BRCA1/BRCA2 patients. One of the genes that have been implicated is the *CHEK2* gene. The significance of changes in the *CHEK2* gene is not well understood. Based on current information, it is indicated that the gene is a risk modifier for developing breast cancer.

Studies have shown that individuals with a *CHEK2* gene fault have increased risk (20–25%) for developing breast cancer in general and cases with a previous diagnosis have an even greater risk (30–40%) to represent with further breast cancer in their lifetime.^{9,10} This increase in cancer risk is also dependent on personal and family history. Other studies have suggested that *CHEK2* carriers also show an increased risk of cancer in the colon, prostate, thyroid and ovary.¹¹

CHEK2 is a tumour suppressor gene that encodes for serine/threonine kinase and plays a major role in the regulation of the cell cycle, apoptosis and DNA repair. Early studies suggest *CHEK2* may have prognostic implications, showing that the use of chemotherapy in combination with *CHEK2* inhibitors has beneficial effects by sensitising tumour cells to the drugs.¹²

One study has shown that there is significantly increased frequency of germline mutations in DCIS under the age of 40. These findings are consistent with our patient's demographics, and similarly in line with the reported peak age of fibroadenoma with malignancy in the literature.

None of the cases of fibroadenoma with malignancy reported in the literature mention molecular findings. It is unknown how many of these cases are associated with germline mutations. Further studies are required to assess this subgroup of patients.

To the authors' knowledge, we report the first case of *CHEK2* mutation present in a fibroadenoma with *in situ* and invasive malignancy. This case illustrates the importance of molecular testing in unusual breast cancers. The identification of germline mutations such as *CHEK2* has current and future merit in management and prognostic implications involving the patient and family members.

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Primary breast telangiectatic osteosarcoma: a rare entity and a potential diagnostic pitfall

Sir,

Telangiectatic osteosarcoma (TOS) is a rare osteosarcoma subtype with an incidence of 2–12% among all cases of osteosarcoma.¹ Considering the rarity, reliable data documenting mammary TOS are scarce. So far, there are only two references which report that breast TOS arises as a result of the very unusual phenomenon of further malignant differentiation within a pre-existing benign or malignant neoplasm of the breast.^{2,3} In this article, we describe a rare case showing the unequivocal morphology of TOS of breast without breast precursor lesions. To the best of our knowledge, this case represents the first case of TOS in breast without breast associated diseases.

A 60-year-old woman presented to our centre for evaluation of a painful lump in her left breast for the previous 10 days. Her medical history was significant for hypertension and chronic bronchitis. Physical examination revealed a fixed mass, 4×3 cm, in the upper outer quadrant of her left breast. Ultrasonography (US) showed a hypoechoic, cystic mass with relatively regular luminal outline and numerous fluid levels at 3 o'clock, 2.5 cm from the nipple. Biopsy revealed a high-grade malignant tumour.

Lumpectomy was performed. Macroscopically, the surgical specimen measured 4.5×4.0×4.0 cm (Fig. 1A). Sectioning revealed a haemorrhagic cystic mass with blood clots (Fig. 1B). Microscopically (Fig. 2), spaces were blood-filled and separated by septa containing highly malignant mesenchymal cells with osteoid. Bone calcification was absent. Mitoses were obvious. Immunohistochemical staining was performed using antibodies against cytokeratins (AE1/AE3, Cam5.2, CK7, CK5/6, CK14, CK17, 34βE12 and CK20), epithelial membrane antigen (EMA), P53, EA, CD31, CD34, ERG, S100, SOX10, Melan A, CD10, CD117, calponin, desmin, CD68, CD163, CD99, IDH1, SATB2, oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).

Fig. 1 (A) Gross appearance of the excised cystic mass. The lesion shows a haemorrhagic cystic appearance. (B) The cyst is filled with blood clot, with no gross evidence of solid tumour.

Fig. 2 (A) Histopathological examination shows the tumour edge is well circumscribed but focally infiltrative. (B) The atypical cells have oval to round nuclei and eosinophilic cytoplasm, some cells are nucleated tumour giant cells. Mitotic figures are frequently seen, but abnormal mitotic figures are not evident.

Antibodies against epithelial markers were all negative, evidencing non-epithelial character of the tumour. Vascular markers (CD31, CD34, ERG), neural differentiation markers (S100, SOX10), and melanoma markers (S100, Melan A), were all negative. The tumour cells were positively expressed in SATB2, but not in desmin. P53 was diffusely positive in most of the neoplastic cells. CD99 was focally positive in the tumour cells. The tumour cell proliferative activity (Ki-67 positivity) was 30%. Fluorescence *in situ* hybridisation (FISH) results were negative for *USP6* translocation. After thorough sampling of the tumour, there were no histopathological findings of breast cancer, malignant phyllodes tumour, or carcinosarcoma. The final diagnosis was high-grade primary breast TOS.

In order to achieve wide resection margins, the patient proceeded to mastectomy and sentinel node biopsy. There was no evidence of metastatic spread in the lymph node or vascular invasion. Whole-body positron emission tomography (PET)/computed tomography (CT) allowed exclusion of primary bone osteosarcoma and did not reveal any evidence of distant metastases. As TOS is a high risk micrometastatic disease, we suggested the patient undergo neoadjuvant chemotherapy; however, the patient refused any further treatment. The patient is presently disease free and is on regular follow-up 3.0 years after surgery.

