

# Clinical and sonographic features of nipple lesions

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## Abstract

**Background:** The aim of this study was to present several cases of benign and malignant nipple lesions and contribute to diagnosis and differential diagnosis.

**Methods:** A retrospective study was conducted on 13 patients. All of the patients were evaluated by ultrasonography, and 11 of them had pathological results. We analyzed the clinical and sonographic features.

**Results:** There were 3 malignant lesions, 7 benign lesions, and 3 congenital nipple dysplasia, listed as follows:

Malignant lesions (n=3, 23%): Paget's disease (PD, n=3, 23%). All of the patients with PD showed unilateral nipple erosion, discharge, and pain. The ultrasound showed abundant blood flow (n=3, 23%); 2 patients (n=2, 15%) had microcalcifications.

Benign lesions (n=7, 54%): Adenoma of the nipple (n=2, 15%). One patient (n=1, 8%) had nipple erosion and discharge. Two patients (n=2, 15%) had a palpable nodule in the nipple. The ultrasound of both patients (n=2, 15%) showed regular-shaped, clear border nodule with abundant blood flow (n=2, 15%).

Leiomyoma of the nipple (n=1, 8%): This male patient was characterized by unilateral nipple enlargement and pain. The ultrasound showed a regular nodule with absent blood flow.

Plasma cell mastitis (n=2, 15%): Two patients showed unilateral nipple inversion and pain. One patient (n=1, 8%) showed swollen and redness. The 2 patients showed a lesion in the gland around the nipple present as an irregular shape and unclear boundary hypoechoic mass.

Nipple wart (n=2, 15%): Two patients showed a unilateral soft exogenous neoplasm. Both of the patients showed a hypoechoic wart; the echo was similar to the nipple, the border was clear, and had no blood flow in the wart.

Nipple Dysplasia (n=3, 23%): Accessory nipple (n=3, 23%). Two patients (n=2, 15%) had accessory nipples in the subcoastal area, 1 patient (n=1, 8%) in the areolar. All of the patients' sonographic features were the same as the nipple.

The positive predict value (PPV) of the clinical symptoms: Erosion and discharge are both 75% ( $P < 0.05$ ). The PPV of the US manifestations: irregular shape, indistinct margin, abundant blood flow, microcalcification, thicken skin in diagnosing malignant lesions are 60%, 60%, 60%, 100%, 100%, respectively ( $P < 0.05$ ).

**Conclusions:** The characteristic sonographic features together with clinical symptoms contribute to the diagnosis of nipple lesions.

**Abbreviations:** CDFI = Color Doppler Flow Imaging, NAC = nipple areola complex, PACS = picture archiving and communication system, PD = Paget's disease, US = ultrasound.

**Keywords:** breast, breast neoplasms, diagnostic imaging, nipple lesions, ultrasonography

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## 1. Introduction

The nipple, also known as the central region of the breast, is the most important part of the breast structure and function. The nipple and areola are composed of pigmented squamous epithelium. The nipple-areolar complex (NAC) contains a layer of circumferential smooth muscle and sebaceous glands that open through small prominences (Montgomery tubercles) that surround the periphery of the areol.<sup>[1]</sup> Due to its special structural features, the lesions of the nipple are major parts of breast disease, and the specific features of the nipple are also associated with breast disease and breast disease treatment. There are many different benign, malignant, and congenital lesions in the nipple. Malignant lesions include Paget's disease (PD), invasive ductal carcinoma, and benign lesions include adenoma, leiomyoma, warts, inflammation, among others. To our knowledge, there is no epidemiological data on benign and malignant lesions of the nipple. For malignant disease, PD is rare and incidences of 1% to 3% have been reported among all the patients with breast cancer.<sup>[2]</sup> Many benign nipple lesions have only been reported in case reports and are generally very rare. Plasma cell mastitis is a type of nonpuerperal benign mastitis with an incidence of 1.1%

to 75% and has a high clinical misdiagnosis rate.<sup>[3]</sup> For congenital nipple lesions, the incidence of polythelia in the general population ranges from 0.22% to 5.6%, depending on factors such as genetics and race.<sup>[4]</sup> The clinical manifestations of the NAC are plentiful and mainly include discharge, nodule, nipple inversion, eczema, and skin rupture. At present, the literature on nipple lesions, in general, is limited. Therefore, we reviewed the clinical and sonographic features of 13 cases of nipple lesions at our hospital with the aim of contributing to the diagnosis and differential diagnosis of nipple lesions.

Commonly used breast examination methods include x-ray mammography, magnetic resonance imaging (MRI) and ultrasound (US). The advantage of x-ray mammography is that it is more sensitive to identify microcalcifications in some malignant lesions, but the structure of the nipple cannot be clearly depicted and it is to reveal the retro areolar mass. MRI has a better resolution for the relationship between the mammary ducts and the range of the malignant lesions; however, a clear presentation of the nipple on MRI requires the use of a dedicated breast coil and an injection of contrast agent.<sup>[5]</sup> Breast ultrasound is of high sensitivity and specificity in the diagnosis of nipple lesions with a high-frequency probe. It can clearly show the structure of the nipple region, the skin changes of the nipple area, the rear catheter, the boundary and morphology of the nodule, which are of great value for the diagnosis of nipple lesions through the appropriate probe angle. Therefore, this study analyzed sonographic features to determine whether ultrasounds have sufficient diagnostic value for nipple lesions.

