Clinical Medicine & Research
Volume 18, Number 1 : 27-32

clinmedres.org

Case Report

First Report of Retroperitoneal Mucinous Cystadenoma in a Patient with Hirsutism

Ciera Danen, BS; Thomas Leschke, MD; Deepa Bassi, MD; and Rohit Sharma, MD

Primary retroperitoneal mucinous cystadenomas (PRMC) are rare benign neoplasms with only 55 documented cases in the English literature so far. A 19-year-old female exhibited hirsutism and was found to have a cystic mass measuring 5.8 cm x 3.9 cm x 5.8 cm in the left retroperitoneum. During subsequent work up, a high pre-operative value of dehydroepiandrosterone sulfate (DHEA-S) was noted. The patient was referred to surgical oncology and underwent an uneventful laparoscopic cystectomy. Pathology classified the cyst as PRMC. Post-operatively, the patient's DHEA-S levels normalized, though there was no appreciable decrease in the patient's hirsutism in the short-term follow-up. The origin of PRMC is uncertain. Due to their unknown biological potential, surgical resection is usually recommended. To the best of our knowledge, this is the first report documenting a PRMC and elevated levels of androgens in conjunction with hirsutism.

Keywords: Benign retroperitoneal tumor; Mucinous cystadenoma; Primary retroperitoneal mucinous cystadenoma; Retroperitoneum; Hirsutism

Primary retroperitoneal mucinous cystadenomas (PRMC) are rare neoplasms of unknown origin most commonly reported in women of childbearing age.[1] Preoperative diagnosis of benign PRMC is difficult based on radiology findings alone,[2] and limited biopsy or laboratory sampling is insufficient for definitively diagnosing PRMC.[3] Therefore, PRMC is generally diagnosed post-surgical resection.[1] Here, we present the first reported case of concurrent presentation of PRMC, elevated pre-operative levels of dehydroepiandrosterone sulfate (DHEA-S), and hirsutism in the English literature.

Case Report

A 19-year-old nulliparous woman presented to her primary care provider for evaluation of hirsutism. Her medical history was significant for primary amenorrhea, obesity, and mitral stenosis with regurgitation. She denied any unexplained weight changes, fatigue, weakness, fever, chills, or night sweats. There was no family history of hirsutism. The patient denied using alcohol or tobacco. She was noted to be obese on the initial physical examination and was mentally underdeveloped. Her body mass index at the time of evaluation was 45.7 kg/m^2, and she was observed to have a weight gain of 28.13 kg over 2 years. In addition, the patient's hirsutism was reported to have begun when she was approximately 17 years old and increased over the preceding 2 years, with increasing severity over the last year. The characteristic hair distribution of hirsutism was noted on examination with thick hair growth on the chin, upper lip, lateral side of the face, and over the midline abdomen. Her Ferriman-Gallwey Score was calculated to be 13-15 (mild hirsutism).[4] The patient's abdomen was soft, not tender or distended, and no masses were palpable. The patient then underwent a laboratory workup for hirsutism, and the observed laboratory values were normal besides elevated DHEA-S and testosterone levels (Table 1). Hyper-secretion of cortisol and non-classical congenital adrenal hyperplasia were included in the differential diagnosis; however, baseline serum cortisol was found to be normal and a cosyntropin stimulation test was negative. The patient did not follow-up for collection of the 24-hour urine cortisol measurement.

Corresponding Author: Rohit Sharma, MD, Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449, Tel: 715-387-5796, Fax: 715-389-3336, Email: sharma.rohit@marshfieldclinic.org,

