

Malignant phyllodes tumor in a patient with hereditary retinoblastoma: a case report and literature review

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Abstract

Patients with hereditary retinoblastoma are at increased risk for second malignancies, most notably sarcomas, particularly after treatment with radiation. Malignant phyllodes tumor is a rare secondary malignancy in these patients. We present a review of the literature and report of a patient with hereditary retinoblastoma who developed two secondary malignancies, including malignant phyllodes tumor. The patient's phyllodes tumor presented as a palpable breast mass with suspicious findings on mammogram and ultrasound. The mass was shown to be at least a borderline phyllodes tumor via sonographic percutaneous biopsy and confirmed malignant phyllodes tumor on final surgical excision.

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Introduction

In the United States, only 250-300 cases of retinoblastoma are diagnosed each year.¹ Patients with hereditary retinoblastoma, representing approximately 40% of patients, have germline mutations in the retinoblastoma gene, *RB1*, and frequently have bilateral or multifocal unilateral tumors.² Due to improvements in diagnosis and treatment, patients with hereditary retinoblastoma are living into adulthood, and secondary malignancies are now the most common cause of death.³⁻⁷ Radiation therapy for hereditary retinoblastoma has been identified as a causative factor in the development of subsequent malignancies.^{3,5,7} The most common secondary malignancies reported include sarcoma, carcinoma, intracranial primitive neuroectodermal tumor, and melanoma.⁵ Breast, lung, and bladder carcinomas have been identified as the most frequent

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secondary epithelial malignancies.⁶

Phyllodes tumors of the breast are uncommon, representing less than 1% of breast tumors.⁸ They usually occur in women 40-50 years of age and often present as palpable masses. Phyllodes tumors are commonly classified as benign, borderline or malignant, with approximately 10-20% of tumors classified as malignant.⁸ The average annual age-adjusted incidence rate of malignant phyllodes is 2.1 per 1 million women.⁹ The database of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program documented only 158 patients with malignant phyllodes from 1973-1981.¹⁰ Phyllodes tumors have been described with alterations in the expression of the retinoblastoma protein.¹¹

The occurrence of phyllodes tumor of the breast in the setting of retinoblastoma has only been reported in two patients.¹² We report a case of malignant phyllodes tumor of the breast occurring in a patient with a history of hereditary retinoblastoma as an infant and leiomyosarcoma of the nasal cavity as a young adult. The imaging findings of phyllodes tumors and the association between these neoplasms are reviewed.

Case Report

The patient was diagnosed with hereditary bilateral retinoblastoma and treated with radiation therapy at four months of age. She then developed a leiomyosarcoma of the nasal cavity at age 29 (Figs. 1 & 2), which was diagnosed on excisional biopsy. She subsequently had a recurrence of the leiomyosarcoma treated with surgery at 30 years of age. The patient was never treated with chemotherapy and no radiation therapy was given for her nasal leiomyosarcoma before diagnosis of phyllodes.



Figure 1. Axial facial CT image demonstrated a 3.4 cm soft tissue mass in the right nasal cavity (black arrow).

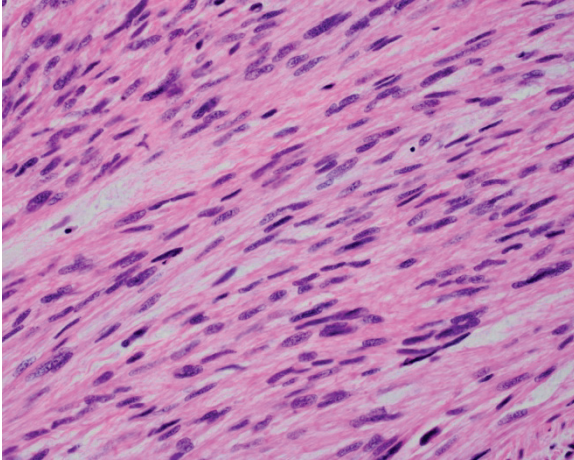


Figure 2. Microscopic examination of the right nasal mass excisional biopsy (hematoxylin and eosin stain; 400x magnification) showing atypical spindle cell neoplasm.

