

## Case Report

# Pathological Nipple Discharge

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**Abstract.** *Introduction:* Pathological nipple discharge is usually of benign aetiology but cancer may be the underlying cause in up to 20% of the presentations. The diagnostic value of discharge cytology and significance of presence of blood remains a topic of interest. Our study sets out to review the distribution of histopathology and diagnostic application of blood-staining and cytology in pathological nipple discharge. *Methods:* We performed a retrospective analysis of those patients that had surgery for pathological nipple discharge. The hospital's electronic medical records and breast cancer information systems were used to identify our study cohort. Parameters evaluated included patient demographics, radiological assessment, if discharge was blood-stained and histological/cytological analysis. *Results:* Of 123 patients, intraductal papilloma was the leading diagnosis ( $n = 62$ ) followed by duct ectasia ( $n = 34$ ). Carcinoma in-situ and invasive carcinoma occurred in nine cases. Seventy-one patients presented with blood-stained nipple discharge of which 41 had a diagnosis of intraductal papilloma, 17 had duct ectasia, and seven cases were due to carcinoma. Two cases of cancer were negative for blood. Cytology was done only in 23 patients and was not diagnostic of carcinoma and identified intraductal papilloma in only 3 cases. *Conclusion:* This study supports the generally accepted view that cytology has very poor sensitivity for detecting breast cancer and has therefore very limited diagnostic value. Nipple discharge that is negative for blood is still associated with cancer. It also confirms that intraductal papilloma is the leading cause of pathological nipple discharge.

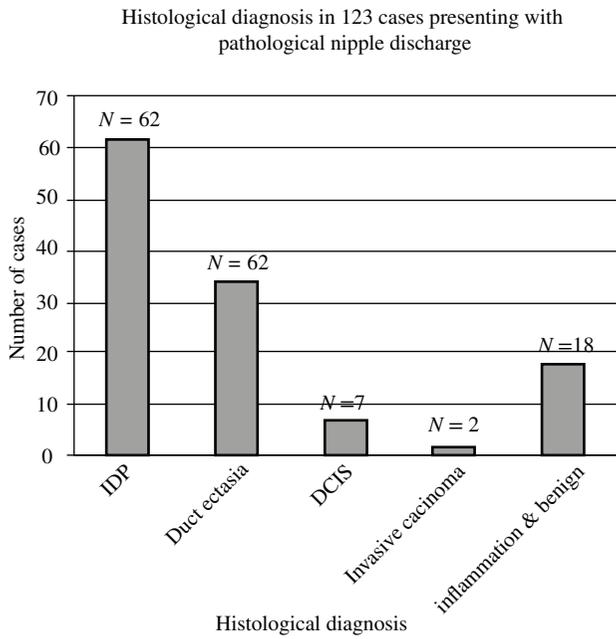
**Keywords:** Breast cancer, nipple discharge, cytology, papilloma

## 1. Introduction

Spontaneous nipple discharge (SND) is a relatively common manifestation of breast disease, accounting for up to 5% of overall breast symptoms [1, 2]. Bilateral nipple discharge involving multiple lactiferous ducts is usually non-pathological and reported by up to 90% of these patients [3–5]. Conversely, pathological nipple discharge (PND) is typically spontaneous, unilateral, uniductal and may be serous or bloody, the latter either overt or occult [1, 3–5]. While the commonest cause of PND is intraductal papilloma (IDP), responsible for nearly 40% of cases [3], an underlying

malignancy, usually ductal carcinoma in-situ (DCIS), has a reported incidence of 4–20% [6–9]. The likelihood of malignancy is greater in women over the age of 50 or those presenting concurrently with a palpable mass [4, 5, 8, 10].

