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A rare case of Rubinstein-Taybi Syndrome and gynecological malignancy

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ABSTRACT

Rubinstein-Taybi syndrome (RSTS) is a congenital syndrome most associated with mutations on chromosome 16p13.3 that can result in both benign and malignant neurologic and hematologic neoplasms of various primary origins. We present the case of a 39-year old female with RSTS who presented with severe abdominal and pelvic pain. Abdominal and pelvic imaging revealed multiple masses involving the uterus, liver and spleen concerning for malignancy. Biopsies from the endometrium and cervix confirmed this as a poorly differentiated, widely invasive squamous cell carcinoma. This represents the first case of primary squamous cell carcinoma of gynecologic origin in a patient with Rubinstein-Taybi syndrome. This case aims to raise awareness of the gynecological malignancy in patients with RSTS as well as serves as a reminder to clinicians to have a broad differential diagnosis in all patients which may help lead to early recognition of pathology.

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BACKGROUND

Rubinstein-Taybi syndrome was first described in 1963 as a symptom-complex with broad thumbs and great toes, facial abnormalities, mental retardation, and other congenital malformations.[1] The syndrome is now known to be associated with a mutations of chromosome 16p13.3 which can lead to alterations in the CREB-binding protein (CBP) or, less commonly, mutations on chromosome 22q13.2, leading to alterations of the E1A binding protein (p300).[2,3] Both proteins are transcriptional coactivators that mediate various signaling pathways. RSTS is of autosomal dominant inheritance, and due to it occurring from a de novo mutation, the recurrence rate in couples with a previous child with RSTS remains low at 0.1%.[4] Overall, life expectancy of individuals with RSTS appears normal, unless they have complex cardiac defects.[5] Several case reports indicate there is increased risk of developing benign and malignant cancers, but the true cancer risk is unknown, therefore no firm cancer surveillance recommendations have been published.[6] We present the case of a patient with RSTS who was diagnosed with squamous cell carcinoma of the endometrium/cervical region after presenting with abdominal pain.

