Original Research

Combining contrast-enhanced ultrasound and blood cell analysis to improve diagnostic accuracy of plasma cell mastitis

Yan Zheng[1], Lin Wang[2], Xiu Han[2], Lin Shen[3], Chen Ling[1], Zhongping Qian[1], Lin Zhu[1], Fenglin Dong[1] and Qingzhen Han[2]

[1]The First Affiliated Hospital of Soochow University, Suzhou 215000, China; [2]Center of Clinical Laboratory, Dushu Lake Hospital Affiliated to Soochow University, Suzhou 215000, China; [3]Suzhou Municipal Hospital, Suzhou 215000, China
Corresponding authors: Qingzhen Han. Email: gyhqz02@163.com; Fenglin Dong. Email: unique5208@163.com

Impact statement

Plasma cell mastitis (PCM), lack of specific biomarkers, is easy to be misdiagnosed and mistreated by present ultrasound and mammography detection. Unfortunately, the incidence rate of PCM has been increasing gradually. In our retrospective study, 331 patients with breast diseases and 100 healthy donors were involved from 2018 to 2020. We first used contrast-enhanced ultrasound (CEUS) to present image of breast lesion for PCM. In addition, we established a combined diagnostic model of promoting diagnostic accuracy of PCM by CEUS patterns and routine blood cell analysis (BCA). It is a promised combination of multiple laboratory methods for differential diagnosis of PCM.

Abstract

Plasma cell mastitis is a benign suppurative disease of the breast, lack of specific clinical manifestations, which is easy to be misdiagnosed and mistreated, often confused with mastitis, breast cancer (BC), and other diseases. Thus, we aimed to establish a combined model of promoting diagnostic accuracy of plasma cell mastitis by contrast-enhanced ultrasound (CEUS) patterns and routine blood cell analysis. Eighty-eight plasma cell mastitis, 91 breast cancer, and 152 other benign breast diseases' patients grouped according to pathological diagnosis underwent CEUS and blood cell analysis examination; 100 healthy female donors were involved. All the plasma cell mastitis and breast cancer patients presented hyperenhancement of CEUS breast lesions compared with others. The majority of plasma cell mastitis (65/88) showed perfusion defect of CEUS patterns with smooth edge (56/65) and multiple lesions (49/65); in contrast, fewer breast cancer patients (30/91) displayed perfusion defect. White blood cell count (WBC), neutrophils, and neutrophils/lymphocytes ratio of blood cell analysis in plasma cell mastitis patients increased significantly compared with other patients ($P < 0.0001$). Combining perfusion defect of CEUS patterns and WBC yielded an area under the receiver operating characteristic curve of 0.831, higher than single 0.720 and 0.774, respectively. The cut-off value of WBC (7.28×10^9/L) helped remaining 65.2% (15/23) atypical cases to be correctly diagnosed as plasma cell mastitis, not misdiagnosed as breast cancer. In conclusion, CEUS presented a clear perfusion defect pattern of plasma cell mastitis lesion for the first time. A precise WBC by routine blood cell analysis test can assist CEUS examination in the differential diagnosis of plasma cell mastitis and breast cancer. It is a promised combination for laboratory diagnostic of PCM.

Keywords: Plasma cell mastitis, differential diagnosis, white blood cell count, contrast-enhanced ultrasound, breast carcinoma, inflammation

Experimental Biology and Medicine **2022; 247: 97–105. DOI: 10.1177/15353702211049361**

Introduction

Plasma cell mastitis (PCM) is a specific type of mastitis that mainly occurs in middle-aged nonpregnant and nonlactating females, occasionally seen in men, and shows an increasing trend in recent years.[1–3] The etiology of PCM remains unclear, but may be due to many factors, such as congenital nipple malformation or dysplasia, mammary gland impairment, inflammation, endocrine disorders, mammary gland degeneration, and autoimmune disorders.[3,4] Since its clinical manifestations lack specificity, it is easy to be misdiagnosed and mistreated, often confused with breast cancer, and other diseases.[5–7] Mostly, PCM presents as a lump or mass in the breast with ipsilateral breast enlargement. It is very similar in terms of clinical

and radiology to breast carcinoma, especially the most common invasive ductal carcinoma (IDC).[8] However, the treatments and prognosis for PCM and breast carcinoma (BC) are significantly different, so if the diagnosis can be confirmed by a non-invasive examination before surgery, that will help clinicians make a reasonable choice of treatment.

Unfortunately, preoperative diagnosis of PCM is very difficult, especially for differential diagnosis with breast cancer. Although ultrasound (US) and mammography of the most commonly used diagnostic techniques for breast diseases have been making continuous progress in techniques, distinguishing the PCM from breast cancer based on the image findings is challenging.[5,9] In recent years, magnetic resonance imaging (MRI) has made some progress in the diagnosis of breast diseases; however, it is too expensive and time consuming to be a routine examination for the diagnosis of PCM in China.[8,10,11] Therefore, contrast-enhanced ultrasound (CEUS) has been tried in the detection of PCM by a few large hospitals in China. In the present study, we firstly present the different features of CEUS pattern between PCM and BC; unfortunately, there are still some atypical cases that cannot be distinguished by CEUS.

