Shiga Toxin-Producing E. Coli O104:H4 Outbreak 2011 in Germany: Radiological Features of Entero-hemorrhagic Colitis

Radiologische Merkmale der enterohämorrhagischen Kolitis beim EHEC-Ausbruch 2011 des enteroaggregativen E.-coli-Stammes O104:H4

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- hemolytic-uremic syndrome
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- CT
- Shiga toxin-producing E. coli
- O104:H4
- enterohemorrhagic colitis

Zusammenfassung


Ergebnisse: Eine Kolondistension wurde bei 16/23 Patienten (69,6 %) beobachtet. Das aszendierende (11/23 Patienten; 47,8 %) und transversale Kolon (12/23 Patienten; 52,2 %) waren signifikant öfter dilatiert (p = 0,006 bzw. p = 0,003) als das deszendierende Kolon (1/23; 4,3 %). Alle 12 CT-Patienten zeigten abnormal wandverdickte Kolonsegmente, 3 (25 %) davon hatten eine Pankolitis und 9 Patienten (75 %) hatten eine segmentale Beteiligung. Das deszendierende Kolon war überwiegend (11/12 Patienten; 91,7 %) und signifikant häufiger (p < 0,001) als die anderen Kolonsegmente betroffen.

Schlussfolgerungen: Bei der STEC-O104:H4-Kolitis findet sich vornehmlich ein segmentaler Befall des deszendierenden Kolons mit vorgeschaltet der Dilatation des transversalen und aszendierenden Kolons, wodurch sich dieser Typ der Kolitis möglicherweise von anderen Kolitiden unterscheidet.

Abstract
Purpose: In 2011 a nationwide outbreak of Shiga toxin-producing E. coli (STEC) O104:H4 infection occurred in Germany with severe hemorrhagic colitis and hemolytic-uremic syndrome (HUS). We defined abdominal radiologic findings in these patients and correlated them with clinical parameters.

Materials and Methods: 23 patients (7 men; age: 48 ± 19 years) with O104:H4 colitis and/or HUS received abdominal CT (n = 12) or radiographs (n = 11). Colonic distension, air-fluid levels, and free intraabdominal air were assessed. Colonic wall thickening, contrast enhancement, pericolic stranding, and ascites were evaluated on CT. Laboratory parameters and clinical presentation were reviewed. Chi-square test, Student’s t-test, McNemar’s test and Spearman correlation were performed.

Results: Colonic lumen distension was seen in 16/23 patients (69.6 %). The ascending colon (11/23 patients; 47.8 %) and transverse colon (12/23 patients; 52.2 %) were dilated significantly more often (p = 0.006 and p = 0.003, respectively) than the descending colon (1/23; 4.3 %). All 12 patients undergoing CT scanning had abnormally thickened colonic wall segments, 3 (25 %) had pancolitis and 9 (75 %) had a segmental involvement. The descending colonic wall was predominantly affected (11/12 patients; 91.7 %) and significantly more often (p < 0.001) than other colonic segments (p < 0.001).

Conclusion: The segmental type of STEC O104:H4 colitis mainly affects the descending colon with upstream distension of the transverse/ascending colon and differs from other types of colitis.
Introduction

