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Radiological characteristics of invasive micropapillary carcinoma of the breast

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AIM: To analyse the various imaging features of invasive micropapillary carcinoma (IMPC), a distinct variant of breast cancer, by mammography, ultrasound, and contrast-enhanced mammography.

MATERIALS AND METHODS: This study included 68 female patients with histopathologically proven invasive micropapillary carcinoma who underwent mammography, ultrasound, and contrast-enhanced mammography examinations. The findings encountered by each imaging tool were analysed using the Breast Imaging Reporting and Data System (BI-RADS) lexicon.

RESULTS: In this retrospective study, 64.7% of cases were of the pure form of IMPC. Most of the cases showed an aggressive clinical course, with lymphovascular invasion noted in 76.5% of cases, while 60.3% of cases showed associated pathological lymphadenopathy. The N3 stage was reported in 25% of cases. On analysing the mammographic and ultrasound imaging findings, a significant association between irregular shape and a non-circumscribed margin with IMPC was found. Associated calcification was noted in 47% of cases. Pathological enhancement of moderate or marked conspicuity was noted in cases that underwent contrast-enhanced mammography, with the most commonly encountered finding being enhancing irregular and non-circumscribed masses.

CONCLUSION: The mammographic and ultrasound imaging features of IMPC are indistinguishable from other aggressive types of breast cancer. At contrast-enhanced mammography examination, pathological enhancement of moderate to marked conspicuity was shown in all cases. The observed strong association of IMPC with lymphovascular invasion and lymph node metastasis with higher nodal stage in this study mandate meticulous sonographic examination of the axilla, as well as the infra, and supraclavicular regions if pathological axillary lymphadenopathy was noted.

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Introduction

Invasive micropapillary carcinoma (IMPC) is a rare distinct variant of invasive breast carcinoma.[1] It is histologically characterised by the presence of tufts of cells arranged in pseudopapillary structures devoid of fibrovascular cores and surrounded by empty, clear spaces formed strands of fibro-collagenous stroma.[2] The cells display an inside-out pattern with the luminal cellular surface being the outermost.[3] Pure IMPC is extremely rare with a reported incidence of <2%, while the micropapillary histological architecture is found in approximately 2–8% of breast carcinomas.[2] The clinical aggressiveness of this variant is owing to its high frequency of lymphovascular permeation, axillary lymph nodal (LN) metastases, and a greater likelihood of loco-regional recurrence.[4] Considering its rarity with resultant limited knowledge about this type of breast cancer compared to the other more common subtypes of breast cancer, this study aimed to analyse the various imaging features noted at mammography, ultrasound, and contrast-enhanced mammography (CEM). To the authors' knowledge, this is the first study to describe the CEM findings of this type of cancer using the recently published CEM Breast Imaging Reporting & Data System (BI-RADS) lexicon.

Materials and methods

This retrospective study was conducted in the period between January 2017 and December 2022 after ethical committee approval.

Patient population

Sixty-eight cases with histopathologically proven IMPC were collected from the pathology database of Baheya hospital, Egypt and included in the study. Those with unavailable imaging information or postoperative final histopathological results were excluded from the study. The clinical and imaging characteristics were reviewed by three experienced radiologists in the field of breast imaging (10–15 years of experience).

Mammography and imaging interpretation

Two standard mammogram views, mediolateral oblique and craniocaudal views, of both breasts were obtained using dedicated digital mammography equipment (Pristina, GE Healthcare, Chicago, USA). Mammography examination was performed in 66 cases, as two cases were <30 years old and proceeded to ultrasound examination followed by CEM. Analysis of the mammographic findings according to the BI-RADS lexicon was undertaken. Accordingly, evaluation of the abnormalities including the shape, size, margin, and density of the masses, presence of asymmetry or architectural distortion, and presence or absence of calcification were reported.

Ultrasound and imaging interpretation

Ultrasound examination was performed on all patients using a high-resolution ultrasound machine (Aplio I700, Canon, Japan) with a high-frequency (18 MHz) linear array transducer. Analysis of the shape, size, margin, and echogenicity of the detected lesions was reported, based on the American College of Radiology (ACR) BI-RADS lexicon. In cases of non-mass findings with parenchymal alteration, the size, echogenicity, and detected vascularity were reported.

