

IS ACUTE APPENDICITIS ASSOCIATED WITH INACTIVE ULCERATIVE COLITIS A PARTICULAR CASE OF DISSOCIATION OF THE MECHANISMS OF IMMUNE DEFENCE WITHIN THE APPENDIX AND THE COLON? IMPLICATIONS IN CLINICAL PRACTICE

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Abstract

Introduction: The presence of a well-known immune system within the bowel and the appendix, a genuine lymphoid organ, imposes a thorough analysis of the inter-relation between those two segments of the digestive tract (in the course of acute appendicitis associated to inactive ulcerative colitis), from an anatomical and functional perspective.

Design. We present a case of acute gangrenous appendicitis in an 80 year-old female patient with ulcerative colitis (UC) and history of repeated

episodes of disease, diagnosed 18 years prior to acute appendicitis. Acute appendicitis occurred with no signs of active UC.

Results. The case presented with diagnostic difficulties which led to delayed surgery.

This was related to the age of the patient (80 years), in which acute appendicitis is very rare. Also, the clinical picture of acute gangrenous appendicitis associated to inactive ulcerative colitis is unusual in clinical practice.

After surgery, the patient developed a suppurated process which required drainage for one month. Despite favouring conditions, activity of UC (an expected phenomenon) was not observed.

Conclusions: This particular situation of an inactive UC associated to acute appendicitis and protracted suppurated process after surgery raised the discussion of the dissociation of the appendicular immune system from that one of the colon in the course of ulcerative colitis (UC).

This case pleads for a strong inter-relation between immunology and clinical practice, both of which are complementary.

Keywords: Acute appendicitis, Ulcerative colitis, Immune response, Toll-like receptors

Introduction

The digestive tract consists of multiple compartments. The immune system is located within these compartments, thus forming the immune compartmentalisation of digestive tract. The compartmentalisation of the immune system has also been described in other organs, such as the lymphoid system, the kidney, etc (Crivellato, 2004; Gluhovschi 2009)

The immune compartments of the digestive tract are responsible for specific immune activities, from anatomical and functional point of view, but they also collaborate with other immune compartments. In fact, the digestive immune system displays an immune compartment within the appendix and another within the colon (represented by Payer plaques and numerous lymphoid follicles).

The appendix is a lymphoid organ that is attributed with the role of “immune sentinel”, due to its location next to the junction point where the small bowel continues with the large bowel. The fact that the appendix communicates directly with the colon through an orifice could explain this relationship between the immune system of the appendix and that of the colon.

Ulcerative colitis (UC) is an inflammatory bowel disease which, in its course, may be associated with inflammation of the appendix. This phenomenon may feature an acute appendicitis, or may be observed during

colonoscopy as an inflammatory lesion, with congestion of the appendiceal orifice. This inflammatory lesion may be framed as “skip lesion”, terminology that defines a situation in which, despite inflammation of the appendix found at colonoscopy, the histopathological examination of the caecum is normal (Perry, 1999). Less is known about association of acute appendicitis with inactive UC.

The diagnosis of acute appendicitis in a patient with UC may encounter difficulties, due the fact that the activation of UC may be mistaken for acute appendicitis, which may delay the decision of surgical intervention, with the deriving consequences.

Although acute appendicitis within an inactive UC should not raise diagnostic difficulties, certain surgeons hesitate to intervene and postpone surgery until activation of UC is ruled out. Moreover, it is considered that acute appendicitis could activate UC through an anatomical communication between the inflamed appendix and the caecum.

Apart from the particularities of this association, in the present paper are discussed the pathogenic mechanisms of the two diseases, with special focus on the immune mechanisms.

This rare clinical condition reported allows illustrating the participation of the mechanisms of defence of the digestive tract under particular circumstances, with implications for the clinical practice.

Objectives and aims

The aim of this presentation is the discussion of the diagnostic difficulties of acute appendicitis associated with inactive UC, from the perspective of the dissociation of immune mechanisms at the level of the immune compartments of the appendix and the colon.

The case (Material and methods)

The 80 year-old female patient, with long history of urinary tract infections, diagnosed early in 1993 (including colonoscopy which showed UC lesions located at the level of the descending and sigmoid colon) with UC, with repeated episodes of activity, was hospitalized for diffuse abdominal pains, more proeminent on the right side, accompanied by nausea, vomiting, and slow intestinal transit. The surgical examination in the emergency unit considered that the symptoms were due to active UC, and hospitalization in the internal medicine department was decided. The patient did not have diarrheic or haemorrhagic stools.