There is still no specific biomarker to monitor PCM till now. Here, some common systemic inflammatory markers are investigated to promote the diagnosis of this inflammatory breast disease, as some reports have shown that breast lesions could alter some routine systemic laboratory indicators.[12] Blood cell analysis (BCA), a very common and simple laboratory diagnostic technique,[13] provides several very important parameters which show a very good diagnostic efficiency of distinguishing the PCM from breast cancer by precise and integrate analysis. In particular, the combined application of BCA and CEUS displays a critical role in accurate identification of PCM. In this retrospective study, 331 patients (88 PCM, 91 breast carcinoma and 152 other benign breast diseases) and 100 healthy female donors were reviewed to determine the improved accuracy of PCM, through interdisciplinary laboratory and imaging combined diagnosis for the first time.

Materials and methods

Clinical case information

From 2018 to 2020, 331 female patients aged 25–80 years underwent contrast-enhanced ultrasound (CEUS) detected with breast lesions and blood cell analysis in our hospital. All the involved patients were divided into several groups according to the consequences of operation, pathological diagnosis, and clinical turnover, 88 PCM (age range: 25–55 years), 91 breast carcinomas (age range: 26–80 years), 70 breast fibroadenoma (age range: 19–66 years), and 82 other benign breast diseases (age range: 20–69 years). One hundred healthy female donors (HLT) without breast disease underwent blood cell analysis and breast ultrasound during routine physical examination (age range: 29–65 years). This study was approved by the institutional review board of the First Affiliated Hospital of Soochow University, and informed consent was waived because of the retrospective nature.

CEUS techniques and analysis

Ultrasonography was performed using MyLab ClassC (Esaote Group, Italy) equipped with a variable frequency probe LA522. Low mechanical index (MI) values were applied (MI 0.02–0.07) to reduce microbubble destruction. A contrast agent of sulfur hexafluoride microbubbles used was produced by Bracco, Italy. After switching to contrast mode, 3.0 mL contrast agent (SonoVue) was injected intravenously, and the tube was flushed with 5 mL normal saline. The contrast agent perfusion of the lesions was dynamically observed immediately for about 90 s.

The lesions were characterized according to location, amount, enhanced intensity, internal homogeneity, perfusion defect, size in diameter, shape, and margin. The examinations were conducted and the ultrasonographic images were determined by two radiologists, at least one of them with more than five years of experience in breast ultrasonography. If any disagreement occurred, a senior doctor with more than 10 years of experience in breast ultrasonography was consulted.

Blood cell analysis

The complete blood count was routinely examined to check the platelet number when the patients needed contrast-enhanced ultrasound. Two milliliters of peripheral blood were collected in hemogram tubes with ethylenediaminetetraacetic acid (EDTA). Blood cell analysis was detected using an automated hematology Sysmex-20 analyzer (Kobe, Japan). A series of hematological parameters were obtained, such as white blood cells (WBC), neutrophils (Neu), lymphocytes (Lym), platelets, red blood cells (RBC), and so on. The NLR was calculated as neutrophils/lymphocytes and the PNR as platelets/neutrophils.

Statistical analysis

Statistical calculations were performed by using SPSS 20.0 and figures for the presented data were performed with GraphPad Prism 5.0 for Windows. The mean values of quantitative datum were presented as mean $\pm$ standard deviation (SD) on the condition of normal distribution. Chi-squared test was applied in categorical variables, while independent *t*-test was applied in comparison of continuous variables. The potential associated factors for identifying PCM and other breast diseases on CEUS and BCA were investigated by a receiver operating characteristic (ROC) curve to observe the diagnostic value by areas under the ROC (AUCs) and calculate the cut-off value on PCM. The most valuable parameters respectively from CEUS and BCA were combined to evaluate diagnostic accuracy of PCM. The cut-off value of the best parameter from BCA combined with CEUS was conducted to especially distinguish PCM and BC. The statistical significance level was defined as 0.05.

Results

Characteristics of CEUS patterns

Of all 331 breast lesions, 88 lesions were pathologically confirmed as PCM, 91 malignant lesions as BC, 70 breast fibroadenoma, and 82 other benign breast diseases. One hundred healthy female individuals were identified with no breast lesion by common ultrasound examination. In contrast to 50% (35/70) fibroadenoma and 59.8% (49/82) other benign breast diseases, CEUS patterns from 100% (88/88) PCM and 100% (91/91) completely presented hyperenhancement. More perfusion defects of CEUS patterns were presented in about 73.9% (65/88) PCM patients, whose edge lines mostly were smooth up to 86.2% (56/65). In BC group, less perfusion defects were presented about 33.0% (30/91) and more less edge lines were smooth about 13.3% (4/30). In addition, more than one lesion could be easy to find in 75.4% (49/65) PCM, and such multiple lesions occurred in 56.7% (17/30) BC. Furthermore, perfusion defect of CEUS patterns was not common in other breast diseases. These characteristics of CEUS patterns were significantly different between PCM and other breast diseases, including the degree of enhancement, incidence of perfusion defect, smoothness of perfusion defect edge, and number of lesions (Table 1). The typical CEUS pattern of lesion as a result of PCM was characterized by perfusion defect, smooth edge line, and multiple defect lesions in contrast to BC are presented in Figure 1. However, it is still difficult to distinguish PCM and BC by these perfusion defect parameters especially for those atypical clinical cases with no perfusion defects.

