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Case Report

Mucinous Carcinoma of the Colon: Clues of Carcinogenesis from A Clinical View Point

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Abstract

Mucinous Carcinoma of the colon (MC) is a subtype of Colon Rectal Cancer (CRC) that occurs in about 10% - 15 % of the CRC in western countries such as Europe, Australia, and North America, but less in Asia averaging in around 4 %. MC distinguish histologically from CRC by presence of abundant of mucin in the tumor, and is more often found in female and younger patients, and found prone to locate at the proximal segment of the colon, when diagnosed often in late stage with a poor prognosis.

MC and CRC both share most common cancer etiologies, such as obesity, DM, smoking, alcohol, physical inactivity, and other genetic disorders etc. However, with those obvious clinical and histological variation between MC and CRC imply some unique different etiological factors are involved in the process of carcinogenesis.

There is sparse information from clinical and basic science research to address the distinct variation in the aspect of gender, age and demographic related to the oncogenesis of MC and CRC.

Recently a patient was treated. Patient's medical history, clinic-pathologic features and treatment course was analyzed with information derived from close observation; this may shed some clue to understand the process of cancer development in MC.

Keywords: Mucinous colon cancer; Obese; Diabetes; Bile acid; Estrogen; Glycocalyx; Dysbiosis

Introduction

MC is characterized with the presence of mucin at least 50% or more spreading in the extracellular space in the whole tumor mass, and incidence is correlated with the incidence of CRC [1-4].

The global epidemiological data shows continued raising incidence of CRC for the last few decades, and remain third most commonly diagnosed cancer and second leading cause of cancer deaths worldwide; In the meantime, the consumption of meat and sugar keep increasing and more obesity and DM developed in the general population [5-8] (Figure 1-5).

Obesity most likely is due to consume excessive calorie dense foods such as those with high-fat content. To digest fat bile acid needed to be produced from the liver as the primary bile acid to resolve the fat with other food and as it goes through the digestive process, most of the bile acid will be re-absorbed in the small intestine especially in the terminal ileum, and return to the liver for recycle as enterohepatic circulation [9,10]. About 10% of the total bile acid pool into the systemic system and only about 5% of the primary bile acid will enter the cecum to the colon, and then deconjugated and dehydroxylated by the microorganism in the colon to become the secondary bile acid as Deoxycholic Acid (DOC) and Lithocholic Acid (LCA). This phenomenon of high fat diet induced high bile acid secretion has been well shown in the clinical study [11], however, data generated from clinical studies also revealed that high level of bile acid in the blood or in the feces were positively relate to the risk factor for CRC and other cancers [12-14], bile acid through it detergent effect on the mucosa of the colon resulting in focal destruction of the intestinal epithelia cell [13,15].

Current research indicates that there are chemical preservatives in the red and processed meat, and during digestive process in the gut, N-nitroso Compounds (NOCs) produced, NOCs have been proven carcinogenic in animal study. When meat cooking in high temperature by frying, grilling and barbecuing, the meat pyrolysis and produced Heterocyclic Amines (HCAs) and Polycyclic Aromatic Hydrocarbons (PAHs) both are potent carcinogen [16]. Red meat contains high concentration of heme in the muscle when digested the heme is degraded in the small intestine by heme oxygenase 1, and releasing free ferrous iron that promote cancer process [17,18].

Obesity with excessive of adipose tissue generate various degree of insulin resistance, chronic inflammation by secretion of pro-inflammatory cytokines, and dysregulate adipokines by increase production of leptin that promote abnormal cell proliferation, and reduce production of adiponectin that show anti-inflammatory effect and limited tumor angiogenesis shown in vitro experiments [19].

Chronic hyperglycemia often leads to hyperinsulinemia and

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Figure 1: Global meat consumption from 1961 projection to 2050.

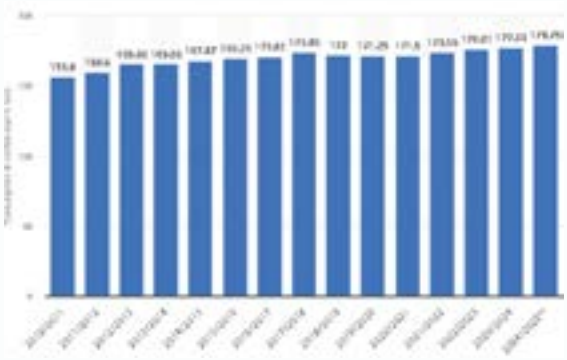

Figure 2: Global sugar consumption 2010 to 2025.

