Case Report

A Successful Approach in Diagnosing Shiga - Toxin Producing Escherichia coli -Induced Colitis

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A Successful Approach in Diagnosing Shiga- Toxin Producing *Escherichia coli* -Induced Colitis.

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Abstract: Shiga-like toxin producing Escherichia coli (STEC) is a well-known cause of foodborne acute diarrheic diseases especially in children and the elderly. The potentially fatal complications associated with toxin production range from bloody diarrhoea and ischemic colitis to kidney failure, haemolytic-uremic syndrome (HUS) and colon perforation. We describe a case and literature review of STEC – induced colitis, highlighting the clinical features, and the necessary tools for the best diagnosis approach and management. Facing challenging differential diagnosis ranging from ischemic colitis, inflammatory bowel disease, to infectious process due to a pathogenic or opportunistic agent, we practiced a step-by-step exploration. Beginning with bacteriological investigation, imagistic screening, and colonoscopy, we could rule out some of initial suppositions and reach the final diagnosis, also considering the pathological results. Although antibiotics are not indicated in this pathology, our patient did receive antibiotics, given the risk of translocation and colon perforation, without associating any complications, as HUS or peritonitis. Detailed and rigorous investigations along with a multi-speciality team are required for a prompt medical support. Coping the symptoms and refraining from further complications are the mainstem of the treatment.

Keywords: STEC; bloody diarrhoea; ischemic colitis; *E coli*

1. Introduction

Escherichia coli strains are commonly found in the human and animal GI tract (1). There are several groups that are pathogenic to humans: enterotoxigenic E coli (ETEC), enteropathogenic *E coli* (EPEC), enterohemorrhagic E. coli (EHEC), enteroinvasive E coli (EIEC), enteroaggregative E coli (EAEC). Some strains of EHEC can produce Shiga-like toxins (STEC), responsible for haemolytic-uremic syndrome (HUS) and ischemic colitis (2). There are two primary serotypes of enterohaemorrhagic E. coli - O157:H7 and non-O157:H7, both generating toxins resembling those of Shigella (3), but the most severe cases are linked to serotype O157:H7 (4). STEC-induced infections are often self-limited or mild and they do not require antibiotic or surgical intervention. Pathogenic strains can also colonise asymptomatic humans, posing at risk their contacts – being they children or adults (5).

This paper aims to highlight the relevance of diagnostic tools in approaching digestive pathology, and also, the importance of the multi-disciplinary team that could successfully manage this disorder.

We reviewed eight cases of STEC-induces colitis in adults, reported in literature in the last 12 years, published on PubMed, in gastroenterology journals, or in medical case reports scientific publications. The keywords used were ischemic colitis, STEC, *E coli*.

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We report a case of colitis, in a patient with no other comorbidities, recovered after a 10-day course of antibiotics, without developing HUS, nor requiring surgical intervention.

2. Case presentation

A retired 64 years-old woman was admitted to our clinic for bloody diarrhoea, intensive abdominal pain, and loss of appetite with a 2-day earlier onset. She had no relevant medical history. The patient stated against smoking, alcohol consumption or substance abuse. She had no allergies. She denied having any autoimmune illness or inflammatory bowel disease in her family. She used to intermittently visit her only 2-year-old niece.

Her daughter in law and her niece had had 2 months and 2 weeks earlier respectively, digestive symptoms like flatulence, abdominal pain, and diarrhoea. They both had been detected with an enterohaemorrhagic E coli non-O157:H7 strains in stool cultures. They both recovered after antibiotic therapy without being hospitalised.

On physical examination the patient had a normal weight, was afebrile, with a pulse of 90 bpm and blood pressure of 115/74mmHg. Abdominal exam showed reduced bowel movements and stubbing pain, given a score of eight out of 10 in severity, without any guarding. She declared frequent bloody loose stools, up to 10-15 times a day.

Laboratory findings revealed leucocytosis, mild electrolytic abnormal values, post-prandial slight hyperglycaemia, inflammatory markers mildly increased, and no other remarkable abnormalities (Table 1).