## 2. Methods

### 2.1. Patient population

The study was approved by the Ethics Committee of Peking Union Medical College Hospital and all the patients gave written informed consent. A retrospective study was conducted on 15 cases of patients visiting hospital due to abnormal nipple appearance from February 2016 to July 2018, 2 patients were excluded for no obvious abnormality in ultrasonography. Finally, 13 patients were included in this study, including 12 females and 1 male, ages 19 to 62 with an average of  $39.1 \pm 13.2$  years of age. All of the patients were evaluated by ultrasonography, and 11 of them were operated and have pathological results.

### 2.2. Clinical history collection

We observed the symmetry of size and shape of the bilateral nipples and whether there was erosion, discharge, pain, or other

**Table 1**

#### Histopathological results.

	Pathological type	N (%)	Total, N (%)
Malignant lesions	Paget's disease	3 (23%)	3 (23%)
Benign lesions	Adenoma of the nipple	2 (15%)	7 (54%)
	Leiomyoma of the nipple	1 (8%)	
	Plasma cell mastitis	2 (15%)	
	Nipple wart	2 (15%)	
Nipple dysplasia	Accessory nipple	3 (23%)	3 (23%)
Total		13 (100%)	13 (100%)

symptoms of the nipple. At the same time, we determined whether there were other palpable masses in the nipple.

### 2.3. Ultrasound examination

Doctors with at least 10 years of experience at the Department of Ultrasound performed the bilateral breast US examinations and blinded the pathological results. Examinations were performed with the patient in the supine position with a scanner using high-resolution linear probes (L12–5 MHz, Canon Aplio 500, Japan). The doctors also performed color Doppler US (CDFI) if a breast mass was detected, using an appropriate Doppler setting after the grayscale US study. The doctors examined the breast in 4 planes (sagittal, transverse, radial, and orthogonal), the nipple, and axilla. If something suspicious was detected, then multiple images in different planes were obtained on grayscale US and CDFI. The grayscale images, the observation of the dilatation of the catheters, the size of the lesion, the contour of the boundary, the internal echo, the error attenuation in the rear, and the calcification were recorded. After the bilateral examination was completed, all images were uploaded to a picture archiving and communication system (PACS) for storage.

### 2.4. Statistical analysis

The data were analyzed using SPSS 12.0 software (SPSS Institute, Cary, NC). Diagnostic efficacy of clinical and ultrasonic symptoms was assessed by Fisher accurate test. Differences were considered significant when the *P* value was  $<0.05$ .

## 3. Results

The pathological findings of 13 patients are shown in Table 1, including 3 malignant cases, 7 benign cases, and 3 nipple dysplasia cases. Twelve patients were female, and 1 was male. The average age of patients with the malignant disease was

**Table 2**

#### Patient sex and age.

Pathological type		Sex		Age (average)	
		Female	Male		
Malignant lesions	Paget's disease	3	0	59 ± 4.4	59 ± 4.4
	Benign	Adenoma of the nipple	2	0	35 ± 4
	Leiomyoma of the nipple	0	1	33	
	Plasma cell mastitis	2	0	35 ± 1	
	Nipple wart	2	0	33 ± 10	
Nipple dysplasia	Accessory nipple	3	0	36.5 ± 0.5	36.5 ± 0.5
Total		12	1	40.8 ± 12.3	40.8 ± 12.3

**Table 3****The clinical symptoms of nipple lesions.**

Clinical symptoms	Pathology			PPV	P
	Benign, N (%)	Malignant, N (%)	Sum, N (%)		
Erosion					
Irregular	1 (8%)	3 (23%)	4 (31%)	75%	.014
Regular	9 (69%)	0	9 (69%)		
Discharge					
Indistinct	1 (8%)	3 (23%)	4 (31%)	75%	.014
Distinct	9 (69%)	0	9 (69%)		
Pain					
Abundant	4 (31%)	3 (23%)	7 (54%)	43%	.192
Absent	6 (46%)	0	6 (46%)		
Inversion					
Present	2 (15%)	0	2 (15%)	0%	1.000
Absent	8 (62%)	3 (23%)	11 (85%)		
Palpable mass in nipple					
Present	2 (15%)	1 (8%)	3 (23%)	33%	1.000
Absent	8 (62%)	2 (15%)	10 (77%)		
Enlargement					
Present	1 (8%)	2 (15%)	3 (23%)	66%	.108
Absent	9 (69%)	1 (8%)	10 (77%)		
Swollen and red					
Present	1 (8%)	2 (15%)	3 (23%)	66%	.108
Absent	9 (69%)	1 (8%)	10 (77%)		

PPV=positive predict value.

59 ± 4.4, and the average age of patients with the benign disease was 34.7 ± 6.0. The details of the patient's sex and age are shown in Table 2.

