ABSTRACT
A 27 year old female presented with pelvic pain and a palpable pelvic mass. Upon histological examination, the cystic mass contained a multi-cellular lining with nuclear grooves. Negative inhibin staining ruled out a follicular cyst and granulosa cell tumor while pan-cytokeratin positivity suggested an epithelial lesion. The lesion stained positive for thrombomodulin, ultimately suggesting a diagnosis of a Brenner cell tumor, although CD56 positivity in the tumor questions the known immunohistochemical profile of Brenner cell tumors. This unusual result opens the door to future research into the role CD56 in the diagnosis of ovarian neoplasms.

INTRODUCTION
A 27 year old woman presented with pelvic pain and a palpable pelvic mass. Ultrasound revealed a 16 cm x 14 cm x 7 cm, thin-walled, cystic mass emanating from the patient's left ovary (Fig. 1). All other pelvic structures appeared normal. Tumor markers (CA-125 and CEA), HCG, and a Pap Reflex HPV screen were negative and her metabolic panel was normal. Surgical excision was recommended in order to rule out the possibility of malignancy. One month later, the patient underwent a laparoscopic ovarian cystectomy. The surgical team visualized the cyst and then performed pelvic washings. The surgeon mobilized the left ovary out of the pelvis and resected the cystic portion, leaving the remaining ovarian parenchyma behind. The specimen was sent to pathology in order to determine a definitive diagnosis.

METHODS
The specimen was sectioned and stained with hematoxylin and eosin (H&E). Based on the gross and microscopic appearance of the tumor, in addition to the young age of the patient, the initial differential diagnosis included a follicular cyst and a granulosa cell tumor. Both of these are known to express inhibin but not cytokeratins (CK).1 Thus, these stains were performed. Because the initial analysis did not definitively determine a diagnosis (see results), additional immunohistochemical (IHC) stains were performed: 1) CK7 and CK20 to confirm the ovarian origin of the tumor cells.1 2) Neuroendocrine markers (CD56, synaptophysin, chromogranin) to investigate the possibility of a small cell carcinoma.2 3) Urothelial markers (uroplakin, thrombomodulin) to investigate the possibility of a cystic Brenner cell tumor.2

RESULTS
Initial microscopic examination revealed a large cystic lesion with a multi-layered cellular lining. The cells had small nuclei, with occasional grooves and nucleoli. There was some vacuolated cytoplasm (Fig. 2). The appearance of the tumor and young age of the patient suggested a follicular cyst or granulosa cell tumor, both of which stain for inhibin and not for pan-CK.1

However, the tumor did not stain for inhibin but did stain for pan-CK (Fig. 3A). This result ruled out the possibility of a follicular cyst or granulosa cell tumor. Additionally, the pan-cytokeratin positivity suggests a tumor of epithelial origin.1 Therefore, the differential diagnosis now had to include epithelial lesions in a young woman: (1) cystadenedoma, (2) small cell carcinoma, (3) cystic Brenner cell tumor. These tumors are especially important to distinguish because while Brenner cell tumors and cystadenomas have a benign course, most patient’s with small cell carcinoma die within 2 years of diagnosis.4

A cystadenoma was ruled out immediately due to the inconsistent histology of the patient’s tumor: cystadenoma’s have a single layer of epithelium (most often serous or mucinous).5 The results of the neuroendocrine staining revealed a CD56 positive (Fig. 3B) but synaptophysin and chromogranin negative tumor. This, in addition to the patient’s normal serum calcium (which is often elevated in patient’s with small cell carcinoma), was sufficient to rule out the possibility of a small cell carcinoma.2

Additionally, CK7 positivity and lack of CK20 staining confirmed the ovarian origin of the epithelial cells. The cells did not stain for uroplakin but stained focally positive for thrombomodulin. Overall, the tumor’s immunohistochemical profile is most consistent with a cystic Brenner cell tumor (Table 1).3

Table 1. A comparison of the immunohistochemical profile of the patient’s tumor and a Brenner cell tumor. CK = cytokeratin, TM = thrombomodulin, UP = uroplakin, (+) = focal staining, ? = unknown.

Of particular interest is the tumor’s expression of CD56, classically a neuroendocrine marker, which in the ovary is usually associated with a granulosa cell tumor or a small cell carcinoma. CD56 positivity in a Brenner cell tumor has never been reported.

CONCLUSIONS AND FUTURE WORK
Based on the immunohistochemical profile and the morphologic features of the tumor, the most likely diagnosis remains a cystic Brenner cell tumor. Brenner (or transitional) cell tumors of the ovary comprise fewer than 5% of ovarian epithelial neoplasms.5 The tumors consist of transitional epithelium, with a uniform population of small, stratified cells containing grooved nuclei (Fig. 4).5,6 The tumors are almost always benign and discovered incidentally.

However, the CD56 positivity of this tumor questions the known IHC profile of Brenner cell tumors. Practically, Brenner cell carcinomas must be differentiated from transitional cell carcinoma metastasis from the urinary bladder, from poorly differentiated serous papillary carcinomas, which may show transitional-like areas, and from small cell carcinoma of the ovary, which may morphologically resemble Brenner cell carcinoma.6 To date, none of these mimics are known to consistently express CD56.2,7,8 We hypothesize that Brenner cell tumors express CD56 and that this marker will be clinically useful in distinguishing Brenner cell tumors from lookalikes. We are currently working on staining multiple Brenner cell tumors, as well as controls, for CD56 to investigate this hypothesis.

REFERENCES

Figure 1. Pelvic ultrasound revealing a large cystic mass (lined in red).

Figure 2. H&E stain of the tumor (40X). Straight arrows = nucleoli, curved = grooved nuclei.

Figure 3. Pan-CK (A) and CD56 (B) positive sections of the tumor (10X).

Figure 4. H&E stain of a known Brenner cell tumor. Figure from Rubin’s Pathology.