

Mammographic and Ultrasonographic Findings in Women with Breast Cancer Diagnosed before the Age of 40

การตรวจแมมโมแกรมและอัลตราซาวด์เต้านมในผู้ป่วยมะเร็งเต้านม ที่ได้รับการวินิจฉัยก่อนอายุ 40 ปี

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ABSTRACT

Objective: The purpose was to evaluate clinical features, imaging findings, and clinicopathological aspect of breast cancer under the age of 40 years in Chaophrayayommarat Hospital.

Method: This retrospective study included 51 patients under 40 years old with pathological diagnosis of breast cancer between September 2014 to August 2019. Thirty-nine patients were investigated by both mammography and ultrasonography. The remaining twelve performed only ultrasonography. The clinical features, imaging findings, and clinicopathological aspects of breast cancer under the age of 40 years were evaluated.

Results: The mean age at diagnosis of breast cancer was 35 years. Only 4 patients (7.8%) had family history of breast cancer in first degree relative. Most of tumors presented with palpable breast mass (88.2%). The most common histological type was invasive ductal carcinoma (82.3%) and 88.2% of tumors were high grade tumors. The ultrasonography showed a higher detection rate of malignant tumors in younger age than mammography (100% compared to 92%). The predominant features suggested of malignant tumors were irregular shape, microlobulated border, hyperdensity of tumor on mammography and hypoechogenicity of tumor on ultrasonography. The tumor size measured by mammography and ultrasound as correlated with pathological size had no statistically significant difference.

Conclusion: Breast cancer diagnosed in women before 40 years usually presents with a self-detected palpable mass. Ultrasonography is the main modality and has slightly superior detection rate for diagnosis of breast cancer in young women than mammography. Most cases of breast

cancer presented more aggressive biological behavior. Awareness of imaging and clinicopathological findings of breast cancer in young women is essential for identifying preventive approaches and helps radiologists to make an early and accurate diagnosis.

Keywords : mammography , breast ultrasonography , clinicopathology , breast cancer , before 40 years

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บทคัดย่อ

วัตถุประสงค์: การศึกษานี้เป็นการศึกษาย้อนหลังเชิงพรรณนา มีวัตถุประสงค์เพื่อศึกษาผลการตรวจแมมโมแกรมและอัลตราซาวด์เต้านมกับลักษณะทางคลินิกและพยาธิวิทยาในผู้ป่วยมะเร็งเต้านมที่ได้รับการวินิจฉัยก่อนอายุ 40 ปี ในโรงพยาบาลเจ้าพระยาอภัยภูเบศร

วิธีการศึกษา: รวบรวมข้อมูลผู้ป่วยหญิงที่อายุน้อยกว่า 40 ปีที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเต้านมรายใหม่ทั้งหมด 51 ราย ตั้งแต่กันยายน พ.ศ. 2557 ถึงสิงหาคม พ.ศ. 2562 โดย 39 ราย ได้รับการตรวจทั้งแมมโมแกรมและอัลตราซาวด์เต้านม, 12 ราย ได้รับการตรวจอัลตราซาวด์เต้านมเพียงอย่างเดียว แล้วนำข้อมูลที่ได้มาศึกษาผลการตรวจแมมโมแกรมและอัลตราซาวด์เต้านมกับลักษณะทางคลินิกและพยาธิวิทยา

ผลการศึกษา: อายุเฉลี่ยของผู้ป่วยคือ 35 ปี โดยมีเพียง 4 ราย (ร้อยละ 7.8) ที่มีประวัติเป็นมะเร็งเต้านมในญาติลำดับที่หนึ่ง ผู้ป่วยส่วนใหญ่จะมาด้วยอาการคลำได้ก้อนที่เต้านม (ร้อยละ 88.2) ผลพยาธิวิทยาที่พบมากที่สุดคือ invasive ductal carcinoma (ร้อยละ 82.3) และเป็นมะเร็งระดับสูงร้อยละ 51 พบว่าอัลตราซาวด์เต้านมมีอัตราการตรวจพบมะเร็งเต้านมในผู้ป่วยอายุน้อยได้ดีกว่าแมมโมแกรม (ร้อยละ 100 และ 92.3) ลักษณะสำคัญที่บ่งชี้ว่าเป็นก้อนมะเร็งเต้านมคือ irregular shape, microlobulated border, hyperdensity ของก้อนจากการตรวจแมมโมแกรม และ hypoechogenicity ของก้อนจากการตรวจอัลตราซาวด์เต้านม ขนาดของก้อนที่วัดได้จากการตรวจแมมโมแกรมและการตรวจอัลตราซาวด์เต้านม เมื่อเทียบกับขนาดก้อนที่วัดได้จากพยาธิวิทยา พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ

สรุป: มะเร็งเต้านมในผู้ป่วยอายุน้อยกว่า 40 ปี มักจะมาด้วยการคลำพบก้อนที่เต้านม การตรวจอัลตราซาวด์เต้านมเป็นการตรวจหลักที่สำคัญ และพบว่าอัตราการตรวจพบเหนือกว่าการตรวจแมมโมแกรมในการวินิจฉัยมะเร็งเต้านมและพบว่าส่วนใหญ่ของผู้ป่วยมะเร็งเต้านมที่มีอายุน้อยกว่า 40 ปี มักจะมีความรุนแรงของโรคมามากกว่า ดังนั้นความตระหนักในผลการตรวจทางรังสีวิทยาและพยาธิวิทยาของมะเร็งเต้านม ในผู้ป่วยที่มีอายุน้อยกว่า 40 ปี มีความสำคัญอย่างยิ่งที่จะช่วยป้องกันโรค และช่วยให้รังสีแพทย์วินิจฉัยโรคได้รวดเร็วและแม่นยำมากขึ้น

คำสำคัญ : แมมโมแกรม อัลตราซาวด์เต้านม พยาธิวิทยาคลินิก มะเร็งเต้านม อายุน้อยกว่า 40 ปี

วารสารแพทย์เขต 4-5 2563 ; 39(4) : 516-528.

Introduction

Breast cancer is the most common cancer among women worldwide and also in Thai women^{1,2} Thai women develop breast cancer in younger age than American or European women. The mean age of breast cancer in Thai women is 55 years^{1,2} The National Cancer Institute of Thailand recognized that the incidence of new breast cancer was 700 patients in 2018³. Despite being a relatively uncommon condition, current statistics indicate an increase in the incidence of breast tumors in the young. It can have a worse prognosis and more aggressive biological behavior than breast cancer in older patients⁴. The delay in diagnosis of breast cancer is a common problem by many factors such as lack of awareness about the disease, lack of screening programs in this age group, rapid tumor growth, and dense breast tissue⁶ The American College of Radiology and Society of Breast Imaging, recommend annual breast cancer screening starting at the age of 40.

The sensitivity of mammography in the detection of breast cancer is lower in young women due to dense breast tissue, the sensitivity decreases from almost 100% in fatty breast to 45% in extremely dense breast⁷. The ultrasonography is the initial imaging modality for evaluate breast problems in young patients. Nevertheless, ultrasonography performed concurrently with mammography increased sensitivity compared with the use of either modality alone. The purpose of this study was to evaluate imaging findings and their correlation with clinicopathological features.

Objective

The purpose of the study was to evaluate clinical features, imaging findings and clinicopathological aspect of breast cancer under the age of 40 in Chaophrayayommarat Hospital.

Method

Study population:

A retrospective, descriptive and single-center study was conducted based on analysis of medical records of Chaophrayayommarat Hospital of patients who were diagnosed with malignant tumors of breast and were under 40 years of age, from September 2014 to August 2019. Among 51 patients, 39 (76%) underwent ultrasonography concurrently with mammography and 12 (24%) performed only ultrasonography.

Imaging protocols:

Mammograms were performed using two mammographic equipments (Hologic Lorad M-IV Analog Mammography and Philips Microdose SI L50 Digital Mammography). Two standard examinations on each breast were obtained using craniocaudal (CC) and mediolateral oblique (MLO) views. Additional views were used for better visualization of the suspicious area and evaluation of microcalcifications.

All breast ultrasound examinations were performed by the interpreting radiologists including real-time bilateral whole-breast scans, using two ultrasound machines (Toshiba's Aplio 500 ultrasound system with 7-12-MHz probe and Esaote Mylab Six ultrasound machine with 3-13-MHz probe).