Received: February 19, 2019
Revised: July 18, 2019
Accepted: August 5, 2019

doi:10.3121/cmr.2019.1488

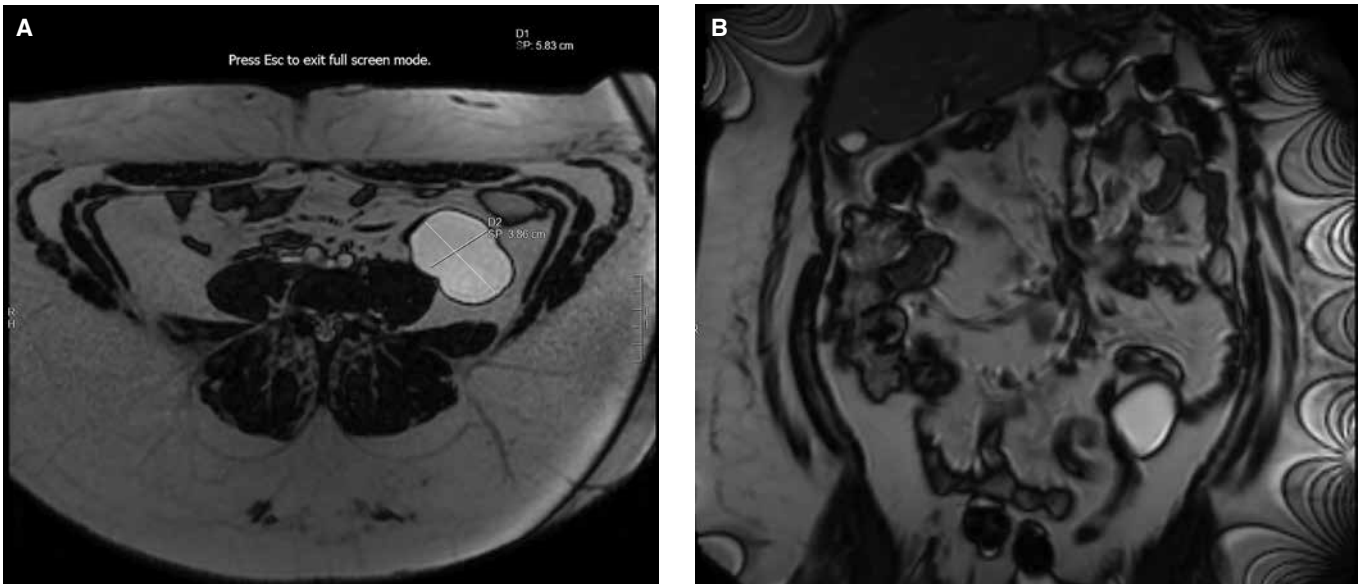

Figure 1. Computed tomography (CT)T imaging highlighted a cystic lesion in the left lower quadrant/upper pelvis region (A). Magnetic resonance imaging (MRI) showing a lobulated thin-walled cyst (B).

A computed tomography (CT) scan with contrast of the abdomen/pelvis was requested to rule out a virilizing tumor of the adrenal gland. CT imaging highlighted a cystic lesion in the left lower quadrant/upper pelvis region (Figure 1A), and normal appearing adrenal glands. The patient also had a pelvic ultrasound to evaluate the ovaries, which appeared normal. At the recommendation of the radiologist, the patient then underwent magnetic resonance imaging (MRI) to determine the exact nature of the lesion. A lobulated, thin-walled cyst in the left retroperitoneum/mesentery, thought to be most likely secondary to a mesenteric cyst or a lymphatic cyst/lymphangioma, was visualized and was measured to be 5.8 cm x 3.9 cm x 5.8 cm (Figure 1B).

Due to the presence of amenorrhea, hirsutism, and elevated androgens, polycystic ovarian syndrome (PCOS) was thought to be the cause of hirsutism. From the radiological images, the cyst was thought to be a congenital anomaly such as an enteric duplication cyst or a primary retroperitoneal cyst. Due to the unknown biological potential of the cystic lesion, an excision was planned for both diagnostic and potentially therapeutic purposes.

The patient was taken to the operating room for a laparoscopic possible open excision of the retroperitoneal cystic lesion. The cystic mass was found to be located lateral to the descending colon and was easily dissected out. It was not attached to the left colon, left ovary, or the pancreas. The specimen was sent to pathology for definitive diagnosis.

Pathology analysis with an initial hematoxylin and eosin (H&E) stain revealed a 5.5 cm x 4.5 cm x 4.0 cm pink-tan cyst with a 0.1 cm thick wall (Figure 2). Cell morphology consisted of columnar cells with basally placed nuclei of mucinous cells, which was consistent with a mucinous cystadenoma. Additional immunohistochemical (IHC) staining for estrogen receptors (ER) and calretinin detected a strong presence of ER on the surface and in the stroma of the cyst (Figure 3A) and only a few stromal cells stained with calretinin (Figure 3B). With no definite ovarian tissue present, the lesion was diagnosed as a benign mucinous cystadenoma arising from the retroperitoneum.

