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Giant Malignant Phyllodes Tumor: A Multi-Recurrent and Metastatic Case

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Abstract

Phyllodes tumor (PT) is a rare fibroepithelial tumor, representing between 0.3 and 1% of all breast cancers. According to WHO classification, PTs are divided into benign, borderline, and malignant, based on histological characteristics. Imaging features on mammography, sonography and MRI are overlapped and do not allow to discriminate between the different subtypes. Malignant PT presents as large mass, fast-growing, with lobulated margins, heterogeneous in eco-structure and signal intensity due to the compresence of solid and cystic components. Sometimes necrosis and hemorrhage may be observed. Anatomopathological examination is mandatory for the correct diagnosis. All PTs have an inherent ability to recur locally and to metastasize, which varies depending on histological grade. Local recurrences usually occur in high-grade subtypes, whilst distant metastases are almost exclusively found in malignant PTs. Lung metastases are the most frequent. Follow-up imaging is not standardized, resulting in lower disease-free survival. Breast MRI every 6 months and chest CT scan annually could ease the identification of common locoregional recurrences and the onset of lung metastases on time for proper assessment.

Keywords: Malignant phyllodes tumor; Local recurrence; Metastasis; Breast imaging; Follow-up.

Abbreviations: PT: Phyllodes Tumor; US: Ultrasound Examination; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; MDT: Multidisciplinary Team; CNB: Core Needle Biopsy; ADC: Low Apparent Diffusion Coefficient.

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Introduction

Phyllodes tumors (PT) are relatively rare tumors, accounting for approximately 0.3 to 1% of all diagnosed breast neoplasms [1]. According to World Health Organization, PTs are classified as "fibroepithelial and hamartomatous neoplasms of the breast", and divided into three subtypes, i.e. benignant, borderline and malignant, based on histologic features, including nuclear atypia, stromal cellularity, mitotic activity, tumor margin appearance, and stromal overgrowth [2].

Most PTs belong to benign subtype, representing between 35% and 64% of cases, followed by borderlines, which constitute between 7% and 40%, while malignant PTs affect up to the remaining 30% of patients [3,4].

The current literature on this topic is scarce, given the rarity of this tumor. Bernstein [5] et al., in a 17-year period study, reported an incidence rate of PTs of 2.1 per million women, with a higher incidence in the Latina White population. Female sex is the most affected by PTs, presenting at a median age of 42 to 45 years [5-7]. Furthermore, older women are usually affected by high-grades PTs [8]. The few reported cases in men breast are usually associated with gynecomastia, which could suggest the potential role of estrogenic/androgenic activity imbalance on disease onset [9].

The disease course is unpredictable and its correlation with histologic grade is not linear: all PTs have a high intrinsic capacity of local recurrence and/or metastatic dissemination, nonetheless malignant PTs have the worst oncological outcomes [10]. Regardless of subtypes, the wide local excision, with clear margins of at least 10 mm, is actually the gold standard treatment [11-13]. Given low incidence of PTs and subsequent paucity of data in the current literature, follow-up is not standardized, resulting in lower disease-free survival, especially for malignant PTs [14].

This study reported clinical pathway, radiological findings, and case-specific assessment of a patient affected by multi-recurrent and metastatic malignant PT.

Case presentation

We reported the clinical and radiological scenario of a 66-year-old woman accepted to Mater Olbia hospital, for a fast-growing breast mass firstly identified 3 months before the consultation, associated with weight loss (8-9 kg) during the past 8 months. Patient's previous medical history included the surgical excision of a right breast fibroadenoma (30 years prior), while no positive family history for malignancies was reported.

On clinical examination, the right breast appeared enormously enlarged due to a complete replacement by a voluminous mass with a maximum diameter of 40 cm. The skin was stretched, thinned and reddish with diffuse signs of superficial ischemia. Furthermore, a dense subcutaneous vascular network was observed. The areola-nipple complex appeared over-sized and tense, with no evidence of infiltrative elements. No suspicious axillary lymph nodes were appreciated (Figure 1).

The ultrasound examination (US) was suddenly performed, showing the complete replacement of the right breast by a circumscribed heterogeneously hypoechoic multi-lobulated solid-like mass, with fluid components. The lesion did not appear to infiltrate the superficial plane along the entire skin covering. Large caliber and high flow new vessels were also observed on color-doppler US. No anomalies of axillary lymph node architecture were detected (Figures 2,3).