Results

She was hospitalized in the nephrology department where she was treated repeatedly for urinary tract infections and for UC, following

recommendations of the gastroenterology department. After two days, the pains concentrated in the right iliac fossa. The attending physician opted, however, for a diagnosis of acute appendicitis and requested repeated surgical examinations. Radiological examination pointed out multiple hydroaeric levels. Acute appendicitis with appendicular block was suspected and the patient was referred to the department of surgery. Laboratory investigations showed leucocytosis and high levels of ESR, fibrinogen, and C-reactive protein.

However, the patient being known with UC, the surgical intervention was postponed. The reasons were the advanced age of the patient and a tumour of the caecum. Computed tomography was performed and showed at the level of the right flank a non-homogeneous mass that included the whole ascending colon, the hepatic angle of the colon, and the terminal ileum. The included bowel segments presented hydroaeric levels, moderate infiltration of the surrounding fat, a fact which brought into discussion the necessity of surgical intervention. Colonoscopy imposes caution in its use. In fact, the patient refused this manoeuvre.

Surgical intervention was performed on the 7th day of hospitalization. An ascending inflammatory tumour block that included the caecum, part of the ascending colon, the last ileal bowel segment, and the epiploon was found. A large mass, of 15/10cm, and pus collection was found in the inflammatory block and the gangrenous, perforated appendix. Appendectomy, evacuation of the pus, and abundant peritoneal lavage was performed. Histopathological examination found acute phlegmonous appendicitis, with extended necrotic-suppurated areas at the level of the meso-appendix. (Figure 1 and Figure 2)

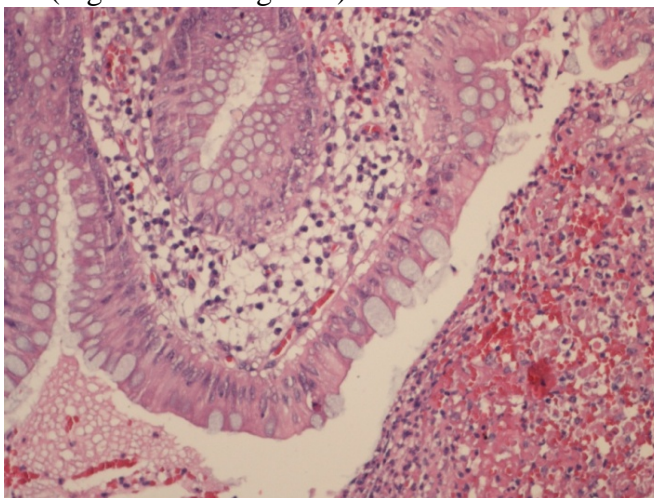


Figure 1. Acute gangrenous appendicitis. Fibrin-granulocyte and erythrocyte exudate in the appendicular lumen, oedema, hyperemia, and inflammatory cells dispersed within the chorion. Exulceration of the epithelium. [HE x 200 ; personal collection]

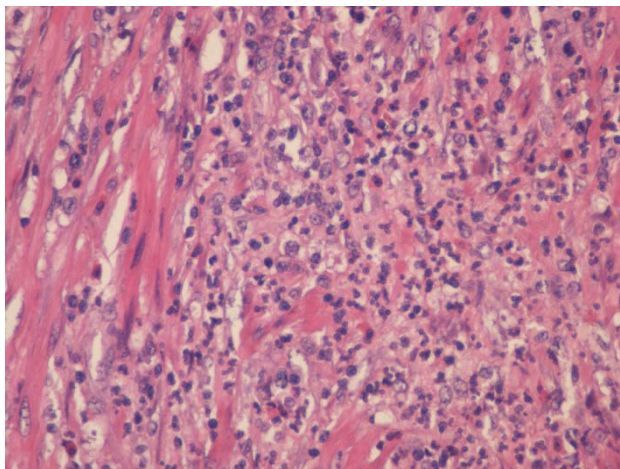


Figure 2. Acute gangrenous appendicitis. Massive granulocyte exudate, with infiltrative aspects, which dissociates to muscular layer of the appendix. [HE x 200 ; personal collection]

Histopathological results concluded that it was acute appendicitis without evidence of elements of ulcerative colitis.

