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Conceptual Paper

The Vascular Imbalance - Ischemic Colitis

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Preface

Ischemic colitis is cogitated as an injury to the colon engendered due to colonic hypo-perfusion. Extent of ischemic injury ranges from superficial colonic degradation and inflammation to necrosis and incriminates full-thickness of the intestinal wall. Nevertheless, ischemic damage enunciated within the colon is attributed to several factors exemplifying a complicated pathophysiology. Ischemic colitis was scripted as a distinct disease in 1966 by Marston., *et al*. and was categorized into gangrenous, stricture formation and transient [1].

Discernment of ischemic colitis is challenging on account of vague clinical symptoms, indistinguishable physical findings and non specific laboratory and radiographic investigations. Assessment of probable factors of disease emergence and a cogent clinical suspicion is essential to formulate pertinent diagnosis and initiate therapy [1,2].

Disease characteristics

Current classification of ischemic colitis is enunciated as gangrenous and partial thickness ischemic colitis. An estimated 50% to 60% instances of gastrointestinal ischemia terminate into ischemic colitis. Ischemic colitis usually arises at 50 years although infants incriminated with necrotizing colitis can be implicated. Intestinal ischemia is enunciated in an estimated 3% of renal transplant recipients [2,3].

Colonic vasculature provides an integral component of the disease process. Superior mesenteric artery sustains vascular outflow from duodenum to the mid transverse colon of the gut. Inferior mesenteric artery supplies blood to the remaining colonic segment and superior aspect of rectum. Internal iliac artery communicates with inferior mesenteric artery through superior and middle haemorrhoidal artery. Collateral blood flow emerges via mesenteric branches which are supplied by marginal artery of Drummond and meandering mesenteric artery or the Arc of Riolan [2,3].

Marginal artery is delineated parallel to the colon and supplies branches to vasa recta. Marginal artery travels along the splenic flexure although it can be absent or insufficiently developed in 5% subjects.

Colonic injury and disintegration typically arises within the "watershed" regions of splenic flexure at Griffith point and sigmoid colon at Sudeck point. Therefore, splenic flexure and transverse colon are commonly implicated and the specific sites configure "watershed" zones arising at the margins of vascular territories supplied by inferior and superior mesenteric arteries. Ischemic alterations within the colon can be confined to mucosa or arise within the mural zone due to hypo-perfusion or as transmural ischemia with incrimination of major blood vessels. Chronic ischemia produces gastrointestinal alterations identical to acute ischemia, although the modifications are segmental and patchy [3,4].

Disease pathogenesis

Ischemic colitis is often engendered as an acute, self- limiting decimation of the vascular supply rather than a particular vascular lesion or an embolic phenomenon.

Cogent angiography demonstrates a narrowing of miniature blood vessels along with a tortuous long colonic artery. Implication of left colon is a classic disease representation. Ischemic colitis incriminates multiple, colonic sites in an estimated 55% instances and is devoid of a preferential location of disease emergence [2,4].

Specific factors incriminated in the appearance of ischemic colitis are gastrointestinal obstruction, diabetes mellitus, cogent medications such as non steroidal anti inflammatory drugs [NSAIDS] or potassium chloride, hypercoagulable states, intestinal Behcet's disease, pseudomembranous colitis, radiation injury, stress ulcer, surgical intervention for adjunctive disorders, vascular disease as with atherosclerosis, dissecting aneurysms, small vessel vasculitis, thromboembolism and uraemia [3,4].

Younger individuals delineate ischemic colitis in association with conditions such as amyloidosis, collagen vascular disease, hypovolemia, phlebitis, thromboembolism, administration of vasoactive drugs, birth control pills, cocaine ingestion, granulomatosis with polyangiitis [Wegener's granulomatosis], in marathon athletes and frequently as an idiopathic disorder [2,4].

Cardiovascular disease associated with development of ischemic colitis are enunciated with diabetes mellitus, dyslipidemia, heart failure, peripheral vascular disease and employment of aspirin and digoxin. Surgical intervention for aortic aneurysm repair frequently compromises vascular flow and induces ischemia. Constipation coagulopathy, consumption of illicit and prescription drugs and extreme physical exertion can induce ischemia in young adults [3,4].

Ischemic colitis is an exceptional, morbid complication of surgical repair of aortic aneurysm and is exemplified in an estimated overall incidence of 2.2% with an incidence of around 8.9% for ruptured aortic aneurysm repair. Prevalence of ischemic colitis is enhanced with open repair at nearly 1.9% rather than endovascular repair at roughly 0.5% [2,4]. Colonic ischemia is associated with enhanced morbidity and two to four fold increase in mortality. Thus, endoscopic assessment is recommended following surgical repair of ruptured aortic aneurysm. Chronic constipation is commonly accompanied by the emergence of ischemic colitis. Enhanced intraluminal pressure exemplifies a decimated blood flow within the mucosa and predisposes to ischemic events, although the exact mechanism remains obscure.

