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Phyllodes tumor with a benign heterologous osseous component: A diagnostic challenge

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Introduction
Phyllodes tumors (PTs) are uncommon fibroepithelial neoplasms that account for 0.3-1% of all primary breast tumors and for 2.5% of all fibroepithelial tumors of the breast in “Western” countries 1, 2. The median age at diagnosis is about 45 years. In Asian countries the median age at diagnosis is 25-30 years, and PTs account for a higher proportion of breast tumors 2.

PTs are characterized by a combination of an expanding hypercellular stroma with enhanced intracanalicular growth pattern with leaf-like projections into irregular, elongated epithelial-lined clefts. The epithelial component consists of a well differentiated luminal epithelialcell layer surrounded by a layer of myoepithelial cells. Great morphological variations can however be seen 2-4.

According to the World Health Organization (WHO) PTs are graded as either benign, borderline or malignant based on features of the stromal component 2, 5.

Heterologous mesenchymal elements such as osteosarcomatous differentiation in PTs is a known but uncommon phenomenon and have been reported in several cases in the literature 6-11. Borderline and malignant PTs with benign osseous metaplasia are exceedingly rare, and to the best of our knowledge, only one other case has been reported in the English literature 12.

Here we report a case that highlights the difficulty in diagnosing and subsequently grading of a PT with a dominating benign heterologous component and with a very unusual metastatic presentation.

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Case report

A 65 year old woman with no prior malignant illnesses attended a screening mammography, showing a 25 mm large area resembling a benign popcorn like calcification in the right breast, assessed as BIRADS 3 (Figure 1). Ultrasonography of the breast showed a tumor measuring 19 mm with no lymphadenopathy in the axilla. Core needle biopsies were obtained and seen primarily to consist of trabeculae of woven bone with a rim of well differentiated osteoblasts on the surface with no lamellar structure or cartilage. No atypia, mitoses or necrosis was observed. Subsequently an excision biopsy was performed. The macroscopic evaluation revealed a firm well circumscribed process measuring 25x17 mm with white nodular areas including foci of hemorrhage. Since the lesion was considered benign, the surgical margins were not meticulously assessed. On microscopic examination the process was well circumscribed without signs of invasive growth and it was dominated by trabecular bone tissue. Only a minor component of spindle-cell stroma between the bony trabeculae was seen, without any glandular structures. No cytological atypia, necrosis or mitotic activity was seen. The final histological report discussed the finding of the unusual bone formation in the breast tissue, and concluded that it was benign osseous metaplasia. Due to the presumed benign nature of the tumor, no clinical or radiological follow up was offered to the patient.

Eighteen months later the patient reported recurrence of the tumor. Conventional and MR mammography revealed a tumor measuring a maximum of 70 mm. Uptake of Gadolinium contrast in a peripheral rim and in deep septae was seen (Figure 2). In addition a F-18-FDG PET-CT scan was performed. Here increased metabolism in the breast tumor was seen and several calcified nodules in both lungs were noted. The nodules contained very little soft tissue and were seen to be metabolically inactive. Due to their morphology and bilateral distribution they were however considered likely to represent metastatic tumors. Needle biopsies were obtained from the breast tumor and a diagnosis of PT was made, classified as borderline but with suspicion of malignancy. A mastectomy was performed and the macroscopic examination of the breast showed a fairly well circumscribed tumor measuring 10x6x6 cm with a firm consistency. Areas of calcification alternating with hemorrhage were seen. Microscopically a rounded but infiltrating tumor was seen dominated by a mixture of mesenchymal components. Throughout the tumor large areas of matured bone and cartilaginous tissue surrounded by a more primitive fibrous component was seen (Figure 3A). Areas of necrosis and a high mitotic count (15 per 10 high-power fields) were found within the tumor. Only in a small area benign glandular structures with intracanalicular growth pattern were seen (Figure 3B). IHC analyses were performed and a negative reaction for cytokeratins, S-100, myogenic markers, CD34 and CD10 was seen in the mesenchymal component, and the Ki-67 index was 33%.

Excision biopsy from the lung was obtained. The tumor had a pale white color resembling cartilage and the cut surface was seen with bone forming tissue centrally and a peripheral cap of cartilage. Microscopically a well circumscribed, slightly lobulated tumor consisting of older and more newly formed well differentiated bone tissue as well as cartilage with endochondral ossification was seen (Figure 4).