Microbiological investigations ruled out *Clostridium difficile, Shigella, Salmonella*, parasitic involvement, and a PCR-based multiplex gastro-intestinal (GI) pathogens detected *Shiga* toxin-producing *Escherichia coli* (STEC) stx1/stx2 genes.

Abdominal CT revealed spastic transverse and descendent large intestine, with a thickened circumferential mucosa, suggestive for an inflammatory and infectious process, that progress the next days. (Figures 1 and 2)

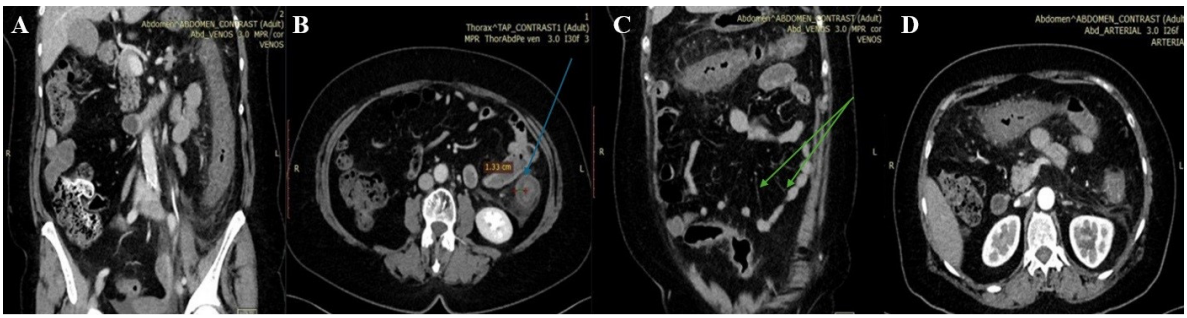

Figure 1. CT scan 1 images. Spastic large intestine, with thickened circumferential mucosa (blue arrow), up to 1.33cm and an incomplete "comb" sign (green arrow).

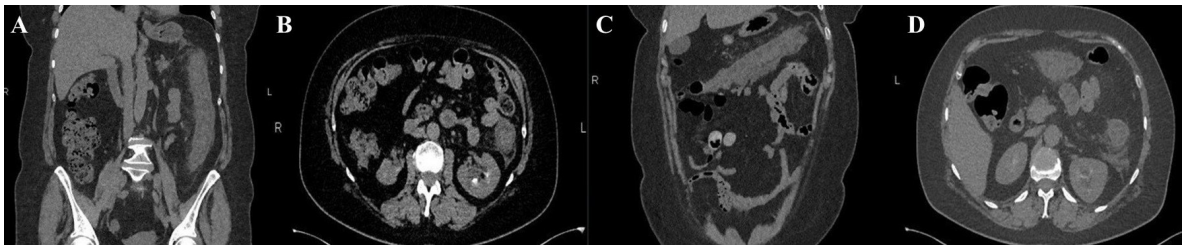

Figure 2. Colonoscopy findings. Sigmoid colon - quasi-normal aspect with erythematous lesions and haemorrhagic debris (A) Descending colon - sections of erythematosus mucosa, with multiple ulcerations (B) Descending colon at 60cm from anal canal – deep ulcerated lesions and friable, haemorrhagic mucosa (C).

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Table 1. Laboratory values during hospitalization.