Diagnostic efficiency of parameters of CEUS patterns in PCM

ROC curve of a simple parameter of CEUS patterns was done to compare the diagnostic efficiency on PCM. Among all the parameters above, perfusion defect showed a high diagnostic performance for PCM with

Table 1. Basic features of CEUS patterns in different breast diseases.

	PCM	Breast carcinoma	Breast fibroadenoma	Other benign breast diseases	Pearson Chi-square	*P* value
Hyperenhancement	88/88	91/91	35/70	49/82	30.993	<0.001
Perfusion defect	65/88	30/91	8/35	14/49	46.215	<0.001
Smooth edge line of perfusion defect	56/65	4/30	3/8	5/14	46.779	<0.001
Multiple perfusion defects	49/65	17/30	4/8	9/14	3.391	0.042

Chi-squared test was applied among different groups and the statistical significance level was defined as $P<0.05$.

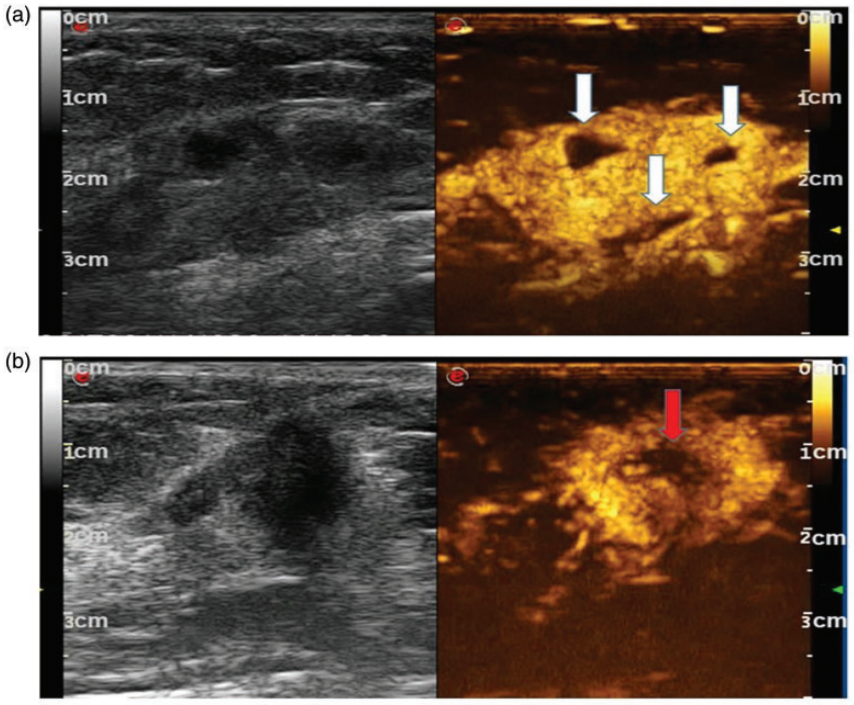

Figure 1. Differences of the typical CEUS patterns between PCM and BC. (a) CEUS pattern of breast lesion caused by PCM showed heterogeneous hyper-enhancement, equal size compared with gray-scale image, irregular shape, uncircumscribed margin, and multiple perfusion defect. The edge of the perfusion defect inside is smooth (white arrow). (b) CEUS pattern of breast lesion caused by BC presented heterogeneous hyper-enhancement, enlarged size compared with gray-scale image, irregular shape, uncircumscribed margin, and single perfusion defect. The edge of the perfusion defect inside is infiltrating (red arrow). All the images were original size in centimeter (cm). (A color version of this figure is available in the online journal.)

AUC of 0.720 ($P < 0.0001$), and smooth margin of perfusion defect was the most important feature of CEUS lesion pattern in PCM with AUC of 0.815 ($P < 0.0001$). In addition, the multiple perfusion defects seemed not to be a significant feature (AUC 0.588, $P = 0.101$). Maybe because both PCM and BC patients completely showed hyperenhancement on breast lesion pattern, hyperenhancement did not show a clear advantage in the diagnosis of PCM (AUC 0.645, $P < 0.0001$) compared with the feature of perfusion defect (Figure 2).

