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# Clinical and Pathological Features of Metaplastic Breast Carcinoma: A Report of Four Case Studies

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## Abstract

**Aims:** The purpose of our study was to research the clinical and pathological aspects of metaplastic breast cancer (MBC).

**Material and methods:** This is a retrospective study of four cases of MBC conducted at the department of pathology of Mohamed Taher Maamouri Hospital in Nabeul, between January 2016 and February 2018. Characteristics of clinical and pathological features were collected from the patient files and histopathological reports.

**Results:** In our study, the mean age of patients was 53 years with extremities ranging from 19 to 89 years old. The most frequent reason for consultation was a nodule with a mean size of 3.87 cm (3 - 4.5 cm) and a localization in the left breast in 75% of cases (n=3). These tumors were classified ACR 5 in 75% of cases. The diagnosis was made in 50% of cases on lumpectomy and 50% of cases on micro biopsies. A metastatic lymph node location was found in only one case (25%). All patients (n=4) had squamous type of metaplastic cell differentiation and only one case was associated with a predominant NST carcinoma. In 100% of cases, it was an SBR grade III carcinoma. At immunohistochemistry, 50% of cases (n=2) had a triple-negative profile (RO, RP and Her2 negative).

**Conclusion:** One of the particularities of our series is the very young age of one of our patients which is rarely described in other series.

**Keywords:** Metaplastic breast cancer; Triple-negative; Squamous cell

## Introduction

Metaplastic carcinoma is a very rare variant of breast cancer that accounts for 0.2 to 5% of all invasive mammary carcinomas [1]. It is an aggressive subgroup with a poor prognosis [2,3] as the majority of these neoplasms are triple negative for estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) According to WHO, it encompasses a heterogeneous group of carcinomas characterized by the presence, in variable proportions, of squamous or mesenchymal differentiation (fusocellular, chondroid, bone or rhabdomyoid) [4]. Because of this variability and the lack of great knowledge of the characteristics of MBC, this study was undertaken through four case studies and a review of the literature to evaluate MBC with regard to its clinical and pathological features.

## Methods

This is a retrospective study of four cases of metaplastic breast carcinoma conducted at the department of pathology of Mohamed Taher Maamouri Hospital in Nabeul, between January 2016 and February 2018.

### Collection of clinical data

They were performed from the patient files and we found the following information:

- Age
- Sex
- Personal and family history
- The seat of the lesion
- The size of the lesion
- unilateral or bilateral involvement
- Presence or absence of inflammatory signs associated with the lesion
- Presence or absence of axillary lymphadenopathy
- The ultrasound and/or mammography aspects
- Presence or absence of metastasis
- Treatment
- Evolution

### Pathological data

The following data were collected from the pathology reports:

- Sampling types
- Macroscopic appearance
- Histological types
- Scarf Bloom Richardson (SBR) grade modified by Elston and Ellis (EE)
- Lymph node dissection
- Vascular emboli
- Immunohistochemistry

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## Results

### Case 1

A 19-year-old woman whose mother was treated for breast cancer at the age of 30, presented with a left breast nodule discovered a week ago. The physical examination found a 45 mm nodule at the union of the upper quadrants of the left breast. This mass was mobile, well limited and without satellite adenopathy. Breast ultrasound showed a 40 mm nodule without lightening of ultrasound, classified ACR4. The patient had, then, a micro biopsy that found an infiltrating carcinoma with squamous metaplasia and was classified grade III according to SBR. The carcinoma was made of large lobule and cords of polygonal cells with distinct squamous differentiation. The mitotic index was 22 mitoses/10CFG. Immunohistochemically, hormone receptors were present (ER: weak expression in 20% of tumor cells, PR: weak expression in 10% of tumor cells), HER2 was not overexpressed (score1), and Proliferation index (Ki67) was at 50%. Tumor extension assessment was negative and the mammary MRI did not show any other lesion. The multidisciplinary consultation meeting indicated a neoadjuvant chemotherapy. The evolution under chemotherapy was unfavorable with clinical progression. A Patey operation was performed. The pathological analysis found an invasive squamous cell carcinoma of 7 cm without therapeutic effect classified in TD according to Sataloff and absence of lymphatic invasion. The patient had radiotherapy and chemotherapy as adjuvant therapy. Currently she takes tamoxifen as a hormone therapy. She had no loco-regional recurrence or remotely with a decline of one year.

