Pseudomembranous colitis complicating the natural course of Crohn’s disease in a pediatric patient

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Abstract: Crohn’s disease usually occurs in adults, at the average age of in between 33 and 39 years old, according to most studies; children are only exceptionally affected, the occurrence within this age group being between 0.6 - 6.8/100,000 children per year. The purpose of this article is to present the rapid evolution of a pseudomembranous colitis, probably with C.difficile – in a body with an early onset of Crohn’s disease (a child of 10 years old), clinically manifested through symptoms that mimicked a perforated acute appendicitis with an immune response previously unaffected by immunosuppressive/ immunomodulatory medication. This case is an argument to support the important role of disorders of the immune system response which is genetically determined in the etiopathogenesis of the diseases associated with the C.difficile infection in children with the severe, ileocolic form of Crohn’s disease.

Key Words: pseudomembranous colitis, Crohn’s disease, children, lethal outcome.
A 10-year old female patient was admitted for abdominal pain, vomiting, diarrhea, fever; the onset had occurred 2 days previous. The clinical and imaging examination led to an acute appendicitis diagnosis; as a consequence, a surgery was performed, during which the doctors found an inflamed appendix located retroceccally, appendicular plastron and purulent peritonitis.

After the appendectomy, the evolution was slowly positive under an antibiotics treatment (Metronidazole, Gentamicin, Cefort). The child was discharged after 2 weeks. 4 days later, the child is admitted with a severe general condition, fever (40°C), pallor, severe diarrhea, vomiting, diffuse abdominal tenderness, accentuated in the right iliac fossa; biologically the doctors found a strong positive inflammatory syndrome, metabolic acidosis, prerenal failure through dehydration; as a result, it was decided to transfer the patient to a higher medical unit; once the stool samples for tests were collected, they set up an emergency course of treatment with acid-base and hydroelectrolytic rebalance, broad-spectrum antibiotics (Ceftriaxone) therapy, antipyretic and gastric protective treatments.

The evolution was unfavorable and her general condition worsened; within a few hours since arriving, the patient became comatose, with hemodynamic instability and cardiac arrest; CPR was applied and followed by the resumption of cardiac activity. The surgical consult and repeated imaging exams (abdominal ultrasounds) raised the suspicion of an acute abdomen which was surgical; it was decided to do, in extremis, an exploratory laparotomy; during surgery the doctors found ascites with serosanguineous fluid (2L), numerous adhesions and loops forming adherential blocks on the right iliac fossa, large intestine with edematous walls of large caliber with megacolon aspect.

Adhesiolysis, omentectomy, lavage, drainage of the peritoneal cavity were performed. Microbiological exams of the stool samples and of the peritoneal fluid taken during surgery were negative.

After the surgery, the evolution was severe, with multiple organ failure - neurological, respiratory, renal, hematologic disorders; 3 hours after the surgery another cardiac arrest occurred, and the patient was unresponsive to resuscitation.

A forensic autopsy was requested; it identified during the macroscopic examination the following: thickened gray-pink parietal peritoneum with multiple blood suffusions occasionally confluent; minimum hemoperitoneum; small intestine with gray-white serosa with multiple blood suffusions located diffusely; a very distended large intestine, with a toxic megacolon aspect, with thickened serosa, occasionally covered with blood clots and false membranes, leading to multiple adhesions and yellowish-brown liquid contents in large quantities.

When the large intestine was opened, it was noticed that the mucosa of the entire colon is lined with a gray-white-yellowish thick membrane, occasionally coarse in appearance, adhering to the mucosa at the level of the transverse and descending colon and rectum, detachable at the level of the cecum and of the ascending colon; the underlying mucosa was thickened, shiny, pink-white, with numerous yellowish dots arranged diffusely. (Fig.1).

The histopathological exam performed on small and large intestine fragments collected during the autopsy (jejunum and ileum, rectum, cecum, ascending colon, transverse colon fragments) showed morpho-pathological aspects typical of Crohn’s disease – granulomatous, transmural, segmental, chronic inflammation with superficial and deep ulcerations in different evolution stages (recent and healing), acute seriositis with false membranes and enhanced hematoedematous infiltration, and acute pseudomembranous colitis - acute inflammation of the mucosa of the ascending and transverse colon with pseudomembranes composed of necrotic cellular debris, fibrin, granulocytes and rare microbial colonies (Figs 2, 3).