CEM and imaging interpretation

CEM examination was performed on 17 patients using digital mammography equipment (Pristina, GE Healthcare). A dual-energy mammogram was acquired approximately 2 minutes after the intravenous injection of iodinated contrast material (standard dose of 1.5 ml/kg at a rate of 3 ml/s). Low-energy images (which have a similar appearance to standard digital mammograms) and high-energy images were obtained in quick succession while the breast remained compressed. The recombined images were used for image interpretation. Findings were analysed using the newly published CEM lexicon, a supplement to the fifth edition of ACR BIRADS. The presence of mass or non-mass enhancement was reported. Analysis of the shape, margin, enhancement pattern, and enhancement extent was undertaken in the case of mass enhancement. In the case of on-mass enhancement, the enhancement pattern and distribution were reported.

Statistical analysis

Statistical analysis was undertaken using IBM SPSS Statistics version 26 (IBM, Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Fisher's exact test was used to examine the relation between qualitative variables. For non-normally distributed quantitative data, a comparison between two groups was undertaken using the Mann–Whitney test (non-parametric *t*-test). A *p*-value <0.05 was considered significant.

Results

This study included 68 female patients with histopathologically proven IMPC. Their age ranged from 28–84 years (mean= 56.2 ± 13.4 SD). There was no predilection to either side (34 cases were comprised of IMPC detected equally on the left and the right breasts). They were most frequently peripheral in location (42/68 cases, 61.8%). Large lesions with no central or peripheral predominance were noted in 5/68 cases (7.4 %). The mean size was 3.8 cm, ranging from 0.8 to 9.5 cm.

Modified radical mastectomy was performed in 52/68 cases (76.5%), while conservative breast surgery was performed in 16/68 cases (23.5%). On reviewing the postoperative histopathological results, the pure form of IMPC

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was more frequently encountered, being reported in 44/68 cases (64.7%). In the mixed subtype, invasive ductal carcinoma (IDC) was the commonest associated type of cancer.

On reviewing the final histopathological results, it was found that associated ductal carcinoma in situ (DCIS) was noted in 14/68 cases (20.6%). Multiple lesions were noted in 14/68 cases (20.6%), while contralateral malignancy was reported in only 4/68 cases (5.9%). Advanced TNM stage at presentation was reported in 31/68 cases (45.6%). Associated lymphovascular invasion (LVI) was reported in 52/68 cases (76.5%), and pathological lymphadenopathy was noted in 41/68 cases (60.3%), with N3 stage reported in 17/68 cases (25%). Considering the hormone receptor status, oestrogen receptor (ER) and progesterone receptor (PR) positivity were reported in 62/68 cases (91.2%), and 63/68 cases (92.6%), respectively. HER 2 expression was positive in only 9/68 cases (13.2%).

Mammography examination

In the current study, mammography was performed in 66/68 cases. Two patients did not undergo mammography as they were <30 years old and proceeded to ultrasound examination followed by CEM.

On reviewing the mammographic imaging characteristics of the study population, it was found that masses were reported in 50/66 cases (75.8%). They were most frequently irregular in shape (40/50 cases, 80%), with a non-circumscribed margin (42/50 cases, 84%; Fig 1. There was a significant association between irregular shape, and non-circumscribed margin with IMPC ($p<0.001$).

In the current study, 37/66 cases (56.1%) presented with non-mass findings, whether asymmetry or architectural distortion, either as a sole finding (16/37 cases, 43.2%), or associated with a mass (21/37cases, 56.8%). Associated calcification was reported in 31/66 cases (47%; Fig 2), out of which 18 cases were of fine pleomorphic morphology (58.1%). Table 1 summarises the mammographic imaging findings of the study population.

Ultrasound examination

Ultrasound examination was performed in all cases included in the present study ($n=68$). Altered parenchymal echogenicity with no definite masses and increased vascularity was reported in 12/68 cases (17.6%). Masses were reported in 56/68 cases (82.4%). Similar to mammographic features, there was a significant association between irregular shape and non-circumscribed margin with IMPC ($p<0.001$). Among the reported masses, 46/56 cases (82.1%) were irregular in shape, and 51/56 cases (91.1%) showed a non-circumscribed margin (Table 2).