The patient had no postoperative complications and was seen at a follow-up appointment 2 weeks later and had normalized levels of DHEA-S from 458 to 300 µg/dL. There was no appreciable resolution in her hirsutism in the short-term follow-up.

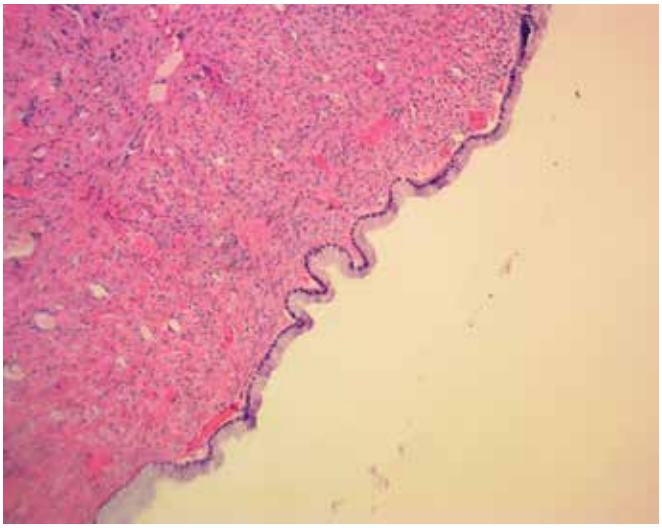

Figure 2. Hematoxylin and Eosin (H&E) staining of the benign cyst wall lined by mucinous cells with basally located nuclei.

Table 1. Laboratory results and normal value ranges

Test	Pre-Operative Observation	Post-Operative Observation	Normal Value Range
Alkaline Phosphate	117 U/L	N/A	42 – 85 U/L
Alanine Aminotransferase	38 U/L	N/A	8 – 22 U/L
Total Testosterone	**113 ng/dL**	**111 ng/dL**	**<10 – 47 ng/dL**
DHEA-S	**458 µg/dL**	**300 µg/dL**	**65 – 380 µg/dL**
Free Testosterone	**3.1 mg/dL**	**3.2 mg/dL**	**0.2 – 1.0 mg/dL**
Sex Hormone-Binding Globulin (SHBG)	17 nmol/L	13 nmol/L	19 – 125 nmol/L

N/A: Not Applicable

Discussion

PRMC are rare neoplasms. Since there is no epithelial tissue in the retroperitoneum, the origin of these lesions is unknown. There are two main hypotheses currently proposed for their origin.[2]

The first hypothesis is that these cysts are ovarian in origin, which is supported by the literature and positive expression of ER in the present case (Figure 3A).[2] Since ER is expressed on cells in both the breast and ovaries, this finding does not definitively mean that the cyst was ovarian in origin, but it supports the first hypothesis. Furthermore, the PRMC resembles ovarian mucinous cystadenomas.[1,5-7] This theory would explain why women have higher reported incidence of being diagnosed with PRMCs.[1]

The second most commonly referenced theory is that these cysts arise from the invagination of the multipotential mesothelium followed by mucinous metaplasia of the mesothelial cell lining, which gives rise to the mucinous cyst.[1,3,5,8-14] Calretinin staining was weak compared to the ER stain, which stained both the mucinous cyst cells and the stroma (Figure 3). Because calretinin stains mesothelial cells, the patient's cyst does not appear to be mesothelial in origin and does not support this hypothesis. The reported cyst may be related to Müllerian/ovarian cell lineages. At this time, there is no universally accepted etiology for PRMCs.