Escherichia coli is a widespread commensal of the mammalian gut and a versatile pathogen [1]. Certain strains of enterohemorrhagic E. coli produce Shiga toxin which inhibits protein synthesis within susceptible eukaryotic cells leading to colitis. Infected patients characteristically have an afibrile illness that begins with abdominal cramps and watery diarrhea, which progresses to bloody diarrhea with high morbidity and mortality [1, 2]. Shiga toxin-producing enterohemorrhagic E. coli (STEC) colitis may be complicated by life-threatening hemolytic–uremic syndrome (HUS) characterized by the triad of acute renal failure, hemolytic anemia, and thrombocytopenia [3, 4]. During previous STEC outbreaks, O157:H7 serotype has been identified as the primary cause of colitis-associated HUS, which occurs primarily in children and is a rare event in adults [5, 6]. From May to June 2011, 3842 cases of infection with an unusual strain of Shiga toxin-producing E. coli, STEC O104:H4, were reported during a nationwide outbreak in Germany and sprouts were finally identified as the most likely outbreak vehicle [7, 8]. The outbreak was characterized by several unusual features: a high incidence in adults (89 %), a greatly increased incidence of post-colitis HUS, a predominance of female patients, and the rare serotype O104:H4. A total of 855 cases of HUS, including 36 (0.6 %) fatal cases, were reported during the outbreak in Germany in 2011. The outbreak was characterized by several unusual features: a high incidence in adults (89 %), a greatly increased incidence of post-colitis HUS, a predominance of female patients, and the rare serotype O104:H4. A total of 855 cases of HUS, including 36 (0.6 %) fatal cases, were reported. This marks one of the largest STEC outbreaks ever described worldwide and indicates a high virulence of the new serotype O104:H4 [7, 9].

Recognition of infection during the outbreak 2011 was initially hampered by the lack of a specific laboratory approach [10]. Later on, the diagnosis was based on one-enzyme (XbaI) gel electrophoresis for confirmation of the outbreak strain [7]. The genome of the German outbreak strain O104:H4 could be distinguished from other strains because it contains a distinct set of additional virulence and antibiotic-resistance factors [9, 10]. In addition to the laboratory and clinical diagnosis of STEC infection, the assessment of gastrointestinal complications including colitis, toxic megacolon and colonic perforation are based on imaging. Early diagnosis and treatment are important to avoid fatal complications and to prevent dissemination of the infection to distant sites [11].

Computed tomography (CT) is widely used to assess patients with nonspecific abdominal pain or those suspected of having complications of colitis [12 – 14]. Therefore, radiologists must be familiar with E. coli colitis to assist in early diagnosis [15, 16]. Clinical and epidemiological findings of the E. coli outbreak in Germany of the O104:H4 strain have been well described [7, 9, 17 – 19], but up to now there are no comprehensive reports of radiological findings of STEC O104:H4 colitis. The purpose of this study was to determine abdominal CT and radiography features of STEC O104:H4 colitis and to compare laboratory and clinical parameters in a cohort of consecutive patients affected during the outbreak in Germany in 2011.

Materials and Methods

Patient population

The local institutional review board approved the retrospective study and waived the requirement for written informed consent. Patients infected by STEC O104:H4 and presenting with colitis or HUS were defined as outbreak cases [7]. 270 patients with STEC O104:H4 infection were treated at our university hospital during the outbreak between May and June 2011. 23 of these patients (8.5 %; 7 men, 16 women; mean age of 48 ± 19 years, range 18 – 83 years) underwent abdominal imaging and were included in this study. 12 patients received abdominal CT scanning and 11 patients received plain abdominal radiographs. The rationale for referral to radiological imaging was clinical evidence of severe gastrointestinal complications in all 23 cases.

Clinical presentation and laboratory tests

Medical records of all 23 patients were reviewed for laboratory parameters, such as hemoglobin, hematocrit, erythrocytes, leukocytes (WBC), platelets, urea, creatinine, C-reactive protein, and lactate dehydrogenase. All tests were performed within 24 hours of radiological imaging. The presence of bloody diarrhea (three or more blood-containing loose stools in a 24-h period) and the clinical diagnosis “acute abdomen” were recorded as well as the duration of hospitalization.