Until 2010 the consensus was that all women with PND should have mammography if they were over the age of 35 years in order to identify ipsilateral lesions [11]. However, in the Association of Breast Surgery's diagnostic guidelines document published in November 2010 the recommended age for mammography was revised to patients over 40 years of age [12]. Ultrasound scan may be helpful in visualising retro-areolar lesions that can potentially be biopsied. Other



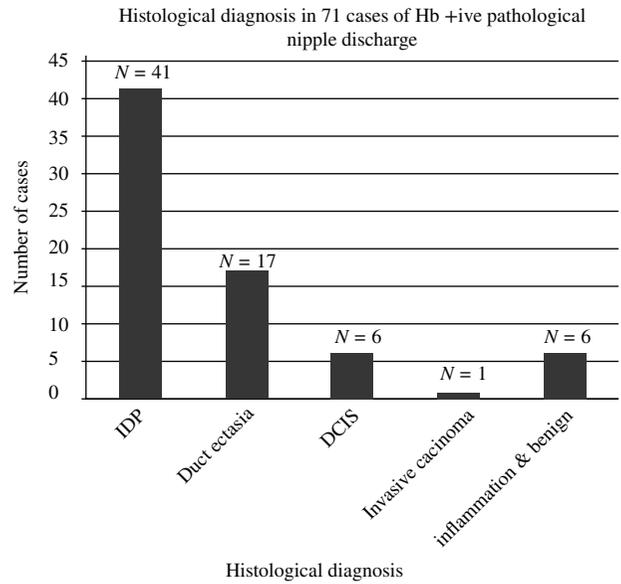
**Figure 1:** Histological diagnosis in 123 cases presenting with pathological nipple discharge.

approaches used in some centres in evaluating PND include ductal aspiration, ductography and ductoscopy. Our own current standard practice, after triple assessment, in appropriate cases that present with PND is to carry out diagnostic microdochestomy (DMD) if the presentation involves a single duct, or total duct excision (TDE). If a concurrent mass is detected on clinical examination and/or imaging it would require tissue sampling as part of the triple diagnostic workup in order to establish the diagnosis [12].

The diagnostic value of nipple discharge cytology (NDC) and the significance of detected blood in the fluid when tested by dipstick remains a topic of interest. Several studies have shown that NDC has low sensitivity rates for malignancy [13, 15–17] while others have conversely, demonstrated a high negative predictive value (NPV) [13]. Furthermore, the presence of blood in the discharge is deemed not to be reliable in predicting breast malignancy [8, 14]. Given that there are discrepancies between centres in the relation to the use of NDC and blood testing we set out to review the distribution of pathologies in cases that present with PND who had had surgical excision and thus had known pathologies, and to assess the diagnostic significance of blood staining and NDC.

**2. Methods**

A review of Guy’s Hospital electronic medical records system, breast clinic data and the Cancer Information System (CIS) was undertaken in order to identify all patients



**Figure 2:** Histological diagnosis in 71 cases of Hb +ve pathological nipple discharge.

Table 1

IDP	Intraductal papilloma
DCIS	Ductal carcinoma in-situ
LCIS	Lobular carcinoma in-situ
EH	Epithelial hyperplasia

presenting with unilateral, single or multi-ductal pathological nipple discharge that needed surgery in the form of DMD or TDE between January 2006 and December 2009. For patients presenting with non-pathological discharge (bilateral discharge, discharge only on expression that is not blood stained and is negative on cytology and/or dipstick) and no other radiological or clinical abnormalities, no other investigations or follow up was deemed needed and they were not included in the cohort. On the other hand, patients that presented with nipple discharge and were found to have malignancy on investigations without the need for DMD or TDE were treated accordingly and also not included in the cohort.

In total, 131 female patients were identified between the ages of 19-82 (mean 46.8) who were assessed and treated for PND at Guy’s Hospital. Eight patients were excluded from the study due to incomplete records, leaving 123 patients. The data collected for each patient was; age, haemoglobin (Hb) positive/negative discharge, cytological evaluation (if performed), imaging studies (USS or mammography), diagnostic procedure (DMD or TDE) and the final histological diagnosis in the excised tissue.

