Low Grade Appendiceal Mucinous Neoplasm with Concomitant Ovarian Mucinous Tumor, Mature Cystic Teratoma and Pseudomyxoma Peritonei

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ABSTRACT
Low grade appendiceal mucinous neoplasms are a challenging entity not just due to their innocent appearance and aggressive extension but also due to their origin dilemmas. We present one such interesting case in a 35-year-old Saudi female who presented to King Abdulaziz University Hospital with acute abdominal pain. The patient presented with the main bulk of the mucinous tumor in the left ovary with extensive pseudomyxoma peritonei. Incidentally there was also a mature cystic teratoma in the same ovary. Appendiceal origin was confirmed on histology and immunohistochemistry. In conclusion our case scenario of low grade appendiceal mucinous neoplasms with concomitant ovarian mucinous tumor, mature cystic teratoma and pseudomyxoma peritonei suggests appendiceal origin both on morphology and immunohistochemistry. As such routine excision of appendix in these case scenarios remains a valid consideration.

Keywords
Ovarian; Mucinous; Appendiceal; Teratoma.
INTRODUCTION

Appendiceal mucinous neoplasms are a spectrum of tumors that keep challenging our knowledge of their existing definitions and classification. One particularly interesting tumor in this group is the low grade appendiceal mucinous neoplasm (LAMN). These tumors attract much interest for the fact that though they have an innocent gross and microscopic appearance they tend to penetrate through the appendiceal wall and disseminate into the peritoneum causing a distinctive syndrome called pseudomyxoma peritonei (PP). Often the pathologist finds him/her self in a diagnostic dilemma when faced with the bland cytological features closely resembling reactive epithelial atypia versus the aggressive behavior when they have disseminated to the peritoneum. This dilemma leads to a series of controversies that surround these tumors such as the classification of LAMN itself, the nature and clinical significance of PP in this scenario, whether the presence of grossly intact and microscopically bland appendix favors or disregards the appendiceal origin and most importantly whether the presence of a concomitant ovarian mucinous tumor (OMT) should be considered a separate primary or a metastasis from the appendix.

CASE REPORT

We present an interesting case of a LAMN arising from an intact appendix with disseminated PP associated with concomitant OMT and mature cystic teratoma (MCT) in a 35year old Saudi female at the time of diagnosis. To the best of our knowledge this is the first such case reported from Saudi Arabia and among the very few reported globally[1-3]. The histopathology slides, report and relevant information were retrieved from the archives of Anatomic Pathology Department at King Abdulaziz University Hospital, Jeddah Saudi Arabia. The clinical history and operative notes were collected from the clinical team in person and from the patient’s hospital file. On history, the patient had four pregnancies all of which were spontaneous live vaginal deliveries. Her last delivery was six years back and had been on oral contraceptives for a period of three years following her last delivery. There was no history of diabetes, hypertension, or any chronic disease.

The patient presented with acute left abdominal pain, distention, which was increasing gradually over two weeks associated with fever and amenorrhea. Laboratory investigations revealed high titer of serum tumor markers such as CA-125 as 35.47 IU/mL (0-35) and CEA 42.47ng/mL (0-3.4). Serum beta HCG was negative. Ultrasound of the pelvis showed a complex left ovarian cystic mass measuring 27x21x12 cm. The right ovary, fallopian tube and uterus were unremarkable. The radiological diagnosis rendered was that of a “left ovarian neoplasm of undetermined significance”. Based on the clinical, laboratory and radiological presence of a mass, a clinical diagnosis of malignant left ovarian mass was made by the gynecologist and the patient was scheduled for left oophorectomy. Over the course of the next few days the patient complained of a severe increase in abdominal pain following which she was rushed for surgical intervention. Intraoperatively the gynecologist found a huge ruptured left ovarian mass. The abdomen was filled with gelatinous mucoid material. Intraoperative frozen section was performed from the ovarian mass which revealed a mature cystic teratoma associated with large mucinous neoplasm. In view of a suspicious OMT and its known association with appendiceal primary, intraoperative staging was performed and the ovarian mass, left and right pelvic nodes, appendix and related omentum was resected and submitted to histopathology for examination and confirmation of frozen diagnosis. The right ovary and tube were found to be uninvolved and were not resected.