The diagnosis of ulcerative appendicitis is not an isolated entity, that it cannot be the sole manifestation of an ulcerative colitis, unlike in Crohn's disease, in which the diagnosis is not seldom established following surgery for „appendicitis“.

The uncertainties of the diagnosis of acute appendicitis determined temporisation of surgical intervention in the department of surgery, a fact which, associated to the severity of the disease, led to worsening of acute appendicitis, with consecutive long-term evolution of the suppurated focus.

The patient required broad-spectrum antibiotherapy and long-term drainage of the peritoneal cavity.

Discussions

Diagnosing acute appendicitis in UC can sometimes be difficult, in spite of up-to-date technical progress, and some incertainties can delay decisions of surgical intervention, with severe consequences on the evolution of the disease. It is known that in UC, the appendiceal involvement may evolve clinically overt or it may be detected at colonoscopy as an inflamed orifice within the bowel. Occasionally, congestion of the appendical orifice is not associated with inflammation of the caecum, condition defined as „skip lesion“. According to Scott et al, the prevalence of appendical inflammation associated to UC is 48%, and of this approximately 37% may be represented by caecum sparing (Scott,1998).

We report an unusual case which reveals the association of acute appendicitis with inactive UC. It should be underlined that UC did not

become active in parallel with the episode of acute appendicitis, despite late surgery, nor with persistent suppurated focus secondary to surgery, which required drainage for one month, with no signs of activity or of further activation.

We also asked ourselves whether acute appendicitis may lead to activation of UC; the immune mechanisms involved in both diseases may associate up to point or they may be dissociated.

There is limited data concerning the role of the appendix in the pathogenesis and activation of UC. Matsushita et al attributed to the appendix the role of "priming site" in the development of UC (Matsushita, 2005).

Also, it has been assumed that appendectomy may have a beneficial effect on the outcome of UC (Cosnes,2002). Recently, Gardenbroek et al, by analysing several databases (PubMed, The Cochrane Library, and EMBASE) observed conflicting data concerning the role of appendectomy in UC (Gardenbroek, 2012). Moreover, Picazo-Ferrero et al observed in Mexican population that appendectomy in patients with UC might have rather a negative effect, by activating the disease to severe form (Picazo-Ferrera,2011). Andersson in his study concluded that appendectomy for an inflammatory condition (appendicitis or lymphadenitis) but not for nonspecific abdominal pain is associated with a low risk of subsequent ulcerative colitis when performed before the age of 20 years. (Andersson, 2001).

Further studies are required in order to clarify the effect of appendectomy upon UC.

It has been expected that two inflammatory processes within the appendix to evolve in parallel, and as such, gangrenous appendicitis should have activated UC. Due to the fact that this condition was not found, the emerging diagnosis was uncertain, with deriving consequences.

Our patient was addressed to the emergency unit with abdominal pains located in the right illiac fossa. These symptoms were mistaken for those of an active UC, possibly associated to the upper urinary tract infection, due to the medical history of the patient with significant urinary tract infections - chronic pyelonephritis with recurrent episodes- , and repeated admissions to the department of nephrology. Also, UC did not display signs of activity, while the appendiceal symptoms were not completely formed. Given the circumstances, the attending physician from the emergency unit decided to refer the patient to the department of nephrology for further evolution, pending the completion of the diagnosis.

In the department of nephrology, the following day the appendiceal signs became clinically overt. As a consequence the patient was referred to the department of surgery. Computed tomography showed in right flank a

non-homogeneous mass including part of the colon and the terminal ileum. Surgery was postponed, given the suspicion of a tumour of the colon, the advanced age of the patient (80), the unusual occurrence of acute appendicitis in the area of the patient's origin, and the fact that tumours may complicate UC and are not rarely observed at this age.

After a few days, the inflammatory phenomena in the right iliac fossa increased in intensity and surgery was performed. Acute suppuration appendicitis was found, appendectomy was performed, and prolonged drainage of the suppuration process was initiated.

This particular condition, a peri-appendicular block associated with UC, is described in the medical literature regarding children (Szigeti, 2011).

The case presented above is meaningful for the clinical presentation of acute appendicitis with inactive UC. The case shares similarities with UC which presents a "skip lesion", namely the appendicular inflammation found at colonoscopy in association with a normal caecum. Another particularity of this case is represented by the initial diagnostic difficulties which resulted in uncertainties and delay of surgery. The suspicion of UC reactivation in a patient with no blood in the stool was not founded.

