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RESEARCH

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Abstract Solitary ductal papilloma of the breast, although considered a benign disorder has a potential association with carcinomas. We studied and analyzed the role of selective ductectomy (SD) for the diagnosis and treatment of intraductal lesions presenting with single duct discharge and ductography suggestive of intraductal (papillary) lesions. During a ten-year-period, files of patients presenting with single (or rarely dual) duct discharge were retrospectively reviewed. The examinations included mammography, ductography and ultrasonography and cytology of the fluid discharged from the duct in all patients. Patients treated with SD were considered further and their histological diagnosis and treatment were analyzed. The series included 100 patients. In 6 cases malignancy was found in the specimen consisting of four in situ and two invasive ductal carcinomas. These 6 patients had a second operation and this was followed by adjuvant treatment. Nine further patients had atypical ductal hyperplasia in or around papillomas and one patient had lobular neoplasia around her papilloma. In the present series, the incidence of carcinoma associated with the clinical suspicion of papillary lesions was 6%, and further 10% had low grade neoplastic proliferations resulting in the diagnosis of atypical papillomas or atypical ductal hyperplasia or lobular neoplasia around the papilloma, indicating that single duct discharge may be a symptom a malignancy, and that ductal papillomas have malignant potential. For such a low risk and grade of malignancy simple follow-up could be one option, but in some cases SD could be applied to relieve the patients from symptoms and establish a diagnosis.

Keywords Intraductal papilloma · Breast cancer · Ductography · Selective ductectomy

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Introduction

Single duct nipple discharge is a common initial symptom of central, subareolar intraductal papillomas [1]. The majority of solitary papillomas are benign, altough they can be associated with cytological atypia, in-situ or invasive malignancy [2]. Most intraductal papillomas are small (less than 5 mm in diameter), however papillomas as large as 10 cm have been reported [3]. Their standard diagnostic work-up includes mammography and ductography. Most women presenting with nipple discharge have normal mammograms, but ductography may visualize intraductal lesions [4]. In addition, some investigators perform ultrasonography of the retro-areolar region to visualize enlarged ducts.

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Recently, magnetic resonance imaging (MRI) has been reported as a useful adjunct to ductograpy in the detection of intraductal papillomas, as well as malignancies with a significant intraductal component [5]. Ductoscopy is a new technical improvement allowing intraductal biopsy and therefore its introduction may be of help in the evaluation of intraductal lesions [6]. Ultrasound guided vacuum assisted biopsy or removal of the lesion is another diagnostic option [7]. An alternative diagnostic procedure is the histological verification of intraductal lesions following selective ductectomy, a conservative surgical excisional procedure aiming at the removal of the discharging duct with a minimal rim of periductal breast tissue. This is a report on a single institutional experience with the latter surgical technique.

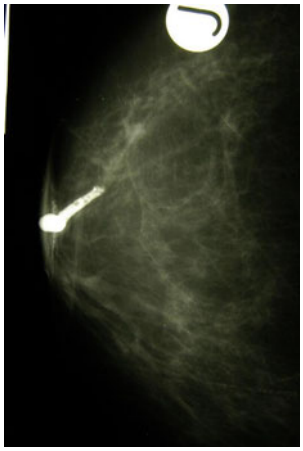

Fig. 1 Title: Example of a typical ductogram of a patient with single duct nipple discharge. Description: The duct fills up partially, is amputated at the end and shows irragularities suggestive of intraluminal protrusions

Patients and Methods

Files of patients presenting with single (or rarely dual) duct discharge at the Department of Surgery or Breast Diagnostics of Bács-Kiskun County Teaching Hospital were retrospectively reviewed. Patients were evaluated and treated within a multidisciplinary setting, an whenever an intraductal obliteration (partial or complete) was evidenced by imaging studies, selective ductectomy was considered as a diagnostic and therapeutic intervention. Only patient undergoing SD were further evaluated in this retrospective analysis.

Bilateral two-view-mammography (craniocaudal and mediolateral oblique), ultrasonography and ductography were performed in all patients. For ductography 2 ml contrast media (Ultravist jopromid, Bayer, Berlin, Germany) was injected through a 27 gauge cannula (Anel, Luer-Lock, Medicor, Debrecen, Hungary) into the discharging duct, then craniocaudal and lateral views of the given breast were obtained. Spot compression magnification views of the area of concern were also analyzed. The suspicion of a papilloma was raised when a regular intraluminar filling defect was seen (Fig. 1).

