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Chemotherapy-Induced Ischemic Colitis: Literature Review and Pooled Analysis

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ABSTRACT

Background: The clinical characteristics of chemotherapy induced ischemic colitis (CIC), as a special type of chemotherapeutic colitis, have important significance for its diagnosis and treatment. In this article, available literatures relating to CIC were assessed to summary its pathogeneses, prognoses and treatment.

Methods: A broad review of the English based literatures on patients with CIC was performed the online PubMed database. Data were collected, including sex, age, clinical presentations, imaging findings, pathological features, and follow-up Discrete variables were expressed as frequencies and percentages, and continuous variables as means ± standard deviations. The Logistic Regression method was used to assess the effect of clinically relevant varieties on prognosis.

Results: To date, 13 related literatures about 16 clinical cases of CIC were reported. By review of these literatures, the clinical characteristics of CIC were summarized. The cohort comprised of 10 male and 6 female patients. The age at presentation was 59.94 ± 15.95 years (range, 20–82 years). The mean of the chemotherapy cycles cases with CIC received was 3.20 ± 4.06. The main clinical symptoms are gastrointestinal and systemic symptoms. The gastrointestinal symptom included abdominal pain (15, 93.8%), diarrhea (11, 68.8%), hematochezia (10, 62.5%) and constipation (1, 6.3%), but no nausea or vomiting. Stool cultures of all cases reported were negative. The abdominal computed tomography (CT) and X-ray revealed the thickened colon wall and the thrombosis in mesenteric vessels. And pathological biopsy was the gold standard for diagnosis of CIC. Histological examination revealed extensive ischaemic damage with or without thrombosis from colonoscopy and hemicolectomy. Moreover, ten patients (62.5%) received medical treatment including total parental nutrition, mesalazin, antibiotic and oral rehydration solutions, which were all recovery. Five patients (31.3%) with acute abdomen received emergency surgery including hemicolectomy/ total colectomy with partial proctectomy/ ileostomy, and only one of them was recovery.

Conclusion: The main clinical symptoms of CIC are gastrointestinal and systemic symptoms. However, laboratory stool tests and bloodwork are usually normal. The main pathological mechanisms of CIC are thrombosis, angiogenesis inhibition, and vasoconstriction. The most common treatments are immediate chemotherapy cessation, medical treatments and surgery.

Keywords: chemotherapy, ischemia, colitis, diagnosis, pathogenesis, treatment

INTRODUCTION

Chemotherapeutic colitis is a major dose-limiting adverse reaction to chemotherapy (Lalla et al., 2014; Peterson, Boers-Doets, Bensadoun, Herrstedt, & Committee, 2015), and few effective

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drugs for this condition are currently available in the clinic (Umang Swami, 2013; Van Sebille et al., 2015). However, chemotherapy-induced ischemic colitis (CIC), a special type of chemotherapeutic colitis, has different clinical characteristics and pathogenesis from well-recognized types such as neutropenic colitis (Al-Dasooqi et al., 2013; Sonis, 2004). CIC has a negative effect on patients' chemotherapeutic tolerance and quality of life. Herein, we summarize existing cases of CIC and provide reasonable medical advice on that basis.

During last several years, numerous chemotherapy agents have been reported to cause CIC, including paclitaxel(Elsayed, Srivastava, Pacioles, Limjoco, & Tirona, 2017), cisplatin(Maggo, Grover, & Grin, 2014), carboplatin(Otsuki, 2003), 5-fluorouracil(Hübner, Handrup, & Vogel, 2006) and etoposide(Tadashi Yokoyama, 1997a). The symptoms of CIC are sometimes nonspecific, presenting as abdominal pain, diarrhea, fever, generalized weakness and fatigue. However, its pathogenesis distinguishes it from other types of chemotherapeutic colitis, giving rise to unique clinical characteristics.

Since CIC 's particular pathogenesis leads to significant uncertainty in its diagnosis and treatment. Therefore, a comprehensive literature review which provide meaningful clinical knowledge on the pathogenesis, symptoms, diagnosis and treatment of chemotherapeutic colitis, are required. In the current study, we assessed the available literatures from PubMed database relating to CIC, and give a complete overview of CIC 's pathogenesis and its management. The main purpose of this review to give a brief overview to clinicians, researchers and other health care providers on the pathogenesis, symptoms, diagnosis and treatment of chemotherapeutic colitis through a discussion of existing case reports and relevant basic studies.