At 32 years of age she presented with a new palpable right breast mass. A 1.6 cm irregular high density mass with microlobulated and ill-defined margins (Figs. 3 and 4) in

the subareolar region was demonstrated on digital mammography. Targeted right breast ultrasound of the subareolar region at the 11:30 position demonstrated a hypoechoic mass with microlobulated margins measuring 1.4 cm (Fig. 5), correlating with the mammographic abnormality. The differential diagnosis for the imaging findings included mammary carcinoma, fibroadenoma, and phyllodes tumor. A BIRADS 4 assessment was given and ultrasound-guided biopsy recommended. A second small 10 mm oval circumscribed isodense mass was also noted on mammogram and ultrasound at the 6:00 position. This mass was determined to be probably benign, a BIRADS 3 assessment given and a 6 month follow-up mammogram was recommended. The patient's physician preferred that both lesions be biopsied.

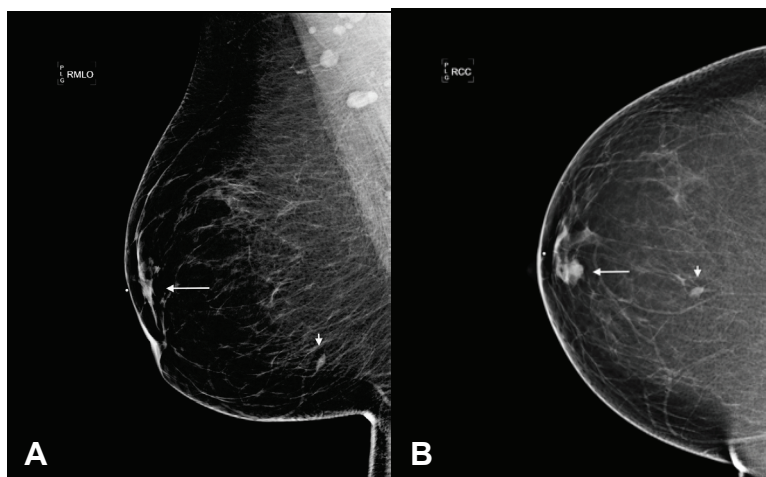


Figure 3. Right CC (A) and MLO (B) views demonstrate a 1.6 cm irregular subareolar mass (white arrow). A second small 10 mm oval isodense mass was also noted at the 6:00 position (white arrow head).

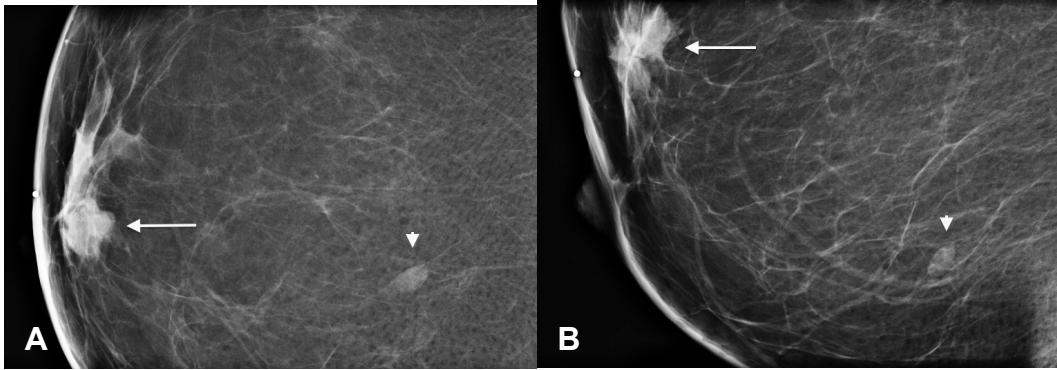


Figure 4. Spot compression right CC (A) and MLO (B) views demonstrate persistence of the irregular subareolar mass with microlobulated and ill-defined margins (white arrow). The second small 10 mm oval isodense mass also persists at the 6:00 position with circumscribed borders (white arrow head).