All of the patients with PD showed unilateral nipple erosion, discharge, and pain (n=3, 23%). One patient (n=1, 8%) with nipple adenoma had nipple erosion, discharge, and pain. Two patients (n=2, 15%) with nipple adenoma had palpable nodules in the nipple and felt pain. The patient with leiomyoma of the nipple was the male patient characterized by unilateral nipple enlargement and pain. Two patients (n=2, 15%) had plasma cell mastitis and showed unilateral nipple subsidence and pain. One patient (n=1, 8%) showed swollen NAC and redness. Two patients (n=2, 15%) with warts showed a unilateral soft

exogenous neoplasm. Two patients (n=2, 15%) with nipple dysplasia had accessory nipples in the inframammary and subcoastal area. One patient (n=1, 8%) had an accessory nipple in the central area of the NAC. The positive predict value (PPV) the manifestations of erosion and discharge are both 75% ( $P < 0.05$ ). The clinical symptoms of nipple lesions are detailed in Table 3.

The ultrasound of the 3 patients (n=3, 23%) with PD showed thicker skin in the unilateral nipple than in the opposite side; 2 patients (n=2, 15%) had microcalcifications at the posterior part of the nipple. In patients with nipple adenoma, 2 patients (n=2, 15%) showed a regular shape, clear border hypoechoic nodule with abundant color Doppler flow. The ultrasound of the patients

**Table 4****The sonography features of nipple lesions.**

Ultrasound manifestations	Pathology			PPV	P
	Benign, N (%)	Malignant N (%)	Sum, N (%)		
Shape					
Irregular	2 (15%)	3 (23%)	5 (39%)	60%	0.035
Regular	8 (62%)	0	8 (62%)		
Margin					
Indistinct	2 (15%)	3 (23%)	5 (39%)	60%	0.035
Distinct	8 (62%)	0	8 (62%)		
Blood flow					
Abundant	2 (15%)	3 (23%)	5 (39%)	60%	0.035
Absent	8 (62%)	0	8 (62%)		
Microcalcification					
Present	0	2 (15%)	2 (15%)	100%	0.038
Absent	10 (85%)	1 (8%)	11 (85%)		
Thicken skin					
Present	0	3 (23%)	3 (23%)	100%	0.003
Absent	10 (85%)	0	10 (85%)		

PPV=positive predict value.

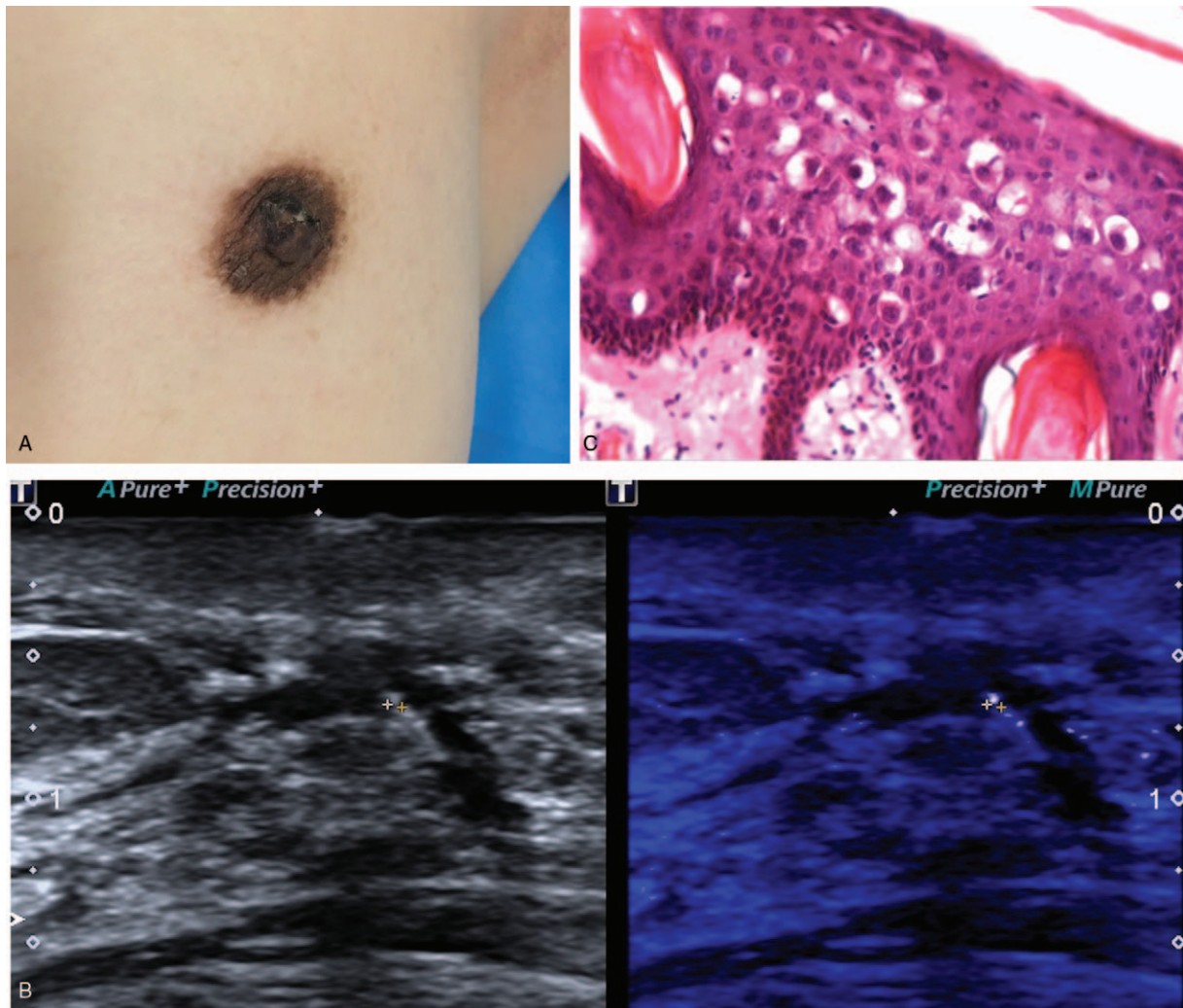
with nipple leiomyoma showed a regular and hypoechoic nodule. Through the color Doppler, rich blood flow could be seen in the surrounding area. In plasma cell mastitis, 2 patients ( $n=2$ , 15%) showed lesions in the gland around the nipple, presented as an irregular shape and unclear boundary hypoechoic mass. Two of the patients ( $n=2$ , 15%) with nipple warts showed a hypoechoic nodule, the border was clear, and there was no blood flow into the wart. All of the patients ( $n=3$ , 23%) with accessory nipples showed sonographic features similar to their nipples, and there were no lesions in the breast. The PPV of the US manifestations: irregular shape, indistinct margin, abundant blood flow, microcalcification, thicken skin in diagnosing malignant diseases are 60%, 60%, 60%, 100%, 100%, respectively ( $P < 0.05$ ). The sonography symptoms of nipple lesions are detailed in Table 4.