Data analysis:

The reports were classified into one category according to BI-RADS by experienced radiologists in Chaophrayayommarat Hospital.

The pathological reports were reviewed to determine histopathological type, tumor grade and immunohistochemical findings including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status. Testing negative for all three hormone receptors was defined as triple negative breast cancer.

Descriptive statistics including patientage, tumor size, clinical presentation, histopathological type, grade, immunohistological, and radiologic findings were presented as percentages of categorical variables mean, and standard deviations of quantitative variables.

Correlation between the size of breast lesions as measured by ultrasound, mammography and pathological examinations were estimated using Pearson's correlation coefficient. p value was considered statistically significant when equal to or less than .05.

Result

Clinical and histopathological data

The age at diagnosis of breast cancer ranged from 21 to 39 years with a mean of 35 years

and was comprised of 7.8% in the age group between 21 to 29 years, 25.5% in the age group between 30 to 34 years, and 66.7% in the age group between 35 to 39 years. Most of the patients (92.2%) had no family history of breast cancer in first degree relatives.

Most cancers were detected from clinical symptoms, especially a palpable mass (88.2%). Additionally, 9.8% of the patients presented with palpable mass and nipple discharge, and 2% of the patients were detected from scalp metastasis.

The mean size of tumors was 3.9 cm. Axillary lymphadenopathy which was also pathologically proven to be malignant was found in 51% of patients. The most common histopathological type of tumor was invasive ductal carcinoma (82.3%), followed by 5.9% was mixed carcinoma, 5.9% was ductal carcinoma in situ (DCIS), and 3.9% was mucinous tumor. About the histological findings, 88.2% of tumors were high grade (grade 2 and grade 3) and 17.6% of tumors were negative immunohistochemistry (triple negative) for estrogen receptor, progesterone receptor, and HER2. The clinical and histopathological features are presented in Table 1.

Table 1 Clinical and pathological characteristics of 51 patients

Characteristics	Number (%)
Mean age (year $\pm$ SD)	35.2 $\pm$ 3.5
Clinical presentation	
- Palpable mass	45 (88.2%)
- Palpable mass and nipple discharge	5 (9.8%)
- Scalp metastasis	1(2%)

Table 1 Clinical and pathological characteristics of 51 patients (Ext.)

Characteristics	Number (%)
Family history of breast cancer	4 (7.8%)
Histopathological type	
- Invasive ductal carcinoma	42 (82.3%)
- Mixed carcinoma	3 (5.9%)
- Mucinous type	2 (3.9%)
- Medullary tumor	1 (2%)
-DCIS	3 (5.9%)
Tumor grade	
- Grade 1	6 (11.8%)
- Grade 2	19 (37.2%)
- Grade 3	26 (51%)
Lymph node involvement	26 (51%)
Immunohistochemical findings	
-ER positivity	26 (51%)
-PR positivity	38 (74.5%)
-HER2 positivity	35 (68.6%)
-Triple negative	9 (17.6%)

Imaging findings

Most patients (76.5%) were investigated by both mammography and ultrasonography. The ultrasonography was the only imaging investigation of the remaining patients (23.5%). Almost all malignancies presented as a mass

(88.2%). Most patients were categorized as BI-RADS 5 (62.7%) and BI-RADS 4C (23.5%).

All the lesions were detected on ultrasonography. Details of ultrasonographic features are shown in Table 2.

Table 2 Ultrasonographic findings of lesions

Sonographic findings (n = 51)	Number (%)
- Mass	39 (76.5%)
- Mass with calcifications	11 (21.5%)
- Mass with calcifications and abnormal duct	1 (2%)

Table 2 Ultrasonographic findings of lesions (Ext.)

