Case Report

Appendiceal Mucinous Adenocarcinoma with Concurrent Tuberculous Appendix: An Unusual Overlap of Two Rare Diseases

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ABSTRACT:
A 52-year-old woman presented with right lower quadrant pain and a palpable mass, and was surgically managed with right hemicolectomy, right en bloc salpingo-oophorectomy, and total omentectomy. Medical treatment with standard quadruple antimycobacterial regimen was also initiated. Histopathologic report showed appendiceal mucinous adenocarcinoma with concurrent tuberculous appendix. Primary tumors of the appendix are rare and present with symptoms of acute appendicitis or a palpable right lower quadrant mass. The appendix is also an uncommon site of granulomatous tuberculosis infection for gastrointestinal extra pulmonary disease. This case report highlights an unusual overlap of the two diseases and a brief review of literature.

Keywords: *Appendiceal tumor; mucinous adenocarcinoma; right hemicolectomy; right lower quadrant mass; right lower quadrant pain; tuberculous appendix; extra pulmonary tuberculosis*

BACKGROUND

Cancer is a major public health issue worldwide. It is the second leading cause of mortality with 8.8 million deaths reported in 2015 due to malignancy. 1 out of 6 death cases is caused by cancer around the world. 70% of cancer-causing death happen in low and middle income countries, and 25% of these cases are cancer causing infections like hepatitis and human papilloma virus [10].

In the Philippines, cancer is the third leading cause of morbidity and mortality after communicable and cardiovascular diseases [11]. In 2012, 59,000 people in the country died due to cancer yearly. Leading cancer sites are the lungs, breasts, liver, colon, cervix, and prostate [12].

One of the risk factors for developing cancer is infection, but this continues to be controversial. Although mutation is a known pathogenesis of cancer, infectious agents may play a role in its development. Prevalence is lower in well-developed countries and higher in underdeveloped countries. Examples of cancer-causing infectious agents are hepatitis B and C virus, Epstein barr virus, human papilloma virus, human immunodeficiency virus type 1, and helicobacter pylori. The mechanism of carcinogenesis may be from chronic inflammation, direct carcinogens, and/or immune suppression. Chronic inflammation not only changes the immune cells that produce inflammatory mediators, but also causes mutation to normal cells, thereby resulting to carcinomatosis. On the other hand, direct carcinogens change the expression of oncogenes that make the cell outgrow cell death; whereas, immune suppression can downregulate the immune response by attacking the cells responsible for protecting the body from cancer development [13].

This paper discusses the association of cancer and infection (mucinous adenocarcinoma of the appendix and its association with tuberculous appendix); however, some studies show that there appears to be no cause and effect.[9]. This paper aims to increase awareness of these diseases and its coexistence at the same location by discussing a recent case in the Philippines that presents as a cecal mass.

Significance
Concurrence of both diseases at the same location is rare and highly unusual. There are only a number of published reports on these diseases in the Philippines; hence, this case may contribute to its research.

CASE

We are reporting a 52-year-old Filipino female who developed right lower quadrant abdominal pain in late 2017. Over the course of two months, she noted a palpable mass which she described as firm, dull, tender, movable, and approximately palm-sized. She underwent an abdominal ultrasound, which showed hypoechoic foci at the right lower quadrant measuring 4.7x 2.2 x 4 cm consider thickened bowel wall with nonspecific sub-centimeter lymph nodes in bilateral inguinal region. CT scan of the whole abdomen with IV contrast was done and showed an intraluminal soft tissue defect in the cecum with surrounding stranding densities and adjacent prominent lymph nodes (Figure 1). Colonoscopy was performed and visualized a distensible colon and redundant sigmoid (Figure 2). A friable circumferential mass was seen at the cecum producing complete obstruction of the lumen.

The patient had no immediate contraindications to surgery. She had an unremarkable obstetric history with regular menses,and had undergone open cholecystectomy and Cesarean section. On physical examination, Kocher scar and a midline infraumbilical scar were noted. The abdomen was non-distended with normoactive bowel sounds, non-tympanitic on percussion, but with a round, firm, movable, tender, 4 cm right lower quadrant mass. Pre-operative laboratory results showed normal CEA at 3.3 ng/ml and normal serum albumin at 4.3. g/dL.