	Day 1	Day 3	Day 6	Day 8	Day 10
WBC (10^3/mm^3)	21.1	18	12.5	9.5	8.3
Neutrophils (%)	77.9	81.4	76	71	60
Platelets (10^3/mm^3)	331	238	238	255	326
Haemoglobin (g/dl)	14.9	12	11.8	11.4	11.8
Fibrinogen (mg/dl)	483	641	469	363	
CRP (mg/dl)	1.4	98.9	69.82	30	
BUN (mg/dl)	25		37		
Creatinine (mg/dl)	0.5	0.5	0.6	0.68	0.5
Na (mmol/l)	133	132			140
K (mmol/l)	3.48	3.56		4.06	4.67
BT (mg/dl)	1.0			0.17	
BD (mg/dl)	0.2			0.06	
BI (mg/dl)	0.8				
AST (U/L)	18			41	19
ALT (U/L)	23	15		28	17
GGT (U/L)	27			59	
ALP (U/L)	74				
Amylase (U/L)	68		27	23	
Lipase (U/L)	13				
Albumin (g/dl)			2.67		3.34
Glucose (mg/dl)	146		73	65	
LDH (U/L)		192			
CK (U/L)		22			
D-DIMER (ng/ml)		1665			
PCT (ng/ml)		< 0.5			

BUN blood urea nitrogen; BT bilirubin total; BD bilirubin direct; BI bilirubin indirect; ALP alkaline phosphatase; PCT procalcitonin.

Despite supportive treatment consisting in rehydration and symptomatic drugs, her conditions worsened the next day, both clinical and biological (Table 1).

On the second day she supported a colonoscopy that revealed a less affected sigmoid colon, but deep ulcerations, dusky areas, necrotic lesions in ascending colon, friable mucosa at 40-60 cm from anal canal (Figure 3), atypical picture for an inflammatory bowel disease. Because of this friability of the damaged mucosa, the gastroenterology specialist could not further advance with the colonoscope, through transverse colon.

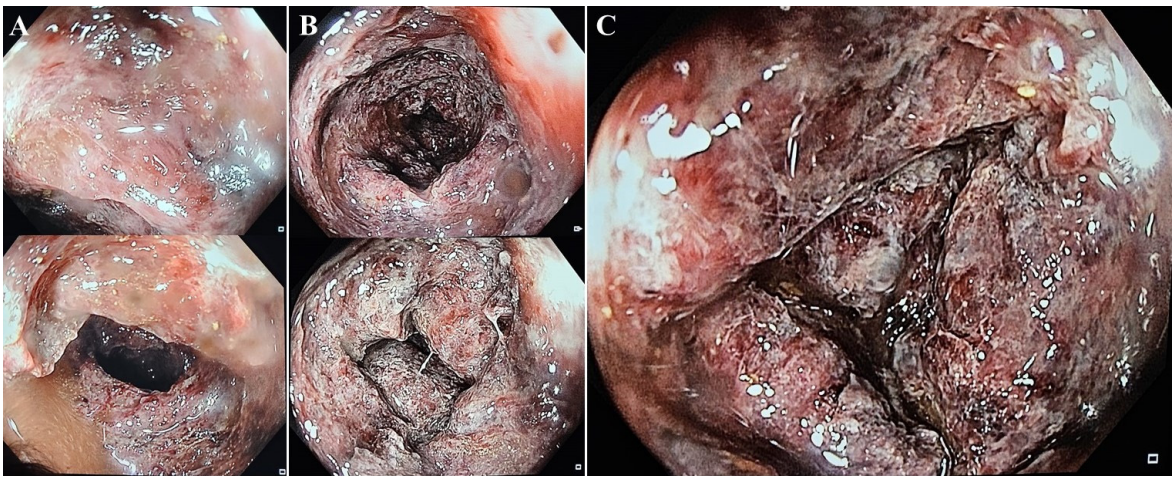

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Figure 3. CT scan 2 images. Extensive and continuous lesions, up to hepatic flexure and down to sigmoid with pericolic fat stranding.

The histological report described focal superficial necrotic lesions in the colonic mucosa, covered by fibrin and haemorrhagic debris, and deep haemorrhagic lesions with cryptic destructions, consistent with an ischemic colitis due to infectious agents (Figure 4).