#### 4. Discussion

Among all the patients, the age of onset of PD is higher than that of other benign diseases; the only male patient was diagnosed with leiomyoma.

In clinical presentations, erosion and discharge of the nipple are more predictive a malignant processes ( $P < 0.05$ ). PD and nipple adenoma may have similar clinical manifestations, such as bloody discharge, erosion, and pain.<sup>[6]</sup> Leiomyoma of the nipple could be asymptomatic for long periods or present as a mass or with specific recurrent spontaneous severe pain when applying pressure or after exposure to the cold. Plasma cell mastitis may present with nipple discharge and nipple retraction, characterized by swollen breasts and redness, although some of the patients do not show these signs of inflammation. Nipple warts are soft and painless skin tags. Polythelia is a rare congenital breast disease.

In ultrasound, irregular shape, indistinct margin, abundant blood flow, microcalcification, thicken skin are more predictive a malignant process ( $P < 0.05$ ). Adenoma of the nipple, leiomyoma of the nipple, wart showed hypoechoic, regular-shaped, and clear border nodules. Leiomyoma and wart showed absent blood flow, however, adenoma showed abundant blood flow. The sonographic features of plasma cell mastitis are easily confused with breast cancer; however, plasma cell mastitis lacked the manifestations that suggest the malignant process.