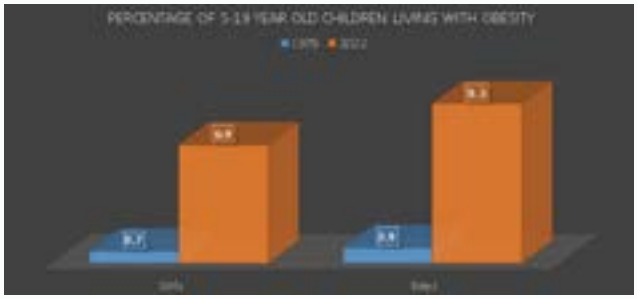

Figure 3: The worldwide prevalence of obesity has more than triple between 1975 to 2022, in 5-19 year olds have increased 10-fold.

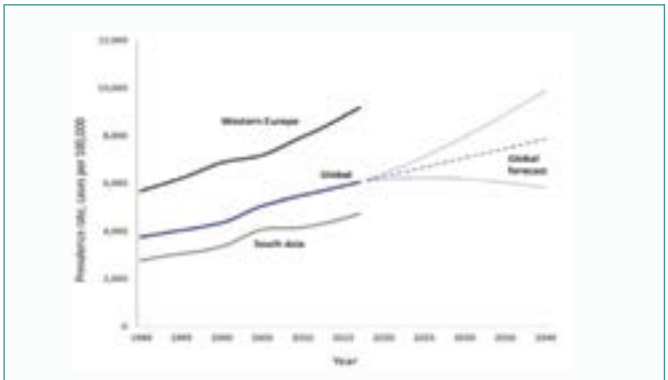

Figure 4: Trends in the prevalence of T2DM from 1990 projected to 2040.

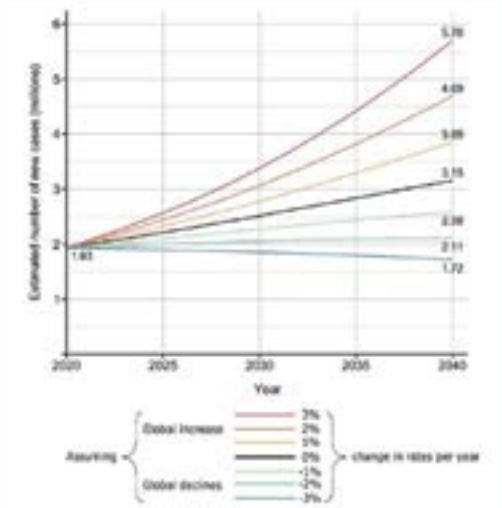

Figure 5: Projected number of cases of colorectal cancer worldwide from 2020 to 2040.

produce insulin -like growth factor-1 these stimulate cell proliferation, inhibit apoptosis and promote angiogenesis and support tumor growth. Elevated blood sugar increase production of Reactive Oxygen Species (ROS) and cause cellular DNS damage that lead to mutation and may promote cancer formation [2].

Hyperglycemia is associated with chronic low-grade inflammation due to production of pro- inflammatory cytokines, create a tumor-promoting microenvironment enhance the survival and proliferation of cancer cell, also lead to formation of Advanced Glycan end products (AGEs) which bind to receptor for AGEs on the cell surface, this inflammatory effect leading to glycocalyx degradation, and interferes the repairing process of glycocalyx [20].

Glycocalyx is a coating layer on the surface of endothelial cell of the entire vascular system and mucosa of the digestive tract, secure the integrity of this protect layer is essential to keep smooth function of the hemodynamic system, and prevent inflammatory factors, toxin, microorganism and others to damage to the interstitial of organs and induce mutagenic and carcinogenic changes [20-23]. Adipose tissues generate multiple hormones, estrogen, testosterone etc. to produced.

These hormones enhance cell proliferation and become carcinogenic factors in certain cancers, pre-menopause female with regular secretion of estrogen to maintain a proper physiological condition, with obesity more estrogen will be produced, this over load of estrogen will make a more favorable condition for cancer to develop.