Mucinous retroperitonal neoplasms are clinically categorized into three different groups that range from benign to malignant based on their histology and clinical behavior (Figure 4). The first type is a benign mucinous cystadenoma. Under microscopic evaluation, these cysts have basally located nuclei, normal cell structure, and normal mitotic rate. Additionally, in these lesions there is no recurrence after surgical resection.[3,15] The second type of neoplasm is borderline mucinous cystadenomas. These neoplasms, unlike the first type, have a low malignant potential. On excision, these lesions have low atypia and pathologically resemble borderline mucinous neoplasms of the ovary.[3] The third type of neoplasm is malignant mucinous cystadenocarcinoma. This type of lesion can be either primary or metastatic.[3,16] Under microscopic evaluation, these lesions have marked atypia, increased pleomorphism, high nuclear cytoplasmic ratio, and either back-to-back glands or stromal infiltration. Areas of necrosis may also be visible in malignant lesions. Since a

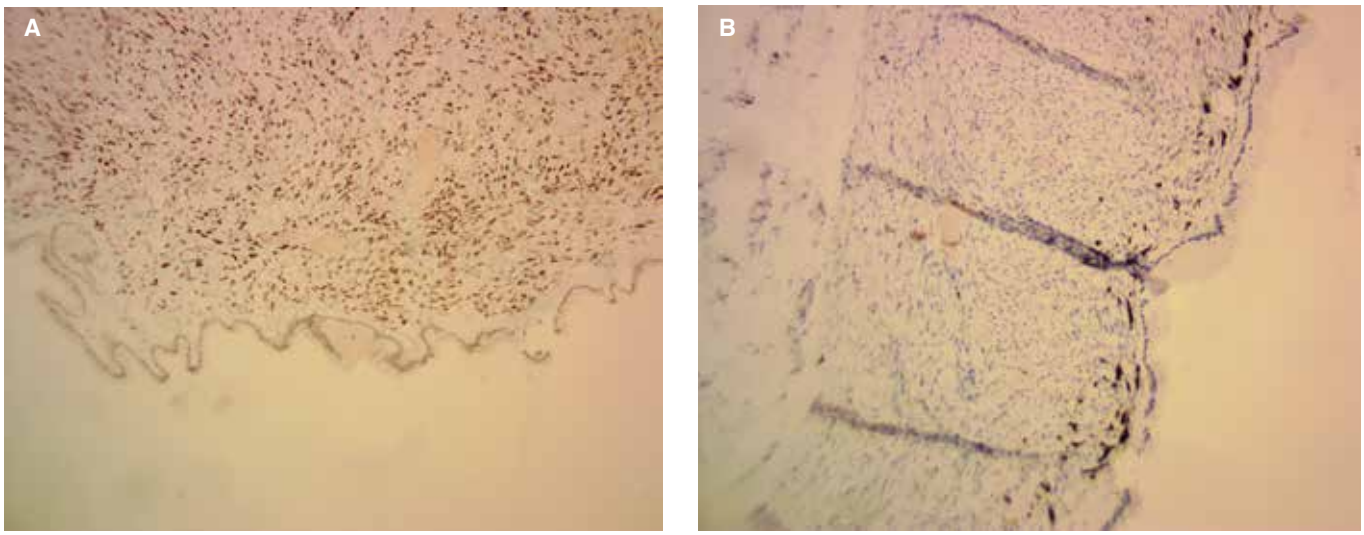

Figure 3. Immunohistochemistry (IHC) staining for (A) estrogen receptor (ER) and (B) calretinin. Strong ER staining is present in both the mucinous cyst cells and stroma.