METHODS

Study identification

A wide search of the English based literatures on patients with CIC were performed the online PubMed database, with keywords of "chemotherapy induced ischemic colitis", or "chemotherapy", "ischemic", and "enteritis" or "colitis". The included literatures in the current study were published in between 1997 to 2017. To prevent missing possible cases, relevant articles from reference lists in the primary literatures were also included. The inclusion criteria in our article are as follow: 1) patients diagnosed with malignant tumors received chemotherapy; 2) excluded prior

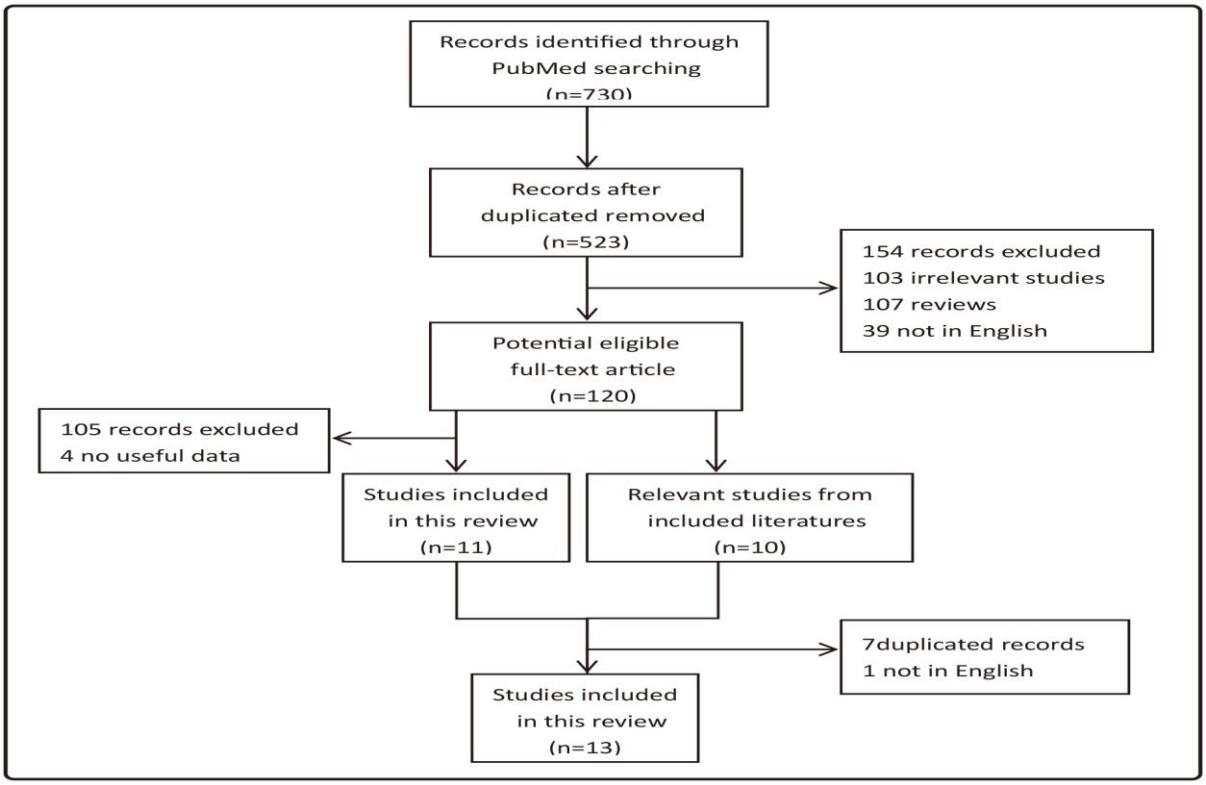

Figure 1. **Flow diagram of identification of studies**

Diagnosis of an inflammatory bowel disease such as ulcerative colitis or Crohn's
disease was identified in the literature. Data were collected, including age, sex, imaging findings, pathological features, clinical presentations, and follow-up (**Fig. 1**).

Statistics

SPSS 16.0 software package (SPSS, Chicago, IL, USA) was used for statistical analyses. Discrete variables were expressed as frequencies and percentages, and continuous variables as means ± standard deviations. The Logistic Regression method was used to assess the effect of clinically relevant varieties on prognosis.

RESULTS

1. Clinical characteristics

This review contained 16 well-described cases of CIC in 13 English language literatures. As shown in **Table 1**, there were 6 (37.5%) cases from Asian region, 4 (25.0%) cases from American region, 3 (18.8%) cases from European region, and 3 (18.7%) cases from Oceania region.