Nipple discharge cytology was evaluated in all cases. Whenever a mass lesion was also identified by ultrasound (US), US-guided fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) was also done. Biopsy of microcalcifications was performed under sterotactic guidance using 14-gauge needle and a biopsy gun.

Surgical excision was recommended on the basis of suspected intraductal papilloma. Selective ductectomy was performed in the following steps. At the beginninig of the operation, the mamilla was compressed in order to visualize the duct with the discharge. One ml of Patent blue dye (Laboratoires Guerbet, Roissy, France) was injected through a 27-gauge cannula inserted into the pathologic duct. Following this vital labeling of the duct, an infraareolar incision was made and the areolar flap was raised. The pathological duct was identified and the dyed 3 or 4 cm long part was removed with a small rim of surrounding breast tissue. The specimens were oriented with a short suture at the mammillary edge and a long suture at the peripheral edge (Fig. 2).

All ducts removed were sent for histological examination. Following fixation in 4% buffered formalin, the ducts were sliced perpendicular to their long axis from the central part towards the periphery, and were blocked in consecutive transsectional planes. The central and peripheral slices were always submitted for histological analysis, whereas the rest of the duct was either submitted in toto or only the slices including the grossly identifiable intraductal lesion were embedded in paraffin. Tissue sections were stained with hematoxylin and eosin (Fig. 3).

Results were categorized as isolated benign papilloma, papilloma associated with high-risk lesions such as atypical ductal hyperplasia (ADH), lobular intraepithelial neoplasia (LN) or ductal carcinoma in situ (DCIS) and papilloma/atypical papilloma associated with invasive ductal carcinoma (IDC). Some non-papillary lesions fell outside of these categories and these also included malignant disease without papillary growths..

Results

The retrospective review of records between January 2004 and January 2011 revealed 100 patients with suspected intraductal papillary proliferations removed by ductectomy. The mean age of the patients was 52 years (range 32–82 years). Nipple discharge was the main clinical symptom in all of them.

Mammography was normal in 83 cases and showed microcalcifications in 17 cases. Ultrasound described a mass in 23 cases.

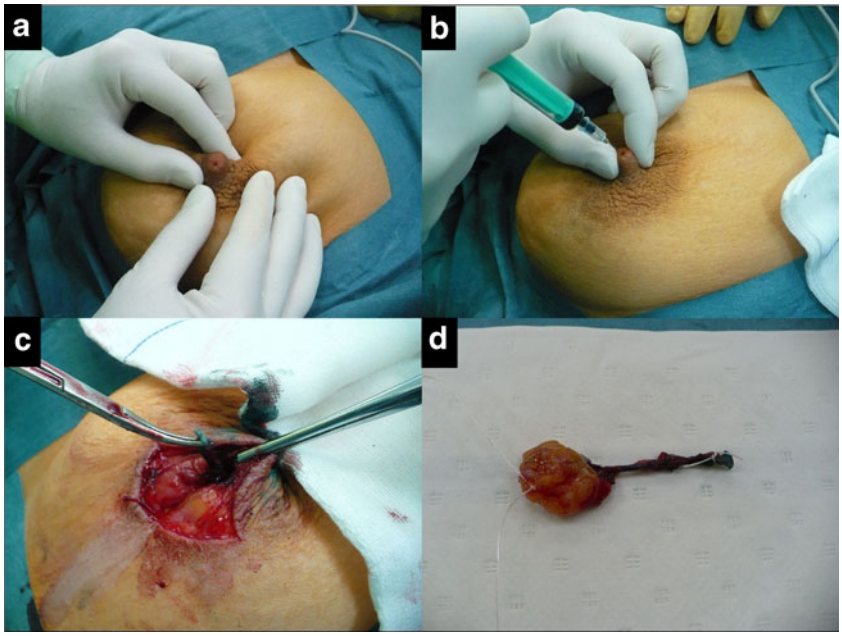

Fig. 2 Title: Selective ductectomy. Description: **a** Identification of the duct responsible for the discharge. **b** Cannulation of the discharging duct and administration of the vital dye into the duct. **c** Removal of the cannulated blue stained duct from an infraareolar incision. **d** The specimens were oriented with a short suture at the mammillary edge and a long suture at the peripheral edge

A single duct discharge was identified in 98 cases and dual duct excretion was seen in 2 cases. The fluid discharged from the duct was serous in 77 cases and blood stained in 23. Cytolgical examination of the fluid discharged from the duct reported normal cells (C2) in 60 patients and showed atypical, probably benign cells (C3) in 40 cases [8]. Core needle biopsy was obtained in 4 cases. All of them were B3 (breast tissue with uncertain malignant potential) lesions, corresponding to intraductal papilloma (n=3) and sclerosing adenosis (n=1) on final histology.