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Discussion

Bone forming lesions of the breast are very rare. As a primary tumor in the breast osteosarcomatous components can occur as osteosarcomatous differentiation in a metaplastic carcinoma, a pure extra skeletal osteosarcoma or as part of the stromal component of a PT 6. Recently published studies reveals that at least malignant PTs possess mesenchymal stem cell features enabling differentiation into various cell lines including osteocytes 13. In our case the dominant osseous component consisted of mature bone, whereas the fibrous component was dedifferentiated and met the criteria for malignancy in the mastectomy specimen. A small focus of benign glandular structures within the tumor excluded a primary sarcoma of the breast. The differential diagnostic consideration of metaplastic carcinoma was rejected due to completely negative reaction for several cytokeratins on IHC staining. In conclusion the tumor in the mastectomy specimen was diagnosed as a malignant PT with benign osseous and chondroid metaplasia. Distant metastases have almost exclusively been reported from malignant PTs and the most common sites are lungs, bone, pleura and mediastinum, due to hematogenous spread 5, 14-18. In a review by Tan et al. metastases were found to be comprised of malignant stromal elements without accompanying epithelium 5. In our case the patient’s lung metastases contained a minor fibrous component morphologically resembling that of the tumor in the mastectomy specimen. Based on this finding and the presence of multiple lesions in both lungs the diagnosis of metastasis from malignant PT was proposed. Since benign PTs rarely undergo malignant transformation the initial excision biopsy was revised 1, 17. Based upon histology and clinical behavior the diagnosis was altered to a borderline PT with benign osseous metaplasia though the lesion doubtfully met the strict diagnostic criteria for PT. According to WHO classification PTs should be graded into benign, borderline and malignant categories based on morphology alone. Each microscopic variable should be assessed as benign, borderline or malignant, however establishing an accurate and reproducible diagnosis can be challenging, and a reliable biomarker to support morphological findings does not exist. Hence PTs with a dominant benign heterologous component comprises a distinct diagnostic challenge for the pathologist, both in terms of recognizing the tumor as a PT and the subsequent grading. If a malignant heterologous component is present the tumor is by definition regarded as malignant 2, 5. The appropriate surgical approach to PTs is a matter of ongoing debate. Previously most institutions have recommended PTs removed with margins of at least 1 cm regardless of histological subtype 1. In the latter years several studies concerning this topic have been conducted. A number of studies found that free surgical margins are necessary to treat PTs, but that the extent of surgical excision does not have an impact on disease free survival 19-23. In one study of 285 Korean patients Yom et al. found tumor size ≤ 5 cm and frequent mitoses (≥ 10/10 high-power fields) to be independent risk factors for local recurrence in PTs. The authors therefore proposed that wide margins should be the goal in treating this distinct subgroup of PTs 24. In another Korean study including 193 patients Kim et al. found that borderline PTs treated with local excision had a higher local recurrence rate compared to borderline PTs treated with wide excision or mastectomy 16.
Conclusion

PTs with heterologous elements are rare neoplasms that pose a diagnostic challenge. Especially PTs dominated by one or more benign heterologous elements can be challenging in terms of both correct diagnosis and subsequent grading. Here we have presented a rare case with a borderline PT that reoccurred as a malignant PT dominated by benign osseous and chondroid metaplasia. Primary diagnosis was unfortunately delayed due to the highly unusual morphology. At recurrence the patient had multiple lung metastases. Due to the metastatic spread of the disease curative treatment was sadly not possible.

References


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Figures

Figure 1
Figure 3A

Figure 3B
Legends

Figure 1
Cranio-caudal mammography of the right breast showing a 25 mm large lesion with popcorn like calcification. Figure 2
Gadolinium contrast-enhanced magnetic resonance image showing a recurrent tumor in the right breast measuring up to 70 mm. Uptake of Gadolinium contrast in a peripheral rim and in deep septae is seen.

Figure 3
The mastectomy specimen containing a tumor measuring 10x6x6 cm. The tumor was dominated by a mixture of mesenchymal components.

Figure 3A. Surrounding the mature bone and cartilaginous tissue is a fibrous component with areas of high cellularity. The cells were plump to spindle shaped with atypical nuclei and with high mitotic activity (hematoxylin-eosin).

Figure 3B. The classical intracanalicular growth pattern of phyllodes tumors was only seen in one small area (hematoxylin-eosin).

Figure 4
Microscopic appearance of a calcified metastatic nodule in the lung. The tumor consists of large areas of well differentiated cartilaginous tissue with enchondral ossification (hematoxylin-eosin).

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