Clinical characteristics of 16 cases with CIC were recorded in **Table 2**. The cohort comprised of 10 male and 6 female patients. The age at presentation was 59.94 ± 15.95 years (range, 20–82 years). 10 (50.0%) cases received platinum-based chemotherapy, and 6 (37.5%) cases received taxane-based chemotherapy, in which 3 (18.8%) cases received platinum combined with taxane chemotherapy (Paclitaxel + Carboplain). 3 (18.8%) cases received 5-azacytidine. The other 2 cases received CHOP (Vincristine + Cyclophosphamide + Doxorubicine + Prednisolone) and FOLFIRI (Irinotecan + Fluorouracil +Leukoverin) chemotherapy. 8(50%) cases were diagnosed as CIC in first cycle of chemotherapy, 1(6.2) case in second cycle, 3 (18.8%) cases in third cycle, 2 (12.5%) cases in sixth cycle, and only 1 (6.3%) case in seventeenth cycle (1 case had no data about the cycle of chemotherapy). The mean of the chemotherapy cycles
cases with CIC received was 3.20 ± 4.06. The median day of CIC onset after chemotherapy was 3 days (4.80 ± 3.66, range: 1–15 days).

2. Clinical complaints

Table 1. **The main information of included literature**

Title	Year	Country	Cases, n
Colonoscopy for Frank Bloody Stools associated with Cancer Chemotherapy(Tadashi Yokoyama, 1997b)	1997	Japan	1
Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer(N. K. Ibrahim et al., 2000)	2000	USA	2
Ischemic Colitis Associated With Paclitaxel(Bruno Daniele, 2001)	2001	Italy	1
Ischemic Colitis Associated With Paclitaxel and Carboplatin Chemotherapy(Mitsuo Tashiro, 2003)	2003	India	1
Symptoms in cancer patients and an unusual tumor: Case 2. Docetaxel-related ischemic colitis(Hussein et al., 2005)	2005	Ireland	1
Extensive colonic ischemia following treatment with bevacizumab, fluouracil and CPT-11 in a young patient with advanced adenocarcinoma of the rectum(Paran, Edelstein, Klein, & Gutman, 2007)	2007	Israel	1
Chemotherapy-Induced Ischemic Colitis in a Patient with Jejunal Lymphoma(Halm, Sack, & Zachaus, 2010)	2010	Germany	1
Ischemic colitis after capecitabine plus cisplatin treatment in advanced gastric cancer(Cetin et al., 2011)	2011	Turkey	1
Complications of 5-azacytidine: Three cases of severe ischemic colitis in elderly patients with myelodysplastic syndrome(Melchardt et al., 2013)	2013	Austria	3
Capecitabine induced colitis(Maggo et al., 2014)	2014	Canada	1
Severe ischemic colitis after treatment of bile-duct cancer using gemcitabine and cisplatin(Osumi, Ozaka, Ishii, & Sasahira, 2015)	2015	Japan	1
Ischemic Colitis Associated with Paclitaxel and Carboplatin Combination(Elsayed et al., 2017)	2017	USA	1
Pemetrexed-associated Ischemic Colitis in Non-small Cell Lung Cancer(Ye, Yang, Fang, & Gu, 2017)	2017	China	1

Table 2. **Clinical characteristics of 16 cases with CIC**

Variables		N (%)
Gender	Male	10 (62.5)
	Female	6 (37.5)
	Median age (y), (mean±SD, y)	62 (59.94 ± 15.95)
Neoplasm	Lung	3 (18.8)
	Breast	3 (18.8)
	Myelodysplastic syndrome	3 (18.8)
	Gastric	2 (12.5)
	Colon/Rectal	1 (6.3)
	Pancreas	1 (6.3)
	Neuroendocrine	1 (6.3)
	Lymphoma	1 (6.3)
Chemotherapy agents	Taxane + Platinum	3 (18.8)
	Other Platinum-based chemotherapy	5 (31.2)
	Other Taxane-based chemotherapy	3 (18.8)
	5-Azacytidine	3 (18.8)
	CHOP (Vincristine + Cyclophosphamide + Doxorubicine + Prednisolone)	1 (6.2)
	FOLFIRI (Irinotecan + Fluorouracil +Leukoverin)	1 (6.2)
	Median chemotherapy cycle (mean±SD)	1 (3.20 ± 4.06)
	Median onset day of CIC after chemotherapy (mean±SD)	3 (4.80 ± 3.66)