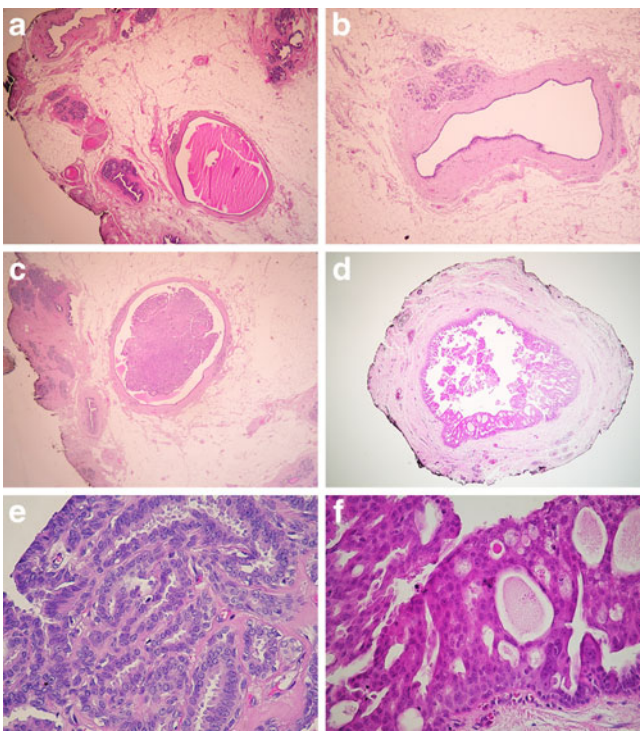

Fig. 3 Microscopy of two representative cases. **a**–**d** Selective ductectomy specimen with intraductal papilloma. A proximal (close to the nipple) (**a**) and distal (away from the nipple) (**d**) transections show a dilated duct with periductal fibrosis, but no intraductal proliferation. Similar findings also suggest proliferation free longitudinal margins. Transections falling between the two edges showed an intraductal papilloma (**b**) without atypia (**c**). **e**-**f** Selective ductectomy specimen with intermediate grade cribriform DCIS. (Hematoxylin and eosin, **a**, **b**, **d**, **e**: ×20; **c**, **f**: ×400)

We made the operations under general anaesthesia. The average operation time was 17 min. We have not got any serious complications. Twelve patients had a mild discomfort in the breast wound for a day or two.

The histopathological findings of the surgically excised lesions revealed benign papilloma in 62 patients, papilloma with atypical ductal hyperplasia within the papillary lesion (atypical papilloma) in 5, papilloma with ADH around the papillary proliferation in 4, papilloma with lobular neoplasia around the lesion in 1, an apocrine papillary lesion without myoepithelium in the central part and with partial lack of myoepithelium at the periphery in 1 [9], DCIS in 4 and IDC in 2 patients (Tables 1 and 2). Three of the DCIS cases and one of the IDC cases were also associated with papillomas (Table 1). Ductectasia was the only finding in 16 patients and other benign changes were seen in 5 cases. This means that out of 100 patients presenting with single duct discharge and ductographic changes suggestive of intraductal (papillary) proliferations, 6 (6%) proved to have malignant disease (4 in situ and 2 invasive carcinomas). Furthermore, 14 intraductal papillomas (18% of papillomas, 14% of all cases) were associated with neoplastic changes: atypical hyperplasia found in 5 and around 5 of them (Table 2), in situ carcinoma associated with 3 and invasive carcinoma with 1 of them (Table 1).