A midline laparotomy from xiphoid to pubis was done. Intraoperatively, a 5 x 5 cm solid, irregularly shaped cecal mass adherent to the posterior peritoneum, lateral peritoneal wall, and right fallopian tube was appreciated. Multiple enlarged lymph nodes were also noted up to the root of the right branch of SMA. No palpable mass on the liver and no carcinomatosis were seen. She was surgically managed with right hemicolectomy, right en bloc salpingo-oophorectomy, and total omentectomy (Figure 3). A five-centimeter margin from the mass was removed proximally from the ileocecal valve and distally from the proximal part of the transverse colon. Side to side anastomosis of the ileum and transverse colon was performed using a 75 mm linear stapler.

Histopathology showed well differentiated mucinous adenocarcinoma with its widest diameter at 5 cm. Invasion of the muscularis propria and subserosa of the appendix was also noted. Results showed negative for tumor in the following areas: surgical margins, twenty-six pericolic lymph nodes, omentum, right ovary, and right fallopian tube (Figure 4). Additionally, granulomatous appendicitis and lymphadenitis with Langhans' type giant cells were seen. Her final diagnosis was mucinous adenocarcinoma of the appendix stage IIA (pT3pN0M0) with GI TB (Appendix).

Her recovery was delayed due to early post-op adhesions. She presented with abdominal bloating and no bowel movement. CT scan of the whole abdomen with IV, oral, and rectal contrast was done and showed no anastomotic leak on the fifth post-operative day. Normal bowel function was restored and bloating decreased on the eighth post-operative day

DISCUSSION

The considerations for painful right lower quadrant mass in a female are either reproductive or gastrointestinal in nature. The most common gastrointestinal mass is cecal mass—appendiceal masses are rare with an incidence of approximately 0.5% of all primary gastrointestinal tumors [14].

Appendiceal tumors are either carcinoid or epithelial neoplasms. The most common malignant neoplasm is an epithelial adenocarcinoma which is further classified by histologic type. The mucinous type and non-mucinous type comprise 37% and 27% of epithelial appendiceal cancers, respectively [2]. Mucinous epithelial neoplasms are further graded into three: (1) low grade appendiceal mucinous neoplasm (LAMN) with well differentiated cells, (2) high grade appendiceal mucinous neoplasm (HAMN) with invasion of the basement membrane, and (3) mucinous adenocarcinoma with poorly differentiated signet ring cells [2].

Tuberculosis (TB) is common in the Philippines and has been found concurrently as pulmonary tuberculosis in cancer patients; however, it is rare for both extra pulmonary TB and a primary malignancy to occur at the same site. It has been suggested that primary TB may cause the development of malignancy through chronic inflammation. Conversely, it has also been theorized that a malignancy may lead to activation of TB due to a decreased immune response. The exact correlation between the two pathologies is still unknown.

Mucinous adenocarcinoma of the Appendix

Mucinous adenocarcinoma grows gradually and presentation may not be evident in the early stage of disease. [1] However, it usually presents as right lower quadrant abdominal pain, a right lower quadrant mass or abdominal distention due to PMP (pseudomyxoma peritonei) where mucin is contained in the peritoneum. In addition to that, patients may experience bloating, ascites, intestinal obstruction or urinary tract obstruction over a period of time [1]. It is commonly detected at advanced stage in 63% of patients with mucinous adenocarcinoma. Upon detection at a later stage, metastatic spread may have developed. Sometimes, it may extend to adjacent organs and around 20-26% of cases is seen with nodal involvement [2].

According to Leonards et al. (2017), mucinous adenocarcinoma occurs at 50 to 70 age group and slightly more predilection to females than males. It is usually well differentiated [1] but may be further subclassified as well differentiated, moderately differentiated or poorly differentiated. Well differentiated mucinous adenocarcinoma corresponds to low grade mucinous neoplasm while moderately and poorly differentiated mucinous adenocarcinoma are high grade mucinous neoplasm. Treatment depends on the type of histologic characteristic of the tumor and peritoneal disease together with TNM staging. For adenoma and LAMN, appendectomy is optimal. However, in cases of LAMN with nodal involvement, HAMN, adenocarcinoma without peritoneal extension, right hemicolectomy with lymph node dissection is done [2]. In mucinous adenocarcinoma of the appendix, due to increasing pressure of accumulation of mucin in the appendix, it may be prone to rupture [4]. When the appendix is not ruptured, complete oncologic surgical resection with appendectomy without spillage of mucin is advised. For localized, non-ruptured low grade (lower than T2 which invades the muscular propria) appendectomy with en bloc resection of cystic lesion is done. However, when the grade is high T2 or greater, right hemicolectomy with excision of 12 or more lymph nodes is recommended to prevent spread [3]. On the other hand, when the appendix is completely ruptured, one should determine whether the rupture is microscopic or gross. For microscopic rupture, resection of residual disease via laparoscopy is done for low grade staging; whereas, laparotomy with gross removal of residual disease also omentectomy, quadrant perintonecotmy, oophorectomy and HIPEC (hyperthermic intraperitoneal chemotherapy) are done for high grade staging. For grossly ruptured appendix, complete cytoreduction and HIPEC are done [3].