Magnetic Resonance Imaging (MRI) was not executed because the large size of the mass exceeded the gantry capacity.

As a consequence, a whole-body computed tomography (CT) with contrast-medium injection was performed to value the loco-regional extent of the disease and the presence of distant metastases. On CT, the breast mass appeared closely to the homolateral pectoral muscle, compressing the right chest wall. Nevertheless, neither lungs' nor other organs' involvement was revealed (Figure 4).

After the Multidisciplinary Team (MDT) discussion the standard pre-surgical biopsy was avoided for several reasons, namely the high risk of superficial ulceration and profuse bleeding, as well as the already clear indication for surgery. After informed consent, the patient underwent nipple-sparing right mastectomy with lymphadenectomy and contextual plastic remodeling with dermal flap. Postoperative course was regular, and no perioperative complications were reported with discharge at the eighth post-operative day. The final anatomopathological examination reported the diagnosis of malignant PT. The diagnosis of malignant PT was then confirmed by two different pathologists.

Six weeks after surgery, MRI showed the presence of three small areas (between 4 and 12 mm) of altered enhancement closely to the fascia of the right pectoral muscle, categorized as disease recurrence (Figure 5).

The patient underwent a second surgical excision a few days later and multiple mesenchymal lesions that deeply infiltrated the striated muscle were detected through anatomo-pathological examination.

According to MDT, 1-month adjuvant radiotherapy using 6 MV photons with 3DCRT technique on the right chest wall was then started.

Another disease recurrence was identified two months later radiotherapy. Indeed, MRI revealed a rounded mass in the right axillary hollow with irregular margins, marked inhomogeneous enhancement, and signs of infiltration of the ipsilateral pectoral muscle. Moreover, the exam showed a satellite smaller nodule localized inside the pectoral muscle (Figures 6,7).

A core needle biopsy (CNB) of the major nodule (5 cm) was then performed, revealing high grade mesenchymal malignant cells, and confirming the diagnosis of malignant PT's recurrence.

The third curative strategy consisted in a two-step procedure: firstly, the oncological resection extended to the pectoral muscle was achieved, and subsequently, the patient received bleomycin infusion with electrochemotherapy.

The subsequent 6-months recurrence-free follow-up was disclosed through mammography and serial sonographies.

Six months after the last procedure, MRI highlighted the appearance of another disease recurrence in the right anterior dentate muscle (Figure 8).

Multiple solid pulmonary nodules were also described as secondary findings. Chest CT scan confirmed these findings (Figure 9).

Given the multiple surgeries and the rapid growth of secondary disease, the patient received chemotherapy treatment.

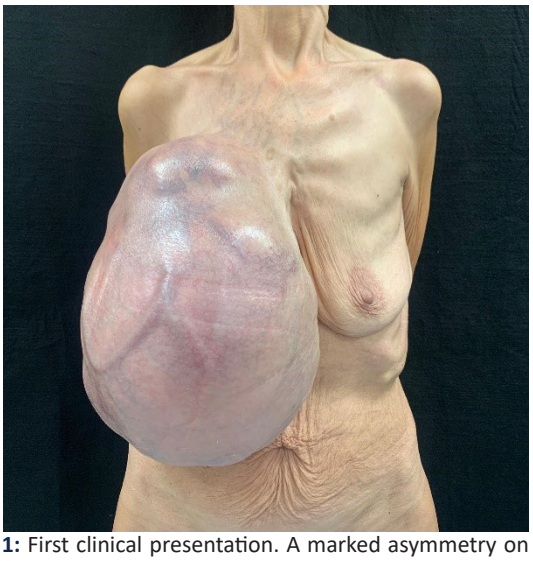

Figure 1: First clinical presentation. A marked asymmetry on breast size can be noticed. A voluminous hard mass replaces the right breast. The overlying skin appears stretched and thinned.

