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Young patients with unilateral breast cancer arising in fibroadenoma: A rare case report

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Abstract---The incidence of breast cancer with fibroadenoma (FAM) in young patients is a rarely reported case, <1% of all cases of women suffering from breast cancer. This case report aims to highlight the importance of considering the presence of FAM and breast cancer at the same time at a young age to be treated comprehensively. A 31-year-old woman with complaints a lump in the breast and pain. Mother has a history of breast lumps. There were no menstrual disturbances and the use of hormonal contraception. The results of breast ultrasound revealed a solid mass with a diameter of 4 cm in the central quadrant of the breast with a hypoechoic mass with malignant features in it according to the Breast Imaging Reporting and Data System (BIRADS) C-4 and enlarged right axillary lymph nodes. Results Fine Needle Aspiration Biopsy (FNAB) unspecified, finally, a wide excision was performed and it was found that there was a solid mass and a smooth mass with a clear capsule. Histopathological report shows invasive carcinoma in right breast fibroadenoma. Young patients with lumps in the breast are not only suspected of being FAM but can be considered an image towards invasive carcinoma.

Keywords---breast cancer, fibroadenoma, invasive carcinoma, young patient, woman.

Introduction

Breast cancer is the most common cancer in women worldwide, where data in Indonesia in 2020 stated that breast cancer was reported as many as 65,858 (16.6%) of a total of 396,914 patients with all cancers, and was the number 1 cause of cancer in women with a total 65,858 cases (30.8%) of 213,546 cancer cases in women with a 9.6% risk of death. (World Health Organization, 2020) Fibroadenoma (FAM) is a type of benign tumor that often occurs in young women under the age of 35 years, with the second most common after fibrocystic (Foxcroft, Evans and Porter, 2004). The most common cause of mammary fibroadenoma is hormonal influences. This is known because the size of the fibroadenoma can change during the menstrual cycle or during pregnancy. Lesions enlarge at the end of menstruation and during pregnancy (Lonare et al., 2020). This fibroadenoma occurs due to an excess of the hormone estrogen. However, there are things that can affect the incidence of tumors, including: genetics and also a predisposition in families suffering from cancer (Salati, 2020). Most often these FAMs are single lesions (simple or complex) or multiple tumors with most being considered benign, but complex or multiple fibroadenomas can turn into invasive carcinoma. Its epithelial components are at risk for malignant transformation. The risk of this transformation is the same for epithelial cells in the breast parenchyma. The incidence of FAM with breast cancer is very rare where it is <1% of the total incidence of breast cancer (Arora et al., 2017).

Fibroadenoma can develop into various types of malignancies, such as lobular intraepithelial neoplasia, lobular carcinoma in situ, phyllodes tumor and microinvasive lobular carcinoma (Zheng et al., 2015). There have been approximately 160 cases of breast carcinoma arising in fibroadenoma cases reported in the UK literature, and in about 100 cases, malignant transformation of fibroadenoma has been reported. This study presents a rare case of unilateral breast cancer arising in a fibroadenoma in a 31-year-old woman. Cases of breast carcinoma with fibroadenoma are indeed a rare breast tumor (Arora et al., 2017).

Breast cancer can be diagnosed by anamnesis, physical examination, supporting examination in the form of; mammography, Fine Needle Aspiration Biopsy (FNAB), Core needle biopsy, Stereotactic biopsy, open or surgical biopsy, Magnetic Resonance Imaging (MRI), Breast Ultrasound (USG). Treatment of breast cancer depends on the size, the presence of pain, the age of the patient, and the results of the biopsy. In young patients treatment is needed in a multidisciplinary manner which includes fertility management, genetic counseling, surgery, and individual psychosocial support. Management of this patient must be based on the Level of Evidence-based international guidelines (Rossi, Mazzara and Pagani, 2018).

Case

A 31-year-old woman with medical record number 164764 with complaints of pain in the right axilla and found a lump in the breast for 1 year. The results of physical examination were palpable lumps of 4 cm, well-defined, rough, rigid and mobile lumps in the middle quadrant of the right breast (Figure 1), no palpable mass on the other side of the breast, enlarged lymph nodes in the right axilla

were found. The patient has regular menstrual cycles since the age of 13 years with a cycle of 28 days and the longest cycle is 30 days. Have mothers with a history of lumps in the breast but it shrinks on its own. Having two children, aged 6 years and 2 years. The patient was not using hormonal contraception.