Sonographic findings (n = 51)	Number (%)
Masses (n = 51)	
Shape	
- Oval	14 (27.5%)
- Irregular	37 (72.5%)
Margin	
- Circumscribed	1 (2%)
- Indistinct	6 (11.8%)
- Microlobulated/angulated	38 (74.4%)
- Spiculated	6 (11.8%)
Echogenicity	
- Hypoechogenicity	38 (74.4%)
- Heterogeneous	12 (23.6%)
- Complex cystic and solid	1 (2%)
Posterior acoustic feature	
- No	26 (51%)
- Posterior acoustic enhancement	21 (41.2%)
- Posterior acoustic shadow	1 (2%)
- Mixed	3 (5.8%)
Associated features	
- Abnormal ductal dilatation	1 (2%)
- Skin thickening	4 (7.8%)
- Axillary adenopathy	23 (51%)

The predominant features on ultrasonography were irregular shape (72.5%), microlobulated border (74.5%), and hypoechogenicity of the tumor (74.5%). Most patients (51%) did not have a posterior acoustic feature and 41.2% of patients demonstrated posterior acoustic

enhancement. About 2%, 7.8%, and 51% of the patients has abnormal ductal dilatation, skin thickening, and axillary lymphadenopathy respectively.

The detection rate of mammography is 92.3%. The predominant mammographic

features were the presence of masses (92%) and suspicious microcalcifications (28.2%). About 5.1%, 15.4%, and 35.9% had nipple retraction,

skin thickening, and axillary lymphadenopathy, respectively. Details of mammographic features are shown in Table 3.

Table 3 Mammographic findings of lesions

Mammographic findings (n = 39)	Number (%)
- Negative findings	3 (7.9%)
- Mass	24 (63.2%)
- Suspicious microcalcifications	1 (2.6%)
- Mass with suspicious microcalcifications	10 (26.3%)
-Axillary lymphadenopathy	1 (2.5%)
Calcifications (n = 11)	
Morphology	
- Fine pleomorphic	10 (91%)
- Amorphous	1 (9%)
Distribution	
- Group	4 (36.4%)
- Segmental	3 (27.2%)
- Regional	4 (36.4%)
Masses (n = 34)	
Shape	
- Oval	8 (23.5%)
- Irregular	26 (76.5%)
Margin	
- Circumscribed	2 (5.9%)
- Obscured	12 (35.3%)
- Microlobulated	2 (5.9%)
- Indistinct	14 (41.2%)
- Spiculated	4 (11.8%)

Table 3 Mammographic findings of lesions (Ext.)

Mammographic findings (n = 39)	Number (%)
Associated findings	
- Nipple retraction	2 (5.1%)
- Skin/trabecular thickening	6 (15.4%)
- Axillary adenopathy	14 (35.9%)

The Table 4 describes the BI-RADS classification adopted for mammography and ultrasonography⁹. Only one of the invasive tu-

mor did not show openly suggestive features and was classified as probably benign finding (BI-RADS category 3).

Table 4 BI-RADS category according to US-MMG

BI-RADS category	Number (%)
BI-RADS 3	1 (2%)
BI-RADS 4B	6 (11.8%)
BI-RADS 4C	12 (23.5%)
BI-RADS 5	32 (62.7%)

The example of BI-RADS 3, BI-RADS 4B, BI-RADS 4C, and BI-RADS 5 in this study were shown in Figure 1, 2, 3, and 4 respectively.

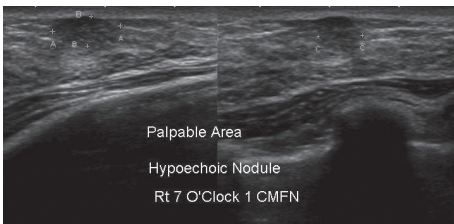


Figure 1A

A 34-year old woman presented with a painless palpable mass in right breast.

Figure 1A. US showed a 1-cm rather circumscribed hypoechoic nodule which was categorized to BI-RADS 3 lesion.

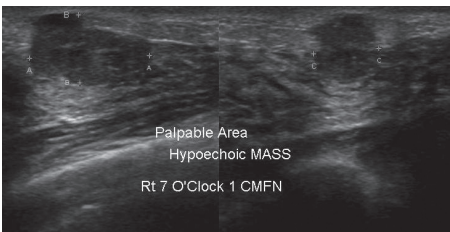


Figure 1B

Figure 1B. About 6 months follow-up US showed an increased size of 1.8-cm hypoechoic nodule with lobulated border which was categorized to BI-RADS 4B lesion and the pathological proven of grade 2 invasive ductal carcinoma.