CEM

In the current study, CEM was performed in 17/68 cases, and the findings were analysed using the newly published CEM lexicon, a supplement to the fifth edition of ACR BIRADS. All of the lesions showed pathological enhancement,

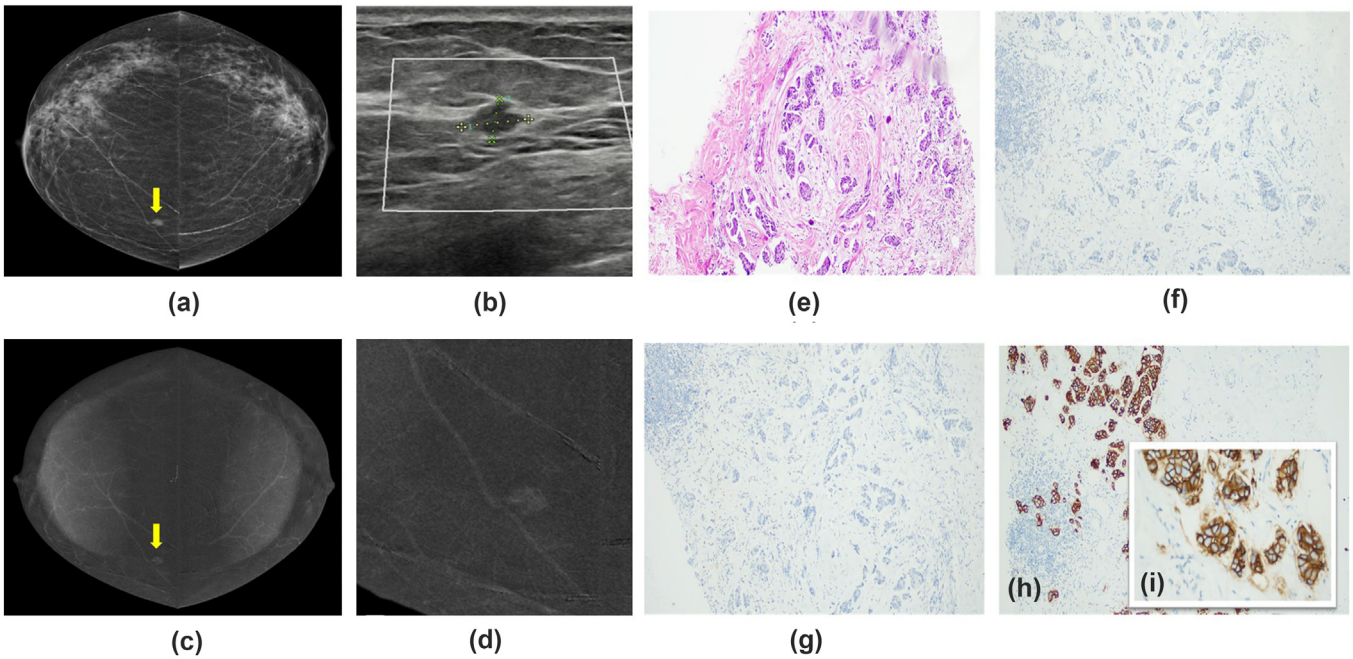

Figure 1 Right breast IMPC in a 51-year-old female (a) Screening mammography shows a right inner small irregular spiculated hyperdense mass (arrowed). (b) A corresponding small hypoechoic mass with an angular margin was noted by ultrasound examination. Contrast-enhanced mammography CC view (c) with zoomed image (d) showing heterogeneously non-circumscribed mass of moderate conspicuity. (e): Hematoxylin & Eosin-stained slide x200 showing small groups lacking fibrovascular cores with surrounding clear spaces with negative ER immunostaining (f) and PR immunostaining (g). (h) HER-2/neu immunostaining: positive, score 3+ with higher magnification slide x400 (i). CC: Craniocaudal view, ER: Estrogen Receptor, PR: Progesterone Receptor, HER-2: Human Epidermal Growth Factor Receptor 2.