Table 1 Summary of patients with a malignant diagnosis

Patient	Age	Imaging	Surgery	Histology/TNM Staging	Size (margins)[a]	Adjuvant treatment
1	76		SD followed by reexcision	IG DCIS pTis pNXM0+ intraductal papilloma ER:pos PgR:pos Her-2:neg	36 (0) [b]	HT
2	33		SD followed by WLE and SNB followed by mastectomy and breast reconstruction	HG DCIS pTis pN0/i-/M0 ER:neg PgR:neg Her-2:pos	44 (0.1 posterior)	
3	48	9-mm-large cyst on US	SD followed by WLE and SNB	IDC Gr.III. pT1c pN0/sn/M0+ intraductal papilloma ER:pos PgR:pos Her-2:neg	13 (0.6 posterior)	WBRT and CT and HT
4	54	25×15 mm mass on US	SD followed by WLE and SNB	IDC Gr.II extensive DCIS component.pT1b pN0/sn/M0 ER:pos PgR:pos Her-2:neg	6 (invasive), 48 (whole) (1 posterior)	WBRT and CT and HT
5	57		SD followed by WLE and SNB	LG/IG DCIS pTis pN0/i-/M0+ intraductal papilloma ER:pos PgR:pos Her-2:neg	29 (>10)	WBRT and HT
6	66		SD followed by WLE and SNB	LG DCIS pTis pN0/i-/M0+ intraductal papilloma ER:pos PgR:pos Her-2:neg	27 (8)	WBRT and HT

CT Chemotherapy; *DCIS* ductal carcinoma in situ; *ER* estrogen receptor; *HG* high grade; *HT* Hormonal therapy; *IG* intermediate grade; *LG* low grade; *neg* negative; *PgR* Progesteron receptor; *pos* positive; *SD* Selective ductectomy; *SNB* sentinel node biopsy; *TNM* Tumor Node Metastases; *WBRT* Whole breast radiation therapy; *WLE* wide local excision

[a] all measures are in mm (closest margin)

[b] reexcision indicated, but patient denying

Considering the six patients with a final diagnosis of DCIS or IDC and the 10 patients with precursor neoplastic lesions (ADH or lobular neoplasia), mammography showed microcalcifications in two cases and ultrasonography found a mass in two (Tables 1 and 2). From the 6 malignant lesions, nipple discharge cytology found normal cells (C2) in three cases and atypical, probably benign cells (C3) in three. The initially performed selective ductectomy was

Table 2 Summary of patients with precursor neoplastic lesions

Patient	Age	Mammography and/or ultrasound findings	Surgery	Histology	margins	Follow-up information
1	68		SD	Papilloma and ADH+CCA around	free, NFS	9 month NED, LFU
2	61		SD	AP, NED around the papilloma	free, NFS	LFU
3	50	4-mm-large microcalcification	SD with wire localization	Papilloma and ADH + CCA around; microcalcification in the papilloma and the CCA	free, NFS	71 month NED
4	55	15-mm-large mass with microcalcification	SD with wire localization	AP, NED around the papilloma; microcalcification in the lesion	free, 2–3 mm	LFU
5	46		SD	AP, NED around the papilloma	duct opened, possibly involved	43 month NED
6	66		SD	Papilloma and ADH+CCA around	0.3 mm	74 month NED
7	61		SD	AP, NED around the papilloma	free, NFS	41 month NED
8	43		SD with wide excision	Papilloma with radial scar associated with ADH around	not assessable, removed in 2 parts	45 month NED
9	32		SD	AP, NED around the papilloma	free, NFS	LFU
10	53		SD	Papilloma with lobular neoplasia outside	crossing lobular neoplasia	36 month NED

ADH atypical ductal hyperplasia; *AP* atypical papilloma (i.e. papilloma with atypical ductal type hyperplasia within the papilloma); *CCA* columnar cell alterations encompassing columnar cell changes and hyperplasia without atypia and flat epithelial atypia; *NED* no evidence of disease; *NFS* not further specified; *SD* selective ductectomy

complemented in all cases with Radioguided Occult Lesion Localisation (ROLL) [10] and breast conserving surgery plus sentinel lymph node (SLN) biopsy. One of the patients needed a third operation, because of the positive margins of the second specimen: due to the extent of the lesion and no signs of it on imaging studies including breast MRI, the third operation consisted of mastectomy, followed by reconstruction with an implant. The SLNs were negative in all cases. Whole breast irradiation was delivered to 4 patients total doses of 50 Gy. Two of them also received boost irradiation to the tumor bed because of close margins. Two patiens were given chemotherapy because of grade 3 IDC and a praemenopausal status. Oestrogen receptor was positive in 5 tumors. All of these patients received hormonal therapy (Table 1).

Discussion

Although nipple discharge is a relatively common symptom and is usually benign in origin, it can also be a feature of intraductal carcinoma of the breast (DCIS). On the basis of previous reports, the incidence of DCIS in patients with nipple discharge varies from 1% to 16% [11, 12].

Ductography plays an important role in the assessment of single duct discharge, because it may visualize intraductal lesions.