Primary breast osteosarcoma is a very rare entity. The exact mechanism of its tumorigenesis is still unclear, but an origin from totipotent mesenchymal cells of the breast stroma or a transformation from a pre-existing fibroadenoma, phyllodes tumour or carcinoma has been suggested.⁴ The lesion in our case showed a characteristic macroscopic appearance as a haemorrhagic cyst. Bone calcification was absent. Unlike osteosarcoma which has high serum alkaline phosphatase (AKP), TOS has normal or slightly increased serum AKP level,⁵ which probably reflects small amounts of neoplastic

bone pathologically, and seldom visible matrix mineralisation. Our patient had normal serum AKP level from beginning to end.

When a malignant tumour with mesenchymal components is discovered in the breast, differentiations between metaplastic carcinoma (MC), malignant phyllodes tumour and sarcomas are necessary. MC are typically triple-negative for ER, PR and HER2 amplification/overexpression. MC always express epithelial markers such as AE1/AE3 and EMA. Primary breast TOS lacks markers of epithelial differentiation, such as cytokeratin and other epithelial markers, and also does not express ER/PR/HER2. Of note, the use of cytokeratin should be applied very carefully because aberrant expression of cytokeratin can be rarely detected in sarcomas including osteosarcoma. Thus, numerous and extensive sampling for the specimen is critical. In our case, there was no neoplastic epithelial component after whole sampling of the tumour. The absence of a preexisting fibroepithelial background made phyllodes tumour an unlikely diagnosis. Although no definite components of metaplastic carcinoma or phyllodes tumour were identified after extensive sampling of this tumour, we still could not exclude overgrowth of the sarcomatous component in a phyllodes tumour or metaplastic carcinoma. However, so far the diagnosis of mammary TOS seems to be the best option.

Another destructive, expansile neoplasm of bone composed of multiloculated blood-filled cystic spaces, aneurysmal bone cyst (ABC), should also be considered as a differential diagnosis. ABC contains cytogenic rearrangements of the *USP6* (ubiquitin specific peptidase 6/Tre-2) gene at chromosome band 17p13. *USP6* rearrangements are found in approximately 70% of primary ABC.⁶ In our case, there was no rearrangement of *USP6*, which could rule out ABC diagnosis.

To date, there are no validated treatment guidelines due to limited data, but the best approach documented for localised disease is a wide local excision or mastectomy with negative resection margins. Removal of axillary lymph node is optional. Crèvecoeur *et al.* reported their patient developed an osteosarcoma in the other breast, 15 months after the discovery of the first tumour, and no axillary lymphadenopathy was observed.⁷ These tumors have a propensity for blood-borne rather than lymphatic spread. Among skeletal osteosarcoma, TOS is exquisitely sensitive to modern chemotherapy but there is no literature about mammary TOS treated with chemotherapy.⁸ The benefits of chemotherapy administration should be weighed against the side effects, especially in older or unfit patients. Indications for radiation therapy, in the absence of specific data on breast sarcoma, probably could follow those for soft-tissue sarcomas in general. We suggested that our patient undergo chemotherapy, however the patient refused further treatment on consideration.

Prognostic factors of primary breast osteosarcoma include tumour size, number of mitoses, presence of stromal atypia, histological subtype and resection margin involvement. Among them, size of the tumour tends to be the most important factor affecting prognosis. A better survival rate for patients with smaller (<4.6 cm) tumours has been observed. The most common sites of metastases include the lung, bone, brain, subcutaneous tissue and heart.⁴ Our patient is presently disease free close to 3.0 years following surgery. The good prognosis is probably associated with small tumour size (<4.6 cm), early diagnosis, no metastasis and clean margin by mastectomy. However, primary breast osteosarcomas are considered highly aggressive tumours associated with early recurrence. Lack of follow-up and late recurrence/metastases are common in osteosarcomas, so our patient still requires close follow-up.

Breast TOS is a very uncommon malignancy where a definitive diagnosis is established on the basis of the typical histological architecture and cellular morphology, coupled with immunohistochemical profile. Surgical excision with clear margins remains the cornerstone of treatment and lymph node dissection could be optional. Further studies are required to clarify the biological behaviour of such tumours and optimise therapeutic strategies. Our case represents a very unusual variant of primary breast osteosarcoma and the first of its kind reported in the literature.

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Histiocytic sarcoma arising from thyroid gland with *BRAF* V600E mutation

Sir,

Histiocytic sarcoma (HS) is a relatively rare tumour composed of malignant cells showing morphological and immunophenotypic characteristics of mature histiocytes,¹ accounting for less than 1% of all malignancies of the haematopoietic system. In this report, we illustrate this rare tumour with its unique location and the presence of the *BRAF* V600E mutation.

A 71-year-old woman presented with a 1-year history of gradually enlarging neck mass. The patient complained of difficulty in swallowing for a month. Physical examination showed a painless mass in the left cervical region and no systemic lymph node enlargements. Laboratory studies revealed TSH was 9.068 mIU/L (normal range 0.350–4.940 mIU/L). Thyroid ultrasound showed a 4.2×3.9×3.0 cm nodule in the left lobe and chest computed tomography revealed a locally advanced thyroid mass producing significant deviation of the trachea (Fig. 1A). No metastases were detected by magnetic resonance imaging (MRI). Aspiration cytology suggested the possibility of a medullary thyroid carcinoma. The patient underwent total thyroidectomy. The patient refused further treatment, and died of pulmonary failure caused by bronchopneumonia at 3 months after the operation.

Grossly, the left lobe of the thyroid measured 5×4×4 cm and the right lobe was 3×2×2 cm. The cut surface of the left lobe revealed a well-circumscribed but unencapsulated tumour measuring 3 cm in diameter, which was golden coloured and soft in consistency (Fig. 1B). The right lobe was unremarkable. Microscopically, tumour cells showed diffuse, scattered or sheet-like growth in the left lobe of the thyroid. They were monomorphic to pleomorphic in shape. The