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Synchronous primary adenocarcinoma of the appendix and colon: Case report and literature review

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ABSTRACT

INTRODUCTION: Primary adenocarcinoma of the appendix (PAA) is rare with fewer than 300 cases reported from 1882 up to 2004. Synchronous occurrence of PAA with a second primary colonic carcinoma is even more unusual. Literature review shows a total of 40 reported synchronous cases in the English literature from the first case reported in 1947 up to 2017. Hereby, an additional case is presented, which is the first case reported in Jordan.

PRESENTATION OF CASE: A 39-year-old woman presented in October 2016 with persistent right lower quadrant abdominal pain diagnosed clinically as acute appendicitis. Abdominal computed tomography showed an oval shaped 3 × 3.4 cm mass at the sub-hepatic region, associated with increased attenuation of surrounding mesenteric fat and multiple enlarged lymph nodes. Three days later, a right hemicolectomy was carried out. A diagnosis of invasive primary adenocarcinoma of the ascending colon with an incidental, microscopic primary adenocarcinoma of the distal part of the appendix was reported.

DISCUSSION: Primary appendiceal adenocarcinoma is rare pathology with an incidence ranges from 0.01% to 0.3% that is characterized by presence of adenocarcinomatous cells originating in the appendix that are in direct continuity with the normal appendiceal mucosa. Even it is less common, synchronous primary adenocarcinoma of the appendix and the colon has been reported in literature, with less than 37 cases being reported in literature so far. PAA are seldom suspected in preoperative phase or even intraoperatively, and it is diagnosed based on histopathologic examination of the resected appendix. Once PAA is diagnosed, a lifelong surveillance with colonoscopy is mandatory to detect synchronous or metachronous colonic malignancies.

CONCLUSIONS: Once a diagnosis of primary appendiceal adenocarcinoma is proved histologically, it is warranted to perform surveillance for synchronous or metachronous tumors because of the increased risk of a second primary malignancy in the gastrointestinal tract.

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1. Introduction

Primary adenocarcinoma of the appendix (PAA) is rare with fewer than 300 cases reported from the first authenticated case reported by Beger in 1882 up to 2004 [1]. PAA is known to have occurred in an appendix stump 35 years after the initial appendectomy [2] and in a 17-year-old patient [3].

PAA is an unusual, rarely diagnosed malignancy, constituting less than 6% of appendiceal neoplastic lesions, and less than 0.5% of all gastrointestinal neoplastic lesions [4–7]. A preoperative diagnosis of PAA is extremely difficult, and has never actually been made before operation since there is no pathognomonic signs or symptoms and the fact that more than 70% of patients with appendiceal adenocarcinoma present with clinical symptoms of acute appendicitis. Presumptive preoperative diagnoses include acute appendicitis, appendiceal abscess, and carcinoma of the cecum [8]. Since there are no imaging studies specific for diagnosing adenocarcinomas, the final diagnosis is most often made postoperatively on microscopic examination [9]. Therefore, the appendix must always be subjected to histological examination as otherwise an appendiceal malignancy can be easily missed [10]. The work has been reported in line with the SCARE criteria [43].

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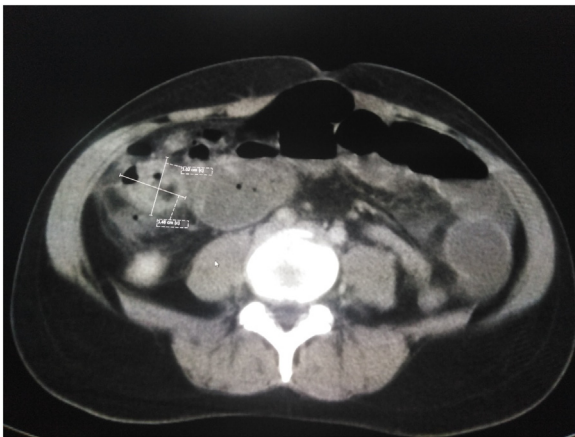


Fig. 1. Axial image of contrast enhanced CT abdomen. An oval shaped structure with thickened enhancing mural wall at the sub-hepatic region measuring 3 × 3.4 cm in antero-posterior and transverse diameters associated with surrounding mesenteric fat stranding and few enlarged lymph nodes.

In this case report, we aimed to highlight the rare occurrence of PAA with colonic carcinoma, and to review available literature regarding patient surveillance and treatment of these cases.