Abdominal CT and radiography

Abdominal CT scans were performed with a 256-slice MDCT (Brilliance iCT, Philips Healthcare, Best, The Netherlands) with the following parameters: gantry rotation time 330 ms, collimation 128 × 0.625 mm, 0.758 pitch, tube voltage 120 kV, automated effective tube current ranging from 40 – 200 eff. mAs. Raw data sets were reconstructed in a soft tissue kernel (B30f) with a slice thickness of 5 mm. The scan range extended from the top of the diaphragm to the bottom of the pelvis. CT images were obtained within a single breath-hold in end-expiration and in a supine position. No patient received oral contrast. 10 of the 12 patients (83.3 %) received 120 ml of nonionic contrast material with an iodine concentration of 300 mg/ml (Imeron 300®, Bracco-Altana Imaging, Konstanz, Germany) administered in an antecubital vein at a rate of 2.5 ml/s via an 18-gauge peripheral intravenous catheter. Abdominal plain radiographs were performed in a supine and lateral position. Coverage included the top of the liver to the pubic symphysis.

Image evaluation

CT scans were assessed by two readers in consensus (with 5 and 7 years of gastrointestinal radiology experience) for the presence of colonic wall thickening as a radiological criterion for the presence of colitis. Based on the criteria from previous reports, an abnormal colonic wall thickness greater than or equal to 4 mm was defined as abnormal [20]. The colon was divided into four segments (ascending, transverse, descending and sigmoid), and any affected segment was noted. Involvement pattern was determined either as segmental or as pancolic. The presence and quantity of ascites (small, moderate, and large) was approximated. CT density measurements of ascites were performed to assess the presence of blood constituent (HU > 40). The presence of pericolic stranding, colonic wall contrast enhancement, and stenosis was assessed. The presence, location and extent of colonic distension, air fluid levels, and free intra-abdominal air were assessed by CT scans and radiographs. A colon diameter greater than 6 cm was considered colonic distension.

Statistical analysis

Discrete variables are given as numbers and percentages, and continuous variables as means ± standard deviation or means (95 % confidence intervals). The distribution of data was tested.
Data not normally distributed were log transformed to reach normal distribution. Univariate analyses were performed using the Chi-square test for categorical variables and Student’s t-test for continuous variables.

The McNemar test [21] was applied to determine whether wall thickening or pathologic colonic distension occurred more often in distinct colonic segments in comparison to other segments. Spearman correlation coefficient $r$ was used to investigate the correlation with laboratory parameters. A nominal $p$-value $< 0.05$, two-tailed, was considered statistically significant. All statistical analyses were carried out using SAS 9.2 software.

Results

Study population

Abdominal imaging was performed within 7.2 ± 9.9 days (range: 1 – 46 days) after hospitalization in all patients. The indications for referral to abdominal imaging were acute abdomen in 10 of the 23 patients (43.5 %), and the search for an infectious focus and/or free intra-abdominal air in the presence of critically elevated WBC or CRP in the remaining 13 patients (56.5 %). WBC was elevated in 20/23 patients (87.0 %) and CRP was elevated in 21/23 patients (91.3 %). Detailed results of laboratory parameters are listed in Table 1. 22 patients (95.7 %) presented with bloody diarrhea at the time of imaging. During the further course of disease, 4/23 patients (17.4 %) were diagnosed with toxic megacolon. 5 of the 23 patients (21.7 %) underwent abdominal surgery due to their clinical condition. In one of these patients hemicolectomy was performed due to extensive segmental inflammation. In another patient subtotal colectomy was performed due to uncontrollable colonic bleeding. The remaining three patients underwent surgical abdominal exploration and lavage. One of the surgically explored patients and one diagnosed with toxic megacolon died during the course of disease (2/23; 8.7 %). 20 of the 23 patients (87.0 %) were diagnosed with HUS and 19/23 (82.6 %) had to undergo plasmaexpansion and/or dialysis. The mean hospitalization time was 25.7 ± 12.6 days (range: 1 – 59 days).