Parameters of BCA in PCM and other breast diseases

Among all the parameters of BCA, WBC and Neu in PCM patients were higher than the healthy donors (WBC 8.82 ± 0.32 VS 5.93 ± 0.12, $P < 0.0001$; Neu 5.65 ± 0.32 VS 3.30 ± 0.19, $P < 0.0001$). In addition, these two parameters in PCM increased significantly compared with that in BC (WBC $P = 0.0247$, Neu $P < 0.001$), as shown in Figure 3. Furthermore, the new calculated parameter of NLR presented better differences between these different groups (Figure 3). The AUCs under WBC ROC curve of diagnostic PCM possessed the highest value of 0.774 (95%CI 0.701–0.829, $P < 0.0001$), and that of Neu and NLR were, respectively, 0.679 and 0.749 ($P < 0.0001$) as shown in Figure 3.

Perfusion defect from CEUS combined with WBC of BCA could significantly improve the diagnosis accuracy of PCM (AUC 0.831, $P < 0.0001$) (Figure 4).

Distinguishing PCM from BC for those atypical cases without perfusion defect lesion

As shown in Table 1, CEUS patterns of PCM and BC patients' breast lesion were 100% hyperenhancement and some cases from both of them showed no perfusion defect as atypical cases, which significantly increased the difficulty of identified PCM simply by CEUS. Fortunately, there were still significant differences in these BCA parameters between these atypical cases. WBC, Neu, and NLR in PCM patients undergoing no perfusion defect were also higher than that in BC group (WBC < 0.0001, NLR $P = 0.0.0139$, Neu $P = 0.0001$), as shown in Figure 5(a) to (c). WBC had a higher diagnostic efficacy in differentiating PCM from BC than that of Neu and NLR, presenting AUC as 0.748 (95%CI 0.627–0.870), 65.22% sensitivity, and 80.33% specificity with the cut-off value of 7.28 (Figure 5(d) to (f)). Therefore, a

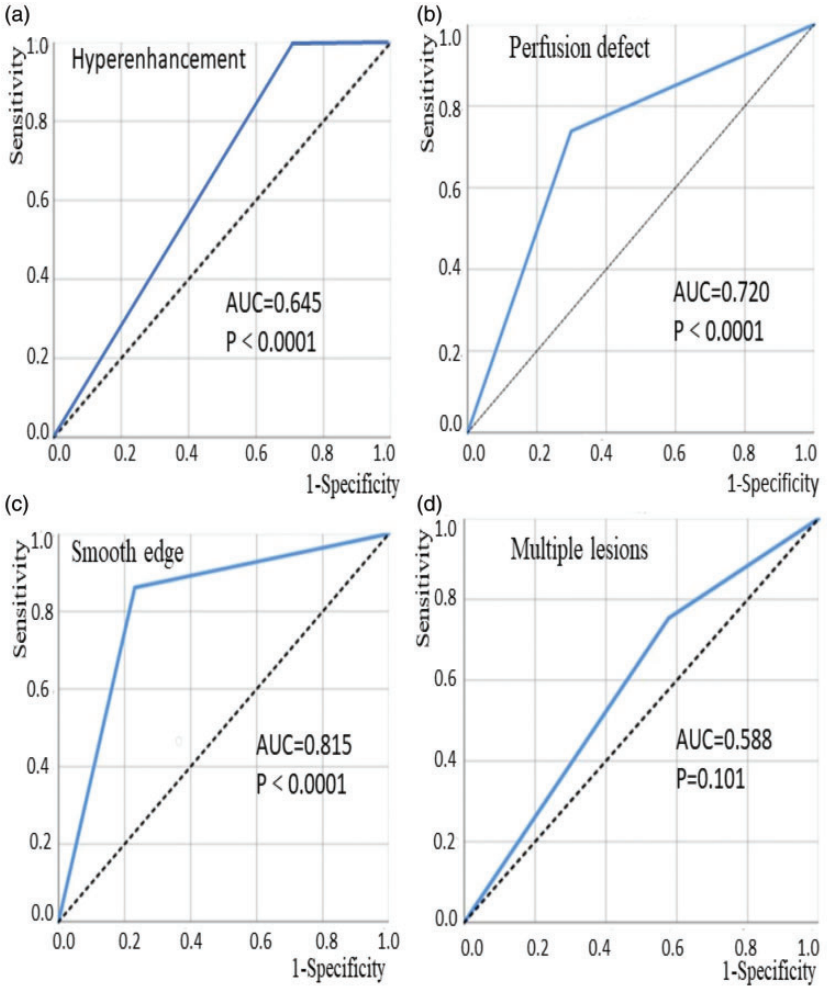

Figure 2. Performances of CEUS pattern parameters for PCM diagnosis. In the ROC curve analysis, the AUCs and *P* values of different pattern features for PCM diagnosis were listed in the corresponding graph, hyperenhancement (a), perfusion defect (b), smooth edge line (c), multiple lesions (d). The statistical significance level was defined as 0.05. (A color version of this figure is available in the online journal.)