2. Case

A 39-year-old woman with unremarkable medical history was admitted to Prince Hamza Teaching Hospital, Amman, Jordan, in October 2016 complaining from right lower quadrant abdominal pain for investigation. Patient was not on medications and her family history was negative for malignancies. On physical examination, patient was vitally stable, afebrile with localized tenderness at the right iliac fossa in association with rebound tenderness. Her blood tests showed leukocytosis with neutrophilia. A clinical suspicion of acute appendicitis was presumed. Radiologic work up showed a normal chest X-ray while the computed tomography (CT) scan for the chest, abdomen and pelvis CT revealed an oval shaped structure with thickened enhancing mural wall at the sub-hepatic region. It measured 3 × 3.4 cm, and was associated with an increased attenuation of surrounding mesenteric fat in presence of multiple enlarged lymph nodes and air-fluid levels (Fig. 1). Normal appearance of the liver, spleen, pancreas, adrenals, both kidneys and lungs. The differential diagnosis was consistent with either an inflammatory process involving the ileocecal junction (i.e. sub hepatic appendix), or colonic malignancy.

On the 3rd day of admission, a diagnostic laparotomy was done. Intraoperatively, a palpable cecal mass with mesenteric lymphadenopathy was identified, for which right hemicolectomy and ileocolic anastomosis was performed with resection of part of the greater omentum. Postoperatively, patient recovered smoothly and was discharged on her 5th postoperative day.

Gross examination of the right hemicolectomy revealed an annular, ulcerating, white tumor 30 mm in length. It was situated in the upper part of the cecum (i.e. Ceco-colic junction) distal to the ileo-Cecal sphincter. It was infiltrating the full colonic wall thickness, serosa and invading the mesocolonic fat. The terminal ileum, the rest of the caecum which showed the site of the appendicular stump and the ascending colon were unremarkable. Ten mesenteric lymph nodes recovered with additionally two firm nodules in the greater omentum, the appendix was normal looking, measuring 35 × 20 × 15 mm and weighing 4 g. The attached omental piece was 40 × 20 × 10 mm, including small lymph node.

Histopathological examination showed a primary, ulcerating, well-differentiated, colonic infiltrating adenocarcinoma of the

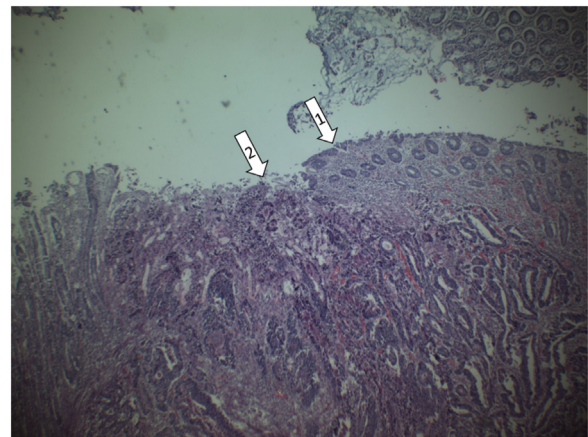


Fig. 2. Low power view of longitudinal section of the primary colonic adenocarcinoma, arrow (1) shows the normal colonic mucosa which is in direct continuity with the transformed colonic adenocarcinoma in the center (arrow 2) which infiltrate downwards in the submucosa (Hematoxylin and Eosine stained section X100).

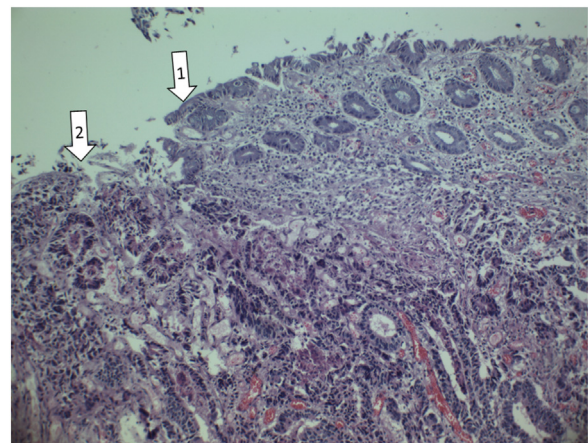


Fig. 3. High power view of the same section shown in Fig. 3, with arrow (1) showing the normal colonic mucosa which is in direct continuity with the transformed colonic adenocarcinoma (arrow 2) which infiltrates downwards in the submucosa (Hematoxylin and Eosine stained section X400).

colon, which was confined to the upper part of the caecum (i.e. Ceco-colic junction), with an evidence of direct continuity of the carcinomatous tissue with the adjacent normal looking colonic mucosa invading the submucosa, colonic muscular wall, serosa and the meso-colic fat (Figs. 2 and 3). Three out of ten mesenteric lymph nodes and the two omental nodules were extensively infiltrated by adenocarcinomatous deposits. Both lines of resections, the small intestine, the colon and the caecum from the appendicular base to the proximal border of the tumor were normal. The colonic tumor was staged as PT4, N1, M0.