Presenting complaints of all cases were recorded, these were collected and carefully examined in **Table 3**. Finally, three categories were summarized: gastrointestinal, systemic symptom and abdominal signs. The gastrointestinal symptom included abdominal pain (15, 93.8%), diarrhea (11, 68.8%), hematochezia (10, 62.5%) and constipation (1, 6.3%), but no nausea or vomiting. The most common gastrointestinal symptom was abdominal pain, which located mainly in lower abdomen (5, 31.2%), especially in left lower abdomen (3, 18.8%), and only 1 case experienced upper abdominal pain. Once abdominal pain occurred, it is not very uncommon to reveal abdominal signs by physical examination. Abdominal tenderness (7, 43.8), distention (2, 12.6) and left side guarding (2, 12.6) with no peritoneal irritation was the signs of CIC. Diarrhea was less frequently than abdominal pain, which always was in coincidence with hematochezia: bloody diarrhea (7, 43.8%). The systemic symptoms were fever (1, 6.3) and fatigue (6.3) which was nonspecific and infrequent.

Table 3. **Clinical complaints of 16 cases with CIC**

Variables		N (%)
Gastrointestinal symptom	Abdominal pain	15 (93.8)
	Diarrhea	11 (68.8)
	Hematochezia	10 (62.5)
	Constipation	1 (6.3)
Systemic symptom	Fever	1 (6.3)
	Fatigue	1 (6.3)
Abdominal signs	Tenderness	7 (43.8)
	Distention	2 (12.6)
	Left side guarding	2 (12.6)

3. Laboratory examination

Laboratory examination was available in 14 patients. Stool cultures of all cases reported for bacterial infections and *Clostrid-ium difficile* enterotoxin were negative. Stool PCR testing of different organisms was negative in one patient, the stool of which was positive for occult blood. Microscopic examination of stool was received by two patients, that exhibited numerous red cells without parasites and ova. Complete blood count (white blood cell, neutrophils, hemoglobin and platelets) revealed increased white blood cell only in one patient. And an elevation of C-reactive protein (CRP) was also detected in one patient.

4. Imaging findings

Imaging findings including abdominal computed tomography (CT) and X-ray were presented in 9 patients. Abdominal X-ray revealed pneumoperitoneum (1 case), air-fluid levels (2 cases), colonic distention (2 cases), and fecal loading (1 case) in the abdomen. But no free air visible on erect-position x-ray chest underneath the diaphragm. The common abdominal CT signs were colon distention (2 cases) and thickening of colon wall (2 cases) with no signs of intestinal obstruction. And only one patient presented ascites for in abdominal CT. Among them, one patient performed CT angiography of abdominal aorta showed proximal segment thrombosis of the celiac artery as a direct evidence on CIC.

5. Pathological characteristics

All patients were diagnosed as CIC via pathological examination of the biopsy specimens from colon. Comprehensive descriptions of pathologic condition is available in literatures 12. All available pathological reports and images were prudently studied.

On sheer pathological existence, segmental colitis or pan colitis with edema (6 cases), ulceration (5 cases), hyperemia (3 cases), erosion (2 cases), petechial bleeding (1 case), erythema (1 case), and friability (1 case) was showed by colonoscopy. This appearance from hemicolectomy underwent by three patients showed similar records as follows: inflammation, serositis, patchy ischemia, perforation, and ulceration were shown in colonial samples removed.

Histological examination revealed extensive ischaemic damage with or without thrombosis from colonoscopy and hemicolectomy. The lamina propria of mucosa contained inflammatory infiltrate with crypt atrophy and crypt dropout. The surface epithelium of mucosa showed necrosis, loss, regeneration of epithelium, inflammatory infiltrate. In submucosa layer presented loss of vascular, hemorrhage and inflammatory infiltrate. The similar appearance also detected in colonial samples removed from hemicolectomy. Submucosa layer showed ischaemic damage with thrombosis, vascular distension and revascularization. And mucosa revealed necrosis with edma, crypt atrophy and regeneration.

6. Treatments and Prognosis

Records of treatments and prognosis were available in 15cases from 12 literatures, as reviewed in **Table 4**. Among them, chemotherapy was discontinued because of CIC accounting for 10 cases (62.5). Ten patients (62.5%) received medical treatment including total parental nutrition, mesalazin, antibiotic and oral rehydration solutions, which were all recovery. Five patients (31.3%) with acute abdomen received emergency surgery including hemicolectomy/ total colectomy with partial proctectomy/ ileostomy, and only one of them was recovery.