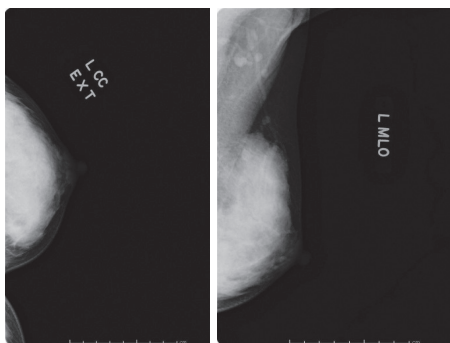


Figure 2A

A 35-year old woman presented with painless palpable mass in left breast.

Figure 2A. MMG showed extremely dense breast tissue with no detectable abnormality.

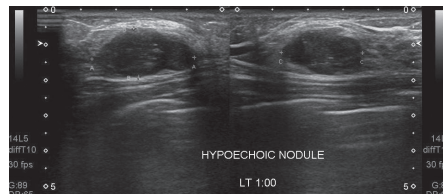


Figure 2B

Figure 2B. US showed a 2.9-cm oval-shaped, hypoechoic nodule with lobulated border which was categorized to BI-RADS 4B lesion.

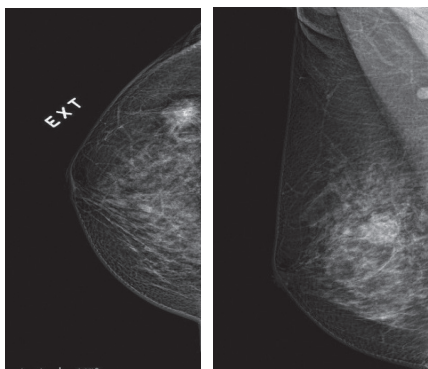


Figure 3A

A 35-year old woman presented with painless palpable mass in right breast.

Figure 3A and 3B. MMG showed heterogeneously dense breast tissue with a 2.1-cm oval-shaped hyperdense lesion with obscured

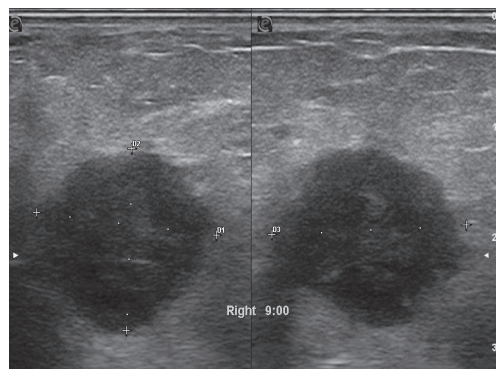


Figure 3B

border. US showed a 2-cm hypoechoic lesion with microlobulated border and posterior acoustic enhancement, categorized to BI-RADS 4C.

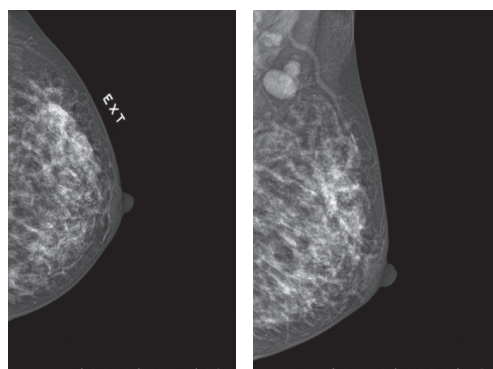


Figure 4A

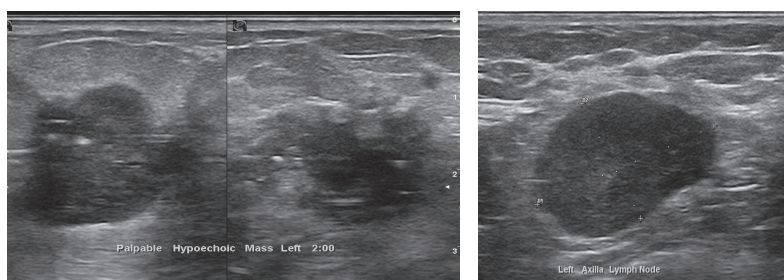


Figure 4B

A 39-year old woman presented with painless palpable mass in left breast.