Radiological findings

All of the 12 patients who underwent CT had abnormally thickened colonic wall segments (Table 2). 9 of these 12 (75 %) had segmental wall thickening, and 3 patients (25 %) had pancolic involvement. The descending colon was predominantly affected (11/12 patients; 91.7 %) and thickened significantly more often than the ascending colon ($p < 0.001$), transverse colon ($p < 0.001$), or sigmoid colon ($p < 0.001$). The maximal wall thickness ranged from 6 – 19 mm (mean: 10.4 ± 4.5 mm). Increased contrast enhancement of colonic wall segments was observed in 4/12 patients (33.3 %). Extensive abnormal wall thickening with subtotal occlusion of the lumen and stenosis was observed in 3/12 patients (25 %). In all three cases the descending colon was involved with consecutive upstream dilatation of the transverse and ascending colon (Fig. 1). The upstream colonic dilatation was significantly higher ($p = 0.012$) in patients with stenosis than in the remaining study population (82.0 mm [95 % CI, 65.7 – 98.3] vs. 55.9 mm [95 % CI, 46.5 – 65.3]). All 12 patients who received CT scanning had peri- colic stranding around the affected segments.

Pathologic segmental colonic lumen distension was found in 16 of 23 patients (69.6 %) who underwent abdominal CT or plain radiographs. The ascending colon (11/23 patients; 47.8 %) and transverse colon (12/23 patients; 52.2 %) were dilated significantly more often ($p = 0.006$ and $p = 0.003$, respectively) than the descending colon (1/23; 4.3 %) (Fig. 2, 3). The mean diameter of the maximal distended colonic lumen was of 64 ± 18 mm (range 33 – 108 mm). The extent of colonic lumen distension was significantly ($p = 0.008$) higher in patients with pathologic air-fluid levels (83.8 [95 % CI, 66.5 – 101.1] cm), which were present in 5 of 23 patients (21.7 %), than in patients without pathologic air-fluid levels (56.3 [95 % CI, 47.2 – 65.4] cm). Colonic lumen distension was significantly higher ($p = 0.0231$) in patients with ascites (67.1 [95 % CI, 57.6 – 76.6] cm) than in patients without ascites (39.0 [95 % CI, 17.7 – 60.3] cm). Ascites was present in 10 of the 12 patients (83.3 %) undergoing CT. The quantity of ascites was considered small in 2/10 patients (20 %), moderate in 5/10 cases (50 %), and large in 3/10 patients (30 %). None of these patients presented with bloody ascites. Free abdominal air was detected on plain abdominal radiography in one patient (4.3 %) who subsequently underwent abdominal surgery and hemicolectomy.

Comparison of radiological findings, laboratory parameters and clinical parameters

In the initial comparison of radiological findings and clinical parameters, pathological lumen distension of the transverse colon was associated with reduced hemoglobin (difference: 1.9 g/dl [0.07 – 3.9 g/dl], $p = 0.059$), hematocrit (difference: 6.4 % [0.5 – 12.4 %], $p = 0.047$), and erythrocytes (difference: 0.88 × 10¹²/l [0.12 – 1.64 × 10¹²/l], $p = 0.025$). Moreover, pathological lumen distension was higher (difference 31.5 mm [0.7 – 62.3 mm], $p = 0.046$) in the two patients who died during the course of disease as compar-

Table 1  Ergebnisse der relevanten Laborparameter.