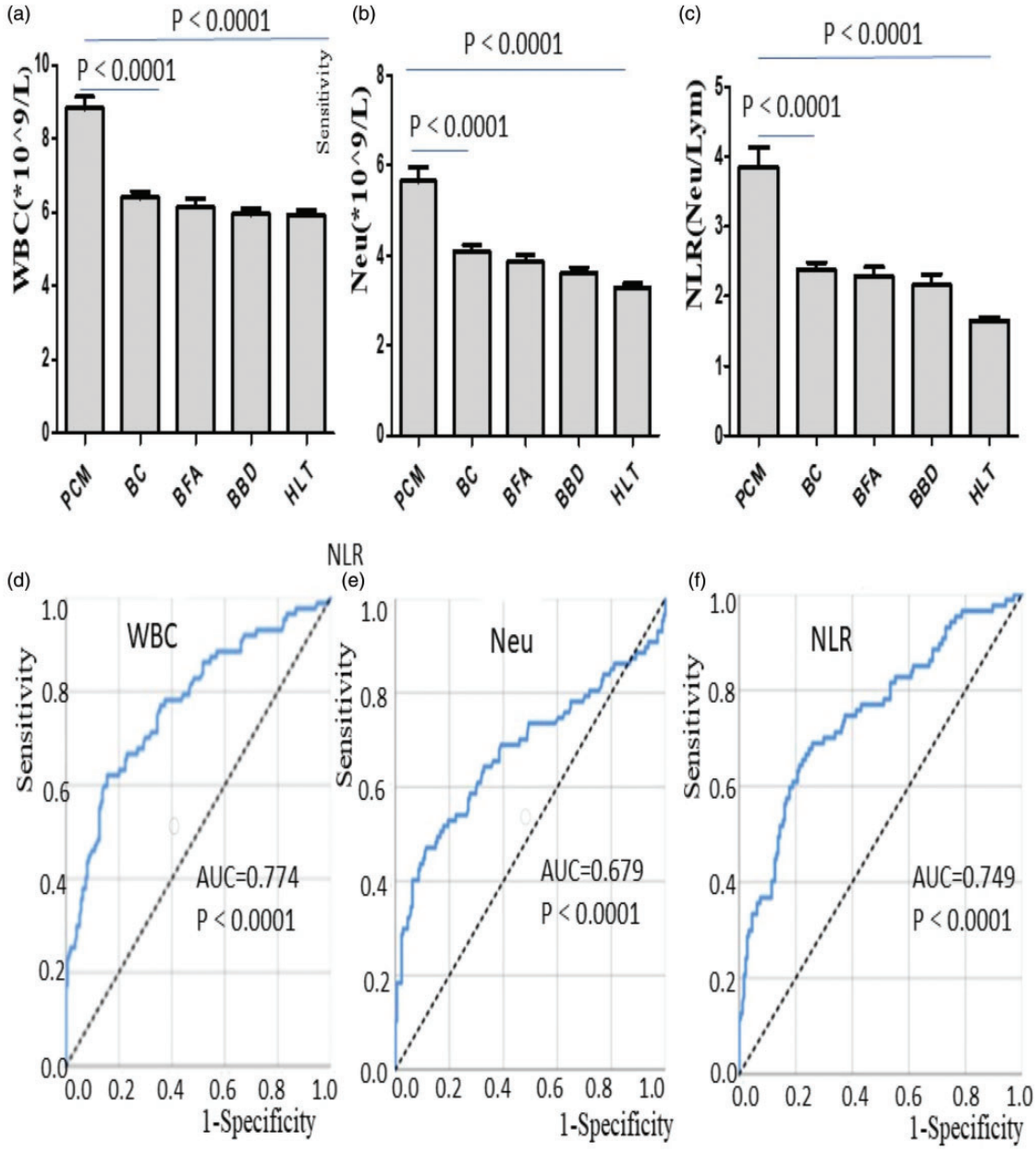

Figure 3. Distributions of BCA parameters in different breast disease groups and diagnostic efficiency of BCA parameters for PCM. WBC (a), Neu for neutrophils (b) and NLR for neutrophils/lymphocytes ratio (c) from routine blood cell analysis were distributed in different ranges. These markers in PCM patients were increased obviously, whose *P* values compared with BC group and healthy controls were clearly marked in paragraphs, not for breast fibroadenoma group (BFA) and other benign breast diseases (BBD). ROC curves of WBC (d), Neu (e) and NLR (f) predicting PCM were analyzed, whose AUCs and *P* values were clearly marked in the corresponding graph. One-way ANOVA was used to analyze the significance among all the groups and independent *t*-test was applied between two groups. The statistical significance level was defined as $P<0.05$. (A color version of this figure is available in the online journal.)

combined diagnosis model based on the significant parameters above was established to help distinguish PCM from BC (Figure 6). Perfusion defect of CEUS breast lesion pattern was firstly referenced by a rough diagnosis of PCM, and then a cut-off value of WBC (7.28×10^9/L in BCA) helps to validate controversial ultrasound findings by radiologists' experiential judgment; 15/23(65.2%) of the remaining atypical cases, easily misdiagnosed as BC with no perfusion defect of hyperenhancement pattern by ultrasonic examination, could be correctly identified as PCM referring to the number of WBC above 7.28×10^9/L (Figure 6). In addition, 4/12 (33.3%) of other breast diseases could be excluded as non PCM breast lesions as a result of WBC below 7.28, who have been misdiagnosed as PCM by CEUS determination (Figure 6). These results demonstrate that WBC can significantly reduce the misdiagnosis of PCM among those atypical patients with no typical CEUS images by initial ultrasound diagnosis.