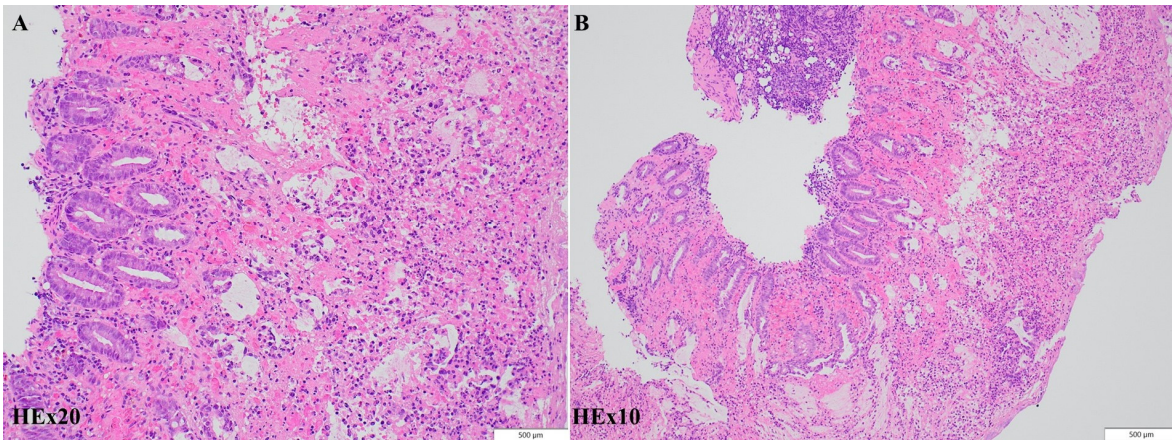

Figure 4. Histological findings. Moderate to severe injury of the colonic mucosa, ranging from acute inflammation associated with focal superficial haemorrhagic lesions to lamina propria necrosis, and cryptic damages, compatible with acute colitis.

The 3rd day she had the second abdominal CT scan which showed extensive colonic lesions up to hepatic flexure, and down to sigmoid and rectum (Figure 2), preserving the mesenteric artery with contrast medium. This picture was compatible with micro-ischemic lesions found in infectious ischemic colitis (6,7).

It was a real challenge to consider whether it was an infectious or an ischemic colitis at the beginning. Her clinical condition seemed more as an ischemic colitis, but biological parameters (LDH, CK, D- dimer) did not sustained this supposition (table 1). On the other side, CT scans revealed inflammatory changes without any large vessel occlusion. Colonoscope images revealed multiple necrotic lesions, inflammatory and haemorrhagic exudate, as those found in ischemic colitis. Tissue biopsies could finally state for micro- ischemic and necrotic intestinal changes, probably due to an infectious agent. The histopathological findings didn't correlate with an inflammatory bowel disease, nor with haemorrhagic colitis due to CMV reactivation. Other infectious agents can cause haemorrhagic or ischemic colitis, like *Campylobacter, Salmonella, Clostridium difficile, Shigella,* but neither of them was found by PCR-based test, nor in stool cultures. The final diagnosis was ischemic colitis due to Shiga-like producing toxin *Escherichia coli*.

Given the unfavourable progress in the first 3 days, with a high risk for bacterial translocation, she was started Tigecycline and Fluconazole for a 10-day course. At the same time, she was transferred from infectious diseases to surgery clinic, since it was possible that she may require a total colectomy.

She continued receiving all parenteral nourishment and bowel rest. Maintaining supportive therapy and antibiotics, she recovered the next days. She was discharged with an improved clinical condition, having normal intestinal transit, with no biological inflammation. She was advised to repeat CT scan and/or colonoscopy in three months.

3. Discussion

It is a real challenge trying to differentiate ischemic colitis *per se* and that induced by infectious agents. Laboratory tests, microbiological studies, and culture for parasitic or bacterial involvement are the first tools to be used (8). Polymerase chain reaction-based molecular methods are the new generation tests that can be helpful and time-sparing, yet, having their limits. In our case the only

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bacteriological results were PCR-based. The final diagnosis was not-culture proven but one can speculate on intra- familial transmission. The two members of the family were successfully treated for enterocolitis due to non- O157:H7 EHEC with amoxicillin-clavulanate and cefuroxime respectively, according to their very distinct antibiograms. Most probably they did not share the same *E coli* strain. It is very unlikely, but not impossible that our patient to get infected with one of those strains. Considering that there was no food incriminated in this case, our patient might have been an asymptomatic STEC carrier, until this episode.