Histopathological examination of the appendix revealed a primary, well-differentiated, infiltrating, colonic type adenocarcinoma that was confined to the distal part (10 mm) of the appendiceal mucosa only, with definite direct continuity of the normal appendicular surface mucosa with the transformed adenocarcinoma (Fig. 4), confirming its primary origin, and excluding an origin from the cecum. According to Guarino and Chitwood [11], this fulfilled the histologic criteria for the diagnosis of primary adenocarcinoma originating within the appendix. The carcinoma invaded and infiltrated the submucosa, the full muscular wall thickness (Fig. 5) and extended very close to, but, not involving the serosa of the distal part of the appendix. No mucocele, signet or goblet cells, mucin collection, or squamous elements were seen. The whole

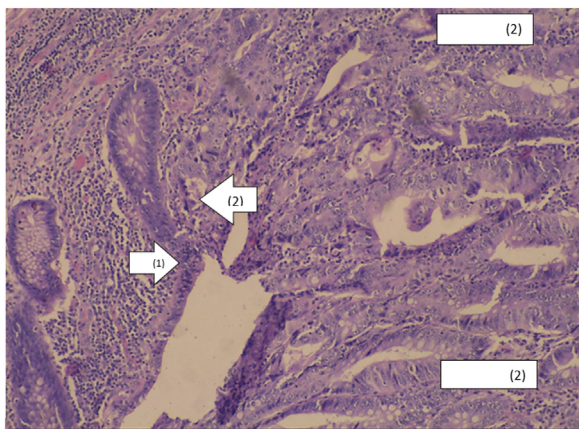


Fig. 4. High power view of longitudinal section of the distal part of the appendix, with arrow (1) showing normal appendicular surface mucosa in direct continuity above with arrow (2) area of transformed adenocarcinomatous tissue, with the carcinoma involving the whole right side part of the section (2 rectangles) (Hematoxylin and Eosine stained section X400).

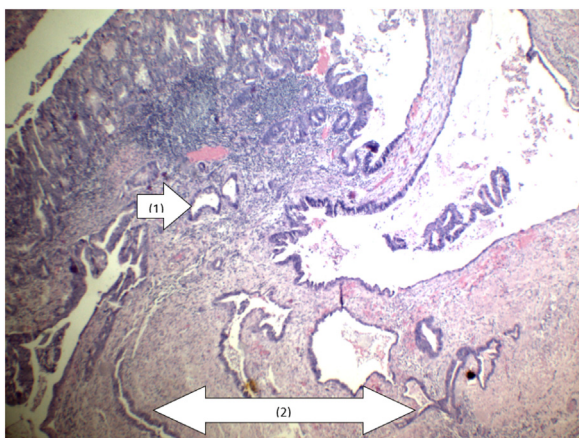


Fig. 5. Low power view of longitudinal section of the primary adenocarcinoma of the appendix with upper arrow (1) showing invasion of the appendicular submucosa and lower arrow (2) showing invasion of the appendix full muscular wall (Hematoxylin and Eosine stained section X100).

rest of the appendix (25 mm) was unremarkable with no evidence of acute appendicitis or of malignancy. Both, the omentum and the lymph node were extensively infiltrated by well differentiated adenocarcinomatous deposits.

Based on her histopathologic findings, patient was referred and followed at the department of oncology for an adjuvant chemotherapy, no interval colonoscopy was performed. Thirteen months later, she presented with bilateral ovarian masses, which were suggestive of ovarian metastasis, for which she was readmitted for bilateral Salpingo-oophorectomy (Fig. 6). Histopathological examination of the right ovarian solid tumor (80 × 70 × 50 mm) and of the left ovarian cystic tumor (50 × 40 × 10 mm) revealed infiltration of both ovaries by adenocarcinomatous deposits of intestinal primary; tumor cells were immuno-stains positive for CDX-2, the key marker to confirm the final diagnosis. In addition, the tumor cells were positive for CK20 and negative for CK 7.