Table 4. **Treatment details and prognosis of cases with CIC**

Variables		**N (%)**
Discontinue chemothrapy	Yes	10 (62.5)
	No	5 (31.3)
Medical treatment	Total parental nutrition	3 (18.8)
	Mesalazin	2 (12.5)
	Antibiotic	2 (12.5)
	Oral rehydration solutions	1 (6.3)
Surgery		5(31.3)
Prognosis	Recovery	10 (62.5)
	Death	5 (31.3)

The effect of each clinical relevant variety on prognosis was statistic in **Table 5**. The difference between treatment of surgery and non-surgery to CIC approached statistical significance (P=0.020, OR=36.000), as the only statistically significant factor. Therefore, the Logistic Regression wasn't operated.

Table 5. **The effect of clinical relevant varieties on prognosis.**

Variables	P	OR	HR(95%IC)
Age	0.410	1.032	0.958-1.113
Gender	0.280	4.000	0.323-49.596
Chemotherapy cycle	0.420	0.769	0.406-1.457
Onset day of CIC after chemotherapy	0.079	1.604	0.946-2.719
Hematochezia	0.274	0.286	0.030-2.692
Surgery	0.020*	36.000	1.772-731.562

DISCUSSION

In the current study, we reviewed 16 cases of CIC from 13 different studies, which were published between 1997-2017. CIC particular pathogenesis leads to significant uncertainty in its diagnosis and treatment, which is a significant challenge for the physicians and other health care providers. To the best of our knowledge, this is the first retrospective study and pooled analysis focusing on CIC. In this study, we summarize the various clinical features of CIC, including clinical presentations, laboratory examination, imaging findings and pathological characteristics, treatments approaches and the prognosis, in order to design a comprehensive rationale for prognostication and diagnosis.

The objectives of current studies was achieved by analyzing the abdominal computed tomography (CT), X-ray, Histological examination, surgery including hemicolectomy/ total colectomy and other laboratory tests of CIC patient from the published reports to provide a brief summary. The various variables obtained were expressed as frequencies and percentages, and a Logistic Regression method was adopted to evaluate the effect of clinical relevant varieties on prognosis. We found that numerous affecting factors for the expansion of ischemic colitis have been identified. Our results show that gastrointestinal symptom included abdominal pain, diarrhea, hematochezia and constipation, but no nausea or vomiting. CT and X-ray revealed the thickened colon wall and the thrombosis in mesenteric vessels. Histological examination revealed extensive ischaemic damage with or without thrombosis from colonoscopy and hemicolectomy. The main pathological mechanisms of CIC are thrombosis, angiogenesis inhibition, and vasoconstriction. The most common treatments are immediate chemotherapy cessation, medical treatments and surgery. Further details are explained below.

1. Definition

Existing guidelines and clinical reports describe CIC from different perspectives. The guidelines of the European Society for Medical Oncology (ESMO) define mucositis as ulcerative and/or inflammatory lesions of the gastrointestinal and/or oral tract during chemotherapy and/or radiation (Peterson et al., 2015). Chemotherapy-induced colitis is a comprehensive description of clinical symptoms such as diarrhea, abdominal pain and bloody stool occurring as side effects of chemotherapy (Chisti, Khachani, Brahmanday, & Klamerus, 2013; Klein & Weaver, 2012),. There are three pathological categories of chemotherapy-induced colitis: pseudomembranous colitis (PMC), agranulocytic colitis and ischemic colitis (IC) (Dosik et al., 1979). IC is defined as injury and inflammation of the large intestine due to shortage of blood supply (Bower, 1993). In the included literature, CIC can be defined, for the drives of clinical treatment and diagnosis, as colitis with a reduction in blood supply due to blockage or narrowing of a visceral artery as a result of by chemotherapy. According to the Common Terminology Criteria for Adverse Events (NCI-CTC), the definitions of visceral arterial ischemia, colitis and diarrhea can also be applied to CIC, as shown in **Table 6** (NCI, 2009).

2. Clinical presentation

Our results revealed that CIC effected mostly old patients, with a average age of 59.94 years, and the patients were predominantly male (male:female, 1.67:1). Patients receiving a regimen of platinum-based chemotherapy accounted for the majority of cases (50%). People received an average of 3.2 cycles of chemotherapy before developing CIC. The incubation period, i.e., the time from the start of chemotherapy to the onset of CIC, was approximately 1 to 15 days, with an average of 4.8 days.