Coagulopathy such as an extensive hypercoagulable state and anomalies of blood coagulation can predispose towards development of ischemic colitis with an estimated 8.4%, in comparison to general population [2,4].

Consumption of illicit and prescription drugs is associated with induction of ischemic colitis. Cocaine associated enterocolitis typically emerges within three days of cocaine consumption and is accompanied by inflammatory modifications upon right colon. Non- operative management is considered appropriate although employment of an abdominal laprotomy is associated with around 50% mortality.

Methamphetamines are synthetic, sympathetic nervous system mimicking agents inducing vasoconstriction and end organ damage along with induction of colonic ischemia [2,4].

Incidence of occurrence of faecal occult blood and ischemic colitis in elevated in athletes involved in endurance sports. Adequate hydration, circumventing consumption of non steroidal anti inflammatory drugs [NSAIDs], caffeine, alcohol and hypertonic or energy enhancing drinks is recommended [2,4].

Clinical elucidation

Geriatric individuals within 60 years to 70 years are commonly incriminated by ischemic colitis and a majority delineate preceding atherosclerotic disease. Clinical symptoms vary from a vague abdominal discomfort to a comprehensive abdominal involvement. Classic clinical representation of ischemic colitis is denominated by an elderly individual delineating abdominal pain, leucocytosis and bowel movements with haemorrhagic excreta. A typical, episode of an acute onset of crampy abdominal pain with excretion of blood mixed stools within 24 hours is preceded by transient hypo-perfusion of the gut. Ischemic colitis characteristically demonstrates abdominal pain and haemorrhagic stools. Subjects with lower gastrointestinal bleeding subjected to colonoscopy can also engender ischemic colitis [4,5].

Individuals demonstrating lower abdominal pain can delineate ischemic colitis particularly subjects on haemodialysis or with diabetes mellitus, hypertension, hypoalbuminemia and administration of constipation inducing agents.

Decimation of a singular, major colonic blood vessel may not engender cogent clinical symptoms on account of an abundance of anastomotic interconnections. However, vascular conditions incriminating end-arteries can initiate miniature, focal ischemic lesions.

Endoscopy exhibits the occurrence of petechial haemorrhages, oedematous and fragile mucosa, segmental erythema, disseminated mucosal erosions and longitudinal mucosal ulcerations [5,6]. Gastrointestinal incrimination is segmental, sharp and distinctive. Clinical symptoms enunciated are an abrupt onset of abdominal pain and bleeding [5].

Histological elucidation

On gross examination, mucosal ulceration can be discrete or serpiginous with the probable emergence of cobblestone pattern recapitulating Crohn's disease or as pseudo-polyps similar to ulcerative colitis. Mucosa appears to be haemorrhagic and erythematous on account of vascular reflow. Intensely tinged mucus or fresh blood can be encountered within the lumen. Segmental attenuation of the gastrointestinal tract can be exemplified in regions of full- thickness bowel infarction and gangrene. Delayed fibrosis and stricture formation can ensue [5,6].

Examination of incriminated gastrointestinal segment necessitates a meticulous dissection of attending vasculature in order to adequately discern adjunctive vascular lesions.

Tissue specimens are beneficial in excluding associated disease processes. Nevertheless, morphological alterations of ischemic colitis are non specific. Histological evaluation is denominated by mucosal erosion, hyperplastic granulation tissue, glandular atrophy, haemorrhage within the lamina propria and submucosal aggregates of macrophages with haemosiderin pigment. With progressive ischemia, submucosal oedema and haemorrhage emerges as bluish- black blebs and protrudes into the intestinal lumen. Aforesaid lesions are consistent with the characteristic 'thumb printing' sign cogitated on radiographic assessment [5,6].

Ischemic segment of the bowel is characterized by occurrence of necrotizing phlebitis and articulation of vascular thrombi. Viable portions of gastrointestinal tract demonstrate a lymphocytic inflammatory exudate whereas ischemic segment is categorized by the occurrence of necrotizing lesions. Necrosis and mucosal ulceration is exhibited. Granulation tissue is extensive and extends into submucosa and encompassing smooth muscle configuring muscularis mucosa. Haemosiderin pigment, haemorrhage and oedema can arise within the lamina propria. Hyaline thrombi are demonstrable within miniature blood vessels. Crypt abscesses are encountered although deep-seated segment of colonic crypts are exempt. Generally, the inflammatory exudate is minimal [4,6].

Occurrence of superficial neutrophilic infiltration, fibrin accumulation or mucosal necrosis is encountered in preliminary phase and transmural fibrosis emerges in the delayed phase. Normal appearing mucosa on endoscopy is essentially devoid of microscopic aberrations [6].