Comparison of different diagnostic models by literature review

It is difficult to distinguish benign PCM from malignant breast diseases solely by conventional ultrasound image.

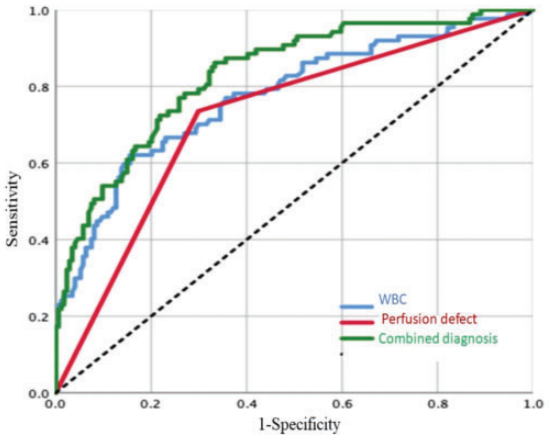

Figure 4. Diagnosis of PCM by perfusion defect combined with WBC. Green line presented performance of combined diagnosis model, whose AUC of 0.831 was higher than single perfusion defect pattern by CEUS (red line) and single WBC (blue line). (A color version of this figure is available in the online journal.)

Many other contrast or imaging technologies have been combined to improve diagnostic accuracy, including mammography, MRI, and superb microvascular imaging (SMI). Here, both CEUS of a clear ultrasound imaging technology and WBC count of a routine laboratory tests were first attempts to predict PCM, presenting a high diagnostic accuracy of 90.9% compared with other diagnostic model reported by other studies (Table 2). In addition, WBC count from BCA is a very easy and wide laboratory test method with no radiation damage to the body.

Discussion

In this study, CEUS tried to determine the breast lesions as a result of PCM, presenting a clear CEUS pattern characterized by hyperenhancement, high incidence of perfusion defect, smooth edge of perfusion defect, more than one focus. Smooth and well-defined perfusion defect of CEUS pattern is the most important feature, maybe because breast lesions of PCM are really closed focal pus cavities full of