Table 6. **The definitions of visceral arterial ischemia, colitis and diarrhea in NCI-CTC**

Adverse Event	1	2	3	4	5
Colitis	Asymptomatic ; diagnostic or clinical observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	critical abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Diarrhea	Increase of <4 stools daily over baseline; average increase in ostomy output compared to baseline	Increase of 4 - 6 stools daily over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; critical ehance in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; Indication of end organ damage; urgent operative intervention required	Death
Definition: A disorder characterized by a reduction in blood supply due to blockage or narrowing of a visceral (mesenteric) artery.					

The clinical symptoms of CIC mainly included gastrointestinal (abdominal pain, hematochezia and diarrhea) and systemic symptoms (fever, generalized weakness and fatigue). Almost all patients experienced abdominal pain, mainly in the lower abdomen, as well as diarrhea with hematochezia or bright red blood in the stool. The NCI-CTC grading of colitis and diarrhea was an appropriate criterion for estimating patients' condition. The systemic symptoms were nonspecific and uncommon. The main clinical signs of CIC were abdominal tenderness and distention without peritoneal irritation.

Laboratory stool tests and bloodwork are usually normal. In reported cases, stool cultures and PCR tests for multiple organisms were negative, and microscopic examination of stool specimens showed that many were positive for red blood cells or occult blood, which was be identified from PMC(DiPersio et al., 1991; Kelly, Pothoulakis, & LaMont, 1994; Tedesco, Corless, & Brownstein, 1982). Moreover, it was also identified from neutropenic enterocolitis(Kazuhito et al., 2010)that complete blood count of almost all cases was normal.

The imaging characteristics of CIC were also summarized. Imaging examinations included abdominal computed tomography (CT) and X-ray. In this article, CT angiography revealed thrombosis of mesenteric vessels, and abdominal CT revealed a thickened colon wall as a particular feature of CIC. CT angiography is the reference standard imaging examination of mesenteric ischemia, with a sensitivity of approximately 90% (Horton & Fishman, 2007; Kirkpatrick, Kroeker, & Greenberg, 2003; Taourel, Deneuville, Pradel, Regent, & Bruel, 1996) In the event of intestinal obstruction, X-ray examination can be used to assess the condition of the gastrointestinal tract. Pathological biopsy is a standard method for the CIC diagnosis. Dosik et al. reported that autopsies of three patients with acute ischemic colitis showed intensely congested and hemorrhagic intestines with irregularly distributed ulcers on gross examination, and thrombosis and hemorrhage were detected in the mucosa and submucosa layer(25).Similar results were revealed in this review: extensive ischemic

damage appeared in the colonic mucosa, with necrosis and ulceration, while thrombosis, hemorrhage and revascularization were found in the submucosa.

3. Pathogenesis mechanism

The pathogenetic mechanism of CIC is still unclear and is not completely accounted for by the current pharmacodynamic or kinetic explanations, such as the theories of ROS, intestinal leakage or inflammatory response (5, 6, 35, 36). Therefore, in this article, we establish a set of assumptions and develop a probable hypothesis regarding the pathogenesis of CIC (**Figure 2**).