Differential diagnosis

Ischemic colitis mandates a segregation from inflammatory bowel disease constituted by conditions such as Crohn's disease which appears in younger subjects and delineates transmural inflammation with an absence of necrosis. Infection with Escherichia coli commonly occurs in younger individuals of specific epidemiological zones and usually implicates right sided gastrointestinal tract.

Ulcerative colitis demonstrates cryptitis, crypt abscess, plasmacytosis of basal epithelium and is devoid of fibrosis of muscularis propria or deposition of haemosiderin pigment [2,4].

Investigative assay

Comprehensive history and physical examination is recommended in subjects delineating abdominal complaints. Vague, non specific clinical symptoms, suspected gastrointestinal ischemia, occurrence of comorbid conditions, administration of various predisposing medications and drugs are incriminated in emergence of ischemic colitis. Physical examination demonstrates sepsis and peritonitis, therefore aggressive therapy with surgical intervention is mandated. As ischemic colitis clinically and morphologically recapitulates ulcerative colitis, gastrointestinal tract infections, diverticulitis or malignant disorders, additional confirmation is mandated.

Complete blood count, metabolic panel, liver function tests, specific biomarkers indicative of lactate production, lactate dehydrogenase, creatine kinase and amylase require evaluation [5,6].

Diagnosis of ischemic colitis is devoid of a specific laboratory investigation. Elevated values of aforesaid markers are indicative of insufficient global perfusion or a non specific tissue injury.

Possible emergence of infectious disease aetiologies require assessment. Stool evaluation for isolation of *Salmonella* spp, *Shigella* spp, *Campylobacter*, *Escherichia coli* and *Clostridium difficile* is mandated. Parasites such as *Entamoeba histolytica, Angiostrongylus costaricensis* and viruses such as cytomegalovirus require discernment [6,7].

Abdominal X-rays usually demonstrate a non- specific gas pattern or the presence of an abdominal ileus. With disease progression, submucosal haemorrhage and oedema can induce a focal, mural thickening of the gut wall, designated as 'thumb printing'. Intestinal perforation and pneumatosis are representative of severe degree of colonic injury.

Computerized tomography [CT] is normal in preliminary or clinically mild instances of ischemic colitis, although it is beneficial in discerning adjunctive causes of abdominal pain or sepsis [6,7].

Segmental thickening of the colon wall or 'pericolic stranding' appears in the delayed phase. However, aforesaid features are non specific and can appear with conditions such as inflammatory bowel disease or gastrointestinal tract infection [6,7].

Pneumatosis or portal venous gas accumulation occurs in delayed stage of disease and are suggestive of infarction of the bowel.

Additionally, serial abdominal magnetic resonance imaging [MRI] and colonoscopy are applicable for adequate elucidation of ischemic colitis. Magnetic resonance imaging [MRI] can be adopted instead of invasive, diagnostic procedures for disease discernment and monitoring.

Adoption of Technetium 99m pertechnetate [Tc-99 m] for a nuclear scan is not beneficial [7,8].

Colonoscopy is a preferred diagnostic modality to be employed in the absence of peritoneal signs of inflammation and hypo-perfusion and is pertinent in evaluation of degree of ischemia. Colonoscopy is sensitive and specific for detecting ischemic colitis as it directly visualizes mucosal alterations. Endoscopic features indicative of ischemic colitis are constituted of petechial haemorrhage, oedematous and fragile mucosa, mucosal haemorrhage, segmental erythema, scattered mucosal erosions and longitudinal mucosal ulcerations. Features consistent with severe ischemic colitis are loss of intestinal haustrations, cyanosis and gangrene [7,8].

Competent colonoscopy requires an avoidance of intestinal perforation. Minimal air insufflation and gentle instrumental passage is necessitated. Evaluation of suspected ischemia by colonoscopy requires the passage of instrument within the ischemic zone while refraining entry beyond the area of injury.

Longitudinal and circumferential mucosal ulcers or erythema and erosions can appear on colonoscopy. Mucosal ulceration is associated with abdominal pain, elevated levels of baseline c-reactive protein [CRP] and extensive hospitalization, in contrast to treatment required for mucosal erythema or erosion [7,8].

Prognostic outcomes

Acute ischemic colitis is usually manageable with adequate medication although morbidity and mortality is enhanced for individuals necessitating surgical intervention. Majority [80.3%] of subjects are amenable to medical management and demonstrate a mortality of 6.2%. Surgical intervention is associated with an estimated 39.3% mortality [2,3].