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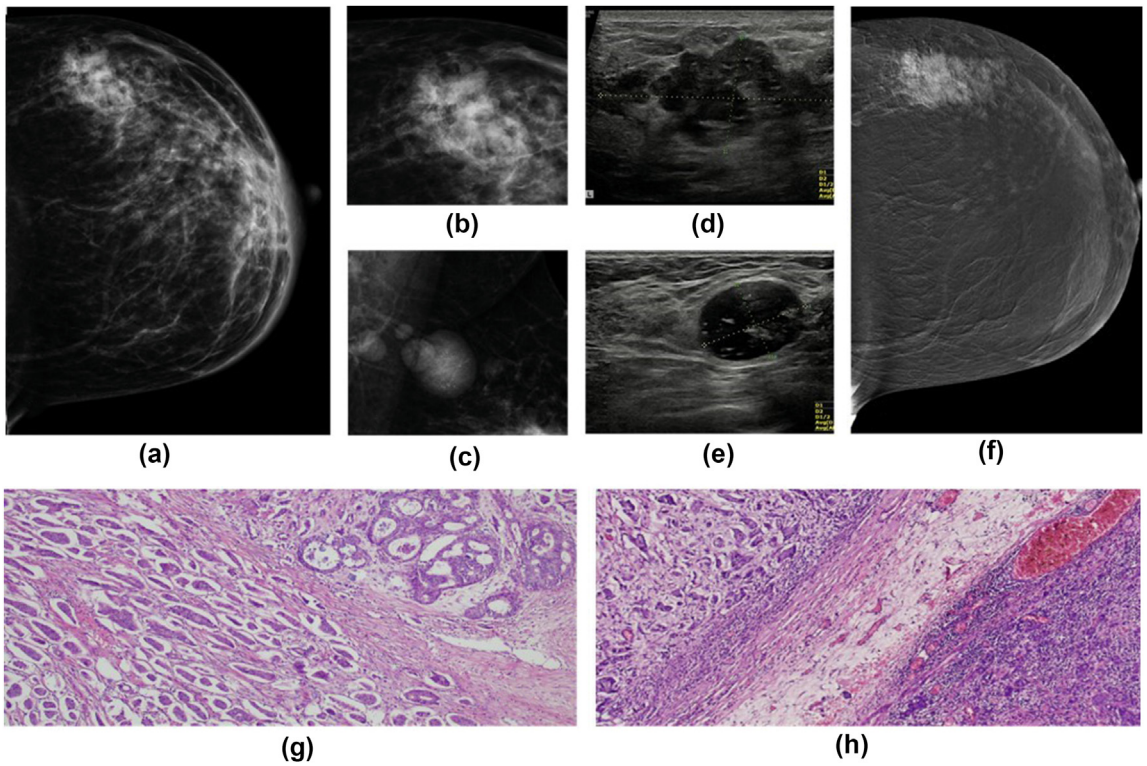

Figure 2 Left breast IMPC in a 43-year-old female (A) Digital mammography, CC view, showed an irregular hyperdense mass with an indistinct margin, associated with diffuse skin thickening. (B, C) Zoomed images of the mass and axillary lymph nodes showed underlying pleomorphic microcalcifications. (D, E) US images showed an irregular hypoechoic mass with a microlobulated margin associated with infiltrated axillary lymphadenopathy. (F) The CEM image, CC view, showed an irregular, non-circumscribed mass with heterogeneous enhancement of marked conspicuity. (G): Hematoxylin & Eosin-stained slide x200 showing invasive micropapillary carcinoma, grade II, with an associated DCIS component of an intermediate-grade cribriform pattern with macrometastatic nodal tumour deposits (H). **CC**: Craniocaudal view, **US**: ultrasound, **CEM:** contrast-enhanced mammography, **DCIS:** Ductal carcinoma insitu.

which are either mass enhancement (12/17 cases, 70.6%), non-mass enhancement (4/17 cases, 23.5%; Electronic Supplementary Material Fig. S1), or enhancing asymmetry (1/17, 5.9%). Most of the reported enhancing masses were irregular in shape (11/12 cases, 91.7%) with all of them showing a non-circumscribed margin (n=12), of which eight cases showed spiculate margins. Extension of the enhancement beyond the mass was noted in 7/12 cases (58.3%). Most of the lesions included in the current study showed moderate or marked conspicuity (15/17 cases, 88.2%), as shown in Table 3.

Table 1
The mammographic imaging findings of invasive micropapillary carcinoma (IMPC).