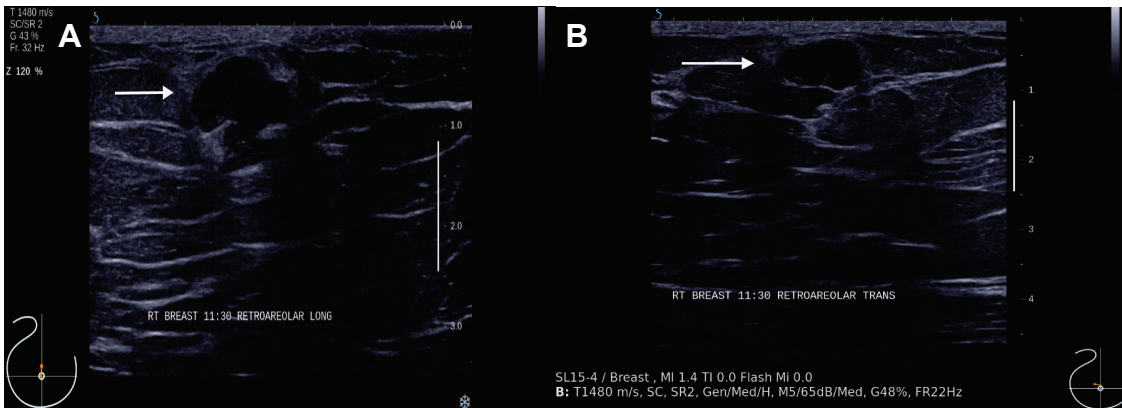


Figure 5: Longitudinal (A) and transverse (B) ultrasound images demonstrate a lobulated hypoechoic mass with microlobulated borders measuring 1.4 cm (white arrow).

Ultrasound-guided core biopsy of both lesions was subsequently performed. Pathology of the smaller likely benign lesion at the 6:00 position showed fibroadenoma. The core biopsy of the palpable mass demonstrated at least a borderline phyllodes tumor on histopathology, and surgical excision was recommended. The patient returned for surgical excision, with pathology demonstrating malignant phyllodes

tumor (Fig. 6). Chromosomal analyses were not reported on any of her tumors. The patient initially underwent lumpectomy with close margin (1 mm from anterior inferior resection margin). Central breast excision was performed six weeks later and no residual tumor was identified. At this time, there is no evidence of recurrence of the phyllodes.

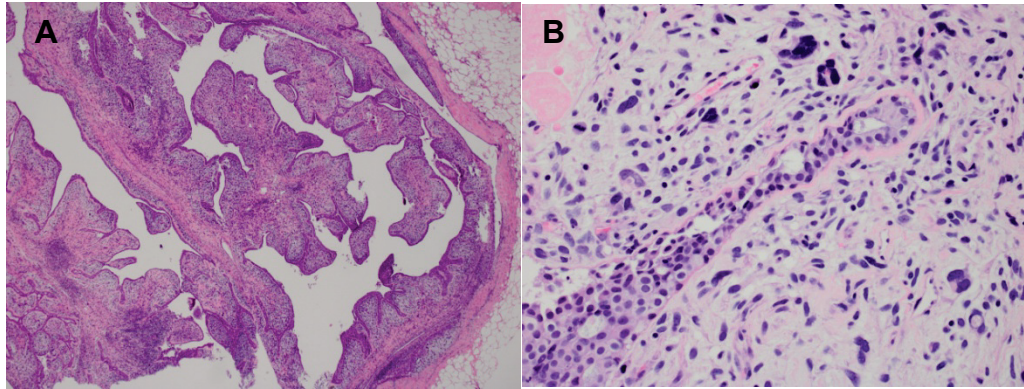


Figure 6: Microscopic examination (hematoxylin and eosin stain) of the palpable breast mass at A) 20x magnification showing a fibroepithelial neoplasm with dilated epithelial lined clefts and B) at 400x magnification with stromal hypercellularity, atypia, and mitoses.

Subsequently, the patient developed a second recurrence of the nasal leiomyosarcoma at the age of 33. She was treated surgically and is currently receiving external beam radiation therapy.