Figure 4A. MMG showed a 5.1-cm irregular-shaped hyperdense mass with indistinct border, associated segmental fine pleomorphic microcalcifications and axillary adenopathy.

Figure 4B. US showed a 4.6-cm irregular, spiculated hypoechoic mass with internal echogenic foci with and axillary lymphadenopathy which was categorized to BI-RADS 5 lesion. The biopsy revealed a 5-cm tumor with grade 3 invasive ductal carcinoma.

The correlation coefficient of mammographic size and ultrasonographic size as correlated with pathological size was 0.65, and 0.50 respectively. High grade tumors were associated with irregular shape (81%), lobulated contour (81%), hyperdensity on mammography

(90%) and hypoechogenicity on ultrasonography (69%).

Discussion

The diagnosis of malignant neoplasm of the breast in women under 40 years is more difficult than in older women^{5,6}. Firstly, benign tumors such as fibroadenomas are much more common in young women. Malignant lesions may be misinterpreted as benign lesions. Secondly, routine screening mammogram is not usually begun until the 40 years old in the average risk women. Thirdly, the sensitivity of mammography declines in dense breasts. Ultrasonography plays a major role in evaluating breast problems in young women because it is not compromised to dense breast tissue and could correlate the ultrasonographic find-

ings with the palpable mass at area of clinical concern, which is the most common presenting symptom. The age at diagnosis of breast cancer in this study was represented by women with an average age of 35 years and the youngest women with the age of 21 years.

In the current study, the majority of the patients had palpable masses (88.2%) and half of the patients (51%) had axillary lymphadenopathy on ultrasonography at the time of diagnosis. All subjects in this study were evaluated by ultrasonography and all malignant lesions were detected as a mass. Most malignant lesions in the presented study showed suspicious features. Most had irregular in shape (72.5%), microlobulated, angular, indistinct and spiculated border (98%), and hypoechogenicity of the tumor (74.5%). Only one patient in this study that ultrasonography was misinterpreted circumscribed-border malignant lesion to benign lesion (Figure 1).

Most of our patients had abnormal mammography (92%). On mammography, the most common findings of the tumors were masses and microcalcifications. The shape of the mass was usually irregular (76.5%) and the margin was indistinct, obscured, microlobulated, and spiculated (98%).

One of the mucinous carcinoma contributed one out of three malignant tumors in the present study which were undetected by mammography. This subtype is well-circumscribed tumor likely to develop by pushing surrounding breast parenchyma outwards

rather than infiltrating. However, it could be detected by ultrasonography. The usefulness of ultrasounds as a supplementary screening method in patients with negative mammographic finding has already been confirmed in the literature, with an increase up to 42% demonstrated in the detection of breast cancers with dense breasts¹².

The correlation coefficient of mammographic size and ultrasonographic size as correlated with pathological size was 0.65, and 0.50 respectively which was no statistically significant difference. (Figure 4).

The findings of the current study showed that breast cancer in women under 40 years old was associated with higher histology grade (88.2%). High grade tumors were associated with irregular shape (71.1%), lobulated contour (80%), hyperdensity on mammography (78.6%) and hypoechogenicity on ultrasonography (75.5%). Breast cancer in the young is reported association with less immunoreactivity for estrogen receptor and progesterone receptor^{10,11}. In the present study most of the patients had positive immunohistochemistry for estrogen receptor (51%), progesterone receptor (74.5%), and HER2 (68.6%).

There were some limitations of the current study. The major limitation was the retrospective study. Secondly, because a long period of data collection with two mammographic and ultrasonographic machines caused dissimilar imaging findings, Thirdly, the number of patients evaluated was low and this

might caused the lack of statistical significance. Future prospective study design along with standardized mammographic and ultrasonographic interpretation should improve the validity of the research.

Conclusion

In conclusion, breast cancer diagnosed in women before the age of 40 years usually presents with a self-detected palpable mass and can show different imaging findings. Ultrasonography is the main modality and has a slightly superior detection rate for diagnosis of breast cancer in young women than mammography. Most cases of breast cancer presented more aggressive biological behavior.

Awareness of imaging and clinicopathological findings of breast cancer in young women is essential for identifying preventive approaches to warn the younger population in our country and helps radiologists to make an early and accurate diagnosis, and the clinician to provide the correct and effective management.

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