The uncertainties in the diagnosis of acute appendicitis associated with inactive UC bring into discussion the following issues:

-not always clinicians are aware of the fact that acute appendicitis may be associated with inactive UC. This association, however, is occasionally signalled in the literature.(Zabana,2007)

-appendicitis is known as a "skip lesion" in which the appendiceal process can be observed, without any lesions of the caecum, UC being located at distance from the inflammatory process. Our patient presented with UC localised within the descending colon and in an inactive form since one year before admission.

-it is not unusual that acute appendicitis may be mistaken for recurrent UC,

-signs related to neighbouring organs, such as kidney in our patient, may raise problems of differential diagnosis,

-the advanced age of the patient delays the diagnosis of acute appendicitis, a rare condition under these circumstances,

-tumours of the caecum and of the ascending colon may be mistaken with UC;

-these may co-exist or they may develop independently: in patients of advanced age, digestive neoplasia should be a diagnosis priority

-computed tomography is not always a reliable diagnostic tool, as was the case with our patient too.

The case presented allows for a critical analysis of the management of a patient who associates acute appendicitis with inactive UC.

Understanding of the relationship between the appendiceal and colonic immune compartments and how these behave in certain situations as two well defined compartments, is the reason why we could explain the association of “skip lesion” with acute appendicitis and concurrent inactive UC. This may develop when the capacity of the immune system is able to control the immune process.

It should be underlined that acute appendicitis does not always evolve in parallel with activity of UC. The lesions of UC may be absent in the vicinity of appendix and may be located at distance within the distal colon and even the rectum.(Olivares, 2007)

Furthermore, it should be mentioned that acute appendicitis in the context of UC may be found even in patients of advanced age, moreover, it may not activate UC. In the elderly, there is an important deficiency of the immune system. Several cases, however, may present clinical signs which do not differ significantly from those described in young persons or adults, in whom the immune system preserves its properties.

The second issue of major import forward by this case is the lack of activation of UC when associated to acute appendicitis, which is expected due to the communication between appendix and the caecum. In the course of acute appendicitis, an inflammatory process of microbial origin occurs within the appendix. The passage of germs through the appendiceal orifice to the caecum could have activated UC in the caecum. It seems that the appendical inflammatory processes were dissociated from those of the bowel, a fact which questions the complexity of the immune mechanisms participating at this level.

The digestive tract presents with an important immune tolerance when subjected to the contact with numerous antigens contained in food (Brandtzaeg, 2001). These complex immune processes within the digestive tract are associated with a well represented immune system.

Since it has been demonstrated that there exists a relationship between immune mechanisms that take place at appendix level and those at colon level, in the present case between acute appendicitis (likely a type 1 immune response) and ulcerative colitis (UC), which would present a type 2 immune response, the fact that UC was not activated during acute appendicitis reflects the complexity of the immune response in immune compartments of the digestive tract.

Furthermore, the bowel (the colon, respectively) is populated with various bacterial species, which constitute a complex ecosystem. This might contribute to maturation of the immune system and the formation of a “direct barrier” against colonization with pathogens (Doré, 2010).

There has been observed that a particular bacterial species, faecalis-bacterium prausnitzi, may protect the bowel from the aggression of several

pathogens. Under certain circumstances, it might occur intestinal dysbiosis, which is associated to inflammatory bowel diseases, such as the case with ulcerative colitis.

The decreased incidence of inflammatory bowel diseases in populations with low level of hygiene compared with their increased incidence in populations with high level of hygiene (such as the countries in North Europe), raises the idea of a “hygienic paradox”. This phenomenon may be related to the protective effect of certain pathogens, of which faecalibacterium prausnitzii is most studied.

The implication of intestinal dysbiosis in the relationship between appendix and ulcerative colitis is not yet elucidated. Absence of activation of ulcerative colitis, however, under the circumstances of severe acute appendicitis, may represent another “paradox” with regard to immune mechanisms at this level.

The appendix is considered a lymphoid organ, well individualized and presenting with B and T cells lymphocytes, and dendritic cells too. (Radford-Smith, 2008).

It is a part of the immune system of the digestive tract, GALT (Gut-associated lymphoid tissue) (Brandtzaeg, 2010). The inflammatory processes which occur within the appendix will associate immune processes which involve the participation of the constitutive immune cells.