Discussion

Phyllodes tumors are uncommon breast tumors that frequently present as rapidly enlarging palpable masses. They average 3-6 cm in size at presentation, although tumor sizes from 1 cm to over 20 cm have been reported. Liberman et al. reported that tumors 3 cm or greater were significantly more likely to be malignant.¹³ Mammography typically demonstrates a large, round to oval, high density mass with circumscribed and lobulated margins. Sonography usually demonstrates a lobulated, well-defined, heterogeneous, hypoechoic mass without posterior acoustic shadowing.¹⁴ There may be internal cystic spaces.¹³ Irregular shape has been significantly correlated with

malignant and borderline phyllodes tumors.¹⁵ Color Doppler imaging frequently demonstrates some degree of internal vascularity. In our case, the malignant phyllodes showed irregular shape with microlobulated and ill-defined borders on mammography and hypoechoic mass with microlobulated borders on ultrasound, consistent with the reported imaging findings of malignant phyllodes tumors. On MRI, phyllodes tumors appear round or lobulated with smooth margins and often demonstrate heterogeneous signal intensity with cystic areas and nonenhancing septations. Signal intensity on T2 weighted imaging is variable and nearly always inhomogeneous. T1 signal intensity is usually iso- or hypointense to adjacent breast parenchyma.¹⁵ Enhancement kinetics are variable.¹⁶

Phyllodes tumors are treated with wide local excision. Margins of at least 1 cm are recommended. Local recurrence is reported to occur in

approximately 3-19% of patients. Sentinel lymph node biopsy or axillary dissection is not routinely performed, unless clinically indicated. There is no role for adjuvant chemotherapy, radiation therapy or hormonal therapy in the treatment of primary phyllodes tumor. Chemotherapy and radiation therapy may be considered on a case by case basis in the setting of recurrence or metastases. The survival rate of malignant phyllodes is much higher than nonphyllodes breast cancer. There is no data regarding differences in prognosis or management of malignant phyllodes in patients with or without retinoblastoma.

Retinoblastoma occurs in both sporadic (somatic mutation) and familial (germline mutation) forms. Knudson's "two hit" hypothesis to explain retinoblastoma tumorigenesis requires two complementary chromosomal mutations.¹⁷ In the familial form of retinoblastoma, the "first hit" is a germline mutation followed by a somatic mutation of the remaining wild-type copy. These individuals are thus more susceptible to second non-ocular tumors because every cell in the body carries the germline mutation.

The retinoblastoma susceptibility gene *RB1*, located on the long (q) arm of chromosome 13 at position 14.2, functions as a tumor suppressor gene. The protein encoded by *RB1*, known as retinoblastoma protein or pRB, is vital to numerous cell processes, including DNA repair, cell cycle

control, DNA replication, and proliferation.¹⁸ Cells with two altered copies of the *RB1* gene produce no functional pRB and are unable to regulate cell division effectively.

It is well known that hereditary retinoblastoma patients are susceptible to a wide variety of second malignancies, particularly soft tissue sarcomas in the setting of prior radiotherapy.³⁻⁷ Phyllodes tumors of the breast, however, are uncommonly reported as secondary tumors in these patients.¹² Recent investigation has identified several chromosomal regions where amplifications, gains and losses were present in phyllodes tumors.¹⁹ In particular, gains of 1q and losses of 13q are hallmark alterations in borderline and malignant phyllodes tumors. Likewise, losses of 13q are identified in approximately 70% of leiomyosarcomas.²⁰ Similar to phyllodes tumor, gains at 1q are identified in 50% of cases of retinoblastoma.²¹ The shared chromosomal alterations in these three tumor types suggest common genetic and cell signaling pathways that are altered and are in need of further study. Clinically, these patients are at high risk for developing a variety of malignancies in multiple sites, and thus close surveillance is necessary.

Conclusion

Retinoblastoma, malignant phyllodes tumor and nasal leiomyosarcoma are rare tumors. It is unlikely that these tumors would sporadically occur in the same patient. Recent chromosomal analysis suggests a

possible common genetic etiology of phyllodes tumor and retinoblastoma, particularly 1q gains and 13q losses with *RB1* alterations. Further evaluation of the role of *RB1* alterations in the oncogenesis of phyllodes tumor is warranted. Furthermore, the differential diagnosis of a breast mass in a patient with a history of retinoblastoma should include phyllodes tumor.

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