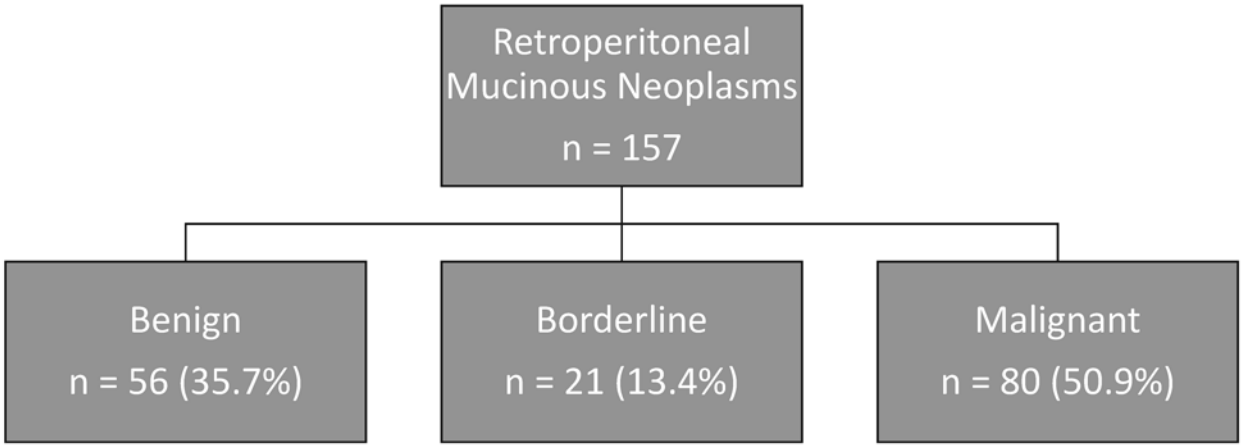

Figure 4. Flow diagram of case reports of mucinous neoplasms of the retroperitoneum split into three categories based on literature review.

definitive diagnosis can only be made through examination of the excised tissue, complete surgical excision is recommended.[1-3]

While most patients are reported to present with pain or other symptoms (Table 2), our patient had no symptoms directly attributable to the retroperitoneal cystic lesion. The patient's DHEA-S levels, which were elevated to 458 µg/dL at the time of initial surgical consultation, normalized to 300 µg/dL following surgical excision of the cystic lesion. This decrease of DHEA-S level, to the best of our knowledge, has not been previously described in the English literature. Thus, the relationship between the tumor and elevated DHEA-S level with subsequent normalization may be incidental and therefore not related to the PRMC resection. In addition, there were other slight abnormalities in the lab values of our patient that are of unknown significance and without specific discussion in the literature that was reviewed; this could be an area of further inquiry (Table 1).

PCOS is associated with elevated androgens, which was noted in our patient (Table 1), and has not previously been reported in conjunction with PRMC in the literature. However, further observations between PRMC and PCOS may elucidate a relationship between the two entities. Whether or not the presence of hirsutism in the current report was related to the PRMC or the coincidental identification of PCOS in the patient is uncertain; therefore, further investigation would be needed to better define this observation.

To put this case report in the context of the current literature on mucinous retroperitoneal neoplasms, we performed a detailed review of the indexed published English language literature from 1989 to January 2018 and only found 55 cases of benign PRMC with the associated characteristics summarized in Table 2.[1-3,5-52] A vast majority of the cases reported (95%) were female (Table 2),[5] which supports the ovarian origin hypothesis for these lesions.

All reported patients had removal of the retroperitoneal cyst, with the majority having open surgical intervention (70%). Of the overall reported cases, only about 14% underwent laparoscopic resection, with most laparoscopic procedures being performed in the last two decades. Recent documented reports of laparoscopic excision suggest that minimally invasive resection may be a safe and effective management strategy for this condition.[2,9,10,24,27,31,34,46,47]

It is important to note that in a comprehensive review of the English literature, there are 21 cases of borderline malignant mucinous cystadenomas and 80 cases of malignant mucinous cystadenocarcinoma.[9,53-55] The presence of these other categories of cystic lesions supports the need for surgical resection to definitively diagnose and reduce the potential for future cancer development in these lesions.

Conclusion

Primary retroperitoneal mucinous cystadenomas are rare neoplasms. All lesions, whether symptomatic or not, should be surgically removed due to their unknown malignant potential. Either open laparotomy or laparoscopic approaches may be used. While the origin of these cysts is unknown, the strong presence of ER and absence of calretinin on the patient's cyst supports the theory that these cysts arise from the ovaries.[2] Additionally, the presence of ER may provide a future link between PRMC and PCOS. This is the first case report of the observation between a PRMC, elevated levels of androgens, and hirsutism. This observation needs to be replicated in order to explore the relationship of PRMC with reproductive hormones and hirsutism.

Acknowledgements

We would like to acknowledge Emily Andreae, PhD and Marie Fleisner for manuscript editing assistance.