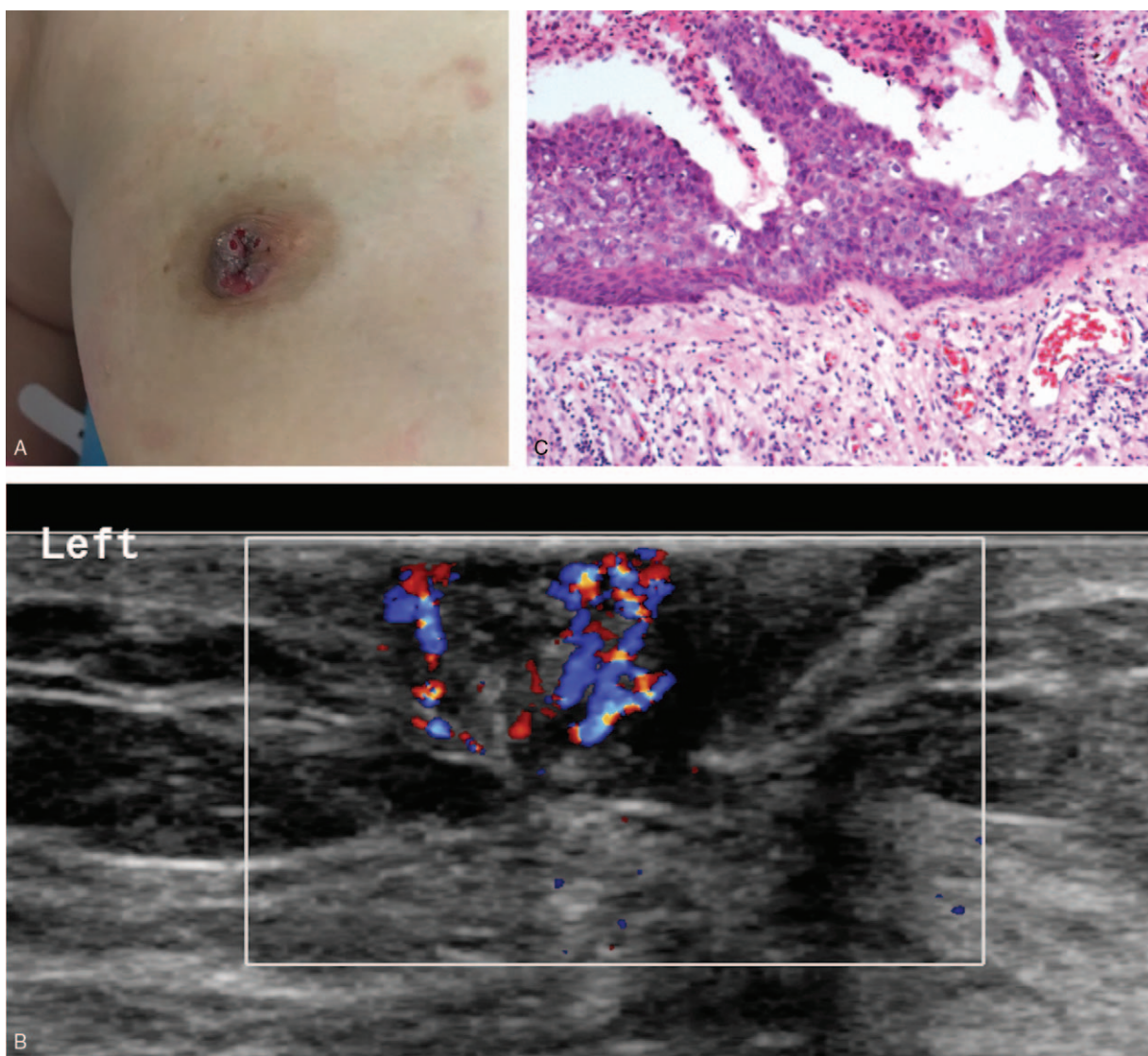


**Figure 1.** (A) A female, 61 years' old, with ulceration, erosion, and pain in the left nipple. (B) Ultrasonography revealed dilated irregular subareolar ducts with microcalcifications in ultrasonic firefly imaging. (C) Paget's disease of the nipple, ductal carcinoma below the nipple. Immunohistochemical results: CK5/6 (+), Syn (-), ER $\alpha$  (-), CK14 (+), Her2 (3+), EGFR (2+), Ki-67 (index 20%), p53 (+), PR (-), and CgA (-).

#### 4.1. PD

This disease occurs most commonly in postmenopausal women, with a peak incidence between the sixth and seventh decade of life at a mean age of 54 years, 5 to 10 years higher than the overall peak incidence of invasive breast carcinoma.<sup>[7-9]</sup> In our study, the average age of onset of PD was 59 years, consistent with the reported literature. PD usually has eczema-ulceration of the nipple (Fig. 1A, 2A), which is the characteristic manifestation of this disease. Pathologic findings consist of tumor cells with glandular features present within the epidermis of the nipple (Fig. 1C and 2C). They are often localized in the basal layer but may also be in the upper portions of the epidermis. With cancer cell infiltration, the formation of new capillaries, serous exudation, and reactive changes such as eczema-ulceration of the dermis can be seen. Approximately 50% of patients with PD also present with an associated palpable mass in the breast.<sup>[10]</sup>

The ultrasound characteristics include irregular shape, indistinct margin, thickening, microcalcifications, as well as hypervascularity of the affected nipple. In dermatology, Doppler sonograms have been evaluated in the past decades; the sensitivity and specificity of hypervascularity detected using Doppler sonography in malignant skin tumors were 90% and 100%, respectively, whereas those of hypervascularity in benign lesions were 100% and 90%, respectively.<sup>[11]</sup> In our research, compared with other benign lesions, the blood flow of PD was abundant ( $P < 0.05$ ) (Fig. 2B); therefore, higher blood flow signals detected by Doppler sonography are useful for differentiation from benign lesions. Two theories have been proposed explaining the pathogenesis of PD: the epidermotropic and the transformation theories.<sup>[12]</sup> All PD patients presented underlying ductal carcinoma behind the nipple in accordance with the epidermotropic theory, which postulates that ductal cancer cells that migrate along the basal membrane of the nipple are the origin of