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>normal range</th>
<th>mean ± SD</th>
<th>range</th>
<th>number of patients with abnormal parameters (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemoglobin (g/dl)</td>
<td>12.3 – 17.5</td>
<td>9.7 ± 2.4</td>
<td>6.1 – 15.3</td>
<td>21/23 (91.3)</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>35 – 48</td>
<td>28.6 ± 7.5</td>
<td>18.6 – 45.0</td>
<td>21/23 (91.3)</td>
</tr>
<tr>
<td>erythrocytes (× 10¹²/L)</td>
<td>4.1 – 5.9</td>
<td>3.3 ± 1.0</td>
<td>2.1 – 5.9</td>
<td>20/23 (87.0)</td>
</tr>
<tr>
<td>leucocytes (× 10⁹/L)</td>
<td>3.8 – 11.0</td>
<td>19.9 ± 7.9</td>
<td>8.8 – 45.6</td>
<td>20/23 (87.0)</td>
</tr>
<tr>
<td>platelet count (× 10¹¹/L)</td>
<td>150 – 400</td>
<td>139.4 ± 112.8</td>
<td>27 – 390</td>
<td>15/23 (65.2)</td>
</tr>
<tr>
<td>urea (mg/dl)</td>
<td>8.0 – 26.0</td>
<td>42.1 ± 22.7</td>
<td>7.0 – 86.0</td>
<td>19/23 (82.6)</td>
</tr>
<tr>
<td>creatinine (mg/dl)</td>
<td>0.5 – 1.3</td>
<td>3.1 ± 2.1</td>
<td>0.5 – 7.4</td>
<td>19/23 (82.6)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>&lt; 5</td>
<td>93.6 ± 68.9</td>
<td>5.0 – 276</td>
<td>21/23 (91.3)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>135 – 225</td>
<td>810.1 ± 574.5</td>
<td>186 – 2019</td>
<td>22/23 (95.7)</td>
</tr>
</tbody>
</table>

1 LDH = Lactate dehydrogenase. Percentages are presented as numbers in parentheses.

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ed to the remainder of the study population. However, the extent of pathologic lumen distension associated neither with the indication for abdominal surgery (p = 0.260) nor with the duration of hospitalization (p = 0.512). Also, neither the indication for surgery nor the duration of hospitalization was associated with any other radiological findings.

**Discussion**

Review of abdominal radiographic findings of 23 patients with STEC O104:H4 colitis revealed a high incidence of abnormal wall thickening of the descending colon with pericolic stranding and upstream abnormal transverse and/or ascending colonic lumen distension. Two patients with a fatal course presented with massive distension of the transverse colon. However, no significant association between radiological findings and clinical parameters was found. One of the 23 patients underwent immediate surgery due to the presence of free abdominal air. The remaining 22 patients did not require immediate surgical intervention. Due to the high percentage of women in the STEC O104:H4 population during the German outbreak 2011 [7, 18], 70% of the patients in this study were female.

There is considerable overlap in the clinical appearance of various infectious types of colitis. They are usually confirmed clinically on the basis of stool and blood analyses and/or colonoscopy supported by biopsy results. All infectious types of colitis share the radiological features of wall thickening, pericolic stranding, and various degrees of ascites [12–15]. In most infectious forms of colitis the distribution is contiguous or pancolic [12, 13, 22]. This is in contrast to the findings of this study, where the majority of patients presented with segmental involvement. Previous imaging studies of E. coli colitis reported contiguous involvement with the transverse colon being most often affected [23, 24]. In contrast, this study revealed a predominance of descending colon wall thickening with abnormally distended but normal wall thickness of the transverse colon, likely due to the downstream constriction of the involved wall of the descending colon. Pseudomembranous colitis also demonstrates marked wall thickening, but can be clinically differentiated due to its association with broad-spectrum antibiotic treatment and the detection of clostridium difficile toxin in the stool. Neutropenic colitis is characterized by right-sided colonic and ileal involvement, which was never observed in the patients of this study with STEC O104:H4 infection [12]. Diverticulitis can be discriminated, since the process is focal and asymmetric with fasicial thickening and inflamed diverticula [25]. Hence, the presence of abnormal transverse and/or ascending colonic lumen distension with a descending colon wall thickening seems to be a characteristic finding in patients with STEC O104:H4.