Tomographic features that are very suggestive for a bacterial colitis are (1) continuous distribution, (2) empty colon, (3) absence of fat stranding, (4) absence of a "comb' sign, and (5) absence of enlarged lymph nodes (2). According to these criteria, our patient had extensive and continuous distribution, collapsed intestine and the absence of enlarged lymph nodes. However, she had contrarily pericolic fat stranding and an incomplete “comb” sign, that made the final diagnosis more difficult to consider.

Rectoscopy or colonoscopy and tissue biopsies complete the investigational plan for achieving the positive diagnosis. In our case, although the entire colon was affected, the endoscope could reveal no further than 40-60 cm from the anal canal, because of risk of iatrogenic colon perforation. Histological biopsies from colon or rectum may show similar patterns as in ischemic colitis - atrophic crypts, coagulative necrosis of the mucosa, hyalinized lamina propria, and fibrin thrombi (6).

The management of the STEC-induced colitis does not imply antibiotics, but fluid replenishment and supportive care. There are some studies conducted on animal models that highlight the benefits of alternative treatment such as monoclonal antibodies aiming Shiga toxins, toxin receptor analogs, or vaccines (9). Antibiotics may increase the risk of haemolytic-uremic syndrome by releasing more toxins while killing bacteria, especially in children (3). Despite that consideration, the risk of translocation of endogenic bacteria through an affected mucosa was too great to be ignored in presented case. We choose an antibiotic with good intestinal penetration, which could cover a large bacterial spectrum, including STEC.

There are few published case reports on ischemic colitis in adults (Table 2), due to Shiga-like producing toxin *E coli* (7, 10-16). The mostly found clinical features were abdominal pain, bloody diarrhoea, with or without fever. Laboratory findings revealed unspecific changes such as mild to intense leucocytosis or slight inflammation. Microbiological assessments provided STEC positive stool cultures in four out of the eight cases (7, 11, 14, 15) and CT scan was performed in six of the cases.

Seven out of eight cases had a colonoscopy performed (Table 3), with tissue biopsy, the last one having macro-/micro histological findings due to exploratory laparotomy (13). In a single patient there was exclusively ileum mucosa affected (11) and another case had extremely severe necrosis up to transvers colon, making impossible further examination, similar to our case (10). In the rest of cases, intestinal mucosa damage was arbitrary scattered all along the colon, sparing the rectum in three patients, affecting possibly more the right side.

Two patients with colon necrosis (14, 15) and one with faecal peritonitis (13) underwent surgical interventions with favourable outcome All of them received at least one day antibiotics: quinolones, cephalosporins, penicillins, metronidazole, known for their risk of triggering HUS, but only the two cases of extreme ages developed HUS (15, 16).

Haemolytic uremic syndrome was found especially in children with acute diarrheic disease due to STEC, according to some studies conducted in Romania between 2010 and 2016 (17, 18). They revealed a high STEC prevalence (6.4%) in symptomatic hospitalized children aged up to 30 months old. Almost one out of four developed HUS. In 2021 there were 6.534 cases of STEC colitis reported by 30 EU/EAA countries. Out of these, there were 365 HUS reported, the majority being in the youngest age group 0-4 years (64%) (19).

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Table 2. Literature review.