The postoperative course was uneventful and the patient was discharged from the hospital 14 days later and referred for adjuvant chemotherapy. She was still living with no long-term postoperative complications 20 months after the initial diagnosis of the appendiceal carcinoma.

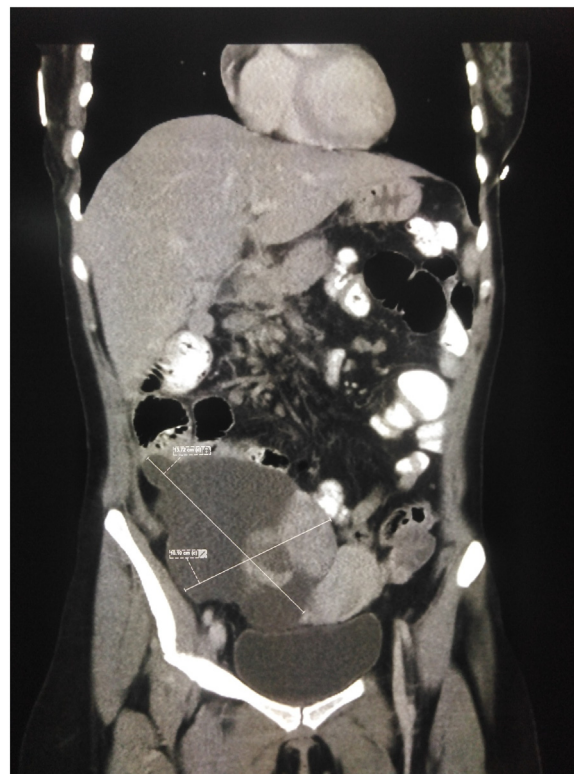


Fig. 6. Contrast enhanced CT scan abdomen & pelvis (Coronal view). Bilateral ovarian masses with cystic and solid component, large Right ovarian mass measures 13 × 10 cm.

3. Discussion

3.1. Epidemiology and incidence

Based on available literature, PAA incidence ranges from 0.01% to 0.3% [12–16]. Beger is generally credited as having reported the first authenticated case of appendiceal adenocarcinoma in 1882 [17]. The routine histologic examination of all surgically removed appendices had resulted in the discovery of an increasing number of PAA cases.

During the period between 1882–1970, the total number of PAA reported in the English literature was 149 cases [8,12], the number increased to fewer than 200 up to 1976, and to fewer than 300 up to 2004 [1,2]. In 2016, Xin Xie et al. reported 1404 patients with adenocarcinoma of the appendix in the Surveillance, Epidemiology, and End Results Program (SEER) database in China during the period between 2004 and 2013. 48.7% of the cases were positive mucinous adenocarcinoma and 51.3% were none mucinous colonic-type adenocarcinoma [19].

PAA is more common in men than in women, with a male to female ratio of 1.4:1 [38]. The mean age of patients in different series ranges between 56 and 61 years, with an age range between 18 and 100 years [12,19,22–25,38], only 15% being younger than 40 years of age [22]. Takahashi reported the youngest patient (13-year-old) with PAA [44].

Guarino and Chitwood [11] presented the histologic criteria for diagnosis of primary adenocarcinoma originating in the appendix. According to them, direct continuity of the carcinomatous cells with the normal appendiceal mucosa is an essential criterion to diagnosis primary PAA, and this criterion was fulfilled in the present case.

Prior to 1943, the classification of adenocarcinoma of the vermiform appendix was in a state of considerable confusion. Clar-

ification began with Uihlein and McDonald [18] in 1943 whom divide appendiceal carcinoma into three categories based on their prevalence; carcinoids (88.2%), cystic carcinomas (8.3%), and appendiceal carcinoma resembling the adenocarcinomas of the colon (3.5%). These figures give an excellent idea of the rarity of the colonic type of appendiceal carcinoma. The authors have tabulated the usual sites of the various types; the colonic type was found to arise in the base or tip of the appendix. In Andesson study, two of the 13 colonic type were confined to the distal third while the remaining 11 were localized to the base [2]. In the present case the PAA was localized in the tip of the appendix.

