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Review Article

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The Link between *Fusobacteria* and Colon Cancer: a Fulminant Example and Review of the Evidence

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ABSTRACT

Systemic infections due to *Fusobacterium* may originate in the tonsillar/internal jugular veins or from the abdomen. We encountered a patient who presented with bacteremia, fulminant septic shock, and extensive soft tissue pyogenic infection due to *Fusobacterium necrophorum*. In addition, there was widespread metastatic colon cancer with the unique finding of pre-mortem co-localization of *F. necrophorum* and cancer cells at a site distant from the colon. We reviewed the literature of the association of *F. necrophorum* and colon cancer, and discuss the evidence of how each of these 2 distinct entities may mutually augment the development or progression of the other.

Keywords: Lemierre's disease; Bacteremia; Anaerobes; Malignancy; Microbiome

INTRODUCTION

Systemic infections due to *Fusobacterium necrophorum* and less commonly with other *Fusobacterium* species typically manifest as internal jugular vein thrombophlebitis and bacteremia in otherwise young, healthy adults (1-4). In this classical description attributed to Lemierre (4), *Fusobacterium* organisms—part of the normal oral flora—invade and precipitate thrombophlebitis of a tonsillar vein, which then propagates to the ipsilateral internal jugular vein. But *Fusobacterium* is also part of the normal colonic flora and thus bacteremia may originate from the lower intestine, with greater than expected association with colorectal cancer (3,5-14). We present a patient with septic shock due to disseminated *F. necrophorum* infection that was associated with previously undiagnosed widely metastatic colon cancer with conspicuous co-localization of both cancer cells and *F. necrophorum* in a purulent axillary lesion diagnosed pre-mortem. We performed immunohistochemistry for specific immune cells of the affected tissues and reviewed the potential mechanisms by which colorectal cancer and *F. necrophorum* infection may each play a role in the pathogenesis of the other.

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Conflicts of Interest
The authors declare no potential conflicts of interest.

Abbreviations
CT, computed tomography; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TMC, tumor-infiltrating myeloid cell

Author Contributions
Conceptualization: Hurley H, Chan ED, Frey A; Data curation: King M, Hurley H, Davidson KR, Dempsey EC, Barron MA, Chan ED, Frey A; Formal analysis: Frey A; Investigation: Hurley H, Chan ED, Frey A; Writing - original draft: King M, Hurley H, Chan ED, Frey A; Writing - review & editing: King M, Hurley H, Davidson KR, Dempsey EC, Barron MA, Chan ED, Frey A.

CASE PRESENTATION

A 53-year-old man was admitted with 2 wk history of severe, intractable pain in the right flank, abdomen, and buttock, and a 20 pound unintentional weight loss accompanied by non-bloody diarrhea, malaise, dyspnea, and generalized weakness. His family history was significant for lung cancer and tobacco-related emphysema in his maternal grandmother. He had a 35 pack-year history of cigarette smoking, drank alcohol daily, and used marijuana, methamphetamine, and cocaine. He had avoided medical contact for many years and took no medications. He lived alone in a remote mountain cabin, was a wood worker, and prided himself on a self-sufficient lifestyle.

The temperature was 39°C, heart rate 135 beats per minute, blood pressure of 90/50 mmHg, respiratory rate 45 per minute, and oxygen saturation of 90% on 2 L per minute of supplemental oxygen. He was cachetic, diaphoretic, restless, and in marked pain. The cardiopulmonary exam was notable for tachycardia and bilateral rhonchi, and the abdomen was soft with normal bowel sounds. Along the right lateral aspect of the body—extending from the axilla to the thigh—were large patches of erythema with palpable crepitus that were acutely tender. He had generalized weakness, and any strength testing was limited by severe pain with any movement of his right arm or leg.

The white blood cell count was 21.3×10^9/L with 89% neutrophils and 8% bands, hemoglobin 8.4 g/dl, and platelets 339,000/μl. Basic chemistry, renal function, and liver enzymes were within normal limits. Abnormal blood tests (and normal range values) included an albumin of 1.1 g/dl (3.4–5.0 g/dl), total protein 4.7 g/dl (6.8–8.6 g/dl), ionized calcium 1.05 mmol/L (1.15–1.29 mmol/L), C-reactive protein >150 mg/L (≤2.99 mg/L), international normalized ratio, 3.9 (0.9–1.1), fibrinogen 580 mg/dl (214–502 mg/dl), and lactate 2.2 mmol/L (0.4–2.0 mmol/L). Chest, abdominal, and pelvic computed tomography (CT) with contrast demonstrated innumerable bilateral pulmonary nodules many of which were cavitating (**Fig. 1A**), mediastinal lymphadenopathy, axillary mass, multiple small hepatic nodules and a large, hypodense mass in the right lobe of the liver (**Fig. 1B**), and perirectal lesion suggestive of an abscess as well as extensive intramuscular fluid and gas tracking along the right side of the body from the axilla to the proximal thigh muscles (**Fig. 1C**) as well as along the iliopsoas, gluteus medius, and pelvic sidewalls (not shown).