Case Presentation

A 47-year- old female presented to the emergency room on July 8, 2024 with complaints of cramp lower abdominal pain with diarrhea on and off for over 3 months, saw by a gynecologist and rule out pelvic organs problem, during this period, patient also treated by LMD as colitis, her symptoms worsen from intermittent attack to more persist with more severe degree, and started to develop fever, nausea and vomiting with progressive continuous abdominal pain to the day of emergency visit.

The patient had 3 children by c/s, age 18,16 and 14 respectively. During the first pregnancy, patient noticed of hyperglycemia that

became normal after baby was born without any therapy, during the labor on her second child patient suffered from eclampsia situation, and after the child was born, patient became a diabetic and receive treatment since, and also noticed of weight gain since that time from average weight of 65 Kgs before the pregnancy to current.pt also receive statin for hyperlipidemia. Patient is a social worker with daily walking to her job, no alcohol, no smoking favor meat beef and pork, drink coffee and tea, no environmental contamination problem.

Physical examination

Temp: 38.5˚C, BP: 139/91 mmHg, HR: 104/min, RR: 20/min, Height:152 cm, Weight: 78 kg, BMI: 34 kg/m^2, GCS: 15.

Abdomen: obese, old surgical scar via c/s x 3 on the lower abdomen, no hernia, hypoactive bowel sound, soft, systemic tender on RLQ and LLQ (++), rebound tender (+) rectal digital exam: no mass, no blood, minimum mucus feces noticed, others none specific.

Imagine findings

!. Chest x-ray was normal, KUB show loop intestinal dilatation, no free air (Figure 6).

Abdominal CT is as follow (Figure 7,8)

Laboratory data

Hemoglobin 10.1g/dl, WBC: 4.90 /ul, Neutrophil-seg 85.7%, CRP 245.6g/dl (normal range: <5), Albumin 3.3 g/dl, sugar: 262 gm/dl (normal range:70-140), sodium 134 mm0/L, potassium 3.6 mm0/L. Urine: protein 2+, glucose +/-, occult blood 3+, ketone 2+, others none specific.

Patient was admitted with impression of Acute appendicitis with focal peritonitis, ascites and mass over the cecal region, nature unclear, Type 2 DM, poor control, Obesity.

Clinical course

Upon admission, patient was kept nothing by mouth, iv hydration, antibiotics, nutritional support and correction of diabetes with insulin. With proper correction of blood sugar and general conditions, patient was operated on the 3rd days after admission, intra operative findings showed purulent fluid flooded over the right lower abdominal space down to the pelvis, a firm indurated and engorged mass fixed on the cecal-ileal region with marked inflammatory change around the area and the right-side colon was adhesed to the lateral abdominal wall tightly (Figure 9a), the induration extended to the right adnexa region, also a large mass on the mesentery of the ascending colon, upon lysed the colon from the lateral abdominal wall

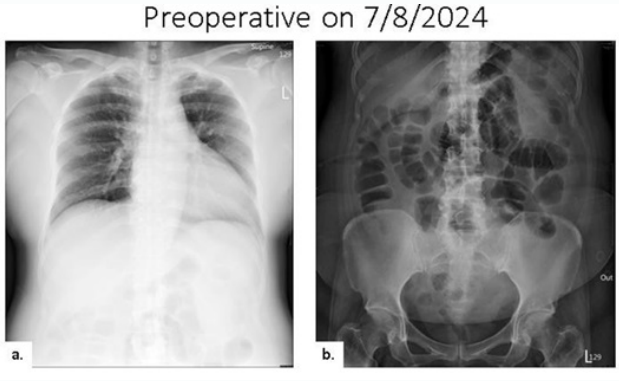

Figure 6: (a). Chest X-ray: normal, (b). KUB small bowel gaseous dilatation.

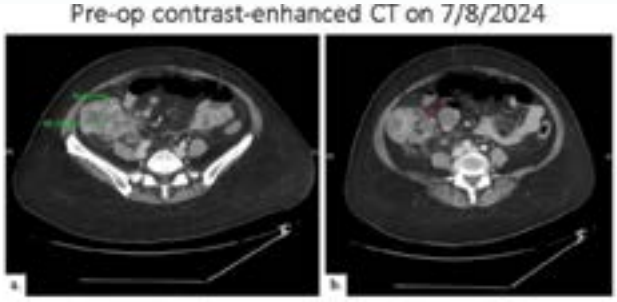

Figure 7: (a). Focal irregular mass formation of the cecum measuring about 6.5 cm × 5 cm, with perifocal and RLQ peritoneal stranding. (b). Two cystic masses in the mesentery at RLQ, 3.06 cm × 2.47cm and 2.04 cm × 2.04 cm in size.