Tuberculous Appendix

Tuberculosis in the Philippines is a major public health dilemma. According to WHO, there are 10.4 million new TB cases in 2016, but only 6 million were notified and diagnosed. It is estimated that 1.7 million died

due to this disease. This is a preventable and curable disease, but still remains to be the most common cause of death of infectious disease [5]. Extrapulmonary tuberculosis in the gastrointestinal tract accounts for approximately 3% of cases. Mostly, extrapulmonary tuberculosis occur in ileum due to several peyers patches that fight off bacteria. Only 1.5-3% of extrapulmonary tuberculosis cases are found in the appendix [7] .

The appendix may either be secondary to ileocecal tuberculosis or other site within the abdomen, or primary tuberculosis where it is an isolated form, which is even more unusual in presentation. Mechanism of spread may be due of hematogenous, by infected intestinal contents or by extension of disease from neighboring organs like ileocecal or genital tuberculosis. The presentation is similar to symptoms of acute appendicitis; hence, diagnosis is made through histopathology. Treatment is appendectomy, but additional tubercular drug therapy (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) for 6 months should be included after surgery [7].

Association of mucinous adenocarcinoma of the appendix and tuberculous appendix

Two rare diseases coexisted and caused a great dilemma on the treatment decision - whether chemotherapy or tubercular drug therapy should be done first. There was a notion that the cancer caused the development of TB in the appendix due to defective immune system. On the stark contrast, some have established that extrapulmonary TB may have caused the cancer in the appendix due to the fact that chronic infection can cause mutation in the cell of the appendix leading to metaplasia or dysplasia. Consequently, this controversy remains unsolved. It may be a coincidence or one may have initiated the other [8].

Another point of concern is the initial medical treatment - chemotherapy or anti-TB drugs. Chemotherapy, when initiated first, can lead to immunosuppression thereby causing further proliferation of tubercular disease. On the other hand, initiating anti-TB medications first will cause a delay in chemotherapy resulting in cancer cells to multiply exponentially.

The timing and regimen of chemotherapy for mucinous adenocarcinoma is still at the realm of research. Usually, 5-fluorouracil with oxaliplatin and other conventional chemotherapy drugs are used for mucinous adenocarcinoma of the appendix [4]. However, it is recommended to complete the anti-Koch's therapy for 6 months prior to giving chemotherapy drugs. Moreover, there are some instances that chemotherapy is not necessary after surgical resection. Adjuvant therapy is not commonly given to low grade mucinous adenocarcinoma [3]. For example, in the case reported by Shaikh et al (2011) entitled Mucinous adenocarcinoma of the appendix. The paper presented with a 32 year old female in diagnosed as a case of mucinous adenocarcinoma of the appendix with an incidental finding of tuberculous abdomen. Hence, treatment was different for this patient. Some studies have shown that adjuvant chemotherapy may prevent the disease progression. Three cycles of Capecitabine 1250/m2 from day 1-14, oxaliplatin 130mg/m2 on day 1 and CAPOX every 21 days with total dose of 50.3 GY external-beam radiation therapy may improve the life span [9].

The patient in this case will be seen regulary every 3 months. Chemotherapy and radiation were not done. Regular surveillance with CT scan of the abdomen after 6 months and colonoscopy after 1 year will be performed. Moreover, the patient still is in good health.

Limitations

There has been a delay in the biopsy result of the colonoscopy done in another institution. Due to several hospital consults and financial constraints, proper management was not done immediately.

Conclusion

Tuberculosis and mucinous adenocarcinoma of the appendix are very rare especially when both occur in one site and in one patient. The causal relationship of tuberculosis and malignancy remained obscure. It may be a coincidence or a cause and effect. Further research between the association of these disease is advised. Moreover, its treatment whether chemotherapy and tuberculous drugs should be given first. Hence, research on these is greatly recommended.