According to the International Classification of Diseases for Oncology [20], appendicular tumors are divided into five classes: Mucinous adenocarcinoma, colonic type adenocarcinoma, goblet cell carcinoma, signet ring cell carcinoma and malignant carcinoid (i.e. adenocarcinoid) [5,20]. Although appendicular carcinomas are classified separately from colorectal carcinomas in the 7th edition of the AJCC Staging Manual [21], both mucinous and non-mucinous adenocarcinomas of the appendix are classified together. The present case and the reported cases mentioned later in the synchronous occurrence with colonic are all of the colonic type of primary adenocarcinoma of the appendix.

3.2. Clinical presentation and work-up

Preoperative diagnosis of PAA is difficult, patient usually present with non-specific presentation. Patients can present with features of acute appendicitis, right lower quadrant mass, urinary frequency, intussusception, hydronephrosis or anemia [13]. Appendiceal adenocarcinoma represents the most common gastrointestinal neoplasm presenting with perforation [22,24,26,38], in some reports, perforation rate was encountered in more than 45% of the cases [22,38]. As the appendix often has deficiencies of both longitudinal and circular muscle fibers, this may not only predispose to perforation but also to apposition of the submucosa and the peritoneum, leading to the potential for early dissemination in seemingly non advanced primary lesions [23,27,28]. In the present case, the PAA was not perforated. So, as PAA are seldom suspected in preoperative phase or even intraoperatively, no established method is currently available for preoperative diagnosis [13].

3.3. Treatment and follow up

Nitecki recommended Right hemicolectomy for all patients with non-carcinoid adenocarcinoma of the appendix because of the risk of overlooked nodal metastases that reach up to 38% [22]. Their findings, and of others, demonstrated that all of these appendicular adenocarcinomas are invasive and that nodal metastases can be found in up to 45% of the adenocarcinoma type, as in the present case. They reported that survival rate was superior after right hemicolectomy versus appendectomy alone (68% vs. 20%, $p < 0.001$) [22], similar results reported by others [29].

Nitecki suggest careful preoperative colonoscopy in the patient undergoing re-exploration for right hemicolectomy after an initial appendectomy alone, in which appendiceal adenocarcinoma ostensibly localized to the appendiceal wall (Dukes A and B lesions), as this is warranted to detect the 12% prevalence of a synchronous colonic or rectal carcinoma [22]. Their advice that surveillance for synchronous or metachronous tumors is warranted because the risk of a second primary malignancy in the gastrointestinal tract is significantly increased. Likewise, a lifelong program of subsequent postoperative colonic surveillance also should be instituted for metachronous tumors.

Given the difficulty in diagnosis of appendicular tumors and the certain risk of synchronous and metachronous neoplasm of the appendix, the question of whether an incidental appendectomy

should be performed in colorectal carcinoma patients has been raised.

The patient in this study presented Thirteen months after hemicolectomy with bilateral ovarian adenocarcinomatous secondaries from intestinal primary. Nitechi advocates' routine oophorectomy (with all types of appendicular adenocarcinoma) in women especially if they are postmenopausal [22]. They found ovarian metastases in 56% of patients subjected to oophorectomy. Although the prognosis is poor when ovarian metastases are present (i.e. mean survival of 30 months), oophorectomy is beneficial for staging, may prevent a potentially privileged site for symptomatic metastasis, and may prolong survival. Indeed, the 5-year survival rate was 31% in this group of patients in whom metastatic ovarian disease was resected [22].

4. Synchronous primary adenocarcinoma of the appendix and the colon

The problem of multiple neoplastic lesions has been present in medicine for over hundred years. Billroth was the first to define the problem in 1889, followed by Warren and Gates in 1932 [30,31]. Both of them provided rounds for the current definition and diagnostic criteria of multiple neoplastic lesions, established by the International Agency for Research on Cancer [32]. By definition, synchronous tumors are distinguished when the time elapsed between the diagnosis of two neoplastic lesions is less than 6 months, while that of metachronous tumors when the period exceeds 6 months. Despite the enormous progress in abdominal imaging techniques, both radiological and endoscopic, the diagnosis of synchronous colon tumors is extremely rare. This is associated with the frequency of occurrence, which for synchronous colon cancer ranges between 0.6–1.4%, while in case of metachronous lesions, between 1% and 8% [33].

Synchronous primary carcinoma of the appendix associated with primary colonic carcinoma is even more unusual than PAA, and is very rare. In the study by Moertel et al., of 261 cases of multiple primary cancer of the large intestine, there were no instances of concurrent primary carcinoma of the appendix [34].