It also showed: an early bronchopneumonia with diffuse alveolar damage, moderate lymphocytic depletion at the spleen level, mild hepatocyte necrosis, acute renal epithelial necrosis, early acute superficial non reactive tonsillitis. The (postmortem) histopathological reassessment of the original surgical piece showed a chronic appendicitis with a periappendicular chronic inflammatory process, as well as features that are typical of Crohn’s disease in the colic wall adjacent to the...
appendix (cecum) at different evolutionary stages, with chronic and acute transmural ulcerations up to the level of the serosa.

**DISCUSSIONS**

Crohn’s disease is a chronic, idiopathic, inflammatory disease of the intestine, the etiopathogenesis of which is not fully elucidated. Most of the clinical and experimental data support the theory according to which Crohn’s disease occurs due to an imbalance of the local immune response in the intestinal mucosa, induced by the intestinal commensal flora in genetically susceptible individuals. Most of the genes associated with Crohn’s disease are involved both in the local immune response and in the barrier function of the intestinal mucosa [13].

There are several forms of Crohn’s disease, classified according to three parameters, namely age of onset (under 16 years old, between 17-40 years old, after 40 years old), localisation (ileal, colonic, ileocolonic, isolated from the upper gastrointestinal tract) and behavior (without strictures and penetration into various structures, with strictures, with penetration) [14].

The type with penetration into the peritoneum is rare; the prevalence is about 1-2% [15], and it usually occurs in people who had the disease as active over a long period of time [11]. It is caused by increased intraluminal pressure, which leads to the appearance of microperforations in the enteric wall; these can be complicated by local inflammatory processes that increase the size of the solution of continuity and in time can lead to a localized or generalized peritonitis. Intestinal perforations in Crohn’s disease in children have been extremely rarely described in the academic literature, especially as the first manifestation of the disease.

For instance Kambouri et al. have described the case of a 11-year old girl who was admitted with symptoms typical of acute appendicitis. Following the appendectomy, the patient's progress was initially slowly positive, but subsequently infectious complications (peritonitis with E. coli) emerged. A CT examination was performed and it identified a pericecal collection, two enterocutaneous fistulas and two ileal strictures, suggestive of a B. Crohn diagnosis. There followed a hemicolectomy, and the diagnosis was histopathologically confirmed over the harvested pieces [16].
In our case as well the reinterpretation of the initial histological evidence, together with the histological examination of the pieces harvested during the autopsy and with the intraoperative macroscopic aspects have suggested the existence of a colonic solution of continuity that led to a peritonitis; the clinical symptoms which are very similar to those of an acute appendicitis led to a diagnostic error; however, the error was not considered to be involved in the thanatogenesis as the pseudomembranous colitis developed due to the antibiotics treatment which was correctly prescribed and performed, but included a substance usually active on C. difficile (Metronidazole).

The pseudomembranous colitis is usually, but not always, caused by Clostridium difficile, a bacteria which normally colonizes the human colon. With antibiotics treatments, other bacteria from the normal local microflora are destroyed, which leads to the excessive multiplication of C. difficile. This bacteria releases two highly potent toxins, A (enterotoxic) and B (cytotoxic).

The toxin A activity is potentiated by preexisting damage of the epithelium of the intestinal mucosa. It binds to receptors located in the intestinal mucosa and causes microruptures of the cytoskeleton, with cell damages that ultimately allow the toxin B to penetrate the lesional mucosa. Inside the cells, the toxins A and B inactivate metabolic pathways mediated by proteins from the Rho family, which are involved in cytoskeleton structure and signal transduction via GTP. Cellular damage activates cell apoptosis and cell retraction (visible as superficial ulcerations on the intestinal mucosal surface) [17].

Both toxins also cause the destruction of intercellular tight junctions [18]. In vivo toxin A causes increased intestinal secretion, mucosal lesions and inflammation [19, 20]. Toxin B is about 10 times more potent in generating colonic mucosal lesions compared to toxin A [21]. However, it can not generate by itself the appearance of clinical symptoms, except when there are pre-existing lesions of the mucosa (such as for instance those of the Crohn’s disease) [22]. The C. difficile diagnosis is usually achieved by identifying the specific toxins (A and/ or B) in feces, as the sensitivity and specificity are usually quite high [15, 16].