Table 2. Benign PRMC Literature Review Summary

Characteristics	n (%)
Sex	
Male	3 (5.4)
Female	53 (94.6)
Presentation	
Pain	23 (41.1)
Other Symptoms*	24 (42.8)
Incidental Finding	7 (12.5)
Unknown	2 (3.6)
Age Range	14-85
Median Age	36
Surgery Type	
Open	40 (71.4)
Laparoscopic	10 (17.9)
Unknown	6 (10.7)
Cyst Largest Diameter	
0-10 cm	12 (21.4)
≥10-15 cm	20 (35.8)
≥15-20 cm	11 (19.6)
≥20+ cm	11 (19.6)
Unknown	2 (3.6)
Median Tumor Size (cm)	12.65
Status at Follow Up	
No Evidence of Disease	25 (44.6)
Not Recorded	28 (50.0)
Not Available	3 (5.4)

*Other symptoms include abdominal fullness, discomfort, distention, flatulence, or mass
Data collected from 51 previous studies[1-3,5-52]

References

1. Nardi WS, Dezanzo P, Quildrian SD. Primary retroperitoneal mucinous cystadenoma. Int J Surg Case Rep. 2017;39:218-220.
2. Pesapane F, Van Renterghem S, Patella F, De Visschere P, Villeirs G. A case report and a literature review of primary retroperitoneal mucinous cystadenoma: the importance of imaging in diagnosis and management. Future Oncol. 2018;14(28):2923-2931
3. Min BW, Kim JM, Um JW, et al. The first case of primary retroperitoneal mucinous cystadenoma in Korea: a case report. Korean J Intern Med. 2004;19(4):282-284.
4. Escobar-Morreale HF, Carmina E, Dewailly D, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2012;18(2):146-170.
5. Subramony C, Habibpour S, Hashimoto LA. Retroperitoneal mucinous cystadenoma. Arch Pathol Lab Med. 2001;125(5):691-694.
6. Lai ECH, Chung KM, Lau WY. Primary retroperitoneal mucinous cystadenoma. ANZ J Surg. 2006;76(6):537.
7. Lee SE, Oh HC, Park YG, Choi YS, Kim MK. Laparoscopic excision of primary retroperitoneal mucinous cystadenoma and malignant predicting factors derived from literature review. Int J Surg Case Rep. 2015;9:130-133.
8. Paraskevakou H, Orfanos S, Diamantis T, Konstantinidou A, Patsouris E. Primary retroperitoneal mucinous cystadenoma. A rare case with two cysts and review of the literature. Hippokratia. 2014;18(3):278-281.
9. Dayan D, Abu-Abeid S, Klausner JM, Sagie B. Primary retroperitoneal mucinous cystic neoplasm: Authors' experience and review of the literature. Am J Clin Oncol. 2016;39(5):433-440.
10. Chen JS, Lee WJ, Chang YJ, Wu MZ, Chiu KM. Laparoscopic resection of a primary retroperitoneal mucinous cystadenoma: Report of a case. Surg Today. 1998;28(3):343-345.
11. Lee SY, Han WC. Primary retroperitoneal mucinous cystadenoma. Ann Coloproctol. 2016;32(1):33-37.
12. Erdemoglu E, Aydogdu T, Tokyol C. Primary retro peritoneal mucinous cystadenoma. Acta Obstet Gynecol Scand. 2003;82(5):486-487.
13. Tapper EB, Shrewsberry AB, Oprea G, Majmudar B. A unique benign mucinous cystadenoma of the retroperitoneum: a case report and review of the literature. Arch Gynecol Obstet. 2010;281(1):167-169.
14. Nam YJ, Kim TN, Kim KH, Gu MG, Lee JY. A case of primary retroperitoneal mucinous cystadenoma arising from the retropancreatic area. Korean J Gastroenterol. 2014;63(3):187-190.
15. Yunoki Y, Oshima Y, Murakami I, et al. Primary retroperitoneal mucinous cystadenoma. Acta Obstet Gynecol Scand. 1998;77(3):357-358.
16. Isse K, Harada K, Suzuki Y, et al. Retroperitoneal mucinous cystadenoma: Report of two cases and review of the literature. Pathol Int. 2004;54(2):132-138.
17. Pennell TC, Gusdon JP Jr. Retroperitoneal mucinous cystadenoma. Am J Obstet Gynecol. 1989;160(5):1229-1231.
18. Rothacker D, Knolle J, Stiller D, Borchard F. Primary retroperitoneal mucinous cystadenomas with gastric epithelial differentiation. Pathol Res Pract. 1993;189(10):1195-1204.
19. de Peralta MN, Delahoussaye PM, Tornos CS, Silva EG. Benign retroperitoneal cysts of müllerian type: a clinicopathologic study of three cases and review of the literature. Int J Gynecol Pathol. 1994;13(3):273-278.
20. Bortolozzi G, Grasso A, Zasso B. Mucinous cystadenoma of the retroperitoneum. A case report and review. Eur J Gynaecol Oncol. 1995;16(1):65-68.
21. Ginsburg G, Fraser J, Saltzman B. Retroperitoneal mucinous cystadenoma presenting as a renal cyst. J Urol. 1997;158(6):2232.
22. Kehagias DT, Karvounis EE, Fotopoulos A, Gouliamos AD. Retroperitoneal mucinous cystadenoma. Eur J Obstet Gynecol Reprod Biol. 1999;82(2):213-215.
23. Balat O, Aydin A, Sirikci A, Kutlar I, Aksoy F. Huge primary mucinous cystadenoma of the retroperitoneum mimicking a left ovarian tumor. Eur J Gynaecol Oncol. 2001;22(6):454-455.
24. Cadeddu MO, Mamazza J, Schlachta CM, Seshadri PA, Poulin EC. Laparoscopic excision of retroperitoneal tumors: technique and review of the laparoscopic experience. Surg Laparosc Endosc Percutan Tech. 2001;11(2):144-147.
25. Song DE, Kim M-J, Khang SK, Yu E, Cho K-J. Primary mucinous cystic neoplasm of the retroperitoneum: A report of three cases. The Korean Journal of Pathology. 2003;37:204-209.
26. Tamura T, Yamataka A, Murakami T, et al. Primary mucinous cystadenoma arising from behind the posterior peritoneum of the descending colon in a child: a case report. Asian J Surg. 2003;26(4):237-239.