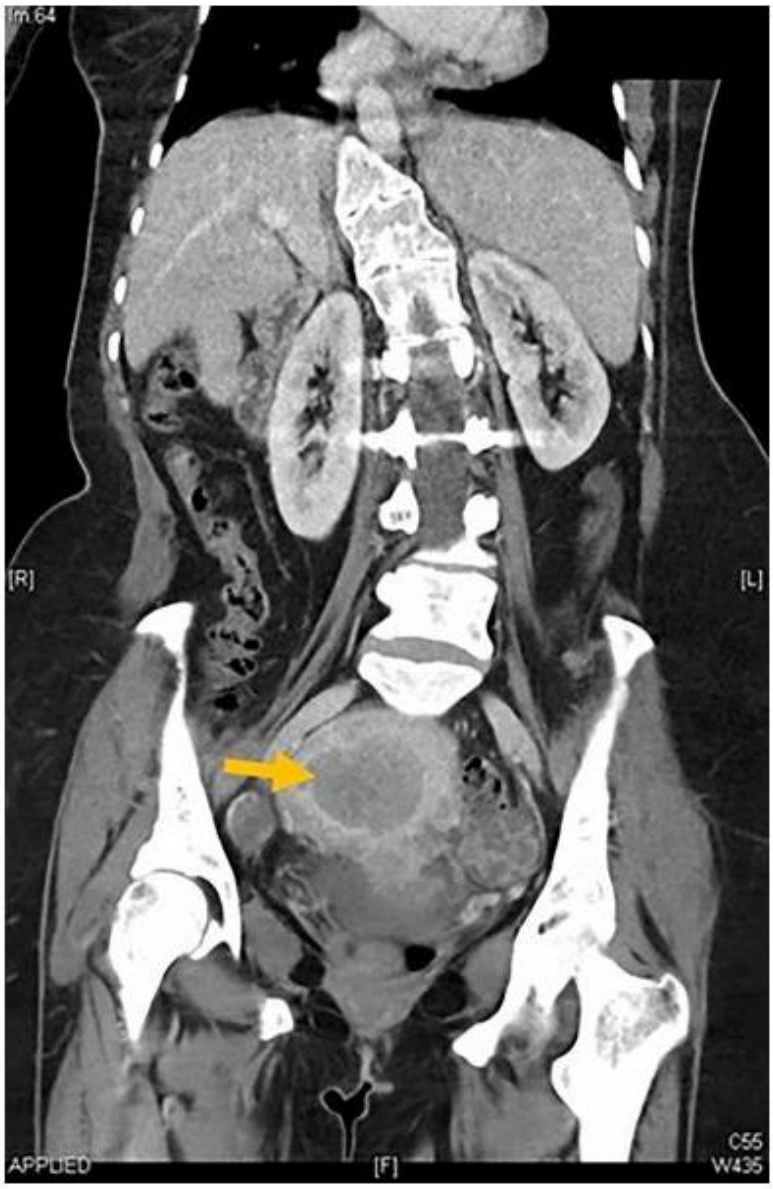


Figure 1: Abdomen/Pelvis CT scan, coronal view, showing heterogenous uterine mass (yellow arrowhead)

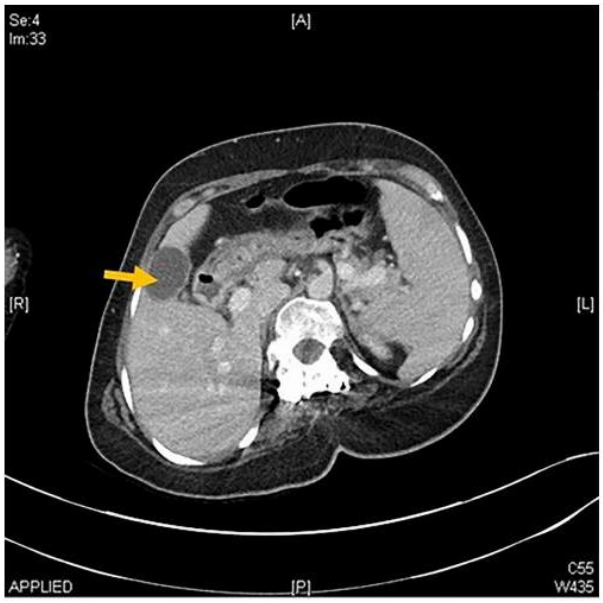


Figure 2: Abdomen/Pelvis CT scan, transverse view, with hypo-attenuating mass in liver (yellow arrowhead)

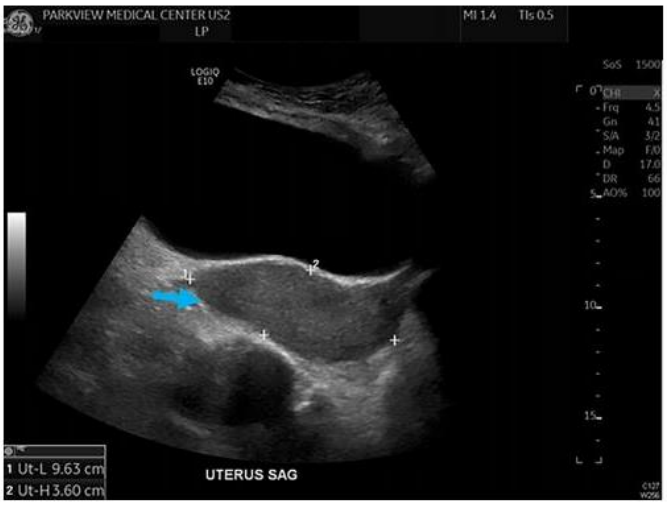
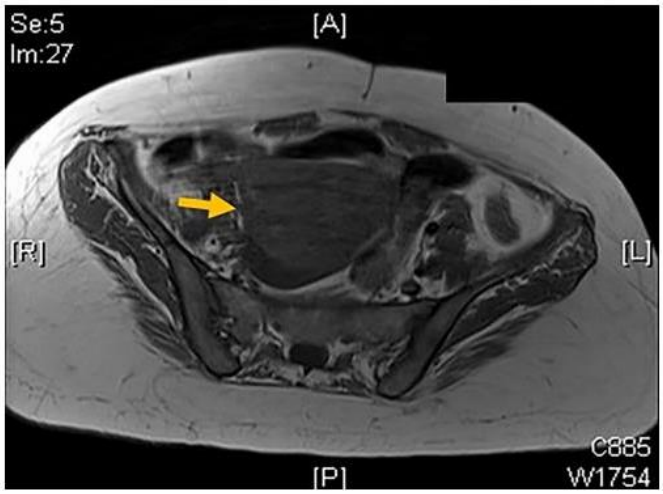


