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Metastatic Phyllodes Tumor in a Patient With Beckwith-Wiedemann Syndrome

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Abstract

Beckwith-Wiedemann syndrome (BWS) is an epigenetic disorder of imprinting on the chromosome 11p15 region that presents with clinical features, such as macroglossia, abdominal wall defects, neonatal hypoglycemia, hemihypertrophy, and embryonal tumors. Phyllodes tumors (PTs) are rare fibroepithelial tumors that account for 0.3% to 1% of breast tumors and present in women aged 35 to 55 years. Here we describe a rare case of metastatic malignant phyllodes tumor in a 27-year-old woman with BWS and uniparental disomy (UPD) of chromosome 11p15.5. To our knowledge, this is the first case report in literature to describe metastatic malignant phyllodes tumor in a woman with BWS.

Keywords

11p15, Beckwith-Wiedemann syndrome, malignant phyllodes tumor

Introduction

Beckwith-Wiedemann syndrome (BWS) is an epigenetic disorder of imprinting on the chromosome 11p15 region that leads to a wide range of clinical symptoms.[1-3] The genes in the imprinted region regulate growth and are associated with tumor suppression, thus leading to features, such as macroglossia, abdominal wall defects, enlarged abdominal organs, hemihypertrophy, and an increased risk of developing embryonal tumors.[1-3] Beckwith-Wiedemann syndrome is present in about 1 in 10 340 live births and most patients are diagnosed at birth or in early childhood.[1]

Phyllodes tumors (PTs) are rare, accounting for only 0.3% to 1% of breast tumors, and occur in women aged 35 to 55 years.[1,4,5] Although there is a wide variety of clinical features associated with BWS, breast lesions are not among the most common. There are case reports describing fibroadenomas and benign phyllodes in females with BWS.[6-9] To our knowledge, there has not been a report of a malignant phyllodes tumor in a patient with BWS. We present the case of a young female with BWS and metastatic malignant phyllodes tumor.

Case Presentation

The patient was a 27-year-old female who was clinically diagnosed with BWS at birth, based on the genetic characteristics of omphalocele, macroglossia, and hypoglycemia. The omphalocele was surgically corrected at birth. She was also noted to have right-sided hemihypertrophy. She was diagnosed with bilateral Wilms tumors at age 2 years and underwent bilateral partial nephrectomy and completed chemotherapy. The patient had a history of a palpable right breast mass since age 16 years, and this mass had rapid growth during her first pregnancy at age 24 years. Ultrasound examination at this time showed the mass to measure 18 cm in maximum dimension. Needle core biopsy was performed but showed only infarcted/necrotic tissue with features suggesting infarcted fibroadenoma, but the necrosis precluded definitive diagnosis. Surgical removal of the mass was recommended; however, the patient experienced a decrease in size of the mass following delivery and chose to wait. She again became pregnant the following year and again experienced growth of the previously biopsied mass, and also developed 2 additional masses in the same breast measuring 6.6 cm and 7.7 cm in maximum dimension per ultrasound evaluation. Needle core biopsy of these 2 masses again revealed necrotic/infarcted tissue and tissue with features of fibroepithelial proliferation. Five months later, 1 month following delivery of her second child, she underwent excision of the largest mass, which at that time measured 27 cm in maximum dimension. This mass was diagnosed as borderline phyllodes tumor with

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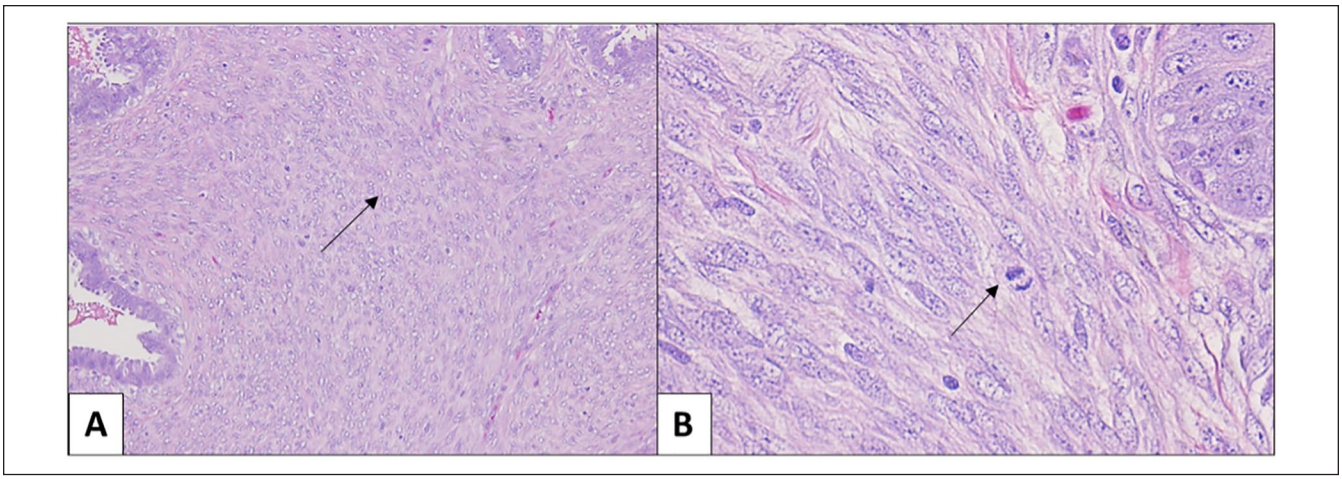