Blood cultures were taken prior to initiation of intravenous vancomycin, meropenem, and clindamycin. He was taken emergently to the operating room for debridement of presumed necrotizing fasciitis but the intraoperative findings revealed the muscles and fascial planes were healthy appearing. Instead, there was a 6-cm axillary mass with a foul-smelling necrotic center, adherent to the pectoralis major muscle. A large amount of pus was found in the right groin with subcutaneous tracking cranially toward the pelvis and caudally toward the mid-thigh. Incision and drainage of the right axillary mass, right groin mass, and right gluteus were performed along with incisional biopsy of the axillary lesion. Both sets of blood cultures were positive in the anaerobic bottles for *F. necrophorum* within 72 h of admission. Gram stain and culture of surgical drainage of the right axillary mass (**Fig. 2A**) and right groin fluctuance were positive for many gram-negative coccobacilli and rods with cultures yielding *F. necrophorum*, the latter identified by matrix-assisted laser desorption/ionization–mass spectroscopy.

Histopathology of the axillary mass incisional biopsy demonstrated a well-differentiated glandular proliferation of malignant cells in a cuboidal to columnar morphology, set in a

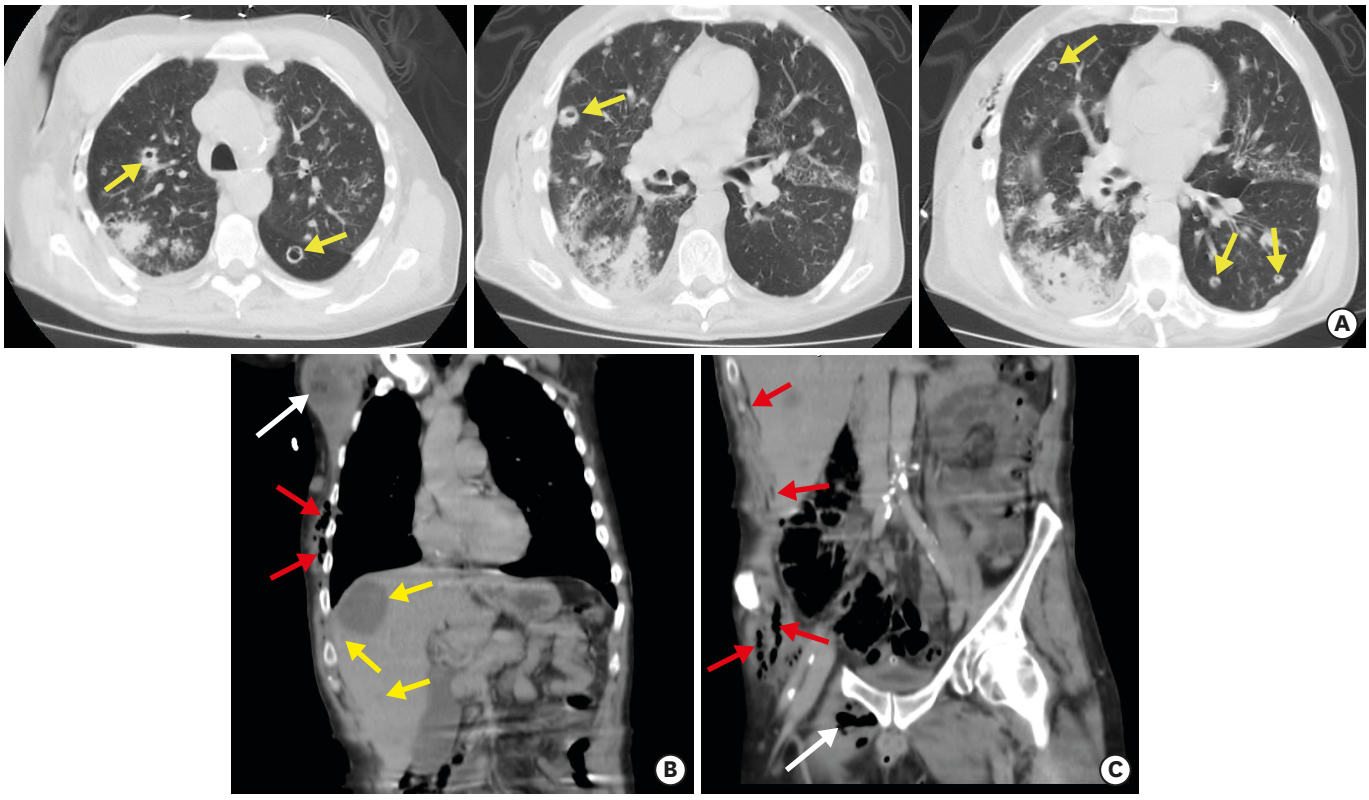

Figure 1. (A) Three panel axial chest CT demonstrating multiple lung nodules—with several that were cavitary (yellow arrows)—with patchy areas of ground-glass opacities and consolidation. Based on histopathology, the lung nodules are more likely to be colon cancer metastases rather than septic emboli. (B) Coronal image of the chest and abdominal CT showing a large right axillary mass with central necrosis (white arrow) with subcutaneous gas tracking inferiorly along chest wall (red arrows). In the liver, there were numerous small hypoattenuating lesions and a large hypodense lesion consistent with an abscess (yellow arrows). (C) Coronal image of the lower abdomen and pelvic CT showing a complicated perirectal collection containing gas and fluid, concerning for abscess (white arrow). Also seen are pockets of soft tissue gas that tracked from the pelvis to anterior thigh and inferior abdominal wall (red arrows).

background of desmoplastic fibrous tissue and abundant necrosis but no evidence of any lymphoid tissue (**Fig. 2B**). The cancer cells were positive for CK20 and CDX2 and negative for TTF-1 and Napsin A, consistent with a colorectal origin. Immunostaining revealed abundant CD-15-positive neutrophils (**Fig. 2C**) and focal clusters of CD-68-positive macrophages (**Fig. 2D**) infiltrating the malignant glands. Scattered CD3-positive T lymphocytes (**Fig. 2E**) and rare CD20-positive B lymphocytes (**Fig. 2F**) were found adjacent to the malignant glands. No CD30-positive T_H2 lymphocytes were identified. PCR for the *16S rRNA* gene of the paraffin-embedded axillary mass tissue identified *Fusobacterium* (University of Washington Medical Laboratories).

Post-operatively, he remained in septic shock and ventilator-dependent. Two days after the initial surgical debridement, he underwent percutaneous drainage of pelvic fluid collections—which also revealed many gram-negative bacilli and gram-positive cocci (**Fig. 2G**) and was culture positive for large number of *F. necrophorum*, *Bacteroides thetaiotaomicron*, and *Clostridium* species (not *C. perfringens*) by matrix-assisted laser desorption/ionization–mass spectroscopy. He continued to decline with severe disseminated intravascular coagulopathy and recalcitrant shock in the setting of metastatic cancer. He was transitioned to comfort care and died on the 10th day of hospitalization.

At autopsy, gross internal examination demonstrated large collections of purulent exudate extending from the right axilla to the right hip subcutaneously. The coronary arteries showed