Figure 1 The patient's right breast appears redder and changes shape.

The results of the pre-operative Ultrasonography (Figure 2) showed the presence of a well-defined solid mass with a diameter of 4 cm in the central quadrant of the breast with a hypoechoic mass in it with malignant features in accordance with Breast Imaging Reporting and Data System (BIRADS) C4 and enlarged right axillary lymph nodes. The patient is examined Fine Needle Aspiration Biopsy (FNAB) before undergoing surgery with the results obtained erythrocyte distribution and few lymphocytes and polymorphonuclear neutrophilic leukocyte (PMN) inflammatory cells, without any specific picture.

The patient underwent a wide excision, in which the lesion was removed, and the tissue sections were pathologically examined. Macroscopic examination showed a brownish yellow mass with a solid and chewy consistency (Figure 3). Microscopic view (Figure 4) shows the presence of fibrocollagenous connective tissue stroma which is infiltrated by malignant epithelial cells, most of which are arranged to form islands of malignant epithelial cells/trabeculae, some are tubular in shape and some foci appear to be arranged in rows and individual cells. These cells had an increased morphological ratio, moderately pleomorphic nuclei, some were hyperchromatic and partly vesicular with prominent nuclear daughters and 21 mitoses/10 fields of view were found. Also seen ductal carcinoma in situ and lymphocyte inflammatory cells around the tumor mass. In other parts of the tumor tissue was also seen covered with fibrocollagenous connective tissue of varying thickness. Subcapsular tumor mass was seen consisting of epithelial and stromal elements. The epithelial elements in the form of mammary glands are tubular in shape, some are dilated and some are pushed by a hyperplastic and myxomatous stroma.