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List of Figures

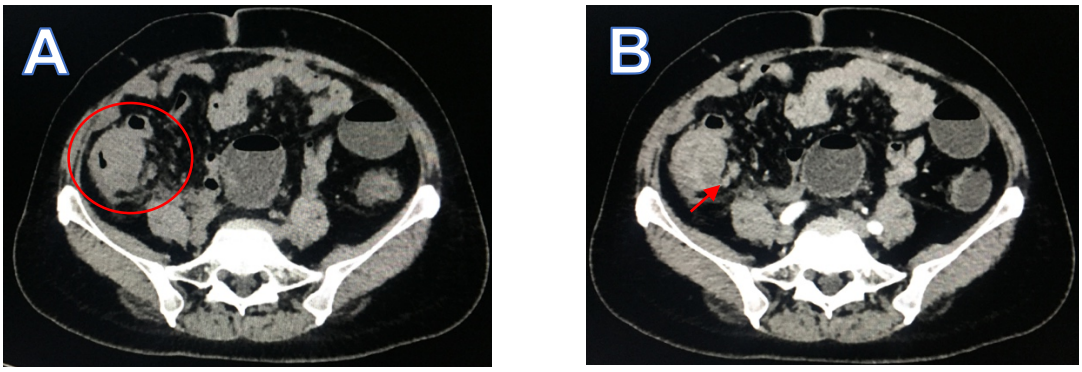


Figure 1. CT scan of the whole abdomen with IV contrast. A. Encircled area showed the mass at the cecal area measuring 4.41 x 3.72 cm. Appendix not visualized. No dilated bowels seen. B. Red arrow points to prominent lymph node with size of 1.13 x 1.09 cm.

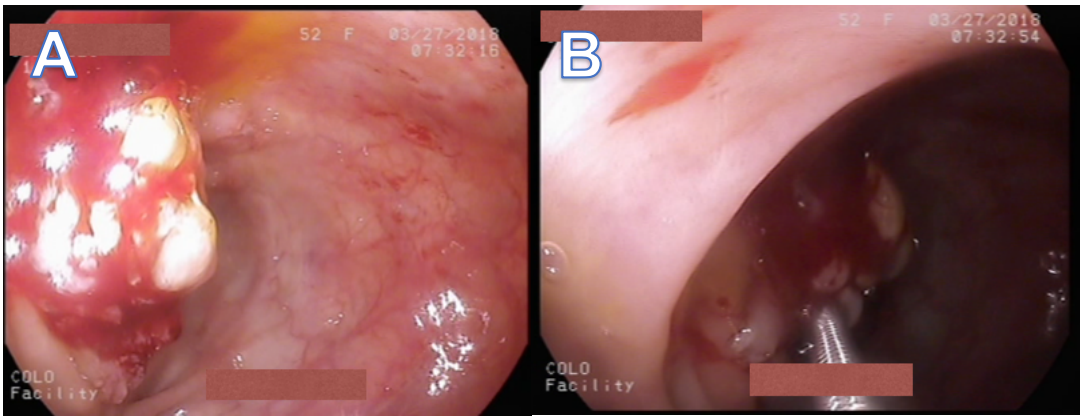


Figure 2. Colonoscopy Finding. A. Mass seen at the cecal area completely obstructing the lumen. B. Taking a sample from the mass.

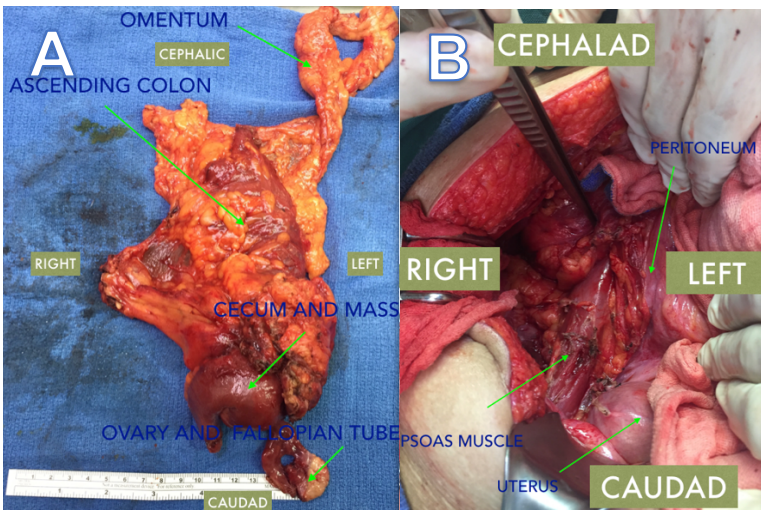


Figure 3. Right hemicolectomy with salpingo-oophorectomy and total omentectomy. A. Gross morphology of the mass shows a 5 x 5 cm solid irregular shape. Right ovary and right fallopian tube are seen at the bottom touching the ruler. B. Location of the mass in the abdomen. Noted densely adherent to the posterior wall of the peritoneum.