### Case 2

A 49-year-old patient with no previous history, consulted for a left breast nodule that had been evolving for 1 month. Clinical examination revealed a 30 mm nodule in the upper left outer quadrant of the left breast, which was poorly defined, indurated and mobile. The examination of the ganglionic airs showed an ipsilateral axillary lymphadenopathy of 1.5 cm, which was mobile. The nodule has been classified ACR5. The extension assessment was negative. The patient had a lumpectomy with left axillary dissection. On gross examination, the piece measured $8 \times 7 \times 4$ cm, with a whitish indurated nodule with a necrotic center, measuring $2.7 \times 2.2$ cm and located 1 cm from the nearest limit. In histology, it was an infiltrating squamous cell carcinoma and was classified grade III according to SBR. The tumor was made of large carcinomatous lobules with distinct squamous differentiation (Figure 1). Vascular emboli were present. Immunohistochemically, Cytokeratin 5/6 was focally expressed (Figure 2). The hormone receptors were negative, HER2 was negative (score 0) (Figure 3) and the proliferation index (Ki67) was 60%. There was a metastatic lymph node (1N+). The patient received adjuvant chemotherapy and radiation therapy. Currently, the patient has no local recurrence or remotely with a decline of 2 years.

### Case 3

An 89-year-old patient with a history of cardiovascular disease consulted for a right breast nodule that has been evolving for 6 months. Clinical examination revealed a nodule measuring $35 \times 30$ mm at the union of the upper quadrants and it was poorly limited and mobile, without skin invasion. The ganglionic areas were free. Radiology concluded a suspicious nodule classified ACR5. The patient had a lumpectomy. The macroscopic examination showed a piece of $7 \times 6 \times 2.5$ cm with a well-defined and yellowish nodule that was measuring $3.3 \times 3.3$ cm. It was distant from the surgical margins. Microscopic examination revealed a metaplastic carcinoma with epidermoid variant and was classified grade III according to SBR modified by EE. It was made of spans and clusters of contiguous polyhedral cells with a large, highly atypical and mitotic nuclei (>10 mitoses/10 CFG). There was no evidence of endovascular tumor emboli. Immunohistochemically, the hormone receptors were negative, HER2 was not overexpressed (score 0), the proliferation index (Ki67) was 60% and there was an intense and focal expression with P63. The patient died after 6 months of diagnosis with a complication of her cardio-vascular pathology.

### Case 4

A 54-year-old patient with no previous history, presented with a left breast nodule that had been evolving for a month. Clinical examination revealed a 45 mm nodule at the upper and lateral quadrant. Mammo-echography showed a poorly defined nodule that was classified ACR5. Micro biopsy concluded to a nonspecific type of infiltrating carcinoma with focal squamous metaplasia. The tumor was classified grade III according to SBR and was made by clusters and trabeculae of cells with focally squamous differentiation (Figure 4). The mitotic index was 17 mitoses/10 CFG. Immunohistochemically, 60% of the cells at the NST type carcinomatous contingent (Figure 5), expressed RO with low to moderate intensity. RP were negative. HER2 was contentious (score 2) and a FISH study is ongoing. The proliferation index (Ki67) was 40%. The patient is currently undergoing treatment.

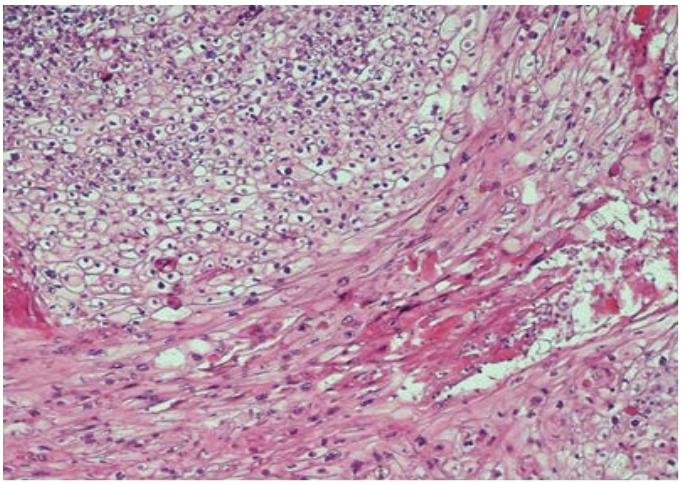

**Figure 1:** Hematoxylin and eosin staining. Invasive squamous cell carcinoma made of large lobule and cords with polygonal cells, eosinophilic cytoplasm and intercellular bridges (10x).

