, possibly owing to the coexistence of other proliferative lesions.[2, 14, 17]

Mammography is negative in most cases, and ultrasonography may or may not reveal a dilated duct with an intraluminal lesion. Galactography has been suggested as a sensitive tool for identifying more peripheral papillomas that would otherwise be difficult to locate. This procedure entails catherization of the duct orifice and the injection of a small volume of water-soluble radiocontrast materials. Papillomas are seen as intraluminal filling defects. Limitations of this study are its relative invasiveness and discomfort and the frequency of false-positive filling defects.[6]

The treatment of an intraductal papillomas is surgical, that is, duct excision. In the absence of a specific mammographic, ultrasonographic, or galactographic lesion, the involved duct corresponds to the duct orifice on the nipple through which the discharge emerges. Palpating in a radial fashion from peripheral to central usually reproduces the discharge. The quadrant and duct are identified, dissected, and excised through a small cirumareolar incision. Injecting a small volume of methylene blue through a 25-gauge angiocatheter into the duct orifice facilitates duct identification and dissection; however, extravasation may complicate the surgical procedure and result in an extensive dissection.

Intraductal and Invasive Ductal Carcinoma

In the absence of a palpable mass or mammographic lesion, nipple discharge is rarely caused by malignancy. Most cancer-associated discharges are the result of ductal carcinoma in situ (DCIS) or papillary carcinoma, and a palpable or mammographic lesion is common.[3, 11] Nipple discharge owing to DCIS has been shown to be a marker for extensive DCIS, which often requires mastectomy to achieve adequate surgical margins.[1, 19]

SPECIFIC DIAGNOSTIC MODALITIES IN THE EVALUATION OF NIPPLE DISCHARGE

The standard diagnostic modalities used in the evaluation of uniductal discharge are the history, physical examination, mammography, ultrasonography, and surgical duct excision. Techniques that more accurately detect early ductal lesions recently have been developed and tested and include galactography, ductoscopy, and ductal lavage.

Ductoscopy is the direct visualization of the ductal lumen with a flexible small fiberoptic scope that is passed through the duct orifice of the nipple. Although studies have shown that ductal lesions may be visualized when other studies are unrevealing, the lack of accessibility to this expensive technology and the discomfort/invasiveness of the procedure raise practical concerns.[23] Currently, this technology is only available in certain centers and should be viewed as investigational.

Ductal lavage is a procedure that entails eliciting fluid from one or more

duct orifices using a suction pump fitted over the nipple, followed by catheterization and irrigation of the duct to obtain cells for cytologic evaluation. Most studies to date have been in asymptomatic, high-risk women for early detection of malignant or precursor lesions.[8] The sensitivity and specificity have yet to be determined. At this time, the procedure is investigational and should be restricted to clinical trials.

NIPPLE DISCHARGE CYTOLOGY

A few words of caution regarding nipple discharge cytology are in order. As is true in any cytologic procedure, skill and experience in sample processing and interpretation are imperative. Even in the most skilled hands, the cytology of nipple discharge lacks the sensitivity to be reliable.[7, 9, 12] A serious diagnostic and therapeutic dilemma is created when atypical or malignant cells are detected from fluid that is pooled from the discharge from multiple duct orifices. In this situation, in the absence of a palpable or mammographic/ultrasonographic lesion, identifying the offending duct without excision of an extensive amount of breast tissue is virtually impossible. Nipple discharge cytology should only be used in cases of reproducible uniductal discharge when skilled cytopathologic interpretation is available and when the information obtained will influence therapy.

SUMMARY

By performing a thoughtful evaluation including a detailed history and careful physical examination, appropriate studies can be selected to allow the practitioner to arrive at the correct diagnosis of nipple discharge in a nonmorbid, expeditious, and inexpensive manner. This article has presented a simple, cost-effective, minimally morbid algorithm for the evaluation of nipple discharge.

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