Grossly the left ovarian mass measured 27 x 20 x 9 cm. The outer surface showed focal rupture and was cystic, smooth and shiny oozing mucoid material. The tumor weighed 2 kg and a small firm hilar ovarian area was identified along with a stump of left fallopian tube. Cut section through the mass showed a multi loculated cyst filled with mature hair shaft; pultaceous material, bony tissue, intermingled with lakes of viscid mucoid material (Fig. 1a, 1b). There were no solid areas or...
necrosis. Representative sections were submitted one per cm of the tumor for microscopic examination. The appendix measured 4x2cm and was grossly intact and unremarkable. Cut section through the appendix revealed only fecolith with preserved lumen. Appendix was totally submitted in six cassettes. The omentum measured 10 x 8 x 5 cms and showed multiple suspicious firm areas which were submitted for histological examination. Four left and eleven right pelvic lymph nodes were identified. Each was bisected, submitted separately and fully embedded.

On histopathological examination; the left ovarian mass revealed benign ectodermal elements including keratinizing squamous epithelium, mature hair shafts, mature brain, sebaceous and apocrine glands (Fig. 2a). Mesodermal element such as calcified bone, cartilage, adipose tissue with giant cell reaction were also present (Fig. 2b). Multiple variable cysts lined by tall intestinal type of epithelium with goblet cells were seen involving most of the ovary surrounded by a large amount of cellular and extra-cellular mucin dissecting the ovarian stroma (Fig. 3a). The glands were elongated exhibiting scalloped lumina and sub epithelial clefts (Fig. 3b, 3c). The epithelium lining the glands showed stratification, mild nuclear atypia with focal micropapillary formation. Psammoma bodies were frequent. There was no mitosis, necrosis, mucin granulomas or ovarian type cellular stroma. The left fallopian tube was uninvolved by the tumor. The appendix revealed intact wall with mucosa lined by adenomatous mucinous columnar epithelium (Fig. 4a) similar to that present within the mucinous areas of left ovary. The epithelium showed crowded pseudostratified villiform...
columnar cells with low grade dysplastic features. The nuclei were basal elongated hyperchromatic with large amount of apical mucin. Muscularis mucosa was thinned out. The submucosa showed marked histocytic response. Mucin lakes were seen focally within the wall of the appendix and focal direct invasion of the muscle wall by jagged neoplastic glands was present (Fig. 4b). The serosal surface showed lakes of mucin (Fig. 4c). Section from the proximal margin of the appendix was also involved by the dysplastic epithelial lining. The omentum showed pools of extracellular mucin, low grade adenomatous mucinous epithelium (Fig. 5a, b) and psammoma bodies with focal mesothelial hyperplasia and giant cell reaction. The lymph nodes showed reactive cellular changes with no metastatic epithelial deposits and negative mucicarmine stain. A panel of immunohistochemical (IHC) markers was performed in an attempt to determine the origin of the mucinous tumor. Immunohistochemical markers were performed separately for section from left ovary, omentum and appendix. The markers included CK7, CK20, CEA, MUC-2, CDX2, CA-125. The epithelium of the mucinous tumor at all three sites was diffusely (more than 50% of the tumor) and strongly (high intensity) positive for CK20, CEA, CDX2, MUC-2 and negative for CK7 and CA125.

In the histopathological diagnostic conclusion, the fact that all the three involved sites showed similar morphological pattern of mucinous tumor and expressed IHC markers supporting appendiceal origin, the final diagnosis was “LAMN with concomitant OMT, mature cystic teratoma and pseudomyxoma peritonei”. At one-year follow-up currently the patient is disease free.
DISCUSSION