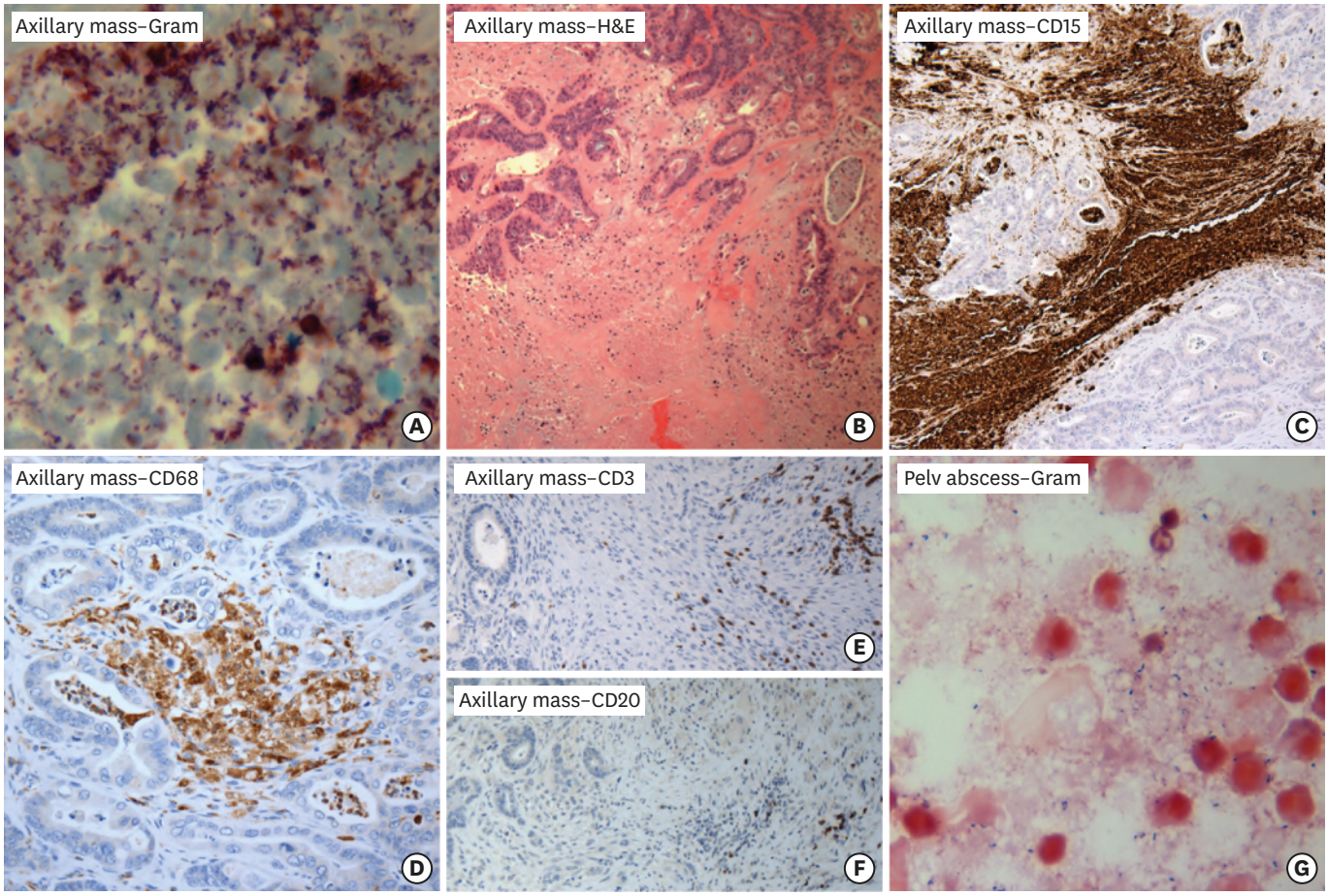

Figure 2. Surgically resected axillary mass and pelvic abscess drainage. (A) Gram stain of the surgically removed axillary mass revealed abundant pleiomorphic, gram-variable bacteria (1,000×). (B) Histopathology of the right axillary mass on the day-of-admission demonstrated infiltration by well-differentiated adenocarcinoma with adjacent necrotic debris (H&E stain, 100×). (C) Tissue of axillary mass immunostained with anti-CD15 antibody revealed abundant neutrophils (100×). (D) Tissue of axillary mass immunostained with anti-CD68 antibody demonstrated macrophages within malignant glands (200×). Axillary mass tissue stained for CD3 revealed few T lymphocytes (E) and rare CD20-positive B lymphocytes (F) adjacent to the malignant glands. (G) Gram stain of pelvic abscess drainage demonstrated gram-negative bacilli and gram-positive cocci (1,000×).

severe atherosclerosis. The distal rectum was involved by a 6.5 cm gray-white, fungating, anteriorly invading, circumferential mass. Four hundred mL and 600 ml of purulent fluid were identified within the right and left pleural cavities, respectively. Gray, fibrous adhesions were present on the right parietal pleural surface. The parietal pleura, sub-pleural surfaces, and the underlying lung parenchyma were studded with firm, white-tan nodules ranging from 0.5 to 3 cm in maximum diameter. Similar looking nodules involved the superior and inferior surface of the diaphragm as well as the liver, adrenals, and kidneys. Hilar and abdominal lymphadenopathy were identified.