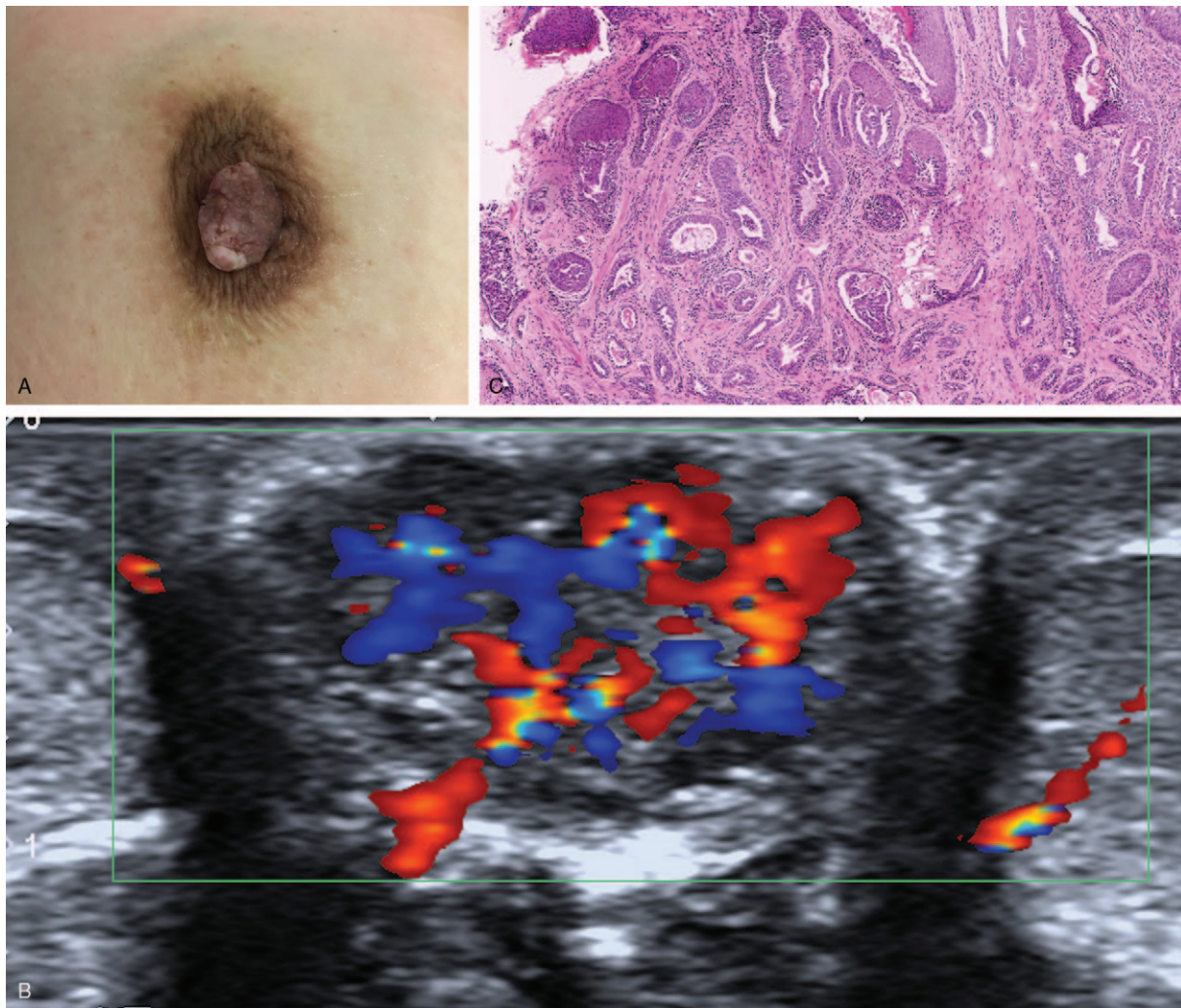
**Figure 2.** (A) A female, 62 years' old, with ulceration, pruritus, pain, and blood in the right nipple. (B) Ultrasonography revealed a hypervascularity lesion in CDFI. (C) Paget's disease of the nipple, ductal carcinoma below the nipple. Immunohistochemical results: CK5/6 (–), CK7 (+), ER $\alpha$  (–), CK20 (–), Her2 (3+), GCDPF-15 (–), Ki-67 (index 60%), S100 (–), p53 (+), p63 (–), and PR (–).

PD. PD has a high microcalcification rate of 37.5% to 86.6%.<sup>[13]</sup> It always occurs within the nipple, within the areola or near the NAC and is present along the lactiferous ducts (Fig. 1B). In our cases, 2 patients present microcalcifications distributed along the lactiferous ducts as observed by ultrasound. The presence of microcalcification suggests malignant progress.

#### 4.2. Adenoma of the nipple

Adenoma of nipple generally occurs in women and can occur at any time after puberty. It is predominantly seen in females and rarely seen in males and adolescents.<sup>[14]</sup> The mean age of the 2 female patients with adenoma of nipple in our study was 35 years. Adenoma of the nipple is a rare benign epithelial proliferation localized within and around the collecting ducts. Its clinical manifestations include nipple discharge, erosion, and bleeding, which were easily confused with PD (Fig. 3A). However, the nodule can be palpated, and the crusting of the ipsilateral nipple was present in both of the patients, which are

different from PD. Histopathologically, adenoma of nipple showed a well-defined tumor containing glandular formation in the whole dermis (Fig. 3C), and it may have sclerotic changes at the border of the lesion.<sup>[15]</sup> The histopathological characteristics are consistent with the clinical features of nodules and crusting. Therefore, during physical check-ups, regular comparative examination between the 2 nipples is particularly important.<sup>[16]</sup> Histological examination is fundamental for the diagnosis. Despite PD and adenoma of the nipple having many analogous features in clinical manifestations, ultrasound can aid in the differential diagnosis. Adenoma of the nipple is characterized by hypoechoic nodules in the nipple, with a clear border, regular morphology, and abundant blood flow. Reportedly, adenoma of the nipple is rich in angiogenesis, even though the tumor is pathologically benign, and the enhancement mode is rim enhancement.<sup>[17]</sup> In our study, both of the patients present abundant flow signals in Doppler sonograms, consistent with literature reports (Fig. 3B). At the same time, they lack the characteristic features of PD, such as thickening of the nipple,



**Figure 3.** (A) Female patient, 31 years' old. A nodule on right nipple with an opening in the center. A yellowish-white liquid can be produced after the extrusion of the nipple, as well as erosion and crusting in places. (B) Sonography showed well-defined hypoechoic nodules in the inferior part of the nipple. (C) The color Doppler revealed increased blood flow signals in the nodule.