Complex immune mechanisms occur within the colon and control the homeostasis at this level. The immune mechanisms are involved in the pathogenesis of UC (Danese, 2011).

The relationship between appendical immune mechanisms in acute appendicitis with inactive UC should be underlined. The entire phenomenon occurs as if the immune mechanisms exert control over inflammation within the colon, while in the appendix these fail to halt the inflammatory process. The dissociation of the immune mechanisms in the two organs has forwarded the concept of immune compartmentalisation within the mucosae. Brandtzaeg et al refer to a regional specialization of the immune system of the mucosae in relation to immune microcompartments which might explain the disparity of the mucosae.(Brandtzaeg, 1999).

According to Roux, a compartmentalisation of the mucosae immune response may be described “between gut and lung” (Roux, 2003). Moreover, the compartmentalisation of the immune system has also been described at other levels, such as lymphoid organs by Crivellato et al (Crivellato, 2004) and the nephron by Gluhovschi et al (Gluhovschi, 2009) .

We showed that in the case of an association between acute appendicitis with inactive UC, the immune system behaves differently in the two compartments; it may control the inflammatory process within the colon, but it fails to do so within the appendix.

In the situation of “skip lesion”, it seems that the immune system behaves differently even within the colon: it may control the inflammation at the level of the caecum, but it fails to control the inflammatory process in other segments of the colon (i.e. the descending colon) or the rectum and the appendix.

Scott et al have reported that the appendiceal lesions associated to UC are very similar to those described in active UC, in contrast to those found in acute appendicitis of other aetiologies (Scott, 1998). In our patient with UC we did not find pathologic lesions different from those described in common forms of acute appendicitis, nor did we encounter lesions of an active UC.

We believe that an analysis of the variability of the immune mechanisms within the appendix and the bowel is mandatory. The observations of Brandtzaeg et al (Brandtzaeg, 2001) regarding the immune compartmentalisation within mucosae, including the one of the bowel, may open a road towards understanding this process, thus providing a diagnostic strategy based on pathogenic explanation.

Another observation deriving from our case is related to the fact that the suppurated process with protracted evolution, which occurred after appendectomy, did not activate UC, a phenomenon which could have been triggered by Toll-like receptors.

According to Danese and Foch, Toll-like receptors within the colon may perform a role in the intestinal homeostasis related to immune processes (Beg, 2002).

These receptors intervene in the interaction of the immune processes with the microbial antigens and with the necrotized tissues resulting from inflammatory processes (Brandtzaeg, 2010).

Although the patient was 80 year-old, an age when appendicitis is rare, diagnosing it should not be missed.

The case presented has both theoretical and practical importance. In clinical practice, the case draws attention on the possibility of acute appendicitis associated to inactive ulcerative colitis. This clinical observation could support an adequate therapeutical decision, appendectomy, respectively. This should be performed as early as possible, in order to avoid complications related to delayed surgery.

Advanced age does not rule out the diagnosis of acute appendicitis, including patients with ulcerative colitis.

From the theoretical standpoint, the case discussed pleads for the dissociation of the immune mechanisms within the colon in the course of ulcerative colitis and those of the appendix. Thus, in the case of microbial aggression, acute appendicitis occurs due to immune deficiency at this level. In contrast, the immune mechanisms of the colon in our patient with

ulcerative colitis seemed to be effective and impeded disease activation by acute appendicitis and the subsequent chronic suppuration.

Understanding the immunopathology of the digestive tract may enhance the dimensions of the competence of those involved in decision-making.

Clinical practice, however, may provide useful observations regarding the functionality of the immune system. These clinical observations might represent an initiating step to complex immunological studies which aim at elucidating the involvement of the immune system in various clinical settings.

Understanding the immunologic particularities of the bowel might provide an explanation concerning the dissociation between the appendicular inflammation and the one of UC.

The patient with UC should be analysed in pathogenic context which allows elucidation of special situations from the perspective of the relationship between acute appendicitis and UC.

Conclusion

This particular situation of an inactive UC associated to acute appendicitis and protracted suppurated process after surgery raised the discussion of the dissociation of the appendicular immune system from that one of the colon in the course of ulcerative colitis (UC).

This case pleads for a strong inter-relation between immunology and clinical practice, both of which are complementary.

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