and free the ascending colon from the retro-peritoneum, a perforation with severe necrotic change on the posterior wall of the cecum with adjacent engorged and indurated appendix sealed tight together, and distended thickened terminal ileum noticed (Figure 9b and c). Right hemicolectomy with large mesenteric mass and surrounding lympho-vascular tissue removed (Figure 9d-f). Pathologic finding showed mucinous adenocarcinoma of the cecum with rupture posteriorly and diffuse peritonitis with peri-appendicitis, lymph nodes 8/10 metastatic (Figure 10-12). Postoperative recovery was smooth, and patient was discharged on July 23, 14 days after admission.

Discharged diagnosed: Mucinous adenocarcinoma of the cecum with rupture posteriorly, stage IIIC. Patient underwent adjuvant chemotherapy plus target therapy, after 6 courses of treatment, a CT of abdomen done on Nov/20/24, and a PET CT scan done on Dec/2024, both showed no evidence of disease, patient is stable without any more GI symptoms and with a proper control of diabetes but obesity remained no change.

Discussion

One of the distinct histological differences in MC compare with CRC is the excessive mucin in the tumor mass as shown in this patient, this excessive mucin was due to the over expression of MUC2 gene to produce mucin in the goblet cell of the colon and more locate on the proximal colon [24-26].

The prone to occur more frequent in the younger patient most likely due to the cancer initiation carry out earlier from obesity as shown the ratio of over weight is higher in the younger generation [27] and obesity often associated with diabetes both are proven risk factors for colon cancer development [2].

Female before menopause, self produces estrogen to maintain normal physiological requirement, however if become obesity, then more estrogen will be produced from excessive adipose tissue, as demonstrated in the lab and clinical studies, estrogen promote cell proliferation, and carry certain risk factors for multiple cancers to developed included colon cancer [1,28,29].

DOC and LCA have detergent effect on the colon mucosa, and the proximal colon is the beginning site to expose to the bile acid flow in from the terminal ileum sustain the most concentrated bile acid degrade the protective layer of glycocalyx on the surface of the endothelial cell and induced mucosa erosion and cause cellular DNA damage and pave the way for development of cancer [30-33].

There are abundant of research data from the basic science and

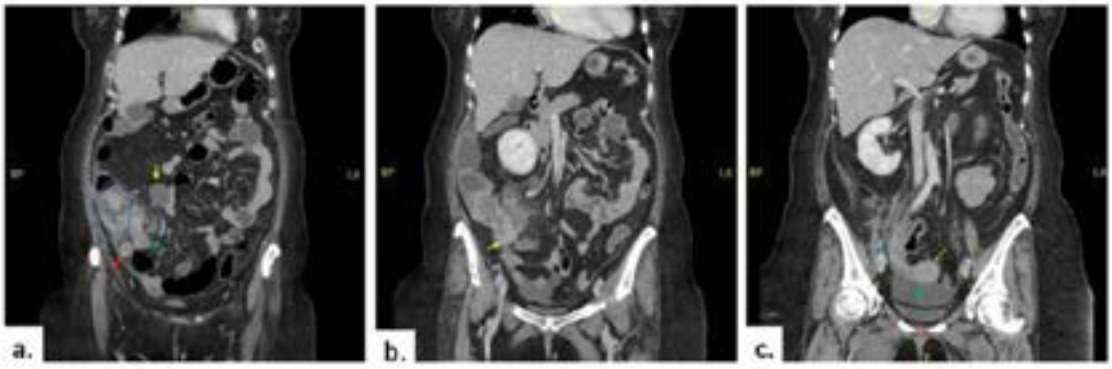

Figure 8: (a). Depicted at ileocecal valve level. Focal irregular mass formation of the cecum (blue circle) with perifocal stranding and mild swollen terminal ileum (green arrow). Also note dilatation of the appendix (red arrow) and cystic mesenteric mass at RLQ (yellow arrow), about 3.7 cm × 3 cm in diameter. (b). Depicted at appendix orifice level. Focal irregular mass formation of the cecum with probable involvement of the appendix orifice (yellow arrow), causing dilatation of the appendix. (c). Contiguous infiltrative soft tissue density from RLQ abdomen to right side adnexa (blue arrow), with pelvic ascites of relative high density (representing exudate) located between the uterus (green star) and collapsed urinary bladder (red arrow).