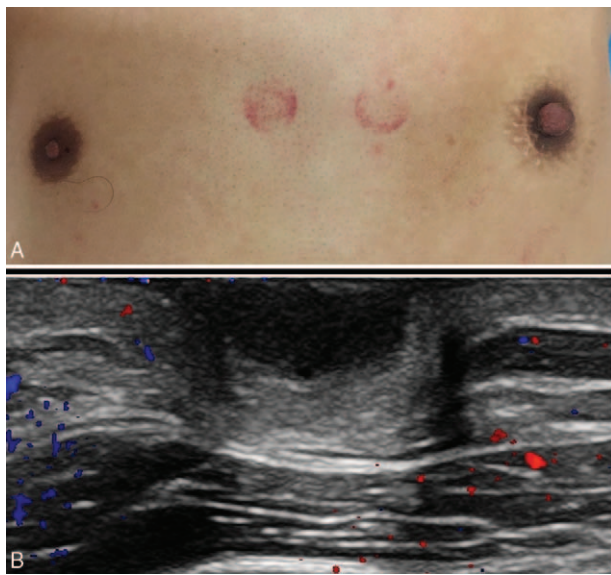
microcalcification or lesions in the gland around the nipple in sonograms.

#### 4.3. Leiomyoma of the Nipple

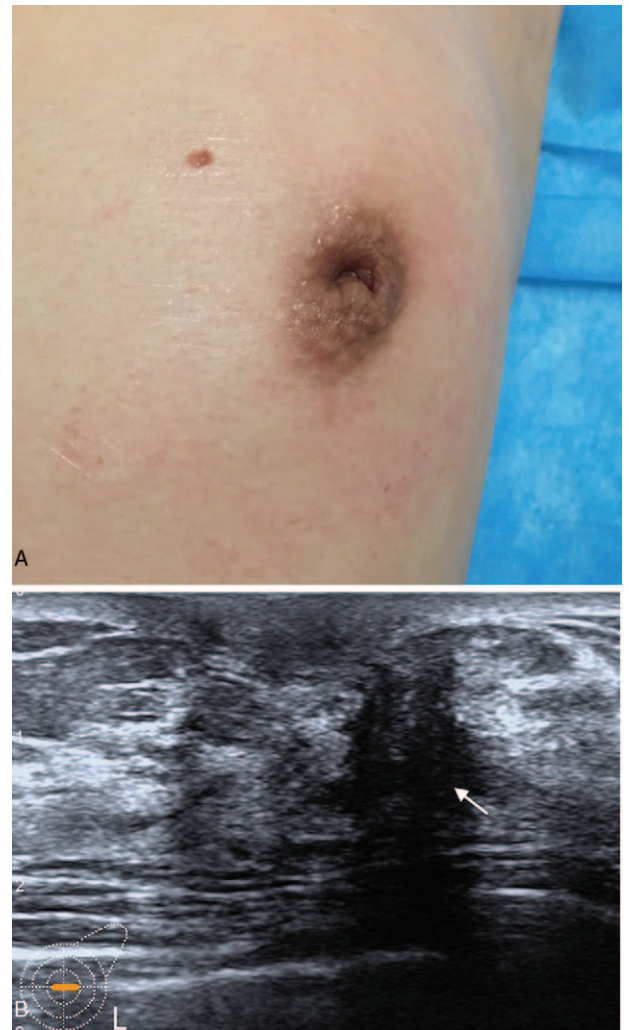
Nipple leiomyoma is a rare, benign, smooth muscle tumor that is subcategorized based on the origin of the nipple smooth muscle within the tumor, often characterized by unilateral enlargement, hardened, and painful nipples. Both men and women can be diagnosed with the disease.<sup>[18]</sup> In our case, the only male patient had leiomyoma of the nipple, which was asymptomatic for an extended period, then it presented as a mass with recurrent spontaneous severe pain while applying pressure or after exposure to the cold (Fig. 4A). This characteristic pain is related to the contraction of smooth muscle cells.<sup>[19]</sup> The main reason that led the patient with leiomyoma of the nipple to the physician was chronic pain.<sup>[20]</sup> A previously published sonography finding has reported leiomyoma to be well-margined, slow-growing, lacking increased blood flow, and posterior echoes may be lacking, decreased, or slightly enhanced.<sup>[21]</sup> In our case, the tumor was a well-circumscribed, hypoechoic lesion with posterior acoustic enhancement. The color Doppler showed less blood flow into the tumor and abundant blood flow signals around it (Fig. 4B).