Microscopic examination of the rectum (**Fig. 3A and B**), diaphragm, chest wall, bilateral lungs (**Fig. 3C**), hilar lymph nodes, kidneys, adrenals, liver, and prostate demonstrated infiltration by well-differentiated adenocarcinoma cells with focal mucinous features, consistent with colorectal origin. Immunostaining of the rectum with anti-CD15 revealed neutrophils adjacent to and infiltrating the malignant glands (data not shown). In addition, focal clusters of CD68-positive macrophages were adjacent to the adenocarcinoma (data not shown). Scattered clusters of CD20-positive B lymphocytes were identified in the benign

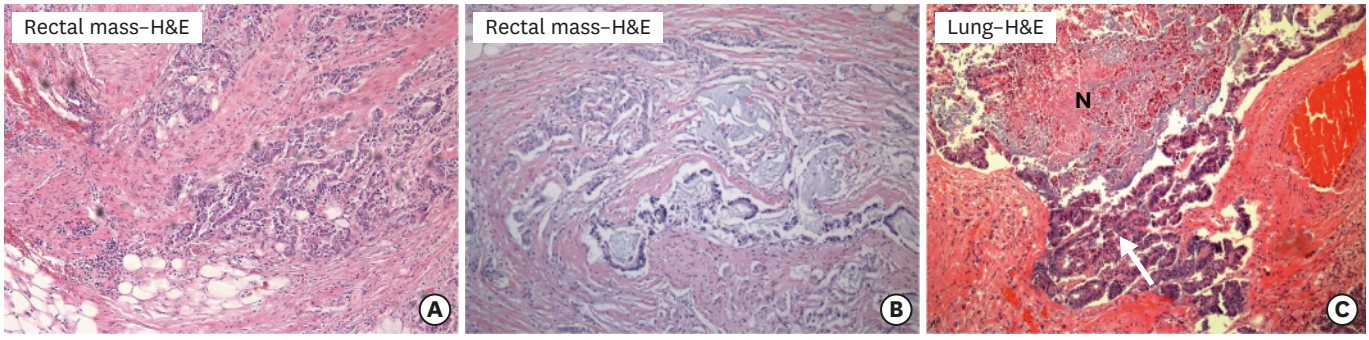

Figure 3. Colonic and lung tissues at autopsy. (A) Histopathology of rectal mass at autopsy demonstrated well-differentiated colorectal adenocarcinoma in the rectal muscularis propria invading into the perirectal adipose tissue (H&E, 100×). (B) Histopathology of rectal mass at autopsy showing mucinous features of the adenocarcinoma (H&E, 100×). (C) Lung tissue (left lower lobe) at autopsy showed well-differentiated adenocarcinoma (arrow) with adjacent necrotic debris (N) (H&E, 100×).

colonic mucosa adjacent to the malignant tissue; however, no CD3-positive T cells were found within or adjacent to the adenocarcinoma. No CD30-positive T_H2 lymphocytes were identified. Tissue gram stain and *16S rRNA* PCR of selected post-mortem tissues (kidney, left hilar lymph node, pancreas, spleen, liver, gallbladder, and lung) were negative for organisms. The rectal tissue was deemed inappropriate for *16S rRNA* gene sequencing, due to potential of contaminating microorganisms obscuring sufficient identification. Furthermore, post-mortem gram stain did not clearly identify *F. necrophorum*, possibly obscured by abundant necrotic debris admixed with the malignant glands. Culture of the post-mortem rectal or perirectal tissues was not performed, due to the non-sterile nature of the autopsy exam.