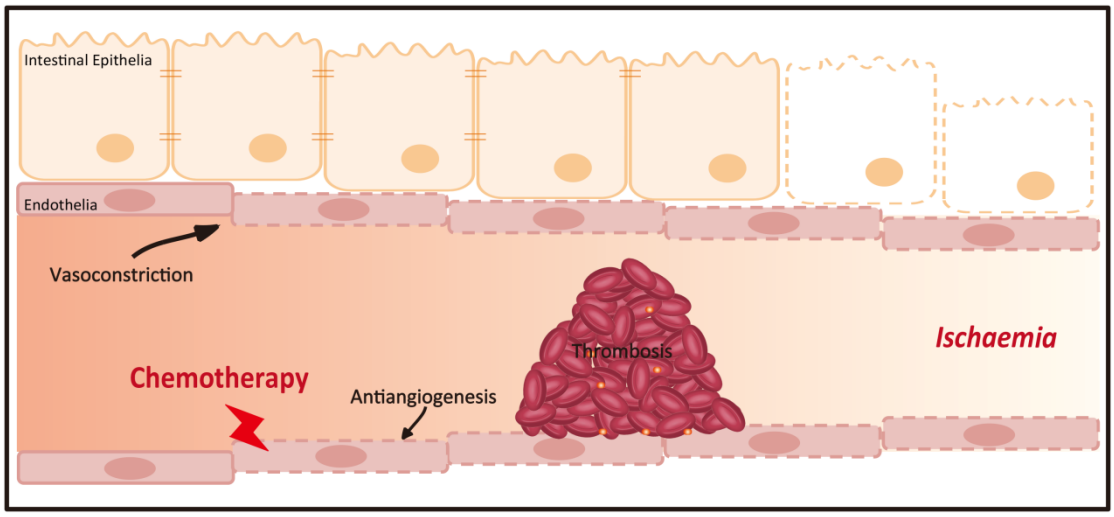

Figure 2. **The pathogenesis of chemotherapy induced ischemic colitis**

3.1 Thrombosis

There is clinical evidence that intestinal thrombosis is involved in the pathogenesis of CIC. We found that CT shown thrombosis in the proximal segment of the celiac artery (Cetin et al., 2011), and extensive ischemic damage with thrombosis was evident in pathological samples of a left hemicolectomy in CIC (N. K. Ibrahim et al., 2000). Moreover, the definition of visceral arterial ischemia in the NCI-CTC guidelines also clearly indicate the occurrence of intestinal thrombosis (NCI, 2009).

Chemotherapy agents can cause injury to the endothelium and disruption to fibrinolysis, leading to thrombosis, which is involved in the pathogenesis of intestinal toxicity (Levine, 1997; Llorca Ferrandiz et al., 2005). There are various recognized mechanisms by which chemotherapy damages the endothelium (Nicolson & Custead, 1985). Some chemotherapy agents, such as bleomycin (Wei et al., 2004), vincristine (Avramis, Kwock, & Avramis, 2001), doxorubicin (Bast, Kaiserova, den Hartog, Haenen, & van der Vijgh, 2007) and adriamycin (Nicolson & Custead, 1985), can directly affect the integrity of vascular endothelial cell membranes. Some chemotherapy agents, such as cyclophosphamide, carbendazim and fluorouracil, can inhibit anticoagulation by decreasing the levels of plasma proteins C and S (Oberhoff, Winkler, Hoffmann, & Schindler, 2000). During coagulation, activated factor VIII (FVIIIa) acts as a cofactor, increasing the activation speed of coagulation factor IX to coagulation factor X (FX) (Ahmad & Walsh, 2005). Activated coagulation factor V (FVA) acts as another cofactor, increasing the activation speed of FX to prothrombin (Autin, Steen, Dahlback, & Villoutreix, 2006). Therefore, FVIIIa and FVa are the rate-limiting factors for the activation of FX and prothrombin, while the protein C system can inactivate FVIIIa and FVa. As a cofactor of activated protein C (APC), protein S can greatly enhance the inactivating effect of APC on FVIIIa and FVa and exerts an indirect anticoagulant effect along with protein C. Protein S can also directly combine with FVa and FXa to directly inhibit the formation of prothrombin complex, thus inhibiting the activation of prothrombin (Brosstad, 1993). Therefore, protein C and protein S play an signicant role in anticoagulation. The deficiency of protein C and protein S induced by chemotherapy can increase the risk of thrombosis.

3.2 Antiangiogenesis

The antiangiogenetic pathogenesis of CIC is mainly revealed by taxane-induced ischemic colitis (C. H. B. a. N. K. Ibrahim, 2012; Klauber, Parangi, Flynn, Hamel, & D'Amato, 1997). Taxane can disrupt the dynamic balance of tubulin and the

tubulin dimer in microtubules, persuade and indorse microtubule assembly and tubulin polymerization, and avert depolymerization, thus inhibiting mitosis, stabilizing microtubules, and effectively preventing the proliferation of cancer cells; in this manner, taxane exerts an anticancer effect (Jordan, Toso, Thrower, & Wilson, 1993; Verweij, Clavel, & Chevalier, 1994). Moreover, angiogenesis involves both the propagation and movement of normal vascular endothelial cells, requiring changes in cytoskeletal dynamics. By acting as microtubule stabilizers, taxanes can downregulate cytoskeleton-dependent functions of vascular endothelium cells, including proliferation, morphogenesis and chemotaxis, by the same mechanism as their effect on cancer cells (Angelo Vacca & Francesca Merchionne, 2002; Ettenson & Gotlieb, 1992; Pasquier et al., 2005). There are also reports contrary to the above literature. The secretion of proteins related to cytoskeleton function, such as urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs), did not change, suggesting that the regulation of the cytoskeleton may not be involved in this process (Stetler-Stevenson, 1999).