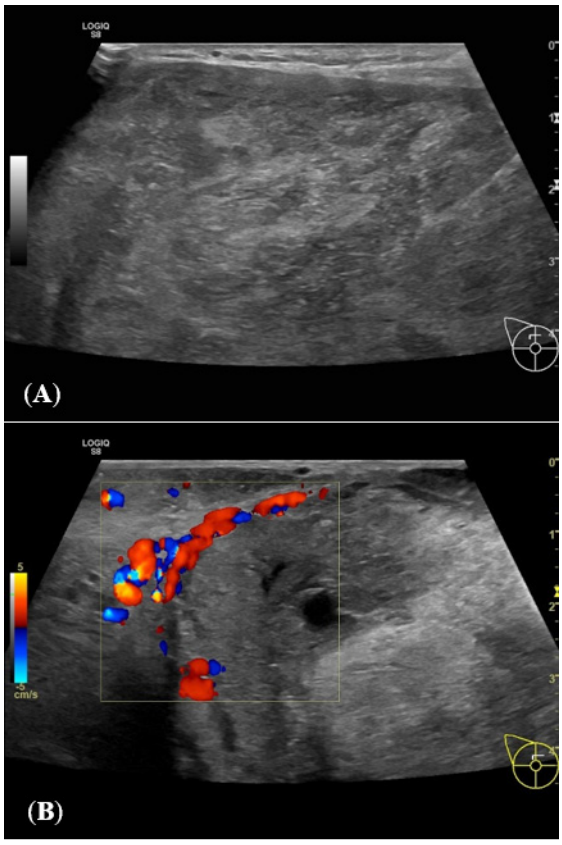

Figure 2: (A) Breast US shows a heterogeneous hypoechoic solid-like mass, with circumscribed margins. **(B)** Color-Doppler US demonstrates internal and surrounding hypervascularity.

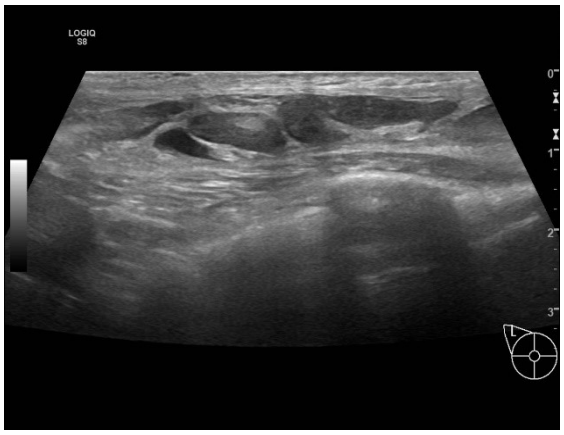

Figure 3: Regular aspect of two lymph nodes in the right axillary hollow at ultrasonography examination.

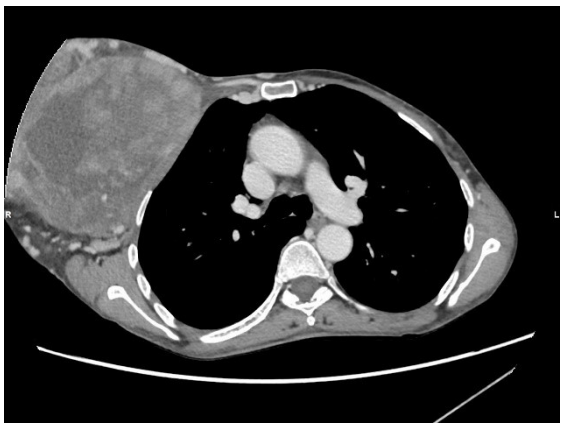

Figure 4: Portal phase of chest computerized tomography (CT) showing a large heterogeneous mass in the right breast. The lesion appears closely to the homolateral pectoral muscle.

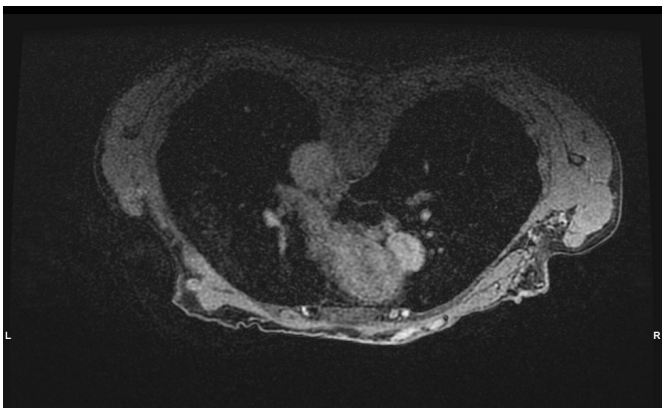

Figure 5: T1-weighted axial contrast-enhanced magnetic resonance imaging (MRI) shows two out of three focal areas of altered enhancement closely to the fascia of the right pectoral muscle, categorized as local recurrences.