Histopathology results in cases where discharge cytology was requested

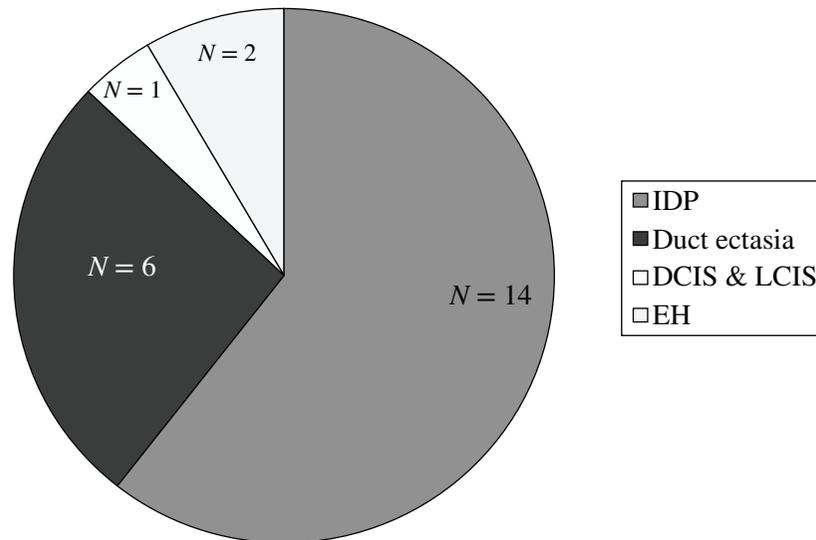


Figure 3: Histopathological results in cases where discharge cytology was requested.

Where NDC evaluation was undertaken, acellular smears were categorized as non-contributory and smears containing epithelial cells and/or blood were considered as abnormal. A fine needle aspiration (FNA) or core biopsy was attempted if an abnormality was identified and the result of this was collected. Operative procedures were either DMD or TDE.

### 3. Results

Of the total ( $n = 123$ ), 67 patients had diagnostic DMD and 56 had TDE in order to make a definitive histological diagnosis. The distribution of histological findings is shown in Figure 1. The commonest diagnosis in this cohort was IDP, accounting for 50.4% of the total ( $n = 62$ ), followed by duct ectasia in 34 patients (27.6%). Ductal carcinoma in situ (DCIS) was diagnosed in 5.7% of cases ( $n = 7$ ) that presented with PND while invasive carcinoma was diagnosed in 1.6% of patients ( $n = 2$ ). Eighteen patients out of a total of 123 (14.6%) presenting with PND had a diagnosis of inflammatory or benign changes on histological analysis.

71 (57.7%) presented with blood-stained nipple discharge (Hb positive [+ve]). Figure 2 illustrates the range of histological diagnoses in this group. The majority of patients with Hb +ve discharge had IDP 57.7% ( $N = 41$ ). The second most common diagnosis in this cohort was duct ectasia, accounting for 23.9% ( $N = 17$ ). Six cases out of a total of 71 (8.5%) were due to DCIS while only one case (1.4%) was the result of

invasive carcinoma. Of note, one case of DCIS and another of invasive carcinoma were Hb-ve.

Of the 123 patients in our cohort, only 23 (19%) had the discharge sent for cytological analysis. The final histopathology results in patients from whom NDC was sent, are shown in Figure 3. Only one of 23 patients had a final diagnosis of DCIS; this was, however, not diagnosed through cytology, which was reported as showing no malignant cells. In 14 out of the 23 specimens sent for NDC, IDP was the underlying pathology. However, cytology was suggestive of papillary lesion in only three, the rest deemed as not showing malignant cells or equivocal.

### 4. Discussion

At present there is no nationally published algorithm regarding the use of diagnostic tests in women presenting with PND. However, it is agreed that patients who are deemed to have PND from the history and examination should have appropriate radiological screening (mammography +/- ultrasonography) with magnetic resonance imaging (MRI) reserved for those requiring further evaluation or following the diagnosis of breast cancer [18]. The key is to identify malignancy, which, according to the literature can be found in up to 20% of women identified as having PND [6–9]. In our series of 123 patients, nine cases (7.3%) were diagnosed with DCIS and/or invasive carcinoma. Most had a diagnosis of IDP (62/123), whilst 34 were found to have duct ectasia. This is in keeping with large studies, which have shown that

IDP is the leading cause of PND (48%), while duct-ectasia is the second most common diagnosis, accounting for 15–20% [4, 19–21]. Interestingly 14.6% of our cohort ( $n = 18$ ) had only inflammatory and/or benign changes in spite of presenting with symptoms and signs of PND.

The value of nipple discharge characteristics such as cytology and blood-staining in investigating PND has long been a subject of debate. NDC is usually only undertaken if patients are having active discharge at the time of assessment in clinic. Of the 123 patients in our cohort, although all were assessed and deemed to have PND, only 23 had nipple discharge that was sent for evaluation at the time of their assessment. Of those, one contained no cellular material.