Figure 1. (A) The malignant phyllodes tumor of breast showed stromal overgrowth (arrow; H&E, 100×). (B) The stroma of the phyllodes tumor showed atypia and frequent mitotic figures (arrow; H&E, 400×).

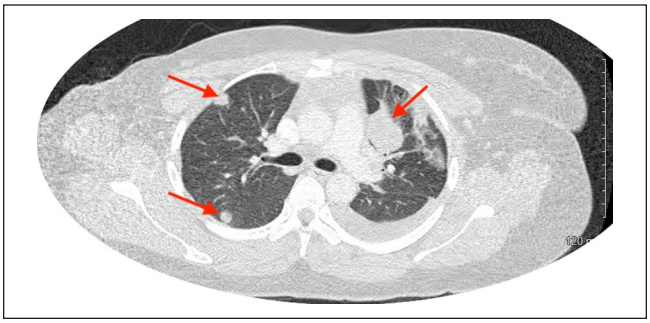

Figure 2. Computed tomography scan of the thorax with contrast showing large left-sided pleural effusion and multiple soft tissue masses in bilateral lung lobes (red arrows).

extensive infarction and lactational changes. Four months later, she underwent mastectomy.

The mastectomy specimen consisted of a breast with axillary tail, and grossly showed multifocal tumor nodules scattered throughout all 4 quadrants, the largest measuring 3.4 cm. Microscopically, the tumor nodules showed fibroepithelial neoplasm with features including areas of stromal overgrowth (Figure 1A). The stroma showed hypercellularity with nuclear atypia and increased mitotic activity (up to 10-14 mitoses per 10 high-power fields were counted in areas of stromal overgrowth; Figure 1B). The tumor nodules were poorly circumscribed with numerous small adjacent satellite nodules. These features are diagnostic of malignant phyllodes tumor. All surgical margins were free from tumor, and no lymph node metastases were present.

She was seen by radiation oncology and completed partial adjuvant radiotherapy to the chest wall. At this time, the patient underwent genetic testing as there is an increased risk of neoplasia in individuals with germline paternal disomy of chromosome 11p15. Genetic testing showed paternal uniparental disomy (UPD) of chromosome 11p15.5 and the molecular diagnosis of BWS was made.

Ten months later, the patient presented for dyspnea and was found to have a large left-sided pleural effusion and multiple soft tissue masses in bilateral lung lobes (Figure 2). The pleural biopsy grossly consisted of a 2-cm aggregate of irregular, hemorrhagic rubbery tissue fragments. Microscopically, sections showed sheets of malignant spindle cells with features including hypercellular stroma with nuclear atypia, similar to the primary malignant phyllodes tumor (Figure 3A and 3B). Necrosis was prominent. Immunohistochemical studies included positive staining for CD10 and WT-1 and negative staining for keratins, consistent with metastatic phyllodes tumor. The magnetic resonance imaging (MRI) of the brain was significant for a 5 mm T2 hyperintense enhancing lesion in the right parietal lobe (Figure 4), also concerning for metastatic disease. Unfortunately, the patient passed away 4 months later, at the age of 27, due to complications from recurrent pleural effusions and encephalopathy from brain lesions.