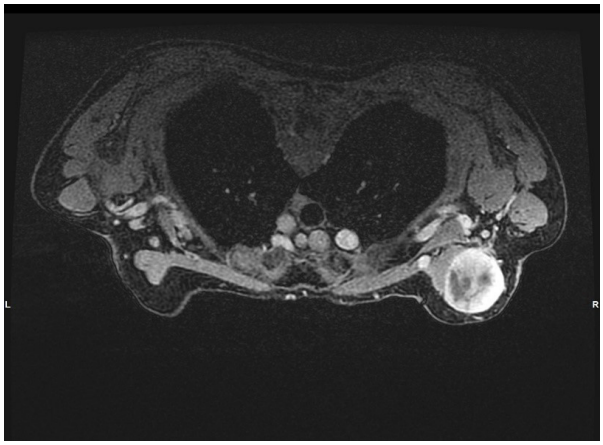

Figure 6: T1-weighted axial contrast-enhanced magnetic resonance imaging (MRI) shows two focal areas of altered enhancement, categorized as local recurrences, with the larger in the right axillary hollow and the smaller in the right pectoral muscle.

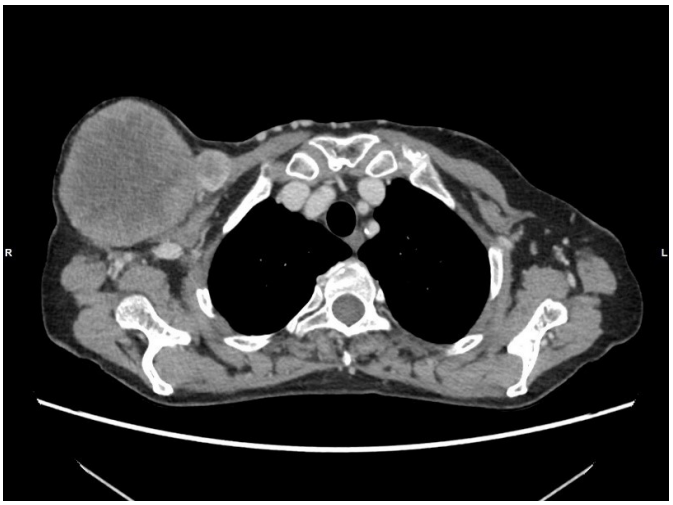

Figure 7: Portal phase of chest computerized tomography (CT) showing the same two nodules seen in figure 6. CT was performed three weeks after MRI: in this little timelapse the two lesions almost doubled their volume.

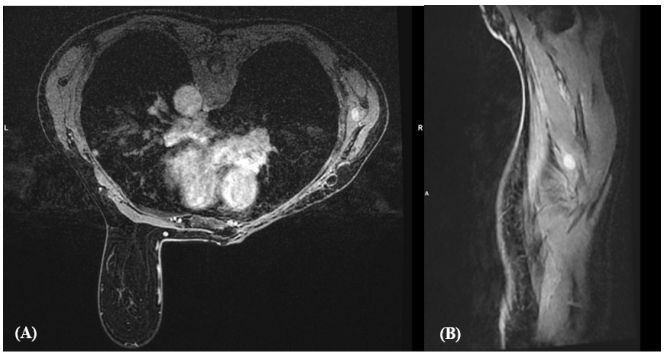

Figure 8: (A) T1-weighted axial and **(B)** sagittal contrast-enhanced magnetic resonance imaging (MRI) showing a focal area of altered enhancement in anterior dentate muscle.

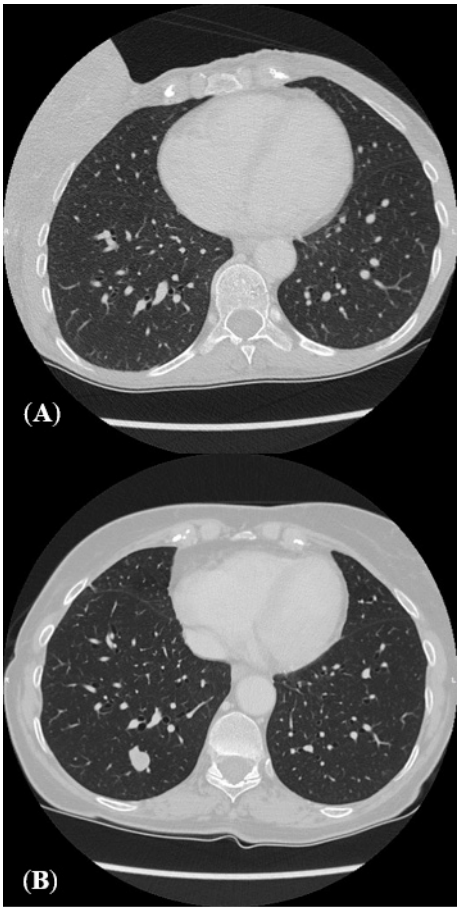

Figure 9: Chest computerized tomography (CT) images demonstrating the appearance of lung metastasis on the right lower lobe. **(A)** First CT **(B)** CT control eight months later.