#### 4.4. Plasma cell mastitis

It is most common in the 40 to 49 years old group who are not in the lactation period. Most of the diseases occur in multiparas around menopause and post-pregnancy women.<sup>[22]</sup> Plasma cell mastitis, also known as duct ectasia or periductal mastitis, is a benign inflammatory disease of the breast. Plasma cell mastitis may be secondary to benign duct ectasia in a patient with pain behind the nipple and the retro areolar region.<sup>[23]</sup> The clinical manifestations are complex and varied, such as nipple retraction,

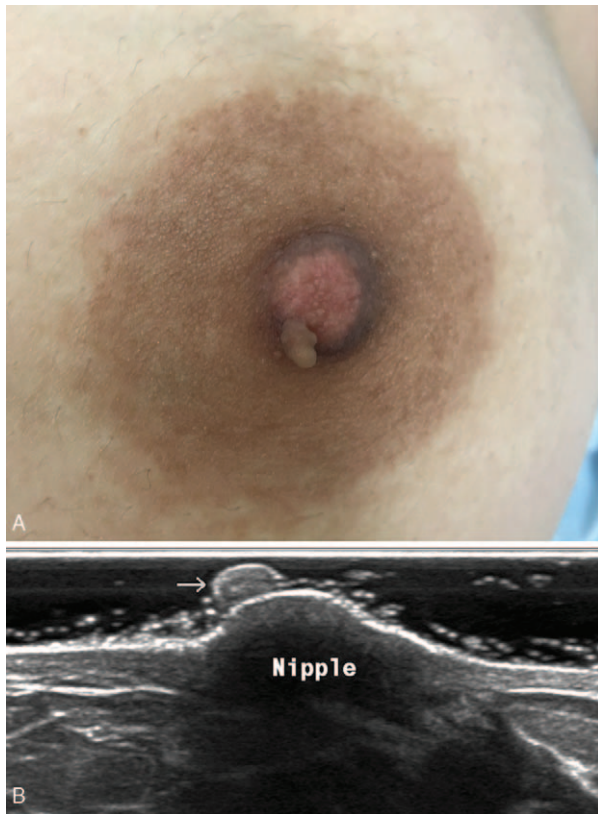


**Figure 4.** (A) Swollen left nipple compared with the right nipple. The male patient's left nipple had an elevated polypoid nodule of light brownish color. (B) Ultrasonography shows an irregular, hypoechoic nodule with rare blood flow into the mass.



**Figure 5.** (A) Female patient, 32 years' old. Presented with left nipple retraction for 2 months. (B) A hypoechoic nodule with unclear margin, irregular shape, and heterogeneous internal echo in the posterior of the nipple (arrow).

pain, nipple discharge, palpable mass below NAC, areola abscess, and nipple fistula (Fig. 5A). In our study, 2 of the patients had palpable masses near the NAC, and 1 patient had redness, swelling, heat, and pain symptoms that are characteristic clinical features of plasma cell mastitis. Plasma cell mastitis may have different types of sonographic findings. On ultrasound, dilated ducts are noted with echogenic material within (debris) and surrounding increased vascularity.<sup>[24]</sup> When it is present as a mass behind the nipple, it can be identified as a malignant disease. In an ultrasound, plasma cell mastitis is characterized by a hypoechoic nodule with unclear margin, irregular shape, and heterogeneous internal echo in and around the areola (Fig. 5B). It can also be cystic-solid mixed. The echoes behind the lesion are not enhanced, but some of them are attenuated. Short blood-flow signals can be detected in the center of the lesion, but surrounding vascularity increases. The sonographic features are easily confused with breast cancer. The sonographic features that favor a malignant process include the location of the ectasia: a peripheral location favors a malignant process, whereas a central location favors a benign process. Other features that suggest a



**Figure 6.** (A) Female patient, 22 years' old. A soft skin tag in the left nipple. (B) Ultrasonography shows a regular, hypoechoic nodule adjacent to the nipple (arrow).

malignant process include the irregularity of the duct margin, focal thickening of the duct wall, and the presence of adjacent hypoechoic tissue.

#### 4.5. Nipple wart

A nipple wart is a harmless, nongender-specific, benign tumor of the skin known as a skin tag.<sup>[25]</sup> The differential diagnosis includes keratoacanthoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). It can be easily removed, mostly for esthetic reasons, with electrofulguration or surgical excision under local anesthesia.<sup>[26]</sup> A nipple wart is a soft papillary external tumor, which is a nonspecific benign tumor of the skin (Fig. 6A). It should be identified with keratoderma and basal cell carcinoma. Ultrasonography showed hypoechoic papillae with regular shape and a clear border. The color Doppler showed no blood signals inside the wart (Fig. 6B).

#### 4.6. Nipple Dysplasia

The pathogenesis of the nipple dysplasia is abnormal development during embryonic development. During embryonic development, the embryological mammary ridge is characterized by 2 ectodermal thickenings on both sides of the embryo, which normally degenerates except for the breast area.<sup>[4]</sup> The abnormality is harmless unless it causes discomfort; thus, the recognition and distinction from other breast pathologies, either benign or malignant, is necessary. The ultrasonographic findings are similar to those of the normal nipples. Most of the polythelia is poorly developed, with bulges (Fig. 7A). In our study, the polythelia grew well near the normal nipple; we have not found similar reports in the literature (Fig. 7B).



**Figure 7.** (A) An accessory nipple in the subcoastal area. (B) An accessory nipple in the areola, similar in size to the normal nipple.



## 5. Conclusion

Characteristic sonographic features together with clinical symptoms contribute to the diagnosis of nipple lesions.

## Author contributions

**Conceptualization:** Hongyan Wang.

**Data curation:** Siman Cai, Hongyan Wang.

**Formal analysis:** Siman Cai, Hongyan Wang.

**Investigation:** Hongyan Wang, Qingli Zhu.

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**Writing – original draft:** Siman Cai.

**Writing – review & editing:** Siman Cai, Hongyan Wang.

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