Reference	Cases (sex, age)	Clinical findings	Biological changes	Microbiological tests	Imagistic investigations	Histological findings	Management	HUS	Other complications
Kravitz, 2002 (13)	F, 48	Pain, fever, vomiting, non-bloody diarrhoea	Leucocytosis, low sodium and potassium level,	Negative stool culture; antibodies to E coli O157 LPS with positive dynamics	Ileus and free subdiaphragmatic air on radiography	Bowel wall rupture, acute haemorrhagic colitis with ischemic features	Imipenem-cilastatin; piperacillin-tazobactam, fluconazole. **Surgical intervention**	No	Colon perforation
Kendrick, 2007 (14)	M, 59	Pain, fever, bloody diarrhoea	Mild leucocytosis	E coli O157:H7 isolated in stool culture	Wall thickening through the entire colon at CT scan	Inflammatory pseudo-membranes, mucosal ischemia, and ulceration	Metronidazole **Surgical intervention**	No	Colon necrosis
Tominaga, 2014 (15)	M, 81	Pain, febrile, bloody diarrhoea,	Inflammatory syndrome, thrombocytopenia	E coli O157 isolated in stool culture; positive verotoxin	Thickening of the entire colon wall and ascites at CT scan	haemorrhagic necrosis into mucosa with subjacent oedema	Cefotiam, levofloxacin **Surgical intervention**	Yes	Colon necrosis, septic shock
Radhakrishnan, 2019 (16)	M, 17	Pain, fever, bloody diarrhoea	Mild leucocytosis,	Positive STEC antibodies	Wall thickening in the ascending colon at CT scan	Haemorrhagic lesions, inflammatory exudate, and atrophic crypts	Cefuroxime, metronidazole, Eculizumab	Yes	Thrombocytopenia, partial-complex seizures
Tanquilut, 2019 (10)	F, 32	Pain, afebrile, non-bloody diarrhoea	Intense leucocytosis, low sodium	GI panel stool positive for STEC Negative stool culture	ND	Superficial mucosal necrosis, haemorrhages into lamina propria	Ciprofloxacin, metronidazole, piperacillin-tazobactam,	No	No
Caldis, 2021 (11)	F, 59	Pain, Afebrile, non-bloody emesis, dark stool	Moderate leucocytosis	E coli O111 isolated in stool culture	Severe colitis, without evidence of large vessel occlusion on CT angiogram	Ischemic colitis in appearance	Ceftriaxone, metronidazole	No	No
Cocca, 2022 (12)	M, 44	Asthenia, Fever, melena	Mild inflammation (CRP)	GI panel stool positive for STEC O157	Thickened wall of terminal ileum at angio-CT	Inflamed and ulcerated mucosa	Azithromycin	No	No
Al-Smadi, 2023 (7)	M, 21	Pain, afebrile, bloody diarrhoea	Mild leucocytosis	Positive stool for STEC	Normal CT scan of large intestine	Erosion and necrosis of mucosa, crypt atrophy	Ceftriaxone, metronidazole	No	No

Table 3. Endoscopic changes.

No	Reference	Cases (sex, age)	Ileum	Ascending colon	Descending colon	Rectum
1.	Kravitz, 2002 (13)	F, 48	ND	ND	ND	ND
2.	Kendrick, 2007 (14)	M, 59	-	++	++	++
3.	Tominaga, 2014 (15)	M, 81	-	++	+	-
4.	Radhakrishnan, 2019 (16)	M, 17	-	+	+	+
5.	Tanquilut, 2019 (10)	F, 32	ND	ND	+++	+
6.	Caldis, 2021 (11)	F, 59	-	++	+	+

7.	Cocca, 2022 (12)	M, 44	+++	-	-	-
8.	Al-Smadi, 2023 (7)	M, 21	-	+	++	-

4. Conclusions

STEC-induced colitis should be considered in patients with bloody diarrhoea, abdominal pain, either having fever or not. Laboratory testing should consist of haematological evaluation, stool extensive culture on MacConkey agar medium and PCR based- multiplex if available. CT scan can rule out obstructive or/and oncologic lesions, ischemic changes on the great arteries and could indicate acute or chronic inflammatory patterns. Colonoscopy should be performed in all severe cases, whose cause is not yet confirmed with certainty. Even though the treatment involves mainly supportive measures, antibiotics can also be cautiously given when anticipating bacterial translocation through an affected intestinal wall. Surgical measures cannot be disregard, when patients' clinical and biological scenario, or CT scan and colonoscopy evidence are alarming for imminent complication such as colonic perforation.

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