In patients with inflammatory intestinal diseases, the ELISA tests have a much lower sensitivity, which can reach up to 54% in identifying the toxins A and B [17, 18]. Repeated testing may increase the sensitivity of detection, but this could not be achieved in this case due to the rapid evolution of the case. The clinical and histopathological aspects, as well as the lack of identification of other potentially involved pathogens, lead to the conclusion that the most likely etiologic agent of the pseudomembranous colitis in our case is C. difficile.

The clinical spectrum of Clostridium difficile infections is very wide, from average forms of diarrhea to severe forms of colitis with toxic megacolon [23]. The toxic megacolon is a potentially fatal complication of both infectious colitis and inflammatory diseases of the colon, characterized by segmental or total non-obstructive colon dilatation associated with general toxicity [24].

The clinical diagnosis of toxic megacolon is done on the following criteria: (1) radiological evidence of colon distension; (2) at least three of the following: fever over 380C, tachycardia (more than 120 bpm), neutrophil leukocytosis (> 10,500 / microL) or anemia, and (3) at least one of the following: dehydration, sensory alterations, dyselectrolytemia, hypotension [25]. The mortality in case of toxic megacolon, caused by complications such as colon perforation, shock or sepsis, varies and depends on the initial cause of the complication.

Thus, in case of toxic megacolon caused by pseudomembranous colitis, a review examining the cases published between 1968 and 1992 identified an overall mortality of 31-35%, the value being higher for those treated medically (42%) than for those treated surgically (18%) [26]. The chronic dilatation of the colon has a poorer prognosis if it is caused by inflammatory diseases of the colon [27]. In adult patients the association between inflammatory intestinal diseases (Crohn’s disease, ulcerative hemorrhagic rectocolitis) and C. difficile infection causes a high degree of morbidity and mortality [28].

The differential diagnosis between the two diseases is often difficult, as the symptoms are similar and C. difficile may precipitate a flare up of the inflammatory pathology [29]. In the case of children very little is known about the association between the two pathologies, as it is rarely described in the academic literature [29]. Nonetheless, it seems that the acute aspect of Crohn’s disease can not controlled in the absence of an appropriate treatment for the C. difficile infection, and the specific treatment for Crohn’s disease (corticotherapy) should be continued with much lower doses in order to decrease the necessity of performing surgery [29].

Both Crohn’s disease and pseudomembranous colitis are pathologies which are relatively rarely encountered in forensic autopsies. In this case the main purposes of the forensic autopsy were to fully and correctly identify the causes of death and to establish the possible existence of a medical error involved in the thanatogenesis. The cause of death in this case was concluded to be Crohn’s disease in its extended ileocecal form penetrating the peritoneum, and complicated amid an antibiotic medication treatment with a pseudomembranous colitis which led to toxic megacolon with consecutive multiple organ failure. Regarding the identification of a possible medical error involved in the thanatogenesis one can make the following comments.

The intra vitam diagnostic difficulties were due to the patient’s symptomatology on first hospital
admission, which was suggestive of the diagnosis of acute surgical abdomen through perforated acute appendicitis; this justified the surgery, during which the doctors found an inflamed appendix located retroceccally, appendicular plastron and purulent peritonitis.

From a surgical point of view, the postoperative evolution was slowly positive, and intestinal transit was resumed without further surgical complications. Therefore there are no causal links between the initial surgery (appendectomy) and the medical cause of death. In the case of the second hospitalization, the toxic megacolon was correctly diagnosed, but the extreme severity of the pathology caused the treatment to fail.

The case illustrates the difficulties to interpret the forensic causality in non-violent pathologies which result in the death of the patient and where diagnostic errors occur. The diagnostic error by itself can be considered as a cause of death from the forensic point of view only if the lack thereof would have resulted in a different prognosis for the patient. Moreover, in this case three colonic pathologies were diagnosed, that is extensive Crohn’s disease, pseudomembranous colitis and toxic megacolon, all with many common histopathological aspects, which made the clinical and even the forensic analysis of the case very difficult.

In conclusion, we have presented the case of a 11-year old girl whose death was caused by a complication (toxic megacolon) of an association of diseases (Crohn’s disease and pseudomembranous colitis) which are very rarely described in children and which raised distinctive problems of forensic interpretation.

References

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