Emergency colectomy is generally required in around 81.6% subjects and displays a morbidity of nearly 85.7% and mortality of roughly 44.9%. Preoperative hypotension ensures a significant probability of concurrent mortality. Nevertheless, extended disease prognosis is favourable. Reoccurrence of ischemic colitis is cogitated at nearly 2.9% at one year interval and almost 9.7% at 5 year interval. Comprehensive five year survival appears at an estimated 69% and morbidity ensues on account of unrelated factors [2,3].

Complications of ischemic colitis are cogitated as intestinal gangrene appearing within one to four days, intestinal superinfection with various bacteria, configuration of enterotoxin as with a pseudo-membrane, stricture formation and intestinal perforation which can be fatal. Severe variety of ischemic colitis is associated with tachycardia and peritoneal signs [2].

Therapeutic options

Following a diagnosis of ischemic colitis, aggressive resuscitation and administration of broad spectrum antibiotics is advised. Subjects who are haemodynamically stable and devoid of peritoneal infection benefit from an urgent colonoscopy.

Cogent therapy is contingent to indicative physical findings and appearance of colonic mucosa on endoscopy. Emergence of peritoneal signs or a non-viable gut on endoscopy mandates an immediate surgical intervention [8,9].

Medical management of ischemic colitis comprises of bowel immobilization, administration of intravenous fluids and broad spectrum antibiotics. Utilization of nasogastric tubes are advantageous in individuals demonstrating gastrointestinal distension or ileus.

Resuscitation based on splanchic innervation with circumvention of vasoconstrictive agents is required. Assessment of mental status, abdominal pain and urine output requires monitoring to evaluate features of adequate end organ perfusion [8,9].

Additional evaluation of therapeutic endpoints such as serum lactate levels and mixed venous oxygen saturation is suggested, contingent to severity of disease.

Therapeutic initiation of supportive modalities of care are necessitated. Ischemic bowel mandates surgical excision, particularly in concurrence with intestinal perforation, peritonitis or transmural bacterial infection.

Surgical intervention of ischemic colitis is pertinent to extent of bowel injury and status of incriminated individual. Non viable gastrointestinal tract necessitates resection. Intraoperative monitoring delineating hypothermia, coagulopathy and acidosis require adequate management. Successive surgery is indicated to evaluate zones of inadequate or debatable perfusion. End to end anastomosis is contingent to medical condition and nutritional status of implicated individual and associated comorbid conditions. Repetitive acute events of ischemic colitis following resolution is associated with occurrence of colonic strictures.

Colectomy is accompanied with an enhanced morbidity and mortality. Colonoscopy with evaluation of tissue specimen is recommended to investigate for malignant conversion or associated diseases. Contingent to severity of clinical symptoms and proportion of intestinal stenosis, colonic dilatation or surgical resection can be indicated [8,9].

Phenteramine
Oral Contraceptives
Pseudoephedrine
Phenobarbitol
Nasal decongestants
Dextroamphetamine
Type 1 Interferons (IFN-α and IFN-β)
Tumour necrosis factor alpha
Antipsychotics * Clozapine
Serotonergic medications *alosetron, *tegaserod
Vasopressors
Cocaine
Methamphetamine

Table 1: Drugs associated with ischemic colitis [2].

Figure 1: Ischemic colitis depicting mucosal ulceration, vascular thrombosis, red cell extravasation in the lamina propria and submucosal haemosiderin [9].

Figure 2: Ischemic colitis demonstrating mucosal ulceration, crypt abscess, lamina propria bleed, vascular thrombosis with excessive granulation [10].

Figure 3: Ischemic colitis with mucosal ulceration, inflammatory exudation, glandular atrophy, submucosal haemosiderin, and abundant granulation tissue [11].

Figure 4: Ischemic colitis with prominent mucosal ulceration, excessive granulation, blood vessel thrombosis and disseminated haemosiderin [12].

Figure 5: Ischemic colitis with mucosal erosion, vascular thrombosis, oedema of the lamina propria and submucosal macrophages [13].

Figure 6: Ischemic colitis with mucosal erosion, oedematous and haemorrhagic lamina propria with excessive granulation tissue [14].

Figure 7: Ischemic colitis with mucosal atrophy, mucosal ulceration, submucosal haemosiderin, abundant granulation tissue and haemorrhage in the lamina propria [15].

Figure 8: Ischemic colitis with mucosal ulceration, crypt abscess, oedematous lamina propria and submucosal haemosiderin with granulation tissue [15].

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9. Image 1 Courtesy: Libre Pathology.

10. Image 2 Courtesy: Slideshare.com.

11. Image 3 Courtesy: Doctorlibinfo.com.

12. Image 4 Courtesy: Dovemed.com.

13. Image 5 Courtesy: Research gate.

14. Image 6 Courtesy: Pathpedia.com.

15. Image 7 and 8 Courtesy: Plaza.umin.ac.jp.