Discussion

Beckwith-Wiedemann syndrome is the most common congenital overgrowth syndrome and increases the risk of embryonal tumors, such as Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma.[10] Beckwith-Wiedemann syndrome is commonly diagnosed from clinical features, but with the availability of molecular genetic testing, specific alterations in the 11p15 chromosome can be identified. Our patient was diagnosed clinically with BWS but only underwent molecular genetic testing after she was diagnosed with malignant metastatic phyllodes tumor. Our patient had a paternal UPD of chromosome 11p15, which is an alteration found in 20% of BWS patients and has an estimated risk of tumorigenicity greater than 25%.[8] There are 2

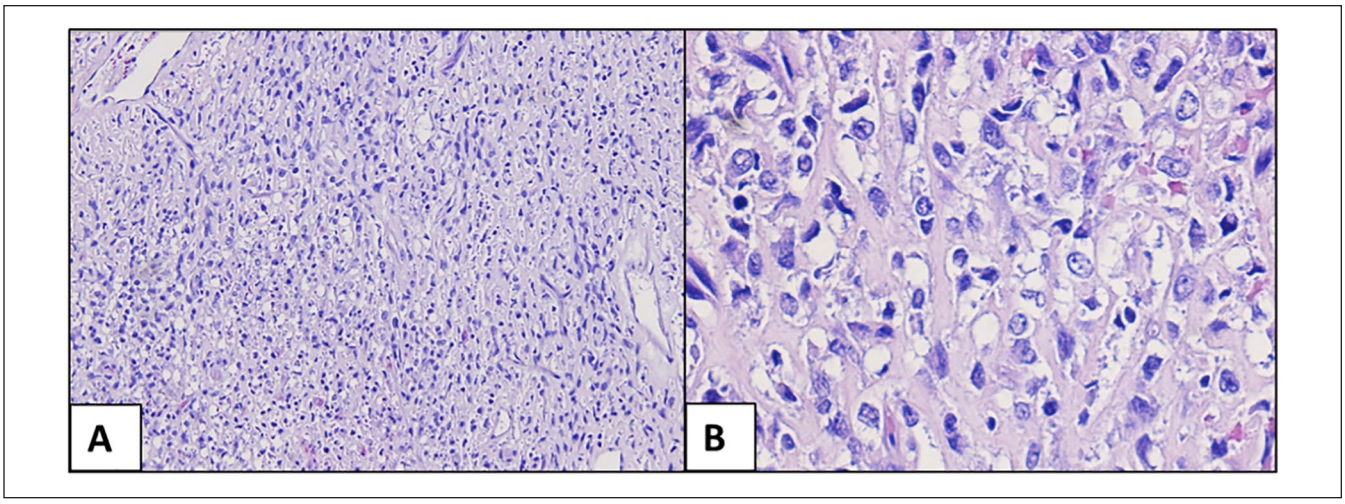

Figure 3. (A) The pleural biopsy showed metastatic phyllodes tumor characterized by sheets of spindle cells (H&E, 100×). (B) The spindle cells showed significant nuclear atypia (H&E, 400×).

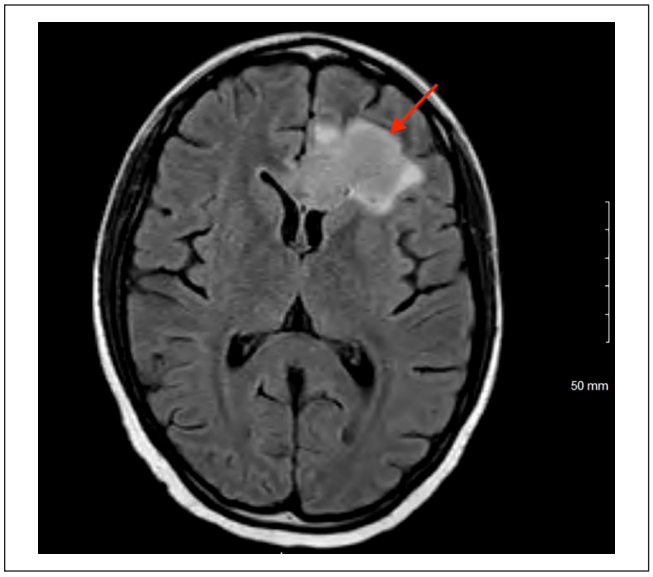

Figure 4. T2 MRI brain showing 5 mm enhancing lesion in the right parietal lobe (red arrow).
Abbreviation: MRI, magnetic resonance imaging.

distinct tumor suppressor loci on chromosome 11p15 that may contribute to tumorigenicity and metastasis in breast cancer.[11] This suggests that women with BWS should have close surveillance for breast masses and diligent follow-up once a breast mass is detected. Furthermore, all patients with BWS should undergo molecular genetic testing to determine the causative alterations in the 11p15 chromosome for risk stratification of tumorigenesis.

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Informed Consent

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