A noteworthy point is that although 50.4 % of our cohort (62/123) was diagnosed as having IDP, NDC indicated a papillary lesion in only three of these. Specifically, none of the seven cases of DCIS or the two cases of invasive carcinoma were detected by NDC. Previous large studies have also shown that NDC has very low sensitivity for the detection of carcinoma among women with PND [22–25]. In the present study, NDC did not detect any cases of carcinoma.

Furthermore, although nipple discharge that is serosanguinous or bloody is reported to be associated with an increased risk of carcinoma [2, 8, 26], in the present series 71 out of 123 presented with Hb +ve nipple discharge, 58% of whom had a final diagnosis of IDP. Only 10% (7 out of 71) of these patients had an underlying malignancy (DCIS or invasive carcinoma), indicating that the majority of cases of blood-stained nipple discharge are benign, mainly IDP and duct ectasia. Conversely, two of the nine cases of carcinoma (DCIS and/or invasive carcinoma) had Hb –ve nipple discharge, demonstrating that the absence of blood-staining does not exclude malignancy; Richards et al. have similarly shown that the presence of red blood cells is in fact not a reliable index for breast cancer [8].

The most reliable tool for definitive diagnosis and treatment of PND is surgical intervention. DMD is less invasive than TDE and may be both diagnostic and potentially therapeutic. In our unit those presenting with PND in the absence of detectable lesions undergo either DMD or TDE in order to investigate the underlying pathology if imaging and cytology/histopathology is not contributory (i.e. normal or benign/atypical). In our series, 67 out of 123 had DMD and 56 had TDE, a decision that was influenced by whether the discharge originated from a single or multiple ducts.

## 5. Conclusion

This study confirms that IDP is the leading cause of PND is the most common lesion to generate blood-stained nipple discharge. Importantly, we conclude that the absence of red blood cells in the discharge is not reliable for excluding breast cancer and therefore both blood-stained and non-blood stained (serous and serosanguinous) PND should still be fully investigated in order to avoid missing an underlying

malignancy. Although few cases had NDC, the study supports the generally accepted view that NDC has very poor sensitivity for detecting breast cancer and is therefore of limited diagnostic value.

## References

- [1] C. D. Haagensen, *Diseases of the breasts*, 253–254, WB Saunders, Philadelphia, 1971, 2nd ed.
- [2] M. A. Chaudary, R. R. Millis, G. C. Davies, and J. L. Hayward, The diagnostic value of testing for occult blood, *Annals of Surgery*, **196**, no. 6, 651–655, (1982).
- [3] M. Gioffré Florio, T. Manganaro, A. Pollicino, P. Scarfo, and B. Micali, Surgical approach to nipple discharge: a ten-year experience, *Journal of Surgical Oncology*, **71**, no. 4, 235–238, (1999).
- [4] S. Lau, I. Küchenmeister, A. Stachs, B. Gerber, A. Krause, and T. Reimer, Pathologic nipple discharge: surgery is imperative in postmenopausal women, *Annals of Surgical Oncology*, **12**, no. 7, 546–551, (2005).
- [5] N. Sharma, T. L. Huston, and R. M. Simmons, Intraoperative intraductal injection of methylene blue dye to assist in major duct excision, *American Journal of Surgery*, **191**, no. 4, 553–554, (2006).
- [6] E. Kapenhas-Valdes, S. M. Feldman, and S. K. Boolbol, The role of mammary ductoscopy in breast cancer: a review of the literature, *Annals of Surgical Oncology*, **15**, no. 12, 3350–3360, (2008).
- [7] T. A. King, K. M. Carter, J. S. Bolton, and G. M. Fuhrman, A simple approach to nipple discharge, *The American Surgeon*, **66**, no. 10, 960–965, (2000).
- [8] T. Richards, A. Hunt, S. Courtney, and H. Umeh, Nipple discharge: a sign of breast cancer? *Annals of the Royal College of Surgeons of England*, **89**, no. 2, 124–126, (2007).
- [9] M. H. Seltzer, Breast complaints, biopsies, and cancer correlated with age in 10,000 consecutive new surgical referrals, *The Breast Journal*, **10**, no. 2, 111–117, (2004).
- [10] M. F. Dillon, S. R. Mohd Nazri, S. Nasir, E. W. McDermott, D. Evoy, T. B. Crotty, N. O’Higgins, and A. D. Hill, The role of major duct excision and microdochectomy in the detection of breast carcinoma, *BMC Cancer*, **6**, p. 164, (2006).
- [11] R. L. Bauer, K. H. Eckhert, and T. Nemoto, Ductal carcinoma in situ-associated nipple discharge: a clinical marker for locally extensive disease, *Annals of Surgical Oncology*, **5**, no. 5, 452–455, (1998).
- [12] A. Willett, M. Michell, and M. Lee, Best Practice diagnostic guidelines for patients presenting with breast symptoms, Association of Breast Surgery, 2010.
- [13] N. Cabioglu, K. K. Hunt, S. E. Singletary, T. W. Stephens, S. Marcy, F. Meric, M. I. Ross, G. V. Babiera, F. C. Ames, and H. M. Kuerer, Surgical decision making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge, *Journal of the American College of Surgeons*, **196**, no. 3, 354–364, (2003).
- [14] D. L. Wahner-Roedler, C. Reynolds, and M. J. Morton, Spontaneous unilateral nipple discharge: when screening tests are negative—a case report and review of current diagnostic management of a pathologic nipple discharge., *The Breast Journal*, **9**, no. 1, 49–52, (2003).