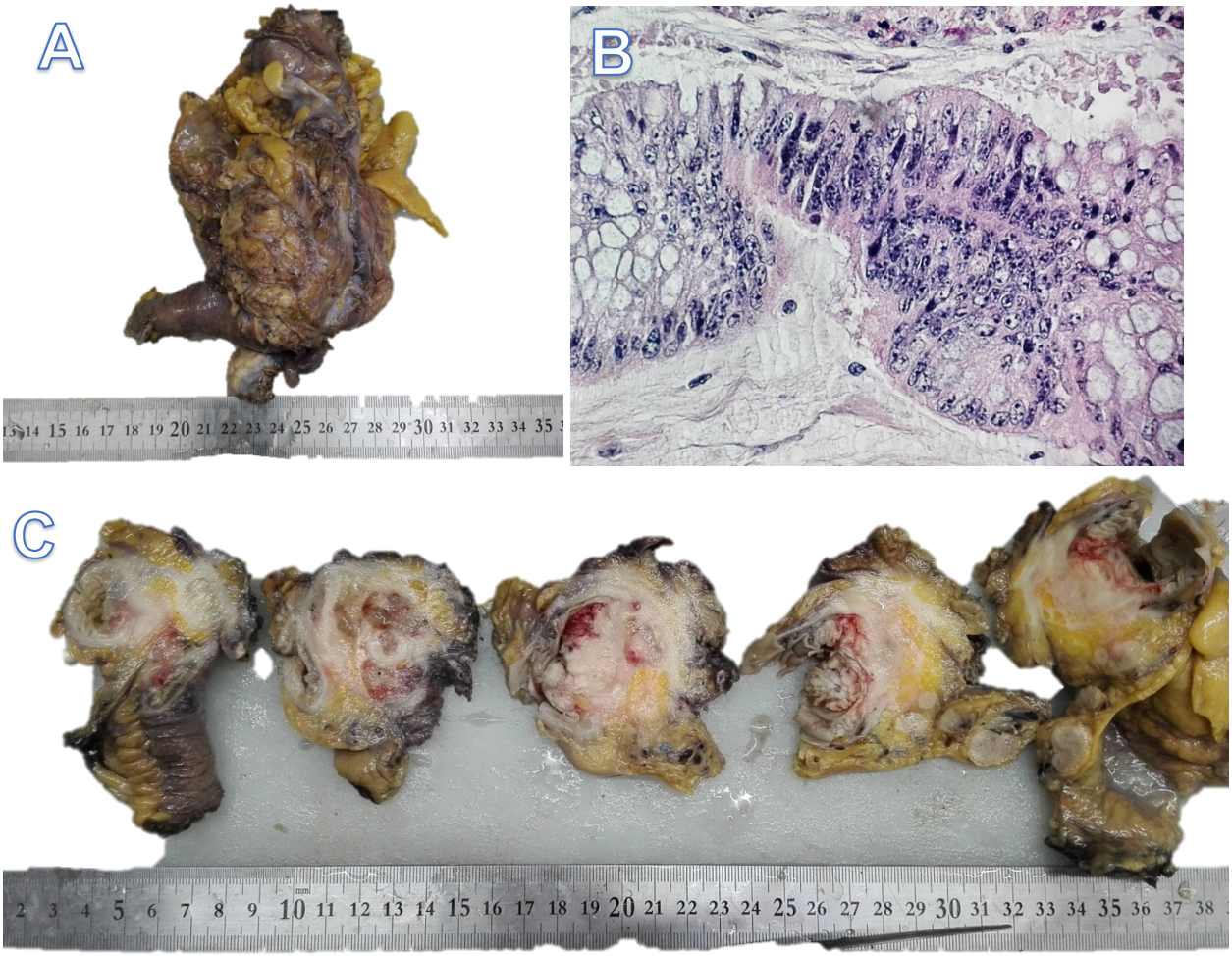


Figure 4. Gross specimens including the ileum, cecum, ascending colon, right ovary, and right fallopian tube. Appendix is not visible grossly. Mass seems to be located at the cecal area but further sectioning reveals that the mass originated from the appendix. Cecal mucosa is not involved. A. Gross anatomy of the mass B. Slide of the sectioned mass with the histopathologic characteristics of adenocarcinoma: mucin-containing signet ring cells and columnar cells. C. Sectioning of the gross specimen.