3.3 Vasoconstriction

Although existing in vivo and in vitro reports provide no direct indication that chemotherapy drugs cause the contraction of intestinal submucosa and mesenteric vessels, the vasoconstriction induced by chemotherapy is one of the pathophysiological mechanisms of coronary spasm (Anne Polk, 2014; Schnetzler, Popova, Collao Lamb, & Sappino, 2001). Chemotherapy may cause vasoconstriction by inhibiting the factors of vasodilation, among which the most important factor is nitric oxide synthase (NOS) (Saad, Najjar, Daba, & Al-Rikabi, 2002).

Three isoforms of NOS, namely, neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and inducible nitric oxide synthase (iNOS) (Capettini, Cortes, & Lemos, 2010), all of which generate nitric oxide (NO) as a gas messenger molecule to regulate vascular function (Forstermann, Mulsch, Bohme, & Busse, 1986). eNOS is regulated via phosphorylation at several protein loci, including threonine (Thr), tyrosine (Tyr), serine (Ser), and residues (Fleming & Busse, 2003). The Thr-495 residue of human eNOS manages to be constantly phosphorylated, exerting a negative regulatory function in endothelial cells. Protein kinase C (PKC) is most possibly the constitutively active kinase involved in its phosphorylation (Fleming & Busse, 2003). Chemotherapy drugs, such as 5-fluorouracil (5-FU), inhibit eNOS by inducing PKC to phosphorylate the negative regulatory site Thr-495. The PKC inhibitor staurosporine decreased 5-FU-induced vasoconstriction, while an activator of PKC, phorbol-12,13-dibutyrate, had the opposite effect on 5-FU-induced vasoconstriction (Mosseri, Fingert, Chokshi, Gal, & Isner, 1991).

4. Treatment and Prognosis

The treatments included in this review were summarized into three categories: immediate cessation of chemotherapy, and surgery. When chemotherapy is immediately discontinued and medical treatment is provided, 62.5% of patients recover. Total parenteral nutrition, mesalazine, antibiotics and oral rehydration solution are the medical treatments recommended by ESMO(Peterson et al., 2015). Notably, however, there is currently no treatment that addresses the underlying pathogenesis (Umang Swami, 2013). Statistical results indicate that treatment is the main factor affecting the prognosis of CIC. However, because of small sample sizes and a shortage of long-term observations in the included literature, this result is still debatable.

Theoretical and practical implications

The current study provides a brief summary of previous numerous cases published from 1997 to 2017, it provides a brief theoretical overview of pathogeneses, prognoses and treatment options of chemotherapy induced ischemic colitis. Which will ease the health care providers to access relevant the data based on patient sex, age, clinical presentations, imaging findings and pathological features. It will also allow the clinician to optimized the treatment approaches and diagnosis modalities for the chemotherapy induced ischemic colitis patients in clinic. Furthermore, it may also help the investigators to distil this information into an accessible form conducive to design future approaches for chemotherapy induced ischemic colitis managements.

Limitations and Future perspective

One of the limitations in the current study is that it only involves the published paper available from 1997-2017. The studies were only included from PubMed database, with keywords of “chemotherapy induced ischemic colitis”, or “chemotherapy”, “ischemic”, and “enteritis” or “colitis”. Furthermore, our scope covers a variable, including sex, age, clinical presentations, imaging findings and pathological features. Further, studies

with a larger data set and multiples variable will be required to get a deeper insight into the CIC pathogeneses, prognoses and treatment. Additionally, analyzing the previous data with more advance statistical tools will help to further strengthen this area of research.

CONCLUSIONS

The main clinical symptoms of CIC are gastrointestinal and systemic symptoms. However, laboratory stool tests and bloodwork are usually normal. Abdominal imaging examination and pathological biopsy reveal a thickened colon wall and thrombosis of the mesenteric vessels. The main pathological mechanisms of CIC are thrombosis, angiogenesis inhibition, and vasoconstriction. The most common treatments are immediate chemotherapy cessation, medical treatments and surgery.

Conflict of interests

None

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Author contributions:

Qingqing Yu and Heng Zhang had the idea for the article and performed the literature search and data analysis. Xiumei Wang participated in the writing and revising of this article Yan Li, Haibo Zhao and Leilei Yuan conceived of the article, and take part in its designing, coordination and wrote the manuscript.

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