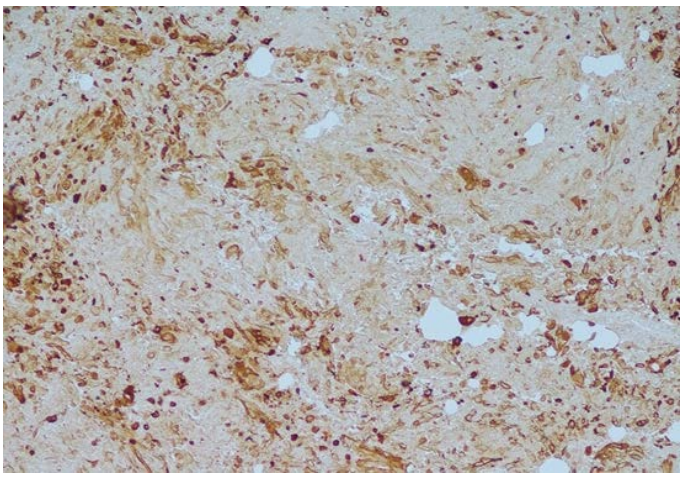

**Figure 2:** Focal expression of cytokeratin 5/6 in carcinomatous cells.

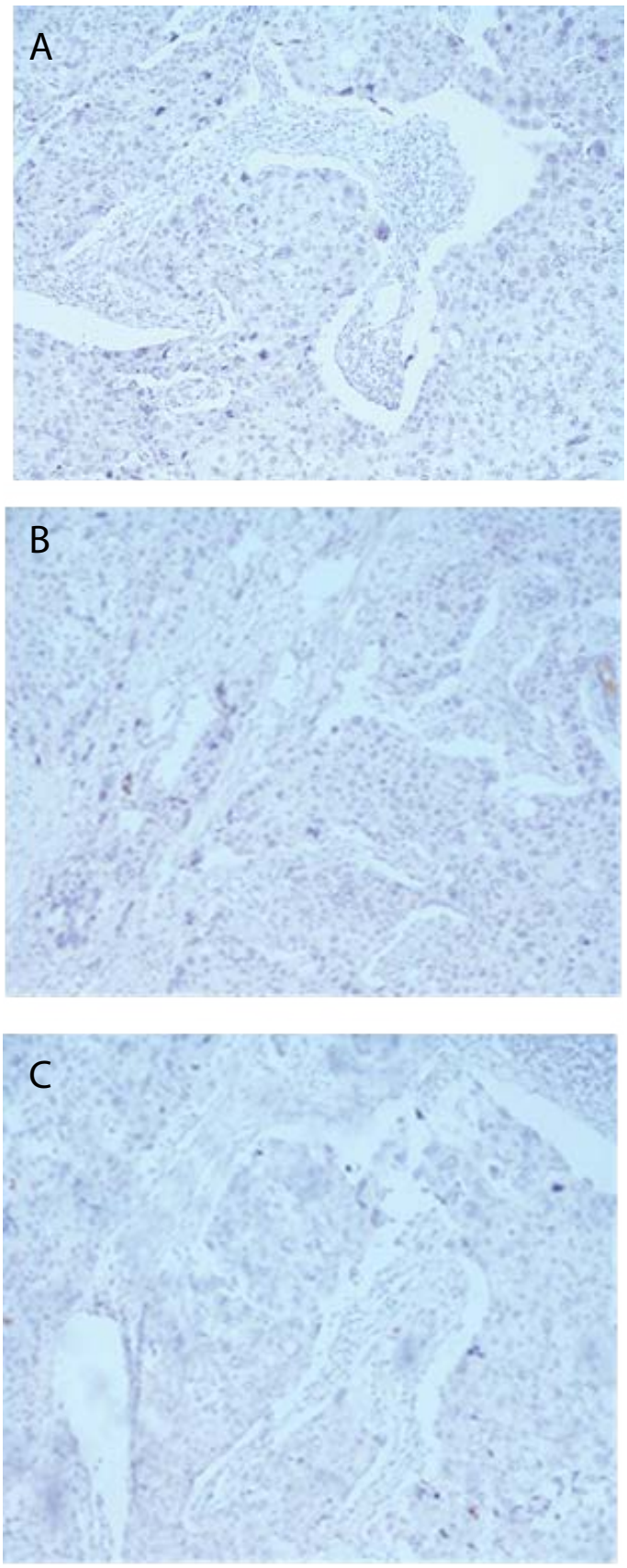


**Figure 3:** Absence of nuclear staining for hormone receptors ER (A) and PR (B); (C) Absence of overexpression of Her2 (score 0).

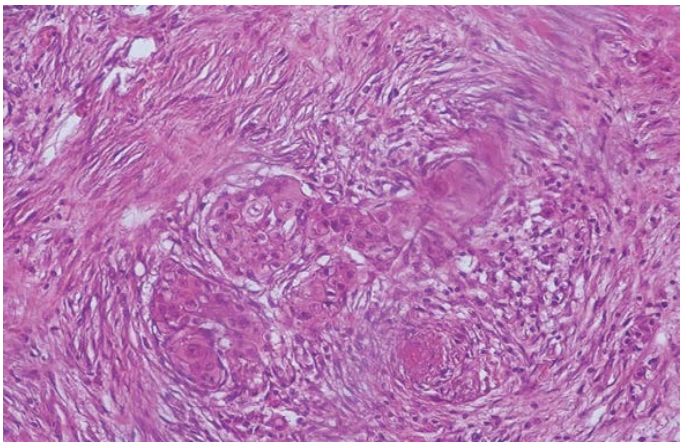

**Figure 4:** Hematoxylin and eosin staining. Invasive Carcinoma with squamous cell differentiation (20x).

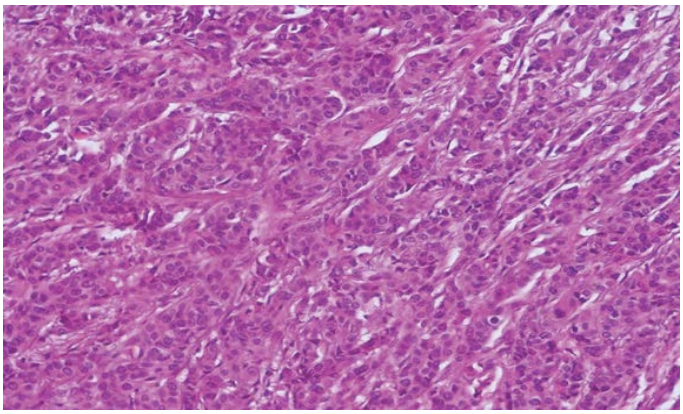

**Figure 5:** Hematoxylin and eosin staining. NST-type carcinoma: infiltrative carcinomatous proliferation made of cords of moderate size cells, with eosinophilic cytoplasm and moderate nuclear atypia (20x).

## Discussion

Metaplastic carcinoma is a very rare subgroup of breast cancers and accounts for 0.2-5% of all invasive carcinomas [1]. It has long been considered as a ductal carcinoma that has undergone metaplastic changes [5,6]. Among the arguments, supporting this hypothesis is the immunohistochemical positivity of cytokeratin in both the epithelial and mesenchymal components. In contrast, other studies suggest that MBC is a clonal entity that is thought to derive from precursors of myoepithelial cells or myoepithelial cells themselves. Several arguments favor this histogenetic hypothesis such as the presence of neoplastic myoepithelial proliferation around ductal structures located on the periphery of certain metaplastic carcinomas of the breast [7,8], the rarity of the association of MBC with ductal or lobular carcinomas *in situ* [9] and frequent positivity and expression of MBC tumor cells for smooth muscle actin and for S100 protein [10,11]. Finally, recent studies show that metaplastic carcinomas, and in particular those with fusiform cells, derive from a transition phenomenon of epithelial cells into mesenchymal cells and can be classified in a recently individualized molecular subtype that is claudin-low [4]. This cancer often affects postmenopausal women over 55 [12,13] In our series all patients were female (100%). The mean age of the patients was 53 years with extremities ranging from 19 to 89 years. It should be noted that the occurrence of this type of cancer at a very young age (19 years old) is rarely described in the literature [13], MBC presents clinically as a mass, which is usually accompanied by inflammatory