- [15] Y. Ito, Y. Tamaki, Y. Nakano, T. Kobayashi, T. Takeda, E. Wakasugi, I. Miyashiro, Y. Komoike, M. Miyazaki, T. Nakayama, T. Kano, and M. Monden, Nonpalpable breast cancer with nipple discharge: how should it be treated? *Anticancer Research*, **17**, no. 1B, 791–794, (1997).
- [16] D. Ambrogetti, D. Berni, S. Catarzi, and S. Ciatto, The role of ductal galactography in the differential diagnosis of breast carcinoma, *La Radiologia Medica*, **91**, no. 3, 198–201, (1996).
- [17] M. Sessa, L. Cerroni, and A. Bertolotti, Proliferative pathology of the mammary ducts. Diagnostic value of ductogalactography and cytologic correlations, *La Radiologia Medica*, **81**, no. 5, 597–600, (1991).
- [18] R. T. Dolan, J. S. Butler, M. R. Kell, T. F. Gorey, and M. A. Stokes, Nipple discharge and the efficacy of duct cytology in evaluating breast cancer risk, *The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*, **8**, no. 5, 252–258, (2010).
- [19] A. N. Hussain, C. Policarpio, and M. T. Vincent, Evaluating nipple discharge, *Obstetrical & gynecological survey*, **61**, no. 4, 278–283, (2006).
- [20] L. D. Louie, J. P. Crowe, A. E. Dawson, K. B. Lee, D. L. Baynes, T. Dowdy, and J. A. Kim, Identification of breast cancer in patients with pathologic nipple discharge: does ductoscopy predict malignancy? *American Journal of Surgery*, **192**, no. 4, 530–533, (2006).
- [21] W. Al Sarakbi, D. Worku, P. F. Escobar, and K. Mokbel, Breast papillomas: current management with a focus on a new diagnostic and therapeutic modality, *International seminars in surgical oncology : ISSO*, **3**, p. 1, (2006).
- [22] J. E. Lang and H. M. Kuerer, Breast ductal secretions: clinical features, potential uses, and possible applications, *Cancer control : journal of the Moffitt Cancer Center*, **14**, no. 4, 350–359, (2007).
- [23] R. Simmons, T. Adamovich, M. Brennan, P. Christos, M. Schultz, C. Eisen, and M. Osborne, Nonsurgical evaluation of pathologic nipple discharge, *Annals of Surgical Oncology*, **10**, no. 2, 113–116, (2003).
- [24] H. F. Newman, M. Klein, J. D. Northrup, B. F. Ray, and M. Drucker, Nipple discharge. Frequency and pathogenesis in an ambulatory population, *New York State Journal of Medicine*, **83**, no. 7, 928–933, (1983).
- [25] T. A. King, K. M. Carter, J. S. Bolton, and G. M. Fuhrman, A simple approach to nipple discharge, *The American Surgeon*, **66**, no. 10, 960–965, (2000).
- [26] H. P. Leis Jr, Management of nipple discharge, *World J Surg*, **13**, 736–742, (1989).

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