The presence of ascites was observed in > 80% of the CT scans. This is an unspecific finding in all types of infectious colitis, but is rarely associated with ulcerative colitis and Crohn’s disease.
Increased contrast enhancement of the colonic wall was observed in a minority of patients and no specific pattern was identified. The degree of bowel wall thickening is said to aid in the differential diagnosis of colonic disease [14, 26]. However, the maximal bowel wall thickening ranged from 6 to 19 mm in this study population, which seems to preclude establishing a specific diagnosis based on the degree of colonic wall thickening alone. Patients with hemorrhagic E. coli colitis are at increased risk for HUS and other severe complications. Therefore, it is crucial to diagnose the disease promptly. The list of differential diagnoses for E. coli colitis includes appendicitis, ischemic colitis, inflammatory bowel disease, as well as infectious colitis due to Shigella, salmonella, Campylobacter, Clostridium difficile or cytomegalovirus [12, 13, 23]. Diagnostic imaging is generally not required for the differential diagnosis of E. coli colitis. The diagnosis is classically established by clinical and laboratory findings. However, the nature of abdominal pain is nonspecific, and abdominal imaging is ordered for its evaluation. Moreover, the spectrum of illness associated with E. coli colitis is broad and may range from asymptomatic infection to hemorrhagic colitis and can rapidly progress to HUS, a life-threatening condition [3, 23]. Hence, not all patients with STEC O104:H4 colitis present with classic symptoms such as cramps and hemorrhagic diarrhea, but rather with generalized constitutional symptoms, constipation or even an acute abdomen [2]. In these patients specific radiological findings could lead to correct diagnosis and appropriate patient management. Clinical history and laboratory testing are critical to exclude other colitides that may mimic STEC O104:H4 colitis. However, the purpose of this retrospective study was not to assess the value of abdominal CT or radiography for aiding the diagnosis of an infection with SO104:H4, but rather to define abdominal radiological findings in these patients. Increased radiologist awareness of STEC O104:H4 colitis will expand the differential diagnosis in patients with suspected colitis and prevent inappropriate medical or surgical treatment. The patients with STEC O104:H4 colitis during the outbreak in 2011 were most often treated medically by supportive measures directed toward maintaining hydration and electrolyte balance. Hence, abdominal imaging played a prominent role in excluding the need for immediate surgical intervention in severe cases. In only one of the 23 studied patients abdominal imaging revealed free abdominal air and immediate surgical treatment including hemicolecction was initiated. In all other cases surgical interventions were performed days later, based on worsening of clinical symptoms and progressive system deterioration. Due to its retrospective nature, there are inherent limitations to this study. Only 8.5% of all E. coli O104:H4-positive patients treated in our institution during the outbreak 2011 underwent abdominal imaging. Only severely affected cases were referred to abdominal CT or radiography which leads to a potential selection bias. Of note, only one patient underwent immediate surgery after imaging. Moreover, this was an observational study, and nominal p-values without adjustment for multiplicity are reported. The study was not powered for a multitude of statistical tests. Although we identified characteristic diagnostic findings for E. coli O104:H4 colitis, the only way to determine the exact clinical impact of abdominal imaging would be a prospective study with colonoscopy as the gold standard for the exact assessment of incidental findings.
flamatory changes, and newer imaging modalities including CT colonography and diffusion-weighted magnetic resonance imaging with the measurement of multiple clinical and radiological parameters [27 – 30]. However, practical considerations preclude such a study.

In summary, the main finding observed in all CT scans of hospitalized patients with E. coli O104:H4 colitis was abnormal wall thickening of the descending colon with pericolic stranding and upstream abnormal transverse and/or ascending colonic lumen distension. While thickening of the descending colonic wall may be seen as a nonspecific sign, the combination with massive upstream dilatation of the transverse and/or ascending colonic lumen can be used to narrow down the differential diagnosis. The final diagnosis concerning the type of colitis is based on clinical and laboratory data, but recognizing specific abdominal imaging features helps to narrow down the differential diagnosis. In conclusion, in the presence of abnormal radiological findings with the proper clinical history, abdominal imaging can aid the diagnosis of E. coli O104:H4 colitis and may prevent unnecessary medical or surgical treatment in possible future outbreaks.

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