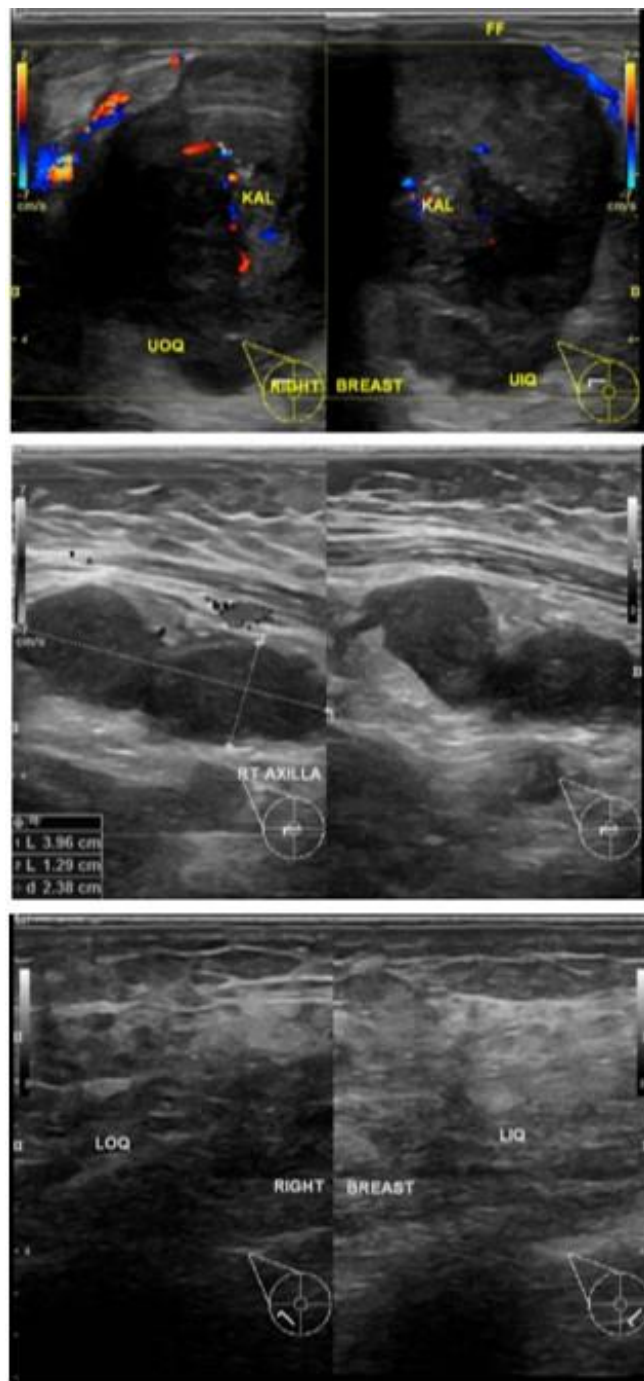


Figure 2. Ultrasound shows a well-defined solid mass with a diameter of 4 cm in the central quadrant of the breast with a hypoechoic mass in it according to Breast Imaging Reporting and Data System (BIRADS) C-4 and enlarged right axillary lymph nodes



Figure 3. Macroscopically it shows a brownish yellow mass with a dense and chewy consistency

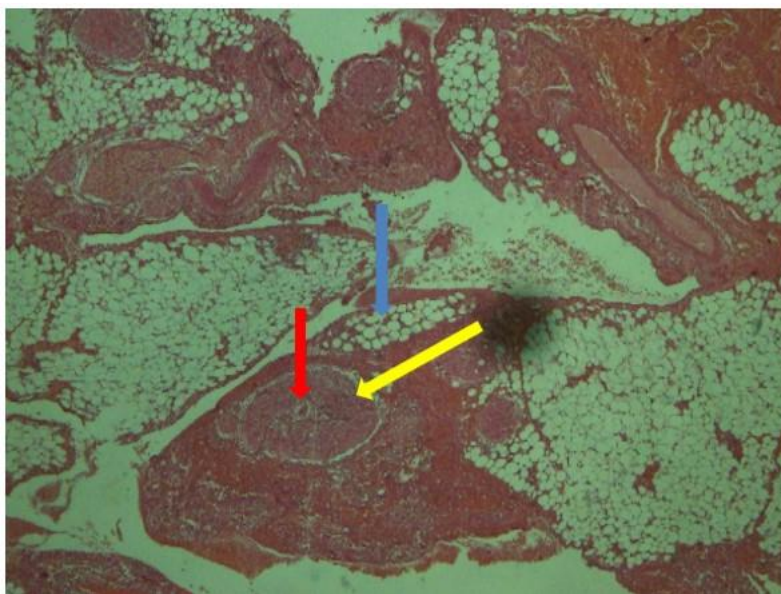


Figure 4. Histopathology with hematoxylin-eosin staining showed fibrocollagen infiltrated by malignant epithelial cells. Blue arrows indicate fibrocollagen, red arrows indicate ductal carcinoma in situ, yellow arrows indicate lymphocytic inflammatory cells.

The gland is lined by columnar epithelial cells that grow hyperplastic with the cell nucleus showing no signs of atypia. Histopathological reports with hematoxylin-eosin staining were consistent with the features of invasive carcinoma and fibroadenoma of the right breast. After knowing the histopathological picture,

patients with a diagnosis of the epithelial elements in the form of mammary glands are tubular in shape, some are dilated and some are pushed by a hyperplastic and myxomatous stroma. The gland is lined by columnar epithelial cells that grow hyperplastic with the cell nucleus showing no signs of atypia.

Discussion

Breast cancer at a young age

Breast cancer in women aged under 40 years old It is known to occur in 18.8 per 100,000 women, for 14% of all cancer cases and for 7% of all breast cancer cases. Cancer found at a young age is associated with an unfavorable prognosis (Al Farisyi and Khambri, 2018). The prognostic relevance of young people <40 years is highly controversial. Some data show poorer outcomes, especially at <35 years of age, while other data suggest a better prognosis with respect to biologics (Ribnikar et al., 2015). Approximately 6.6% of all cases were diagnosed in women <40 years, 2.4% in women <35 years and 0.65% in women <30 years (Al Farisyi and Khambri, 2018). Data in the United States shows women aged <40 years approx 14,000 are diagnosed with breast cancer each year, and nearly 3,000 young women die each year. Recent studies have shown that age as a prognostic factor differs from biological subtypes. In recent years, there has been an increase in biological understanding in young women (Foxcroft, Evans and Porter, 2004).