Figure 3: Transabdominal pelvic ultrasound with 6.6 cm diameter hyperechoic central uterine focus (blue arrowhead)



Figures 4 & 5: Pelvic MRI with both transverse and sagittal slices showing low-attenuating mass in endometrial canal (yellow arrowhead)

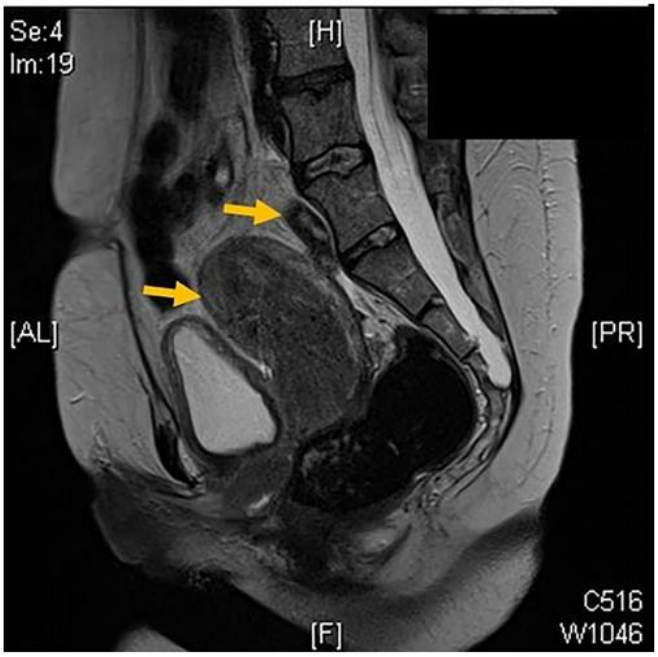


Figure 6: Chest contrast tomography angiogram with solitary pulmonary nodule in the right lower lobe (yellow arrowhead)

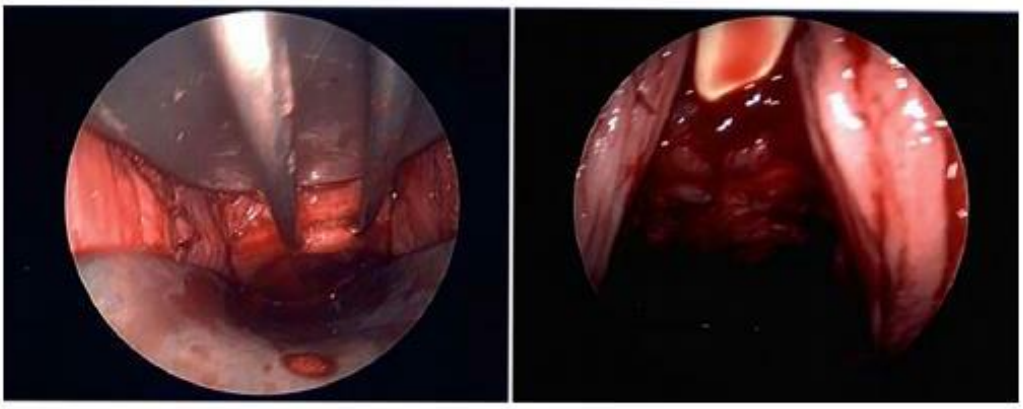


Figure 7: Hysteroscopy showing extensive bleeding from vaginal canal

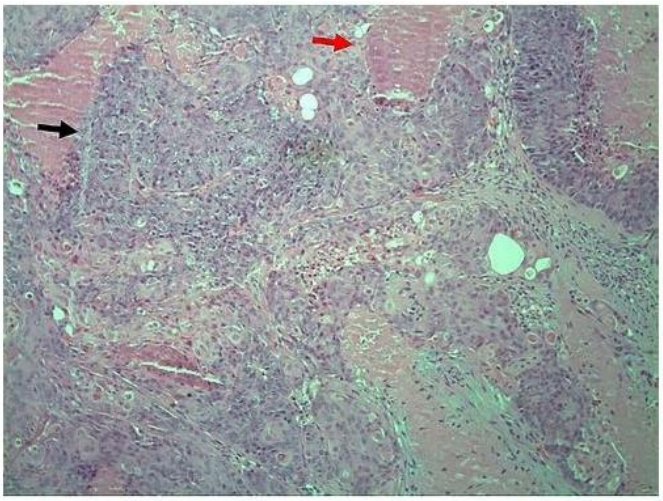


Figure 8: Endometrial curettage biopsy slide showing poorly differentiated squamous cell carcinoma (black arrow) and areas of tissue necrosis (red arrow).