signs, ulceration of the skin, nipple retraction or discharge [14,15]. In our series, all patients (100%) consulted for breast mass without inflammatory signs or other associated signs. The tumor size varies, according to the literature, between 1.2 to >10 cm with an average of 3.9 cm [4]. Our series showed a mean tumor size of 3.87 cm with extremes of 3 to 4.5 cm. Metaplastic carcinomas are characterized by a less frequent and axillary lymph node involvement than other common breast cancers and it is seen in 8-40% of cases at the time of diagnosis according to the literature [16,17]. It is absent in 70% of cases during axillary dissection [18]. The rarity of lymph node metastases is due according to some studies to the presence of a mesenchymal component, mainly the sarcomatous one. In addition, some authors note that the risk of lymph node metastasis goes hand in hand with the percentage of the carcinomatous component in a given tumor [19]. Wargotz et al. reported in their studies an incidence of axillary lymph node metastasis ranging from 6% to 26%, depending on the subtype of metaplastic carcinoma of the breast [20]. Paradoxically, MBC is characterized by a high rate of haematogenous metastasis [21]. In our series, we found through the clinical examination a single case with lymphadenopathy (25%). WHO has defined MBC as a heterogeneous group of tumors that are characterized by differentiation of neoplastic epithelium into squamous cells and/or mesenchymal-looking-elements, including but not limited to spindle, chondroid, osseous and rhabdomyoid cells. These tumors can be either entirely composed of metaplastic elements, or a complex admixture associating a carcinoma and metaplastic areas [4]. Macroscopically, metaplastic carcinoma of the breast has no specific appearance and may correspond to a well-limited or not. Sometimes there may be a degenerative cystic appearance with necrotic changes mainly in squamous cell carcinoma. Generally, the size of this type of carcinoma is relatively larger than that of non-specific infiltrating carcinoma with an average size of 3.9 cm [4] (Tables 1-3).

In our series, well-limited character was found in 25% of cases (n=1). Histologically, we will detail the MBC with squamous cell metaplasia because we found this sub type in 100% of our cases. Squamous metaplasia carcinoma often occurs in a cystic form with a cavity bordered by atypical or even pleomorphic squamous epithelium. It infiltrates the adjacent tissue in the form of cords or nests associated with an important stromal reaction. It is associated with a significant inflammatory infiltrate. The diagnosis of primary breast squamous cell carcinoma can only be retained after having eliminated a secondary localization of squamous cell carcinoma in another organ, particularly the skin. The degree of squamous differentiation of this type of tumor is variable allowing to individualize: The fusiform subtype: the fusocellular aspects are observed especially at the level of the invasion front of the tumor. The acantholytic variant is characterized by the formation of irregular slits bordered by atypical squamous cells having a pseudo glandular or pseudo angiosarcomatous appearance. This form poses a problem of differential diagnosis with angiosarcoma. Squamous metaplastic carcinoma may be pure or associated with a non-specific infiltrating carcinoma as it was found in one of our cases [4]. Immunohistochemical analysis shows that more than 90% of breast metaplastic carcinomas are negative for ER, PR and Her2 and are positive for cytokeratin 5/6 and 14 and EGFR. In our series, hormone receptors were present in two cases. For HER2, it was negative (no overexpression, score0 in 2 cases and score1 in only one case) in 3 cases and litigious (score 2+) in a case requiring the use of a FISH analysis. The breast metaplastic carcinoma proliferation index is high in our series with an average value of 52.5%, which is consistent with the data of the literature. To confirm the epithelial differentiation of these tumors, it is recommended to use more than an immunohistochemical marker [4]. The most frequently used antibodies are: cytokeratin of high molecular weight and particularly: 34betaE12, cytokeratin 5/6, cytokeratin 14 and AE1/AE3. Low molecular weight cytokeratins are negative. P63 is expressed in more than 90% of metaplastic carcinomas. In our series the CK5/6 and the P63 were requested in two out of four cases and were positive. The immunohistochemical study plays an important role in the elimination of different differential diagnoses. The most frequently used antibodies are cytokeratin, P63, CD34, bcl2. The majority of MBC belong to the spectrum of 'basal-like' tumors, triple negative breast cancers (RO-, RP-, HER2- and express high molecular weight cytokératins CK5/6 and CK14 [4] (Tables 1-3).