STUDIES LINKING *FUSOBACTERIA* WITH COLORECTAL CANCER

While *Fusobacterium* species—mostly *F. nucleatum* and *F. necrophorum*—are part of the normal gut flora, there is accumulating evidence that the proximation of *Fusobacteria* and colorectal cancer are not just mere coincidences but that *Fusobacteria* may be an inducer of colorectal cancer. The co-occurrence and co-localization of systemic *Fusobacterium* infection and widely metastatic colorectal cancer in our patient would lend further support for this paradigm that *Fusobacteria* and colon cancer may be pathobiologically linked. In a prospective study of 100 cases of disseminated *F. necrophorum* infections, 58 of the cases were associated with foci in the head and neck and occurred in young individuals (3). The remaining 42 were described as "disseminated *non*-head-and-neck-associated *F. necrophorum* infections" and they occurred predominantly in older men with 30 (71%) having foci of infection that originated from the gastrointestinal tract and one-third of these were noted to have "gastrointestinal cancer" (3). Similarly, in a retrospective study of *Fusobacterium* species bacteremia, malignancy and end-stage renal disease were the most common comorbidities among older individuals (1). Other studies provide additional link between the over-representation of *Fusobacterium* species in the gut flora of patients with advanced colon cancer (15). A case-control study compared the fecal microbiota of 42 subjects with colorectal cancer and 89 matched controls and found an association of colorectal cancer with *Fusobacterium* and *Porphyromonas* species (13). *Fusobacterium* species have also been demonstrated to be more abundant in the actual colorectal tumors than in adjacent normal colonic tissues as examined by whole exome sequencing, PCR amplification of the *16S rRNA* gene, quantitative PCR for *Fusobacterial* DNA, and by fluorescent *in situ* hybridization analysis (6,7). In addition, *Fusobacteria* were found to

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be inside colonic cancer cells by z-section analysis and *Fusobacterium* DNA was identified in metastatic colon cancer lesions (6). Mima and co-workers (9) analyzed *F. nucleatum* DNA by quantitative PCR of a large number of colorectal cancer tissues and equally divided positive cases as high or low levels of *F. nucleatum* DNA. While most colorectal cases in their cohort were negative for *F. nucleatum* DNA, the number of tissues with high levels of *F. nucleatum* DNA progressively increased from the rectum to the more proximal colon cancers, with the highest percentages of cases with high level of *F. nucleatum* DNA in cecal cancers (9). *Fusobacterium* species were also abundant in colonic adenomas—a potential precursor to colon cancer—compared with adjacent normal tissue as well as in stool samples of patients with colonic adenomas compared with healthy controls (5). Clinically, patients with the presence of *F. nucleatum* DNA in their colorectal cancer tissues were significantly more likely to have lymph node metastases (7,10).

Much of the descriptions of the association between *Fusobacteria* and colon cancer were confined to colonic tissues, whereas systemic *Fusobacterium* species infections as seen in our patient have been rarely reported to be associated with colon cancer. A 65 year-old man with disseminated *F. necrophorum* infection—manifested by bacteremia and abscesses in the brain, lung, and liver—was found to have large, dysplastic colonic polyps with intramucosal malignant transformation but no evidence of spread of the colon cancer outside the colonic mucosa (16). Another patient with widely metastatic colon carcinoma developed a fatal *F. necrophorum* septicemia but no mention was made of whether the infection co-localized with the metastatic cells (17). A study of nosocomial infections in cancer patients showed that while *F. necrophorum* was the most frequent anaerobe isolated, mostly from solid-tumor patients, the infections involved the skin or gastrointestinal tract and not the blood; whether there was co-localization of the *Fusobacterium* infection in tissues invaded by cancer cells was not mentioned (18). Thus, the description of our patient with co-localization of colonic cancer and *Fusobacterium* outside the colon is unique.

PURPORTED MECHANISMS BY WHICH *FUSOBACTERIA* INCITE DEVELOPMENT OF COLORECTAL CANCER

If there is purported bi-directional synergy between *Fusobacteria* and colorectal cancer, what are the possible pathogenic mechanisms? From the perspective of *Fusobacterium* species predisposing to colonic carcinogenesis and metastasis, over-abundance of *F. nucleatum* or *F. necrophorum* in the gut flora may play an active role in oncogenesis and/or a permissive role via its deleterious effect on host immunity. One of these possible mechanisms is the ability of the FadA adhesin molecule of *Fusobacterium* species to bind to E-cadherin on the colonic epithelium to activate the Wnt/β-catenin oncogenic pathway (**Fig. 4**) (19). Another is the ability of *Fusobacterium* to inhibit T-cell proliferation and induce T-cell apoptosis (12), impairing host immunity in eliminating transformed cancer cells (**Fig. 4**), and supported by the evidence that tumors enriched in certain T-cell subsets are associated with a better prognosis. This paradigm is also supported by a quantitative PCR analysis of up to 600 colorectal cancer samples revealing that those tissues with high levels of *F. nucleatum* DNA were associated with lower density of $CD3^+$ T cells (11). The paucity or absence of $CD3^+$ T cells in our patient with the *F. necrophorum*-infected, cancerous axillary lesion and the primary rectal cancer, respectively, is consistent with this hypothesis. In a murine model of intestinal tumorigenesis ($Apc^{Min/+}$), exposure of colorectal tumors to *F. nucleatum* resulted in increased tumor multiplicity and recruitment of tumor-infiltrating myeloid cells (TMC); *e.g.*, tumor-associated macrophages (TAMs) and dendritic cells, phenotypic cell types

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known to promote tumor progression (5,20). Such activation of macrophages may result in the production of mediators such as Bcl-2, cyclooxygenase-2, STAT2, and IL-17 (produced by T_H17 cells) that promote tumorogenesis (**Fig. 4**, inset).