			IMPC	
			Count	%
Mass (n=50)	Mass shape	Round	7	14%
		Oval	3	6%
		Irregular	40	80%
	Mass margin	Circumscribed	8	16%
		Non-circumscribed	42	84%
	Mass density	High	33	66%
		Equal	17	34%
Non-mass findings (n=37)	Asymmetry		20	54.1%
	Architectural distortion		17	45.9%
Calcification (n=31)	Morphology	Punctate	2	6.4%
		Amorphous	7	22.6%
		Coarse heterogeneous	4	12.9%
		Fine pleomorphic/linear	18	58.1%
	Distribution	Diffuse	1	3.2%
		Regional	8	25.8%
		Grouped	2	6.4%
		Segmental	6	19.4%
		Within the mass	14	45.2%

Table 2
The ultrasound imaging findings of invasive micropapillary carcinoma (IMPC).

			IMPC	
			Count	%
Mass (n=56)	Mass shape	Round	6	10.7%
		Oval	4	7.1%
		Irregular	46	82.1%
	Mass margin	Circumscribed	5	8.9%
		Non-circumscribed	51	91.1%
Altered parenchyma Echogenicity			12	17.6%
		Heterogenous	25	36.8%
		isoechoic	4	5.9%
		Complex	4	5.9%
		Hypoechoic	35	51.5%

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Table 3
The contrast-enhanced mammography imaging findings of invasive micropapillary carcinoma (IMPC).

			IMPC	
			Count	%
Mass enhancement (n=12)	Mass shape	Rounded	1	8.3%
		Oval	0	0%
		Irregular	11	91.7%
	Mass margin	Circumscribed	0	0%
		Non-circumscribed	12	100%
	Mass internal enhancement	Homogeneous	1	8.3%
		Heterogeneous	11	91.7%
		Rim	0	0%
Non-mass enhancement (n=4)	Non-mass enhancement distribution	Linear	0	0%
		Regional	3	75%
		Multiple regional	1	25%
		Segmental	0	0%
	Non-mass internal enhancement	Homogeneous	0	0%
		Heterogeneous	3	75%
		Clumped	1	25%
Enhancing asymmetry (n=1)			1	5.9%
Lesion conspicuity (n=17)		Low	2	11.8%
		Moderate	4	23.5%
		High	11	64.7%

Discussion

According to the 2003 World Health Organization (WHO) histological classification of breast cancer, IMPC is considered a rare histopathological subtype of invasive breast carcinoma.[5] It is classified as either pure or mixed subtypes depending on the extent of the micropapillary component. According to several studies, the mixed type is more common than pure IMPC. In the present study, the pure form of IMPC was more frequently encountered, being reported in 64.7% of cases. In the mixed subtype, IDC was the commonest associated type of cancer, and that was similar to what was reported by Nassar *et al.*, and Guo *et al.* in their studies.[6,7]

IMPC breast cancer was reported to have an aggressive clinical course, with a greater potency to LVI and LN metastasis than IDC attributing to its poor prognosis. In the present study, LVI was reported in 76.5% of cases, and this was in agreement with the study of Shi *et al.*[8] who stated that LVI was confirmed in 74.5% of cases and that LVI frequency rates were higher in IMPC compared to IDC cases. Vingiani *et al.*,[9] Gokce *et al.*,[10] and Hashmi *et al.*[11] also reported similar results. Axillary LN metastasis was reported in 60.3% of the present cases, which was in accordance with the study of Guan *et al.*,[12] who confirmed regional LN metastasis in 60.9% of cases at the time of the diagnosis. In a large sample size, 2,660 cases of pure IMPC were included in the study of Lewis *et al.*,[13] and they confirmed regional LN metastasis in 55.2% of cases. Pettinato *et al.*,[14] Paterakos *et al.*,[15] and De La Cruz *et al.*[16] reported a higher percentage reaching 90%, 94%, and 92.9%, respectively. N3 stage with supraclavicular or infraclavicular LN involvement was reported in 25% of the present cases, which is higher than that of Adrada *et al.*,[17] who observed suspicious supra- or infraclavicular LNs in 14.3% of their cases, while Hashimi *et al.*[11] reported N3 stage in 33% of their IMPC group.