These tumors often express EGFR, especially in metaplastic squamous cell carcinoma or MBC with fusiform cells. This overexpression has been

| Variables | Sex | Age (Year) | Clinical presentation | Seat of the Lesion | Size of the lesion (mm) | Inflammatory Skin Signs | Axillary Lymphadenopathy |
|---|---|---|---|---|---|---|---|
| Case 1 | Female | 19 | Nodule | Left Breast | 45 | Absent | Absent |
| Case 2 | Female | 49 | Nodule | Left Breast | 35 | Absent | Ipsilateral |
| Case 3 | Female | 89 | Nodule | Right Breast | 30 | Absent | Absent |
| Case 4 | Female | 54 | Nodule | Right Breast | 45 | Absent | Absent |

**Table 1:** Clinical features.

| Variables | Sampling Type | Macroscopic Aspect | Histological Type | SBR Grade | Axillary Lymph Node Dissection | Vascular Emboli |
|---|---|---|---|---|---|---|
| Case 1 | Micro Biopsy | Well Limited | Squamous Cell Carcinoma | III | Yes (Negative) | Absent |
| Case 2 | Lumpectomy | Poorly Limited | Squamous Cell Carcinoma | III | Yes (Positive) | Present |
| Case 3 | Lumpectomy | Poorly Limited | Squamous Cell Carcinoma | III | No | Absent |
| Case 4 | Micro Biopsy | Well Limited | NOS Type Carcinoma With Focal Squamous Cell Metaplasia | III | No | Absent |

**Table 2:** Pathologic features.

| Variables | CK 5/6 | P63 | RE (%) | RP (%) | Her2/neu (Score) | Ki67 (%) |
|---|---|---|---|---|---|---|
| Case 1 | Not Made | Not Made | 20 | 10 | 1 | 50% |
| Case 2 | Positive | Not Made | 0 | 0 | 0 | 60% |
| Case 3 | Not Made | Positive | 0 | 0 | 0 | 60% |
| Case 4 | Not Made | Not Made | 60 | 0 | 2 | 40% |

**Table 3:** Immuno-histochemical features.

linked to EGFR amplification, particularly in squamous metaplastic carcinomas. In our series, 50% of cases presented a basal-like profile. According to the literature, no series is sufficient to determine the prognosis of MBC. The 5-year survival rate is 54.5%, which is lower than that of non-specific infiltrating carcinomas (85.1%) and non-metaplastic triple negative breast carcinomas (73.3%) [22]. Chao et al. report that the duration of clinical signs, tumor size and lymph node status are the determinants of survival [23]. In the case of squamous cell carcinoma, tumor size and axillary lymph node involvement are considered as the main prognostic factors in the literature [24]. Some authors consider that the predictive factors for a bad evolution of epidermoid cancers are fusiform component, necrosis, and cellular acantholysis [25]. The presence of distant metastases is a pejorative prognostic element. In fact, metaplastic carcinomas of the breast have a high metastatic potential, despite the rarity of regional lymph node involvement with frequent bone and lung localization [19].

## Conclusion

In summary, we report the clinicopathologic features and prognostic factors of MBC which remains poorly known because the rarity of this entity and its heterogeneity. Our results were generally in agreement with those of the literature. Nevertheless, one of the particularities of our series is the very young age of one of our patients (19-year-old woman) and which is rarely described in other series. The diagnosis is made thanks to the pathological examination. The lack of expression of Hormonal receptors and HER2 limits the therapeutic management which is still poorly codified. Thus further studies are required to identify the particular molecular features of this tumor in order to develop more effective agents and improve its prognosis.

### Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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