The presence of a significant neutrophilic infiltrate in both the metastatic axillary lesion and the primary rectal cancer of our patient is typical of the immune response to colon cancers. But because *F. necrophorum* was present in the axillary metastasis, the neutrophilic response in the axillary lesion may be secondary to the infection as well. Well-to-moderately-differentiated colonic adenocarcinomas commonly exhibit central and adjacent foci of necrosis, sometimes extensively with a concomitant acute immune response. Analogous to that seen with TAM, immunosuppressive tumor-associated neutrophils (TANs) have been implicated to facilitate metastatic tumor spread and poor clinical outcome (21). Furthermore, peripheral blood neutrophilia as well as elevated neutrophil to lymphocyte ratio are poor prognostic indicators in cancer patients (22-24).

In addition to the TAM and TAN phenotypic responses, a significant lymphocytic response is identified within colonic adenocarcinomas with microsatellite instability; *e.g.*, due to mutations of *MLH1*, *MLH2*, *MSH6*, or *PMS2* genes (25). Indeed, such evidence of "tumor infiltrating lymphocytes" is a morphologic feature of such tumors present in patients with Lynch syndrome, who have germline mutations in these mismatch repair genes and are vulnerable to carcinomas of the colon, stomach, and hepatobiliary tract (26). Our patient's

