

## Yolk sac tumor of the ovary in a young girl with tuberous sclerosis: A case report and review of the literature <sup>☆, ☆☆</sup>



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Tuberous sclerosis (TS) is a relatively common neurocutaneous genetic disorder affecting 1 in 10,000 people and has a spectrum of manifestations due to incomplete penetrance (Crino et al., 2006). Common features include cognitive and behavioral problems, seizures, hypomelanotic “ash-leaf” spots, facial angiofibromas, hamartomatous and choristomatous tumors. Lesions commonly associated with TS include subependymal neural tubers, renal angiomyolipomas (rAMLs) and cardiac rhabdomyomas (Crino et al., 2006).

Gynecologic neoplasms in TS patients have also been reported (Gyure et al., 1995). To date, there are three previous reports of ovarian malignancies: juvenile granulosa cell tumor, epithelioid AML, and adenocarcinoma (Gyure et al., 1995; Guo et al., 2006; Anderson et al.,

2001). Herein, we report the first case of an ovarian yolk sac tumor (YST) in a TS patient.

### Case report

An 11-year-old female with TS presented with a one day history of worsening nausea, non-bloody, non-bilious emesis, and abdominal pain. She also had three months of worsening enuresis, constipation, and abdominal distension. Her menses were normal with LMP of two weeks prior to presentation.

On exam, she was afebrile, normotensive, tachycardic at 125 bpm, and tachypnic to the mid-30's. She had facial angiofibromas, ash leaf macules on the trunk and a large, non-tender mass in the suprapubic region extending towards the right iliac fossa. Her bowel sounds were normal and cardiac auscultation was negative for murmurs. She had normal external female genitalia. Serum chemistry tests and beta-HCG were normal however her serum alpha-fetoprotein (aFP) level was 280,003 ng/mL (normal: <15 ng/mL). A non-contrast computed tomographic (CT) scan revealed an 8.6 cm × 18 cm × 18 cm abdominal mass with solid and cystic components and internal septations (Fig. 1). Multiple enlarged left paraaortic and left common iliac lymph nodes (measuring up to 13.0 mm × 8.5 mm) were also noted. Bilateral renal lesions measuring 1.7 cm on the left and 1.9 cm on the right were also noted without evidence of rupture or hemorrhage.

At laparotomy, bloody ascites and peritoneal inflammation were found. The mass originated from the left ovary and was adherent to the omentum, large bowel, small bowel, and sigmoid colon. There were no signs of invasion into the adjacent pelvic structures and the uterus and contralateral ovary were unremarkable. A left salpingo-oophorectomy was performed along with peritoneal lymph node biopsies, diaphragmatic scrapings, omentectomy, and an appendectomy.

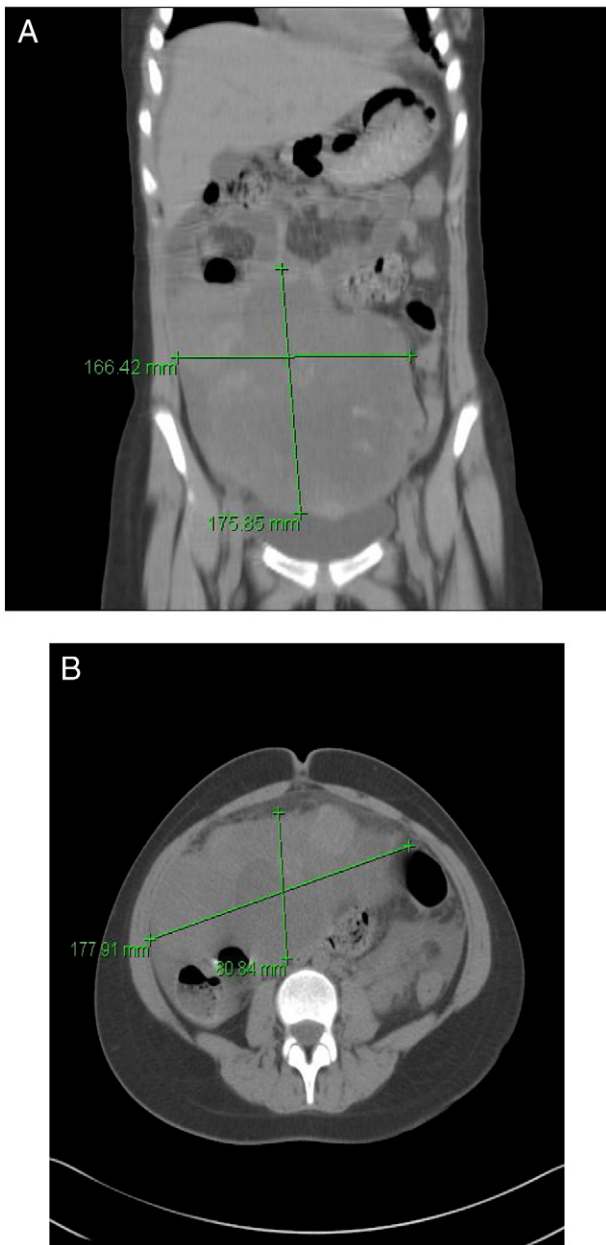
Final pathology showed a ruptured 25 cm × 18 cm × 9 cm ovarian mass weighing 2250 g. There were large areas of necrosis and hemorrhage with a mixture of solid and cystic components and no evidence of fallopian tube involvement. Microscopically, the tumor had an epithelial cell type appearance in a vitelline pattern with Schiller-Duval bodies (Fig. 2). In addition, focal areas of multinucleated cells suggestive of syncytiotrophoblast without villi were seen. Peritoneal