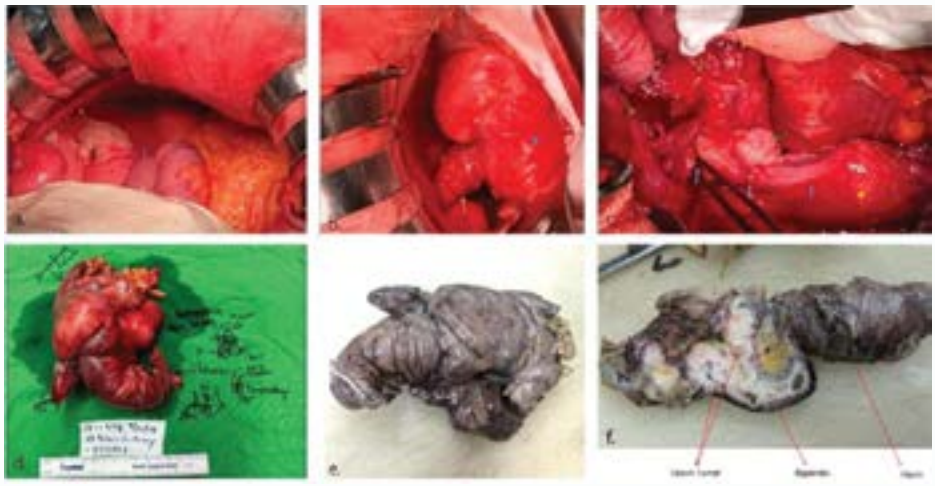

Figure 9: (a). Purulent fluid over the right lower quadrant (blue arrow). Necrotic fibrinous tissue coating on the surface of colon mucosa (black arrow). (b). Engorged appendix (yellow arrow), swelling and indurated cecum (blue cross). (c). Perforated posterior wall of cecum with necrotic tissue change on the opening (yellow arrow), marked induration over the right adnexa region, fallopian tube (blue arrow), ovarian (green arrow), uterus (asterisk). (d). Gross resected right colon and with its mesentery. (e). Formalin fixed specimen. (f). Whitish cecum tumor occupied portion on the orifice of appendix, indurated swelling terminal ileum.

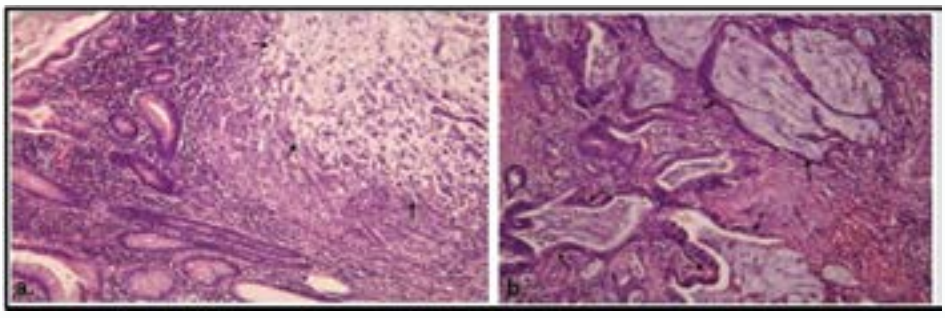

Figure 10: (a). Upper right: tumor with mucin pool, lower left: normal mucosa (100x). (b). Cancerous glands with extracellular mucin production (200x). (mucin pool: black arrow).

clinical studies recognized that the microorganisms in the gut play a significant role in the maintain of energy homeostasis, nutritional metabolism, anti- inflammation, enhance immunity, and secure an integrity of intestinal barrier, violate the balance of the organisms in the gut (dysbiosis) lead to multiple illness, include cancers [34,35]. Inactive life style, obesity and diabetes are all associated with dysbiosis.