CASE PRESENTATION

A 39-year-old female with past medical history of Rubinstein-Taybi syndrome presented to our institution with a chief complaint of acute abdominal and pelvic pain that had been present for 3-4 weeks prior to presentation. She complained of concurrent dysuria, urinary urgency and urinary retention. She had no prior history of similar complaints. She was seen by her gynecologist a year prior to this presentation due to abnormal uterine bleeding and was started on Medroxyprogesterone 20 mg daily. There was no prior history of Pap smear or pelvic examination. Surgical history included recent left parietal scalp mass removal and biopsy, thoracolumbar fusion surgery, hand surgeries to repair her thumbs, and foot surgeries to repair her big toes. She had no prior history of substance use including tobacco, alcohol, and illicit drugs. Family history was significant for unknown cancers in her grandparents. She had no known drug allergies. She did not have any known diagnosis of malignancy on presentation though the pathology on her previously biopsied scalp mass did subsequently come back as invasive sebaceous cell carcinoma. On presentation, her blood pressure was 115/80 mmHg, pulse 100 beats per minute, respiratory rate of 20 breaths per minute, saturating 92% on room air, with a temperature of 97.9 degrees Fahrenheit. Upon examination, the patient was in moderate distress, appeared anxious, and was grimacing in pain while holding her lower abdominal region with both hands. She was able to communicate that she was in pain but otherwise, due to her syndrome, she was largely non-vocal. She had micrognathia, downslanting of palpebral fissures, a protruding beaked nose and low-set ears. There was a healing wound on her left parietal scalp from a recent parietal mass excisional biopsy. Lung examination demonstrated clear breath sounds without wheezing. She had no rashes on the exposed skin. Cardiac examination was significant for sinus tachycardia without abnormal heart sounds or murmurs. Abdomen was soft but diffusely tender to palpation as indicated by patient's facial grimacing. Pelvic examination was not done due to patient's discomfort and family's decision.

INVESTIGATIONS

Complete blood count demonstrated significant leukocytosis of 26,000 uL, hemoglobin count of 16.4 g/dL and basal metabolic panel was unremarkable with the exception of a calcium of 11.3 mg/dL. Vitamin D 25–hydroxy level was 20.1 ng/mL. Serum pregnancy test was negative. Urinalysis demonstrated ahigh specific gravity of 1.026, positive urine nitrite, large urine leukocyte esterase, urine WBC 73/HPF, urine hyaline casts 65/LPF and urine bacteria 29/HPF. Routine blood and urine cultures showed no growth for any organism. Abdomen/pelvis CT scan with contrast revealed a 9.7x4.4x7.3cm heterogeneous pelvic mass in the area of the uterus (see Figure 1)and lobulated, centrally hypo-attenuating bilateral adnexal masses as well as a 2.3cm mass in the right pelvic sidewall and lobulate mass in the pelvic retroperitoneal fat. It also noted a 2.5cm diameter heterogeneous, hypoattenuating mass in the liver (see Figure 2), splenomegaly with a 3.0cm heterogeneous hypo-attenuation focus in the interior spleen, and bilateral lower lung nodules. Transabdominal pelvic ultrasound showed a 6.6 cm diameter hyperechoic central uterine focus (see Figure 3). This corresponded to a region of decreased attenuation on the preceding CT potentially representing a focus of endometrial neoplasia/uterine cancer and/or leiomyoma not well delineated with this transabdominal technique. MRI pelvis with and without contrast showed a 3.2 x 6 x 7.3 cm heterogeneously enhancing low attenuation mass filling the endometrial canal (see Figure 4). Additional rim-enhancing, low-attenuation masses were identified in the bilateral adnexa, measuring up to 3.2 cm. Cervix was enlarged and ill defined. A possible 1.5 x 3.4 cm soft tissue lesion was seen in the vagina. Moderate free pelvic fluid was present. Ovaries were not well-visualized secondary to patient motion artifact and bilateral adnexal masses (see Figure 5). Chest CTA showed multiple pulmonary nodules