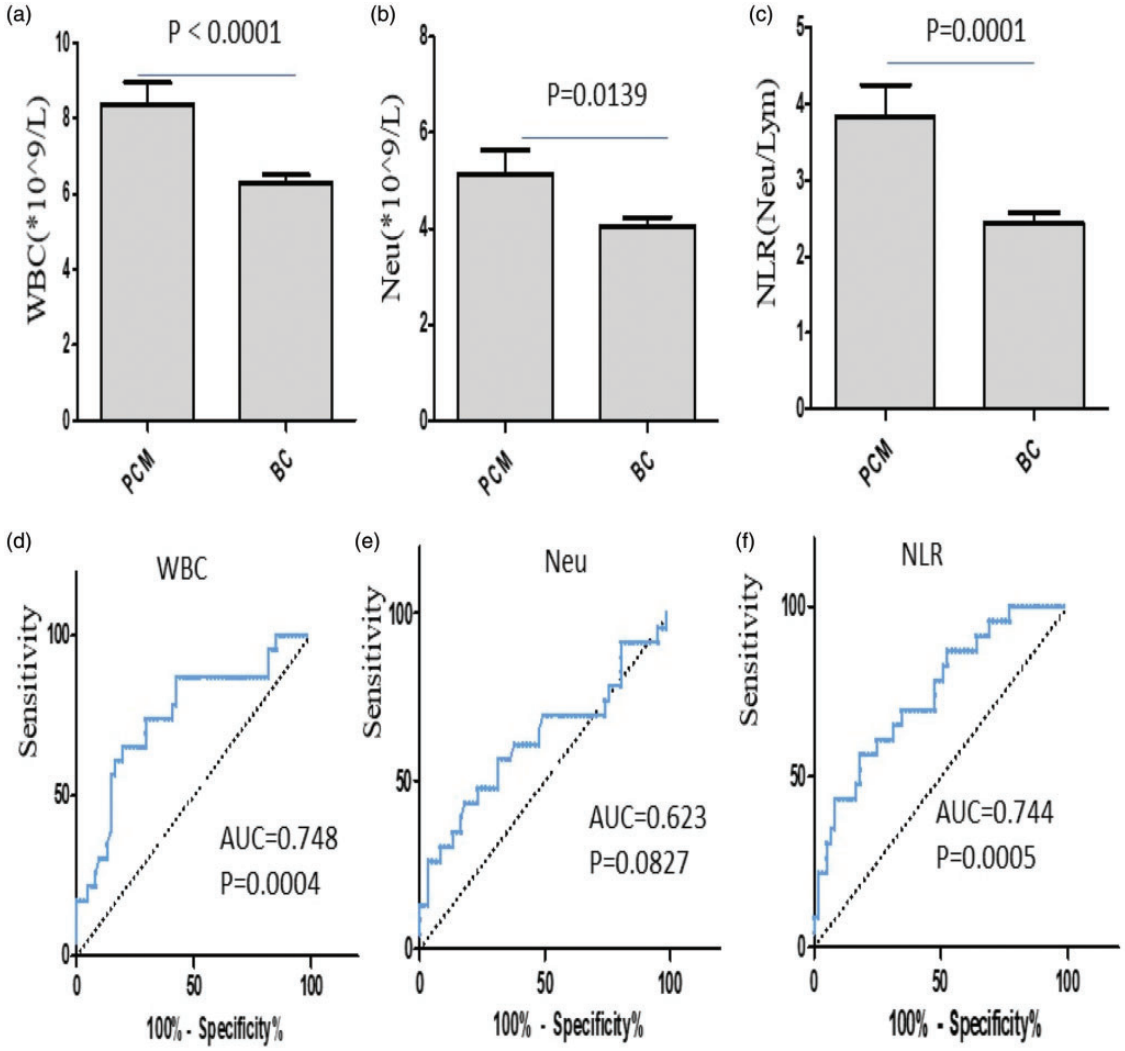

Figure 5. Distributions of BCA parameters in those atypical patients and their diagnostic efficiency of distinguishing PCM from BC. Those atypical patients with no perfusion defect of CEUS pattern were divided into two groups correctly identified according to the pathological results, including 23 PCM and 61 BC patients. BCA parameters from PCM patients have been still higher than BC group, whose *P* values were marked in the paragraph, WBC (a), Neu (b) and NLR (c). ROC curves of WBC (d), Neu (e), and NLR (f) predicting PCM among these 84 cases were analyzed, whose AUCs and *P* values were clearly marked in the corresponding graph. The cut off value of WBC ROC curve (d) was 7.28×10^9/L. Independent *t*-test was applied between two groups and the statistical significance level was defined as $P<0.05$. (A color version of this figure is available in the online journal.)

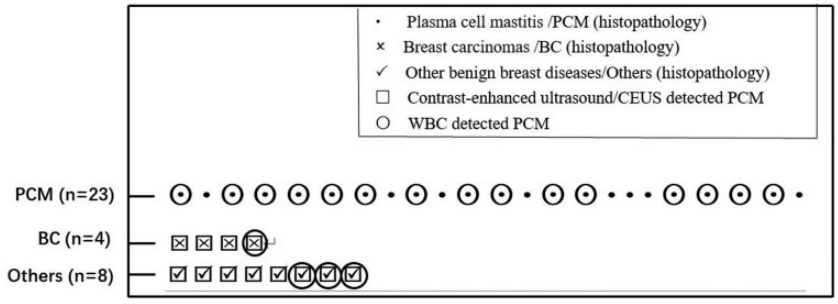

Figure 6. Classification results of misdiagnosed cases, including undetected PCM and misdiagnosed as PCM by CEUS. Patients with breast lesions misdiagnosed by CEUS were further identified by WBC counts to improve diagnostic performance of the model, referring to the results of histopathological examination. PCM and other benign breast diseases are marked as dots and checkmarks respectively, while breast carcinomas are marked with crosses. Squares, detection of PCM using the CEUS method. Circles, detection of PCM using WBC counts. WBC above 7.28×10^9/L was used to support PCM diagnosis.

Table 2. Accuracy rate and misdiagnosis rate of different diagnostic models by literature review.

Models	No. of PCM	Accuracy rate (%)	Misdiagnosis rate (%)	Literatures
CEUS+WBC	88	90.9	9.1	Present study
US+mammo-graphy	111	91.9	8.1	Combining ultrasonography and mammography to improve diagnostic accuracy of plasma cell mastitis[5].
multiparametric MRI	197	83.2	16.8	Differential diagnosis of plasma cell mastitis and invasive ductal carcinoma using multiparametric MRI[8].
US+SMI	17	83.2	16.8	Evaluation of plasma cell mastitis with superb microvascular imaging[11].

PCM: plasma cell mastitis; CEUS: contrast-enhanced ultrasound; WBC: white blood cells; US: ultrasound; MRI: magnetic resonance imaging; SMI: superb microvascular imaging.

secretions caused by intense chronic inflammation.[14–16] In contrast, perfusion defect patterns of breast lesion in human breast cancer tissue are mainly caused by ischemic tissue necrosis, as they mainly present irregular and bad-defined perfusion defects.[17–19] In addition, incidence of perfusion defect is not high and mainly occurs in patients with invasive ductal carcinoma (IDC), which is mainly due to the abnormal vascular in breast cancer like vessel dilation, tortuosity, and poor perivascular coverage.[20,21] Therefore, different CEUS patterns are commonly observed between PCM and BC. Our data clearly demonstrate that it is easy to distinguish PCM from other breast diseases by CEUS. Compared with widely used magnetic resonance imaging (MRI), for the differential diagnosis of PCM and breast carcinoma, CEUS also presents a very clear picture and equal diagnostic efficiency; however, the latter is more convenient, fast, and inexpensive.