Diabetic and overweight patients as mentioned before usually due to higher consumption of dense calories food such as meats with low fruit and vegetable fiber diet, this kind of eating habit influence the balance of microorganism in the colon and disrupted the normal fermentation process in the gut as dysbiosis. In animal studies showed increased dietary fiber intake leading to higher Short Chain Fatty

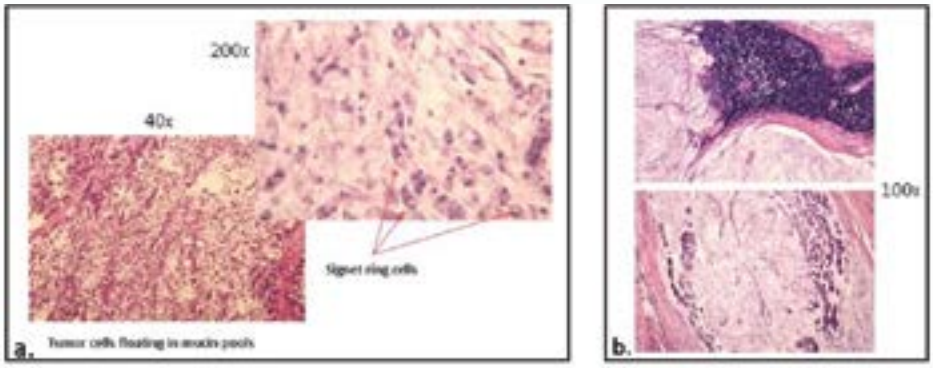

Figure 11: (a). Mucin pool with tumor cells. (b). Lymph node with mucinous metastatic carcinoma.

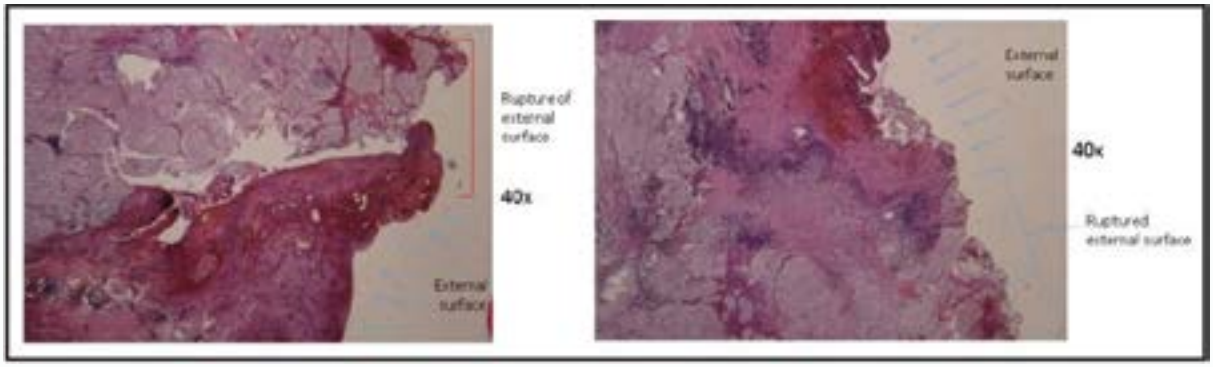

Figure 12: Ruptured posterior wall of the cecum with ulcerative necrotic change on the surface.

Acid (SCFA) production, and reduces the incidence and progression of colorectal cancer [36]. In clinical correlation that lower level of SCFAs and reduced fiber intake are associated with higher incidence in colorectal cancer in humans [5]. SCFAs are microbial metabolites produced by fermentation of dietary fibers by gut bacteria, and the primary SCFAs are butyrate, acetate and propionate, the butyrate has most anti-cancer effects by anti- inflammation effects, enhance immunity, promote gut barrier integrity and enhance mucosa repair and reducing epithelial cell damage, which lower the risk of cancer [37].

The poor prognosis of MC as shown in the literature were most likely due to the delayed in diagnosis just as in this patient in spite of lower abdominal pain with mucus diarrhea for 3 months patient only came to ER after the peritonitis was developed with impression of peritonitis from perforated acute appendicitis, it turns out, the perforation was due to the sever mucosa erosion through the full thickness of the posterior wall of the cecum from the cancer.

Conclusion

MC and CRC both share most cancer risk factors, to delineate some possible difference risk factors need more clinical study specific analyses in gender, age, and different geographic location in relate with the occurrence of MC, currently lacking this kind of study due to the limit number of MC as shown in the epidemiologic data., however, judge from the already known proven risk factors that indicate the abnormal life style contribute most to the carcinogenesis in most cancers and specific in CRC and MC. By improve life style to more physiological suitable to health will certainly reduce most of cancer development globally [38].

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