In the current study, 76.5% of the cases underwent modified radical mastectomy owing to the advanced locoregional stage at presentation, presence of multiple lesions, and presence of intra-ductal extension with nipple involvement noted. Based on the current clinical guideline, breast-conserving surgery was recommended for early-stage breast cancer, yet it may be considered in stage III after downstaging by neoadjuvant chemotherapy.[18] Wang *et al.*[19] reported equivalent results regarding the survival of patients with early IMPC who underwent breast-conserving surgery and mastectomy, yet their study population included early-stage IMPC only; however, considering the high rate of LVI associated with IMPC, the reported likelihood of locoregional recurrence, and the decreased knowledge about the surgical approach of choice in this distinct rare subtype, breast-conserving surgery remains challenging for some surgeons and extensive resection margin is preferred.[20,21] Conversely, some studies reported no improvement of the prognosis with extensive surgical approach.[22,23]

IMPC was characterised by a high rate of ER and PR expression. In the current study, most cases showed positive expression of ER (91.2%), and PR (90.6%). Zekioglu *et al.*[24] reported a percentage of ER and PR positivity as 68% and 61%, respectively. Walsh & Bleiweiss[25] reported high percentages of ER and PR positivity (90% and 70%, respectively). In the present study, HER 2 expression was only found in 13.2% of cases, and this is discordant with the studies of Cui *et al.*,[26] and Pettinato *et al.*,[14] who observed a much higher percentage of HER 2 positivity. Similar to the present results, Nangong *et al.*[27] reported HER 2 positivity in only 26.4% of cases.

Mammography was able to depict an abnormality in all cases, which was either a mass (75.8%) or a non-mass abnormality as asymmetry or architectural distortion (24.2%). Masses were detected in 73.5% of cases, being most frequently irregular in shape (40/50, 80%), and of non-circumscribed margin (42/50, 84%), which was consistent with the studies of Adrada *et al.*,[17] and Jones *et al.*,[4] that stated that the most predominant mammographic feature was an irregular, spiculate, high-density mass. In the present study, associated microcalcification was noted in 31/66 cases (47%), with fine pleomorphic morphology being the commonest (58.1%), which was similar to the study of Günhan-Bilgen *et al.*[28] in which associated microcalcification was noted in 43% of cases. Similarly, Yun *et al.*,[29] and Adrada *et al.*,[17] reported a predominance of fine pleomorphic morphology of microcalcification.

Considering the sonographic imaging characteristics, hypoechoic mass (35/68, 51.5%), irregular mass (46/68, 82.1%), and non-circumscribed margin (51/68, 91.1%) were the commonest features in the present study, which was in accordance with the studies of Alsharif *et al.*,[30] and Jones *et al.*[4]

Several studies discussed the magnetic resonance imaging (MRI) features of IMPC and reported that the commonest imaging characteristics were an irregular, spiculate

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mass with malignant kinematic features, as reported by Yun *et al.*,[29] and Kurtoğlu Özçağlayan *et al.*[31] Nanoong *et al.*[27] reported the absence of non-mass enhancement in their study, contrary to what was reported by Yun *et al.*,[29] and Jones *et al.*[4]

To the authors' knowledge, this is the first study discussing the CEM imaging features of this distinct subtype of breast cancer, using the newly published CEM BI-RADS lexicon. In the present study, all the included lesions showed pathological enhancement whether mass enhancement (70.6%), non-mass enhancement (23.5%), or enhancing asymmetry (5.9%). The commonest findings were irregular enhancing mass (64.7%), and non-circumscribed margin (70.6%). Considering cases presenting by non-mass enhancement, regional distribution (75%), and heterogeneous enhancement (75%) were most frequently encountered. It was reported that the degree of lesion enhancement on CEM may be related to the biological aggressiveness of breast cancer.[32] The majority of the lesions included in this study showed moderate or marked conspicuity (15/17 cases, 88.2%), and this may be attributed to the aggressive nature of this type of breast cancer and the observed higher grade at the time of the diagnosis.

Some limitations were noted in this study. The small sample size owing to the rarity of this specific type of breast cancer. The lack of a control group of patients diagnosed with the more frequent IDC not otherwise specified (NOS) was also another limitation. In addition, the small number of cases that underwent CEM interfered with drawing conclusions concerning the CEM imaging characteristics of IMPC.

In conclusion, the imaging findings of IMPC either by mammography, sonography, or CEM indicate the aggressiveness of this subtype of breast cancer. The observed strong association with LVI and LN metastasis with higher nodal stage mandate meticulous nodal assessment with sonographic examination of the axilla, as well as the infra- and supraclavicular region if pathological axillary lymphadenopathy was noted. Despite the indistinguishable imaging features from other aggressive subtypes of breast cancer, increasing awareness and knowledge about the radiographic and pathological features of this unusual variant allows better comprehensive management, prediction of its prognosis, and improvement of overall survival.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2023.09.010.

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