Some studies report breast cancer at a young age has a more aggressive character. These include higher estrogen receptor (-), higher histopathology, more triple negative subtypes (38%) than older age (26%). Low outcome factors were found at a young age due to high clinical stage at diagnosis, with larger tumor size and more positive axillary lymph nodes (KGB). From several studies, it is concluded that young breast cancer has a higher recurrence rate with shorter disease free survival (DFS) and overall survival (OS) than older breast cancer (Al Farisyi and Khambri, 2018). In the results of this case report, the patient was diagnosed with breast cancer when he was 31 years old.

The most common age for breast cancer is the 35-40 year age group. Differences in breast cancer based on age, distinguished by menopausal status when first diagnosed as breast cancer. This difference is not only relevant to premenopausal and postmenopausal age differences, but also to differences in hormonal status in pre and postmenopause. In premenopause, women are still exposed to cyclical hormones produced by the ovaries, in contrast to postmenopausal women whose main source of endogenous estrogen comes from fat tissue. Premenopausal breast cancer is associated with more aggressive tumors than postmenopausal breast cancer (Nassar et al., 2015). Although it is said that the patient is still experiencing a good menstrual cycle, it does not rule out the possibility of breast cancer, this is in accordance with Farisyi's research (2018) where 71 patients (80.3%) are known to be not related to hormones with $p = 0.132$ (Al Farisyi and Khambri, 2018).

In this case report, it was also reported that the patient's mother also had a lump in the breast and it disappeared on its own, this shows that the patient does have genetic factors for cancer. SA woman will have breast cancer if her mother, sister

or direct relatives have suffered from the same disease. According to clinical trial research, about 5-10% of breast cancer cases are associated with genetic changes (RISKESDAS, 2017)

The relationship between fibroadenoma and breast cancer

In this study, the results of the diagnosis of patients with invasive carcinoma and fibroadenoma were obtained. Fibroadenoma is a type of benign breast tumor and is often associated with a young age and has a tendency to become breast cancer (Lonare et al., 2020). The histopathological appearance of fibroadenoma varies widely from the most common type, about 70-90% simple fibroadenoma, then followed by giant juvenile fibroadenoma type which in the picture can reach more than 5 cm and weighing > 500 grams with skin ulceration and enlarged veins, the least common is multicentric fibroadenoma which can occur 0.5% to 2% (Begum, Thomus and Babu, 2017; Kartini. et al., 2021).

The relationship between fibroadenoma and breast cancer is associated with changes that occur in fibroadenoma that develop into malignant cells. The incidence of these changes is very rare and is most often diagnosed incidentally on examination of postoperative excisional biopsy specimens in only about 0.002% to 0.125% incidence (Foxcroft, Evans and Porter, 2004). The risk factor for changing from FAM to cancer increases from 3.1 to 3.7 times if the FAM is complex. Of all breast carcinomas arising in fibroadenoma, lobular carcinoma in situ is the most common (50%), followed by ductal carcinoma in situ (20%), invasive ductal carcinoma (20%), and invasive lobular carcinoma (10%) (Arora et al., 2017). The median age of cancer reported in the various case series was 42.5 years, which is about 20 years later than the peak age of fibroadenoma occurrence implying that there should be a high index of suspicion for malignancy in fibroadenoma occurring in older women especially in who have associated risk factors such as a strong family history (Zheng et al., 2015).

Breast carcinoma and epithelial fibroadenoma experience the same stimuli and triggers as the rest of the breast. Carcinomas can arise in the adjacent breast tissue that compresses or infiltrates the FAM or is completely limited, or at least predominant, in the FAM (Arora et al., 2017). Several reports have described a higher risk of subsequent breast carcinoma among patients who have FAM, with relative risk (RR) ranging from 1.48 to 1.7 times. At the tissue level, a fibroadenoma is a benign tumor consisting of an epithelial and stromal component. Complex fibroadenomas are fibroadenomas with associated histologic characteristics, including cysts (>3 mm), sclerosing adenosis, epithelial calcification, or papillary apocrine metaplasia. A previous report from Dupont et al. showed that the relative risk (RR) of invasive breast cancer was 2.17 times higher for patients with fibroadenoma than for matched controls (95% CI 1.5–3.2) (Dupont et al., 1994). The relative risk increased to 3.10 times for women with complex fibroadenoma (95% CI 1.9-5.1) and remained elevated for more than 20 years after diagnosis (Nassar et al., 2015).