Payumo and McManus stated that as far as we can determine, only two previous examples of coincidental carcinoma of the appendix and colon have been reported up to 1970 [8], the First was reported by Maisel and Foot and the second by Seddon [35,36]. Payumo and McManus add one further case of their own which brought the total number synchronous cases to three, from 1947 up to 1970 [8].

Following literature review for an additional synchronous case reports from 1971 up to 2017, we collected 37 cases which brought the total number of synchronous PAA associated with primary colonic carcinoma reported in the English literatures during 70 years, from 1947 to 2017 to 40 cases listed in chronological order in Table 1. Hereby, we present an additional case which is the first case reported in Jordan.

Due to the possibility of synchronous tumors after histological confirmation of appendiceal adenocarcinoma, it is necessary to complement diagnostics by endoscopy or abdominal CT images. Usually, during surgery performed because of a neoplastic lesion, the surgeon identifies the existence of a second gastrointestinal tumor. Such a situation requires a change in the management strategy and extends the duration of the operation, increasing the risk of complications. In case of a synchronous tumor, both lesions should be excised. Postoperative colonoscopy is valuable and acceptable, in order to evaluate the remaining part of the colon [22].

Table 1
Synchronous occurrence of Primary Adenocarcinoma of the Appendix and of the colon in different studies, arranged in chronological order.

Author	Year of Publication	Study Year/s	No. of patient	No. of PAA	PAA%	Synchronous Colonic Ca	Colonic Ca/PAA Rate	Country
Maisel [35]	1947		1	1		1	1/1 = 100%	New York Hospital, NY, USA
Seddon [36]	1965		1	1		1	Abstract not available	Abstract not available
Payumo [8]	1970	1963	1	1		1	1/1 = 100%	French Hosp. New York USA
Brozinsky [37]	1977	1976	1	1		1	1/1 = 100%	Brooklyn, New York USA
Cerame [38]	1988	1960–1985 (25y)	316	316		8	8/316 = 2.5%	Ohio, USA
Nitecki [22]	1994	1976–1992 (16y)	32	32		10	10/32 = 31%	Mayo Clinic, USA
Connor [39]	1998	1979–1994 (16y)	7970	8	0.1%	7	7/8 = 87.5%	Dundee, Scotland,
Bucher [40]	2004	(10y)	20	20		3	3/20 = 15%	Geneva, Switzerland
Kim [41]	2009		1	1		1	1/1 = 100%	Korea
Benedix [4]	2010	2000–2004 (5y)	31,341	99	0.316%	5	5/99 = 5%	German Multi-center Study
Goryn [42]	2012	2012	79	2	2.53%	2	2/2 = 100%	Poland
Present case								
Total 40 cases			1510	1	0.066%	1	1/1 = 100%	Jordan

5. Conclusion

The need for histological examination of all appendectomy specimens is stressed. The operation of choice for PAA is right hemicolectomy, either as a primary or as a secondary procedure. This is associated with better survival rates than when the condition is treated by appendectomy alone. Following the diagnosis of PAA, it is warranted to perform surveillance for synchronous or metachronous tumors because the risk of a second primary malignancy in the gastrointestinal tract is significantly increased.

Patient: A 39 years old female

Final Diagnosis: Synchronous Primary adenocarcinoma of the appendix (PAA) and the right colon

Symptoms: Presented as a case of acute appendicitis

Medication: No chronic medications

Clinical Procedure: Right hemicolectomy with bilateral Salpingo-oophorectomy for secondaries thirteen month later.

Specialty: Surgery and Pathology

Objective: Rare disease

Learning points / highlights: as PAA is rare pathology that is discovered usually on histopathologic examination of resected appendix, it is important to report all pathologic reports to the primary physician in order to confirm primary diagnosis and discuss it with their patients. If a diagnosis of PAA is reported, a surveillance lifelong colonoscopy screening is mandatory to rule out synchronous or metachronous occurrence of colonic malignances.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

Ethical approval was granted from the institution review board (IRB) of Hashemite University and Prince Hamzah Hospital.

Consent

Patient agreed publishing this case.

Registration of research studies

N/A.

Guarantor

Mahmoud Al-Balas.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRedit authorship contribution statement

Mohammad K.M. Al-Wiswasy: Conceptualization, Methodology, Writing - original draft, Supervision. **Hamzeh Al-Balas:** Writing - original draft, Writing - review & editing. **Raith A.S. Al-Saffar:** Conceptualization, Data curation. **Mahmoud Al-Balas:** Data curation, Writing - review & editing.

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No.

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