Our case supports the currently established concept that OMT with PP almost always results from the spread of primary gastrointestinal tract tumor usually of appendiceal origin[1]. The ovarian tumors in such cases are large in size mimicking a primary while on the other hand the primary appendiceal tumors may arise in a grossly unremarkable and intact appendix[1] and frequently lack classic infiltrative invasion of the appendiceal wall yet managing to seed the peritoneum causing PP[2], as in our case. Although clinicopathological, IHC, molecular and genetic studies have established the concomitant OMT with PP as being of metastatic nature from an occult appendiceal primary[1] yet an element of reasonable doubt of it being vice versa remains in the minds of many pathologists to date. The reason for this being the presence of diversity among such case reports in literature that convincingly seem to support the opposite origins. To add to the confusion is the fact that isolated cases of histologically benign, borderline, or malignant OMT may as well be associated with MCT and PP[1]. Our detailed knowledge regarding these tumors and their biological behavior however remains limited since much of it is derived only from individual case reports or case series. Ronnett and Seidman[3] reported a subset of OMT arising in a background of MCT associated with PP and exhibiting an IHC expression more supportive of gastrointestinal origin rather than ovarian. Stewart et al.[1] reported two cases of primary OMT arising in MCT with PP and compared it with four cases of OMT secondary to primary LAMN by using IHC markers. Interestingly both categories of primary origin tumors expressed the same set of IHC markers such as CK 20, CEA, CDX2 and MUC2. Thus IHC markers are reasonably helpful to differentiate the origin in such complicated case scenarios. A study by McKenney et al.[4] targeting 42 patients with OMT arising in MCT and associated with 24% PP showed no significant risk for intra-abdominal recurrence. In their case series Stewart et al.[5] reported that primary OMT arising in MCT and associated with PP were similar in morphology and IHC expression to those arising secondary to LAMN by using IHC markers. Interestingly both categories of primary origin tumors expressed the same set of IHC markers such as CK 20, CEA, CDX2 and MUC2. This raises the possibilities that IBMT arising in MCT or may not result from LAMN and that they may be associated with PP in either case. A morphological study by Stewart et al.[6] compared 16 cases of ovarian involvement by LAMN associated with PP with 18 cases of primary ovarian IBMT devoid of PP and 6 ovarian IBMT arising within MCT associated with PP. They concluded that the presence of scalloped glands with sub epithelial clefts were more frequent in LAMN than ovarian IBMTs. On the other hand, ovarian IBMT more frequently showed cellular ovarian type stroma with formation of mucin granulomas. In our case, although we found scalloped glands with sub epithelial clefts in the ovarian involvement by LAMN, the interpretation of applying these microscopic features as solely reliable criteria to consistently differentiate the origin would require validation by large case studies.

The plethora of conflicting evidence in literature[7-27] and the reconciliation with the fact that both tumors appear similar in morphology and IHC expression regardless of origin raises important research questions. First; if these tumors are so mysteriously similar in morphology and IHC expression, do they have a similar biological behavior? Second; does their origin, similarity or difference impact clinical outcome and management? Third; should appendiceal resection be routinely considered in all such cases? Fourth; what prognostic impact does LAMN with concomitant OMT, MCT and PP have? With the best of our efforts we found no convincing answers to our questions worth scientific documentation.

CONCLUSION

In conclusion all these questions could be reasonably answered by more comprehensive studies involving large number of cases targeting the detailed clinicopathological, immunophenotypical and prognostic comparison of the two categories LAMN with concomitant OMT, MCT, PP and LAMN without concomitant OMT, MCT, PP. Our case scenario of LAMN with concomitant OMT, MCT and PP suggests appendiceal origin both on morphology and IHC. As such routine excision of appendix in these scenarios is clinically warranted.

Conflict of Interest

The authors have no conflict of interest.

Disclosure

None of the authors received any type of commercial support either in forms of compensation or financial for this study. They have no financial interest in any of the products or devices, or drugs mentioned in this article.

Ethical Approval

Obtained.

REFERENCES


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ورم الزائدة الدودية من الدرجة المنخفضة مصاحبا لورم مخاطي بالمبيض بالإضافة إلى ورم مسخي ناضج وورم مخاطي صفافى كانب

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المستخلص:

أورام الزائدة الدودية المخاطية من الدرجة المنخفضة تعد إحدى الأشكال التشخيصية من حيث صفاتها التشريحية الحميدة وانتشارها الخبيث ومصدرها، ومن هنا تتعذر لكم حالة نادرة لسيدة بلغ من العمر 35 عاماً سعودية الجنسية، أدخلت إلى مستشفى جامعة الملك عبد العزيز بجدة من ألم شديد في البطن، وكان معظم أعراضها مصلبة في المبيض الأيسر، إضافة إلى استكشاف وجود ورم مسخي ناضج في نفس المبيض الأيسر، ويعود مصدر الورم الذي تم إبتهله بفحص الخلايا والأنسجة بالإضافة إلى صبغة الكيمياء الهيستولوجية المناعية إلى الزائدة الدودية.

نستخلص من هذه الحالة المماثلة في ورم الزائدة الدودية من الدرجة المنخفضة بالإضافة إلى ورم مخاطي في المبيض، وورم مسخي ناضج، وورم مخاطي صفافى كانب، بأن مصدر الورم في الزائدة الدودية استنادا إلى شكل الخلايا والأنسجة وصبغ الكيمياء الهيستولوجية المناعية، ولذا فإن استئصال الزائدة الدودية لا يزال يعتبر من الإجراءات المفيدة في مثل هذه الحالات.