The role of investigations in breast cancer patients

Patients with complaints of lumps in the breast should immediately take a history, clinical examination and support to be able to determine the cause of the lump. In this case report, the supporting examinations that have been carried out before the surgical removal of the tumor include ultrasonography and FNAB examination. Early diagnosis of lesions in the breast can be done using the FNAB method or known as a fine needle biopsy. The advantages of FNAB are non-invasive and have a reliable accuracy of 78%. Basically FNAB serves to obtain a sample of nodule cells in the aspirated breast by inserting a needle into the breast nodule tissue (Widarso, Norahmawati and Setijowati, 2015; Samosir et al., 2018; Kartini. et al., 2021). The results of the patient's FNAB were not specific, so a wide excision was performed to directly remove the pathological tissue in the patient.

Investigations that are usually done at a young age are ultrasonography (USG) because it will clearly show the density of breast cancer and free of radiation (Wang et al., 2019). In high-density breasts, ultrasound is known to have a sensitivity of 88%, higher than mammography which is the gold standard for breast cancer screening, which is only 56% (Geisel, Raghu and Hooley, 2018). Breasts with high gland density are often found in women under the age of 50 years and are more common in Asian populations than in European or American populations, so that they represent the breast characteristics of the Indonesian people (Rahayu et al., 2020). The patient's results obtained BIRADS C-4 which means the abnormality leads to malignancy. Breast Imaging Reporting and Data Category is used to predict the degree of malignancy of breast cancer patients in screening which starts from C-0: without further examination; C-1: normal; C-2: benign disorder; C-3: abnormality that is benign, with strict evaluation, C-4: abnormality suggesting malignancy and finally C-5: malignancy (Ramli, 2015).

Mammography is not recommended before the age of 40 years because patients of this age group generally have increased breast density and mammography has decreased sensitivity for detecting breast cancer in this setting. There is also a risk of false-positive mammography findings, which could potentially require follow-up imaging (Sardanelli et al., 2017). Sydney Breast Imaging Accuracy Study found that in women 45 years of age or younger, the sensitivity of sonography was significantly better than that of mammography. Mammography is less sensitive and less specific (especially in young women with dense breasts), but can be used to detect the presence of the smallest detectable lesions (eg. small areas of microcalcification). The use of mammography should be based on the results of the biopsy; in cases of malignancy, mammography is indicated to determine the extent of the disease, the type of breast cancer and to determine the presence of bilateral axillary spread (Foxcroft, Evans and Porter, 2004; Sardanelli et al., 2017; Geisel, Raghu and Hooley, 2018). Examinations that can be used to determine primary oncogene factors of breast cancer can include examination of disease immunophenotype (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 index (Ribnikar et al., 2015)).

Histopathological picture

In the histopathological description of this case, it was found that invasive carcinoma arising in FAM, which were rare cases <1% of all breast cancer features (Zheng et al., 2015). The results of the largest prospective observational study evaluating the pathological characteristics of 2,956 women under the age of 40 years had ductal histology (86.5%) and grade III tumors (58.9%). Of the patients, 50.2% had node-positive disease, and multifocality was observed in 27% of the patients. One-third of tumors were ER negative and one-quarter were HER-2 positive (Copson et al., 2013). Similar results were found among 399 patients with high rates of lymphovascular invasion (34%) and lymphocytic infiltration (24%). Many other retrospective studies have evaluated differences in pathological features according to age. Collins et al. showed that younger patients were diagnosed with larger tumors, nodal involvement, grade III tumors, and ER-negative disease (Collins et al., 2012).

Conclusion

Patient 31 years old female diagnosed as breast carcinoma, with unilateral invasive carcinoma arising in fibroadenoma. Young patients with lumps in the breast are not only suspected of being FAM but can be considered an image towards invasive carcinoma.

Acknowledgments

Patient and all author

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