Although nipple discharge obtained by sqeezing should be smeared and submitted for cytology in all such cases [13], this approach was not very helpful in our hands, as suspicion for malignancy (C4) was not raised in any of the patients. In lesions with associated atypia, the cytomorphologic features may overlap with those of low-grade intraductal carcinoma, and tissue biopsy might be considered for a definitive diagnosis [14].

Image-guided needle biopsies are generally the next step to get a diagnosis. Leah at al suggest excisional biopsy to be considered when a papillary lesion (caterogized as B3, lesion of uncertain malignant potential, because of the probability of associated malignancy [8]) is identified at percutaneous image-guided breast biopsy [7], although these issues are somewhat controversial. Good sampling may allow the diagnosis of a benign papilloma (B2) [8]. Mammary ductoscopy (MD) or fiberoptic ductoscopy (FDS) is an endoscopic technique that allows direct visualization of the mammary ductal lining using sub-millimetre fiberoptic microendoscopes inserted through the ductal opening onto the nipple surface. These scopes also provide working channels for insufflation, irrigation, ductal lavage, and possible therapeutic interventions. MD can be performed under local anaesthesia in the office setting [15]. Although nipple discharge is an unusual presentation for DCIS, FDS with ductal lavage cytology can be a useful technique for the diagnosis of DCIS prior to surgery [16] in patient with nipple discharge.

There was a wide divergence of opinions with regard to the treatment of nipple discharge in cases of suspected intraductal papilloma. The various methods of treatment included observation with no treatment; infraareolar incision with removal of a small area which contains the duct and the intraductal papilloma; wide wedge-shaped incision, removing the offending papilloma and several ducts; and a more radical procedure, resection of the nipple and areola complex. However, in the last 30 years, a more conservative approach has been accepted, stemming mainly from the studies of Haagensen in the USA and Atkins and Wolff in the UK [17]. These authors all recognized that patients whose discharge was due to intraductal papilloma were cured by the removal of the papilloma. Atkins developed microdochectomy through a small cut removal of a single duct following the circular line of the areola and Haagensen [3] used a procedure that is between Atkins' microdochectomy and the excision of the major duct performed by Urban [18]. If the discharge can be localized to a single duct, microdochectomy gives satisfactory results in younger patients with minimal or no change of the breast shape and function. SD can be considered as a variant of microdochectomy in which the surgeon removes the given duct and a small rim of surrounding breast tissue with the guidance of a vital dye (sometimes combined with radiocontrast material). MD as a new alternative in the management of intraductal proliferations offers the advantages of accurate localization of pathology, ductal lavage under direct visualization, and intraoperative guidance especially for lesions deep within the ductal system [19].

In our hospital, the general work-up of single duct discharge through the nipple includes mammography, ultrasonography, ductography and discharge cytology. Image guided FNAC or CNB are also used for cases with identifiable mass lesions. When these examination suggest intraductal proliferations (papillomas in general), selective ductectomy, a conservative surgical excision of limited extent was our method of choice for diagnosing and treating the lesion behind the symptom. When malignancy was proven preoperatively, breast conserving surgery with the ROLL technique or mastectomy with sentinel node biopsy (SNB) were advocated. In six cases malignancy was discovered in the surgical specimens removed by selective ductectomy and initiated a second operation in all but one patient who had a mastectomy in a third step.

Breast papillomas may be either solitary or multiple. Solitary papillomas are usually found in a subareolar location within the larger ducts, and more than half of the patients present with spontaneous nipple discharge. In contrast, multiple papillomas usually arise within the terminal duct lobular units and are most frequently peripheral in location. These patients rarely present with nipple discharge [20]. Some studies have shown an increased potential for malignancy associated with multiple (peripheral) papillomas