27. Arribas D, Cay A, Latorre A, Córdoba E, Martínez F, Lagos J. Retroperitoneal mucinous cystadenoma. Arch Gynecol Obstet. 2004;270(4):292-293.
28. Yang DM, Jung DH, Kim H, et al. Retroperitoneal cystic masses: CT, clinical, and pathologic findings and literature review. Radiographics. 2004;24(5):1353-1365.
29. Sheen-Chen SM, Eng HL. Retroperitoneal mucinous cystadenoma. Dig Dis Sci. 2006;51(4):752-753.
30. Bakker RF, Stoot JH, Blok P, Merkus JWS. Primary retroperitoneal mucinous cystadenoma with sarcoma-like mural nodule: a case report and review of the literature. Virchows Arch. 2007;451(4):853-857.
31. Ishikawa K, Hirashita T, Araki KI, et al. A case of retroperitoneal mucinous cystadenoma treated successfully by laparoscopic excision. Surg Laparosc Endosc Percutan Tech. 2008;18(5):516-519.
32. Yan SL, Lin H, Kuo CL, Wu HS, Huang MH, Lee YT. Primary retroperitoneal mucinous cystadenoma: Report of a case and review of the literature. World J Gastroenterol. 2008;14(37):5769-5772.
33. Prabhuraj AR, Basu A, Sistla SC, Jagdish S, Jayanthi S. Primary retroperitoneal mucinous cystadenoma in a man. Am J Clin Oncol. 2008;31(5):519-520.
34. Abedalthagafi M, Jackson PG, Ozdemirli M. Primary retroperitoneal mucinous cystadenoma. Saudi Med J. 2009;30(1):146-149.
35. Roma AA, Malpica A. Primary retroperitoneal mucinous tumors: a clinicopathologic study of 18 cases. Am J Surg Pathol. 2009;33(4):526-533.
36. Rifki Jai S, Bouffetal R, Chehab F, Khaiz D, Bouzidi A. Primary retroperitoneal mucinous cystadenoma. Arch Gynecol Obstet. 2009;280(3):479-483.
37. Wiesel O, Spector D, Klausner JM, Sagie B. Mucinous cystadenoma of the retroperitoneum, laparoscopy or an open approach? Two case reports and review of the literature. Gynecol Surg. 2011;8(1):41-43.
38. Del Gobbo A, Bimbatti M, Ferrero S. A case report of mesenteric mucinous cystoadenoma with review of the literature. BMC Gastroenterol. 2010;10(1):105.
39. Papadopoulou D, Chatziralli I, Filitatzi Ch, Demertzidis Ch. Primary retroperitoneal mucinous cystadenoma. Hippokratia. 2011;15(2):191.
40. Fujita K, Yamamoto Y, Yamaguchi S. Laparoscopic resection of primary retroperitoneal mucinous cystadenoma by retroperitoneal approach. Int J Urol. 2011;18(8):607-608.
41. Fujita N, Nishie A, Asayama Y, Kiyoshima K, Kubo Y, Honda H. A male case of primary retroperitoneal mucinous cystadenoma: a diagnostic dilemma. Jpn J Radiol. 2012;30(7):594-597.