scattered throughout the bilateral lung fields. Larger nodules included right upper lobe nodule measuring 12 mm, right lower lobe nodule measuring 13 mm (see Figure 6). Mildly enlarged scattered mediastinal lymph nodes were noted. Patient's CA-125 antigen came back elevated to 109 U/mL.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for pre-menopausal women presenting with acute abdominal and pelvic pain is broad. Cervical cancer is associated with Human Papillomavirus (HPV) infection worldwide. Of the different genotypes, HPV 16 and 18 are associated with the highest risk for progression to cervical cancer.[7] Our patient's presentation with pelvic pain, history of abnormal uterine bleeding, imaging suggesting abnormal pelvic masses and subsequently histopathologic findings from endometrial curettage allowed us to reach this final diagnosis. Leiomyomas are common benign uterine neoplasm, composed of smooth muscle with fibrous connective tissue. Leiomyomas can be asymptomatic or present as a palpable abdominal-pelvic mass.[8] Magnetic resonance imaging (MRI) is the most sensitive modality to detect and localize leiomyomas. Our patient's MRI and histopathologic findings make this a less likely cause of her uterine masses. Adenomyosis results from direct invasion of endometrium into the myometrium. It can cause a diffuse abnormality or can also occur as a focal mass.[8] Histopathologic analysis shows ectopic endometrial glands within the myometrium. Our patient's histopathologic analysis was not consistent with this diagnosis. Focal myometrial contractions can appear as mass of low signal intensity on MRI.[8] Transient nature and resolution of mass at subsequent imaging differentiates this from other focal lesions, as in our patient's case.

TREATMENT

Initially, there were concerns for underlying urinary tract infection and patient was started on intravenous ceftriaxone. With her abnormal imaging results and acute symptoms, Gynecology was consulted and pelvic exam was performed under anesthesia with hysteroscopy, dilatation and curettage, and biopsies of the anterior vaginal wall and endometrium. Hysteroscopy showed extensive bleeding from vaginal canal (figure 7). Biopsies from endometrium and anterior vagina showed poorly differentiated, widely invasive, squamous cell carcinoma (figure 8). The cytology from her cervix was also consistent with poorly differentiated squamous cell carcinoma with a positiveP16 immunohistochemically stain, confirming HPV16 associated cervical cancer as most likely primary source. The patient's case was discussed with gynecologic oncology and decision was made for outpatient follow-up for decision on further treatment versus palliative options. Her daily medroxyprogesterone 20 mg was resumed upon discharge under the consideration that squamous cell carcinoma is not hormonally active.

OUTCOME AND FOLLOW-UP

Five days after discharge from our institution, prior to her appointment with gynecologic oncology, the patient passed away.

DISCUSSION

In 2015, Johannesen et al., presented a case of low-grade serous carcinoma of the ovary and an endometrioid adenocarcinoma of the uterus.[9] Boot et al., studied incidence and character of neoplastic tumors in all known individuals with RSTS in The Netherlands until 2015. They found that 35 benign and malignant tumors were observed in 26 of the 87 individuals included. Of those, five malignant tumors were found including medulloblastoma, diffuse large-cell B-cell lymphoma, breast cancer, non-small cell lung carcinoma and colon cancer.[10] Gynecological malignant tumors are not commonly reported in patients with RSTS. Hence, this case highlights the importance of primary gynecological malignancy in such patients. As discussed above, there are no guidelines currently which recommend cancer surveillance in patients with RSTS, but there should be a low threshold for screening in patients with RSTS. Age appropriate cancer screenings (such as Pap smear for cervical cancer) should be done in these patients. Seven

days prior to her presentation to our institution, this patient had a left parietal scalp mass removed and sent for pathology. Pathology results came back later, which showed invasive sebaceous carcinoma. This also highlights the possibility of two different primary carcinomas in patient with RSTS as presented by Book et al.

LEARNING POINTS/TAKE HOME MESSAGES

1. Rubinstein-Taybi syndrome (RSTS) can be associated with gynecologic malignancy.
2. Patients with RSTS can have more than one primary malignancy.
3. Early recognition of symptoms can prompt further investigation and medical attention, which could lead to the diagnosis of cancer in its early stages.

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