compared to solitary (central) papillomas [3, 21, 22]. The B3 diagnostic category comprises a variety of lesions, including papillary lesions which have a lower rate of associated malignancy than the B4 (suspicious for malignancy) category, but this rate is still up to 25% [8]. Histopathologically, papillary lesions also comprise a variety of lesions which are classified into different diagnostic entities [23]. Benign papillomas, hyperplastic rather than neoplastic lesions, are characterized by the presence of a dual population of luminal epithelial and myoepithelial cells both at the periphery and in the papillary areas. These were the most frequent in our series. Papillary DCIS is relatively rare in its pure form, but can be admixed with other patterns of DCIS. It is characterized by the absence of myoepithelium in the papillary projections, but its presence at the periphery of the involved duct. No such lesion was encountered in our study. Invasive papillary carcinomas retain the papillary architecture, but have no myoepithelial component. There are also specific lesions like the encapsulated papillary carcinoma (also known as intracystic or encysted papillary carcinoma) and the solid papillary carcinoma of which the real nature is still a matter of debate. They may represent either a form of invasive carcinoma with excellent prognosis as would suggest the total or nearly total absence of the peripheral myoepithelial layer, and very rare occasions of metastatic disease, but they may also represent specific forms of in situ carcinoma as suggested by their indolent clinical behavior and their circumscribed structure suggesting an intraductal origin. Experts tend to classify them on the basis of the latter approach [24]. It must also be remembered that papillomas may be associated with neoplastic proliferations within the lesions themselves (giving rise to atypical papillomas or papillomas with atypical ductal hyperplasia or frank in situ carcinoma) or around the lesions. Finally, some papillary lesions may defeat current categorization guidelines [9]. No encapsulated, solid or invasive papillary carcinomas were seen in this series.

Our data suggest a 6% (95% confidence interval: 3–12%) in situ or invasive malignancy rate for patients presenting with simple rather than multiple duct discharge, and a suspicion of intraductal proliferation (papilloma) on ductography. For the histopathological entitiy of intraductal papilloma (77 in this series), the rate of neoplastic changes was 7.8%, with four overlapping cases having both DCIS and intraductal papilloma. Therefore, the clinical presentation we discuss in our series was associated with neoplastic epithelial changes in 16 cases (16%): 2 cases without histologically identified papillary lesions, and 14 with papillomas (5 fitting into the frames of atypical hyperplasia, 5 with ADH or lobular neoplasia around the papilloma and 4 cases associated with DCIS or invasive carcinoma). Whether this incidence of malignancy and its predominantly low grade justifies selective ductectomy for the management of single duct discharge raising the possibility of intraductal proliferations consistent with central papillomas is a matter of perception. It was felt that the answer to this question was positive, but on the other hand, patients with nothing more than inspissated secretion related ductal obliteration and ductectasia as final diagnosis were overtreated. Clearly, selective ductectomy is just one possible approach to manage single duct discharge with papillary lesions suspected in the background, and patients should be informed about the pros and cons of this minimally invasive intervention, the low rate of malignancy associated with this clinical setting and an informed consent should naturally be obtained. Owing to the rather uncommon association with malignant findings a watchful waiting policy could also be a viable alternative, although this does not relieve the leading symptom of nipple discharge.

Whether surgery is needed for a disease or a symptom associated with such a low incidence of malignancy, can be questionable. However, after meeting the patients it became clear, that nipple discharge can be very unpleasant and this minimal diagnostical operation promptly cease the symptom. Considering the possibility of the oncoligical overtreatment (93% of the patients had no malignant lesion, and the importance of the five in situ carcinomas is unclear) it is very important to inform the patients about the magnitude of the risk of malignancy. Some authors make the diagnosis with core biopsy, others with vacuum assisted biopsy. The treatment of these B3 risk lesions is contradictional, there are authors who suggest a surgical excision [7, 25],. others do not find this necessary, only in the case of papillary lesions [26]. The indication for the operations in this series was very similar, although the diagnosis of intraductal papilloma was not estabilished by using core biopsy, but was raised with high suspicion with ductography performed for single duct discharge after previous mammographic and ultrasound examinations. After informing the patients about the alternatives, one option can be ductoscopy, but this is not available in some countries including Hungary. Biopsy of the papillary lesion if it can be visualised by mammography or ultrasound. is the most followed option,but there was no such visible lesion amoung our cases. Another alternative can be the radiological follow up.

Conclusion

Single duct nipple discharge with no obvious mammographic or ultrasonographic lesions, but a ductographic finding suggestive of intraductal proliferation was associated with malignancy (most of the time in situ carcinoma) in 7% of the cases and atypical hyperplasia in 9% of the cases. For such a low risk and generally low grade of malignancy, simple follow-up could be offered from a surgical and an oncological point of view, but in some cases, considering the patients' request to get rid of the symptoms, SD could be applied. Whenever

associated mass lesions or microcalcifications are identified, these require separate work-up, including non-operative guided biopsies, or surgical excisions for both high risk lesions on non-operative diagnostics and lesions with inconclusive non-operative assessment. Our retrospective analysis suggests that SD is well tolerated, has no major complications and might be a realistic diagnostic and therapeutic approach in the clinical situations described above.

Conflict of interest statement None declared.

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