42. Navin P, Meshkat B, McHugh S, et al. Primary retroperitoneal mucinous cystadenoma—A case study and review of the literature. Int J Surg Case Rep. 2012;3(10):486-488.
43. Stranz CV. Asymptomatic large retroperitoneal cystadenoma. ANZ J Surg. 2012;82(7-8):558-559.
44. Bosisio FM, Estevez S, Segura J. Mucinous cystadenoma of the retroperitoneum. Int J Surg Pathol. 2013;21(2):150-152.
45. Demirel D, Gun I, Kucukodaci Z, Balta AZ, Ramzy I. Primary retroperitoneal mucinous cystadenoma with a sarcoma-like mural nodule: an immunohistochemical study with histogenetic considerations and literature review. Int J Gynecol Pathol. 2013;32(1):15-25.
46. Chen CH, Chiu LH, Lin JY, Liu WM. Pelvic retroperitoneal cyst during pregnancy. Taiwan J Obstet Gynecol. 2013;52(1):117-119.
47. Mattei J, Kim FJ, Phillips J, et al. Male primary retroperitoneal mucinous cystadenoma. Urology. 2013;82(1):e1-e2.
48. Santo-Filho MA, COLLEONi R, Shigueoka DC, Artigiani R, Scalabrini M, Lopes-Filho GJ. Primary retroperitoneal mucinous cystadenoma - case report. ABCD. Arq Bras Cir Dig. 2014;27(3):224-226.
49. Singh AK, Luhadia N, Agrawal A, Pahwa HS. Primary retroperitoneal mucinous cystadenoma: A rare case report. Scholars Journal of Medical Case Reports. 2014;2:609-611.
50. Heelan Gladden AA, Wohlauer M, McManus MC, Gajdos C. A primary retroperitoneal mucinous tumor. Case Rep Surg. 2015;2015:1-3.
51. Knezevic S, Ignjatovic I, Lukic S, et al. Primary retroperitoneal mucinous cystadenoma: A case report. World J Gastroenterol. 2015;21(17):5427-5431.
52. Zevallos Quiroz JC, Toran Monserrat FJ, de Santiago Urquijo FJ, Cormenzana Lizarribar EP, Arrinda Yeregui JM. Primary retroperitoneal mucinous cystadenoma. Cir Esp. 2016;94(6):365-366.
53. Myriokefalitaki E, Luqman I, Potdar N, Brown L, Steward W, Moss EL. Primary retroperitoneal mucinous cystadenocarcinoma (PRMCa): a systematic review of the literature and meta-analysis. Arch Gynecol Obstet. 2016;293(4):709-720.
54. Tokai H, Nagata Y, Taniguchi K, et al. The long-term survival in primary retroperitoneal mucinous cystadenocarcinoma: a case report. Surg Case Rep. 2017;3(1):117.
55. Nuhi A, Altarac S, Nuhii N. Extraovarian primary retroperitoneal mucinous cystadenocarcinoma; Case report. Journal of Surgical Arts. 2018;11(2):39-42.

Author Affiliations

Ciera Danen, BS; Thomas Leschke, MD*; Deepa Bassi, MD†; Rohit Sharma, MD**

**Department of General Surgery, Marshfield Clinic, Marshfield, Wisconsin, USA*
†Department of Pathology, Marshfield Clinic, Marshfield, Wisconsin, USA