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**Fig. 1.** Non-contrast (A) coronal (B) axial CT scan of abdomen and pelvis showing large tumor with multiple cystic components and peritoneal inflammation.

lymph node biopsies showed no metastases. Immunohistochemical stains were strongly positive for keratin and weakly positive for CD30. A mixed germ cell tumor with primary yolk sac and minor dysgerminoma components was diagnosed. She was referred to oncology and given chemotherapy according to the Children Oncology Group (COG) AGCT0132 protocol, consisting of three cycles of cisplatin, etoposide and bleomycin. She attained complete radiologic and biologic remission with AFP <1 ng/mL after 3 cycles and did not require consolidation chemotherapy.

Three months after completing chemotherapy her AFP rose to 65 ng/mL, but there was no radiologic evidence of recurrence. Her 6 month post-chemotherapy AFP was 6390 ng/mL suggesting recurrence, despite both CT and MRI scans being negative. A positron emission tomography scan showed a 2 cm × 0.7 cm lesion in the left ovarian bed for which she was given salvage chemotherapy (COG AGCTO 521 protocol) consisting of paclitaxel, ifosfamide and carboplatin. Currently,

she is in complete remission 49 months post chemotherapy completion and remains well.

## Discussion

Tuberous sclerosis has a well-documented association with a number of tumors. Tuberous sclerosis complex (TSC), specifically TSC1 or TSC2 mutations or sporadic events is a potential causative oncogenic factor in patients with TS. TSC1 and TSC2 encodes hamartin and tuberlin proteins, respectively (Crino et al., 2006). The pathophysiologic basis for tumor formation is due to derangements in these cellular proteins which, under normal conditions, combine to form a functional protein complex important to negatively regulate cell growth, differentiation, and proliferation in a wide variety of tissues (Crino et al., 2006). Mutations in either protein give rise to abnormal protein complex formation and function resulting in hamartomatous and choristomatous tumors, most commonly cortical tubers, subependymal giant-cell astrocytomas, renal angiomyolipomas, cardiac rhabdomyomas, and renal cell carcinomas (Napolioni & Curatolo, 2008; Nelson & Sanda, 2002).

Acute abdominal pain in 80% of TS patients is associated with renal angiomyolipomas (Nelson & Sanda, 2002). Independent of TS-related lesions, spontaneous rupture of rAML lesions is estimated in as many as 15% of patients presenting with acute symptoms. This happens even with no history of trauma, and may or may not present with gross hematuria. Lesions greater than 4 cm have shown a greater risk of rupture (Nelson & Sanda, 2002). While the natural history of rAML is poorly understood, TS-associated rAMLs at diagnosis are more often bilateral, earlier in onset, larger in diameter (average 8.9 cm) and at a greater risk of spontaneous hemorrhage compared to the generally solitary, sporadically occurring rAML (Nelson & Sanda, 2002). In spontaneous ruptured rAML, the classic triad of flank pain, a palpable, tender mass, and a gross hematuria are noted in 11% of patients (Nelson & Sanda, 2002). Wunderlich syndrome or hemorrhagic shock may occur in 20% of TS patients (Nelson & Sanda, 2002). This is a major consideration in TS patients presenting with shock. In our patient, there was little clinical or radiographic evidence for rAML rupture as her clinical parameters and CT images were not consistent with a rAML or with an ectopic focus on angiomyolipoma.

The incidence of pediatric ovarian neoplasms is 2.6 per 100,000 girls (Dallenbach et al., 2006). Yolk sac tumors account for 1% of these pediatric ovarian neoplasms and are more commonly noted among patients between 18 and 25 years. We report the first case of a patient with TS presenting with YST. These tumors usually present with a 2–4 week history of progressive abdominal pain and a rapidly enlarging abdominal mass (Dallenbach et al., 2006). CT scans and magnetic resonance imaging (MRI) are the most widely used imaging modalities but pre-operative diagnosis remains challenging, as no studies distinguish YST from other ovarian masses. Our study in conjunction with others indicates that serum AFP is elevated in tumors containing a yolk sac component and may serve as both a diagnostic tool and marker for disease progression (Dallenbach et al., 2006). Post-operative serum AFP levels are more sensitive than radiologic studies in detecting response to chemotherapy and disease recurrence. The median time to recurrence is between 4 and 6 months (Dallenbach et al., 2006).

Surgical resection and combination chemotherapy are the mainstay of therapy (Dallenbach et al., 2006). Survival rates have improved greatly since the introduction of platinum based chemotherapy in the late 1970's. Survival is closely related to tumor stage, surgical resection and response to chemotherapy but other genetic factors are being studied for prognostic value (Dallenbach et al., 2006). Importantly, patient age and fertility sparing surgery have not been associated with decreased survival (Low et al., 2000).

Gynecologic ovarian neoplasms in patients with TS have been previously reported (Table 1). Our PubMed and MEDLINE search was conducted on August 2013 and utilized the keywords "neurofibromatosis or neurocutaneous and yolk sac tumor or Endodermal

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