Discussion

The discrimination between malignant PTs and the other two subtypes (benign and borderline) is even nowadays challenging, especially considering two cornerstones in tumor identification and surveillance as mammography and US. Besides, MRI can be really helpful to clarify the risk of PT malignancy [15,16].

PTs are mostly perceived as breast bumps during physical examination. However, around 20% of PTs are diagnosed occasionally as abnormal findings on screening mammography [17].

At clinical presentation, PTs usually present as large masses with regular or lobulated margins. Most of cases, these breast lesions are mobile and painless [4,18]. Ancillary features may include nipple retraction, ulceration, nipple discharge, or tumor fixation on chest wall [19].

As reported by Foxcroft [20] et al, PTs are characterized by a rapid growth during the surveillance period. Consequently, the identification of a fast-growing pattern in the differential diagnosis between PTs and other lesions, such as fibroadenomas, could be crucial in the decision-making process.

Suspicious breast nodules on physical examination should be investigated with mammography and US.

A well-circumscribed oval or lobulated opacity, considerable in size, is the most common presentation at mammography. Further

rare radiological findings are the presence of a lucent halo of fat and calcifications. At sonography, PTs appear as heterogeneous hypoechoic solid-like masses, with circumscribed margins, lobulated, with round or cleft-like cystic spaces and posterior acoustic enhancement. Color-doppler US can reveal hypervascularization inside solid areas [15,21,22].

Breast MRI may be helpful to value the extent of the disease, guiding in therapeutic assessment, and to highlight some features that can be addressed to high-grade PTs. Malignant PTs are characterized by cystic changes with irregular walls and septa on T2-weighted images. T1-weighted images could identify intra-cystic hemorrhage as a high signal intensity. After contrast-medium injection, altered and heterogeneous enhancement is peculiar to malignant subtypes due to the compresence of solid and cystic components [16,23,24]. Additionally, Yabuuchi [16] et al. underlined the low apparent diffusion coefficient (ADC), tumor signal intensity lower on T2-w and higher on T1-w images compared with the normal breast parenchyma can also suggest a high-grade lesion.

When a PT is suspected, core needle biopsy is required and mostly diagnostic [25]. On the contrary, fine needle aspiration is less accurate with a high false negative rate [25]. If the sample gives an indeterminate or discordant result, excision biopsy is mandatory. At anatomopathological examination, Malignant PTs are characterized by invasive tumor borders, marked degree of hypercellular stromal overgrowth, number of mitoses greater than five per 10 high-power fields, and stromal cellular pleomorphism [1].

All PTs have an intrinsic ability to recur locally and metastasize at distance, which varies according to their histological grade. Local recurrences usually occur within 2-3 years from diagnosis in about 21% of cases, reaching 30% in malignant PT. Distant metastases are found almost exclusively in malignant PTs: lungs (66%), bones (28%) and brain (9%) are the most affected organs [26,27].

A wide surgical excision represents the first-line treatment: margins must be greater than 1 cm to be curative and lower the risk of local recurrence [4,28,29]. Axillary dissection is not routinely recommended considering the rarity of lymphatic and node metastases [27,30]. In case of unclear preoperative diagnosis, with consequent non-oncological resection, a further surgical procedure is mandatory to obtain clear margins [31].

Adjuvant radiotherapy may be required in high-grade PTs, especially when negative surgical margins are not achieved [32]. On the other hand, the use of systemic chemotherapy is still a matter of debate and its administration has to be decided on a case-by-case basis, especially in multi-recurrent and metastatic diseases [4,33-35].

Conclusions

Malignant PTs are characterized by high incidence of local recurrence, even in case of adequate surgical excision. Furthermore, the development of metastatic disease should not be understated.

Given the rarity of the disease, follow-up recommendations are not standardized resulting in multiple surgeries and low disease-free survival.

The introduction into follow-up protocols of breast MRI every 6 months and chest CT scan annually could ease the identification of common locoregional recurrences and the onset of lung metastases on time for proper assessment.

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