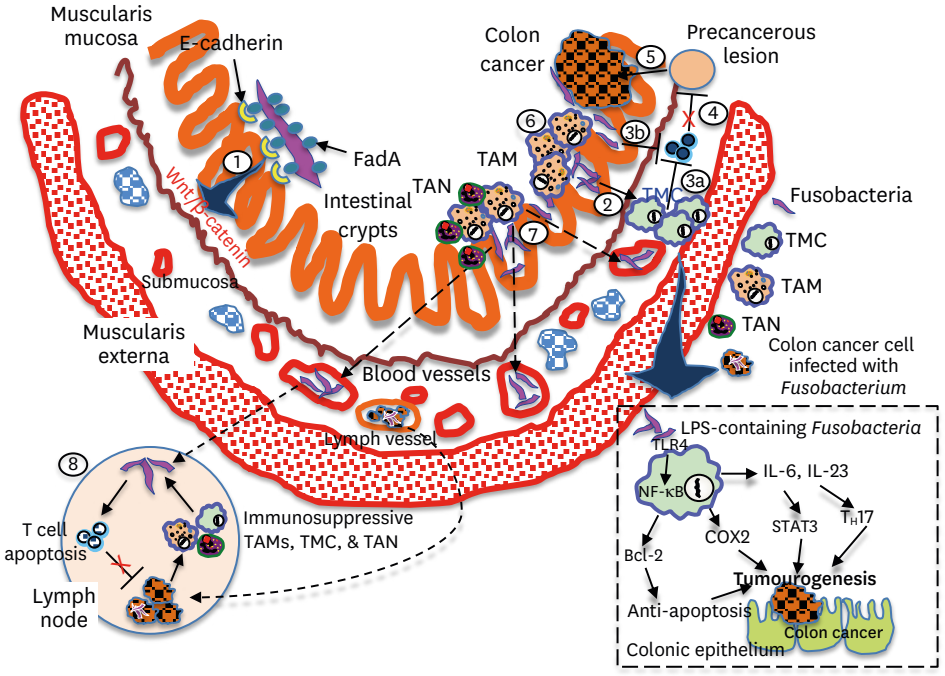

Figure 4. Diagram of the hypothesized, mutual synergism between *Fusobacterium* and colon cancer. (1) With regard to possible direct oncogenic effect of *Fusobacterium*, the FadA adhesin molecule of *Fusobacterium* binds to E-cadherin molecule on the colonic epithelium to trigger the Wnt/β-catenin oncogenic pathway. More indirect oncogenic effects of *Fusobacterium* include the following hypothesized sequence of events: (2) *Fusobacterium* recruits TMC to the intestinal submucosa, (3a) TMC inhibition of T effector cell and (3b) *Fusobacterium* inhibition of T cell proliferation and induction of T cell apoptosis, (4) loss of inhibition of T effector cells on any premalignant cells that begin to transform into cancer cells, (5) transformation and growth of pre-cancerous lesion to colon cancer, (6) infiltration by immunosuppressive TAM and TAN, (7) immunosuppression caused by TAM and TAN allows *Fusobacteria* to invade the submucosa and enter the blood stream, and (8) spread of both *Fusobacterium* and cancer cells to regional or distant lymph nodes may occur independently or the *Fusobacteria* may be transported inside cancer cells. Within the lymph node, induction of immunosuppressive TAM, TMC, and TAN by the cancer cells and induction of T effector cell apoptosis by *Fusobacterium* may lead to a mutual synergism between cancer cells and *Fusobacteria*. Inset: Diagram showing the purported molecular mechanisms by which *Fusobacteria*, via induction of NF-κB in tumor-infiltrating myeloid cells, may facilitate tumorigenesis.

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cancer was not tested for microsatellite instability, but the paucity of lymphocytes in both the primary rectal cancer and metastatic lesions makes microsatellite instability less tenable. The relative lack of a T cell response in this case may also be a feature of immunosuppression by *F. necrophorum*. Thus, one prevailing hypothesis is that individuals who have an over-representation of *Fusobacterium* species have increased immunosuppression of host immunity by the bacteria or express an immunosuppressive phenotype, intensifying the formation, growth, and spread of colonic cancer (5).

MECHANISMS BY WHICH COLORECTAL CANCER PREDISPOSES TO SYSTEMIC *FUSOBACTERIA* INFECTIONS

The finding in our patient of the presence of both metastatic cancer cells and *F. necrophorum* in the axillary mass—and likely at other sites although we were technically unable to confirm—would also lend credence to the hypothesis that colon cancer may, conversely, predispose to systemic *Fusobacterium* infection (**Fig. 4**). We posit that this may occur by several mechanisms. First, any predisposing immunodeficiency (*e.g.*, lymphopenia) as a result of the cancer and associated malnutrition may allow normally commensal bacteria to invade the colonic mucosa and become opportunistic infections. Second, invasion and disruption of the colonic submucosa by the colon cancer may also provide a portal of entry for *Fusobacterium* to gain access to the systemic or portal circulation. Third, increased infiltration of the colonic mucosa with TAM and TAN—especially if they are of the immunosuppressive M2 macrophage and N2 neutrophil subtypes—may permissively allow *Fusobacterium* to proliferate and invade the colonic submucosa, entering the blood circulation and subsequent dissemination (**Fig. 4**). At the extracolonic site (*e.g.*, regional or distant lymph nodes), the bi-directional synergy between *Fusobacteria* and cancer cells may also be occurring; *i.e.*, infiltration by immunosuppressive TAM and TAN at metastatic cancer sites creates an environment that is conducive for *Fusobacterium* invasion and, in turn, *Fusobacterium* inhibition of T cell activity generates a favorable milieu for cancer cell metastasis, the so-called "fertile soil hypothesis of cancer metastasis" (**Fig. 4**, lymph node diagram). This paradigm is similar to the concept of *locus minoris resistentiae* wherein physical trauma—associated with the influx of "wound-healing" immunosuppressive macrophages that are phenotypically similar to TAM—predispose to cancer metastasis or infection at the site of the trauma (27-29). Fourth, because *Fusobacteria* may reside intracellularly within colon cancer cells in actual clinical tissues, it is plausible that colon cancer cells transport *Fusobacteria* in a Trojan Horse-like fashion to sites of cancer metastases via lymphatics and blood vessels.

CONCLUSION

In conclusion, there is increasing evidence that over-abundance of *F. necrophorum* may play a role in the pathogenesis of colon cancer. Our patient with concomitant fulminant *F. necrophorum* septicemia and newly-diagnosed widely metastatic rectal cancer support the hypothesis that these two disorders are not a mere coincidence but that there may be a mutual synergism. Systemic *Fusobacterium* infection in the elderly, especially without evidence of internal jugular vein thrombophlebitis, should prompt clinicians to consider an underlying colonic malignancy. This association should be further studied in experimental animal models and in patients with colon cancer as greater understanding of this link may lead to greater innovative methods in preventing, screening, and treating colorectal cancer including interventions to alter the microbiome.

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