The etiology of PCM remains unclear, but may be due to many factors.[2,22] At present, autoimmune disorders and local bacterial infection of breast tissue are widely recognized conditions to attribute to a periductal inflammatory reaction caused by extravasation of duct contents.[1,2] PCM is a benign inflammatory disease, different from breast cancer in nature, and therefore blood cell analysis as indicators of systemic inflammation is postulated to distinguish PCM from breast cancer. Our data demonstrated that the white blood cell count (WBC) increased significantly in peripheral blood of PCM patients compared with breast cancer (BC) group, whose diagnostic efficiency was similar to that of contrast-enhanced ultrasound (CEUS). The cut-off value of 7.28×10^9/L also presented a good specificity of identifying PCM from BC. As a non-specific inflammatory marker, the diagnostic performance of WBC is often underestimated in laboratory diagnosis, which has been gradually alerted with the development of laboratory diagnostics. In the last decades, many intelligent means have been used to improve the diagnostic value of these routine diagnostic parameters, such as precise reference intervals for regional or particular crowd, personal health level, and intercellular ratio.[13,23–25]

Here, our results indicate that an accurate reference ranges for specific diseases and a recommended level (cut-off value) are inevitable to become very useful of boosting the clinical diagnostic value of routine laboratory test indicators like BCA; 95% confidence interval (CI) of WBC for PCM is 8.19 to 9.45×10^9/L locating in the reference interval of normal population, but significantly higher than BC, whose diagnosis value is easy to explore by comparison of different diseases and establishing distribution ranges in specific diseases. The establishment of personal health basic data files is also an important means to promote accurate diagnosis and analysis, because the alternations of routine parameters may be significant in specific disease but within the normal reference intervals. In addition, a recommended cut-off value can well help doctors make correct judgments on the basis of many examination results. Of course, such increasing leukocytes, but not far beyond the upper limit of normal reference interval, well support chronic inflammation etiology of PCM. For some PCM patients (22/88) involved here, their WBC beyond the up limit of 10×10^9/L may indicate active bacterial infection, which favor the infection incidence of PCM.

In the present study, CEUS combined with BCA significantly improved the ability to accurately identify PCM, reducing the probability of misdiagnosis as breast cancer. Compared with routine ultrasound examination, CEUS can present a clear pattern of breast lesion due to PCM, mainly characterized with perfusion defect and smooth edges, which helps radiologists be more sure and easier to make a conclusion. Although PCM is a specific type of mastitis with breast duct dilatation and plasma cell infiltration in nature, it always presents a diverse array of clinical presentations. PCM often presents as a lump or mass in the breast with ipsilateral breast enlargement, but sometimes without any signs of inflammation such as red swelling and fever of the skin. In addition, CEUS does not show perfusion defect in some cases of a typical PCM, when it is not easy to distinguish PCM from BC by single ultrasonic examination and clinical manifestations. For the inflammatory etiology of PCM, inflammatory markers are bound to change to some extent. Here, WBC count of routine BCA test really helps 65.2% (15/23) atypical PCM with no perfusion defect to be correctly diagnosed as PCM consisting with pathological diagnosis results. Maybe, the remaining 8 from these 23 atypical cases can only refer to the invasive core needle biopsy.

Conclusions

A clear CEUS pattern of PCM lesion is characterized by high incidence of well-defined smoothly edged perfusion defect, different from low incidence of bad-defined perfusion defect in human breast cancer lesion. In addition, an integrated and precise analysis of leukocyte parameters by routine BCA test can thus assist CEUS examination in the differential diagnosis of PCM and BC lesions. BCA parameters are easily detected to monitor treatment response of PCM patients due to its benign inflammatory breast lesion in nature. It is a promised combination of different detect methods for laboratory diagnostic of PCM by multidisciplinary and inter-disciplinary research. Of course, misdiagnosis is inevitable for some cases due to the diverse clinical manifestations and controversial pathogenesis of PCM, thus, further invasive biopsy and histopathological examination are necessary.

AUTHORS' CONTRIBUTIONS

QH conceived the project and wrote this manuscript. FD and YZ designed the study. LW, XH, and LS collected the patients' characteristic data, analyzed data and prepared tables. CL, ZQ and LZ prepared figures and analyzed the imaging. QH and FD as the corresponding author approved the final version to be submitted

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

Qingzhen Han is supported by Jinjihu talent training project of Suzhou Industrial Park (2020), Suzhou, China. This work was supported by Suzhou science and technology planning project (SLT201921).

ORCID iD

Qingzhen Han https://orcid.org/0000-0001-7373-891X

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(Received July 24, 2021, Accepted September 8, 2021)