A rare case of *situs inversus totalis* associated with sigmoid diverticulitis and appendicular agenesis. Embryological, clinical considerations and literature review

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**Abstract**
The revelation of *situs inversus totalis* by a peritoneal syndrome is an extremely rare event. The association of this condition with sigmoid diverticulitis and agenesis of the vermiform appendix has not been described in the literature. This paper aims to present the first case of this type while screening the literature on this topic. The authors present the case of a sigmoid diverticulitis associated with *situs inversus totalis* and agenesis of the vermiform appendix, in a 44-year-old male patient. Because of abdominal pain located in the right iliac fossa, elevated temperature (38.2°C) and biological examinations, acute appendicitis was rather simulated and considered as a presumptive diagnosis. Diagnostic accuracy was achieved during laparoscopic exploration of the peritoneal cavity, which proved the coexistence of visceral transposition, appendicular agenesis and sigmoid diverticulitis, usually noted as a rare finding. Secondly, we performed a systematic search on PubMed® and Google Scholar® databases introducing the following terms: *situs inversus totalis*, acute appendicitis. Given the time span of the last 30 years, we have obtained a small number of cases in which symptoms that are specific to acute appendicitis have been found in patients with *situs inversus totalis*. Due to the rare number of cases, it is difficult to establish a preoperative diagnosis. Usually, this diagnosis is revealed as an intraoperative surprise. A careful clinical examination and a set of standardized paraclinical examinations can guide the diagnosis. The patient’s evolution was favorable, without any other changes at the subsequent examinations.

**Keywords**: *situs inversus totalis*, appendicitis, sigmoid diverticulitis, appendicular agenesis.

**Introduction**
*Situs inversus* is a transposition of the abdominal and thoracic viscera as opposed to their common position. First described by Aristotle in animals, it was discovered in humans by Fabricius in the 17th century and later described in detail by Matthew Baillie [1].

It is an autosomal recessive pathology, but it can also be an X-linked condition. Approximately 25% of those with *situs inversus* also have a dysfunction called primary ciliary dyskinesia. Fifty percent of the patients with primary ciliary dyskinesia develop *situs inversus*.

The association of abdominal *situs inversus* with dextrocardia is called *situs inversus totalis* and has an incidence of one in 200 000 inhabitants. In the absence of imaging investigations to guide the diagnosis, considering the anatomical particularities of these patients, the diagnosis is difficult to establish, symptomatology being sometimes unspecific and inappropriate for the actual real topographic projection of abdominal viscera [2].

The association of an acute diverticular inflammatory process with the abdominal *situs inversus* is extremely rare. Appendicular agenesis represents a developmental arrest resulting in total absence of the vermiform appendix. These cases are intraoperative surprises with an incidence of 0.001% in patients where surgery is performed for presumed acute appendicitis.

The clinical diagnosis of this type of pathology is difficult to establish in the absence of a previous imaging, especially if the given condition is atypically located in the right iliac fossa. This diagnosis is usually coming as an intraoperative surprise [3]. The diagnostic enigma in our case, which represented an acute abdominal condition, arises out of visceral transposition.

In the process of presenting such a rare case, it is important to remind the need for a careful both clinical and imaging diagnosis.

**Aim**
The purpose of this report was to describe a unique association of *situs inversus totalis*, sigmoid diverticulitis and appendicular agenesis. We also conducted a literature review on this topic to analyze different diagnostic and therapeutic modalities, in situations that are somewhat similar to our case.
Case presentation

We present the case of a 44-year-old male patient, with no history of any health concerns or surgical interventions in the past. He arrived at the Emergency Room of the Emergency County Hospital, Sibiu, Romania, in March 2017, complaining about abdominal pain of eight hours duration, located in the right iliac fossa.

Clinical examination of the abdomen revealed signs of peritoneal irritation in the right iliac fossa and elevated body temperature: 38.2°C.

Biological assessment noted modified inflammatory samples with white blood cell count at 14.6×10³/μl and left shift neutrophilia 87%. Urinalysis was normal. The diagnosis of acute surgical abdomen was established, raising the suspicion of an acute appendicitis. The Alvarado score for acute appendicitis was 8 points (tenderness in right lower quadrant – 2 points, nausea – 2 points, elevated temperature – 1 point, leukocytosis – 2 points with left shift – 1 point). At this value, Alvarado score has 78% sensitivity and 100% specificity, with 93% predicted number of patients with acute appendicitis. An electrocardiogram (ECG) was carried out. Because acute appendicitis was initially suspected, radiography was not performed, not being considered a routine investigation in the diagnostic process of acute appendicitis. Afterwards, the patient was referred to the Department of Surgery.

We decided to perform surgery under general anesthesia with orotracheal intubation. During the exploration of the peritoneal cavity, laparoscopic surgical approach revealed an abnormal position of the stomach, being placed on the right of the round ligament. The liver was found on the left of the median line, with the cholecyst projected in the left hypochondrium and the spleen was located in the right hypochondrium.

The cardiac apex beats were revealed transdiaphragmatic on the right side. An adherent block in the right iliac fossa was highlighted, intimately adhering to the abdominal wall. The right iliac fossa and the right colic flexure were occupied by the sigmoid, which presented multiple diverticula in its terminal part (Figure 1). Cecum with vermiform appendix agenesis were highlighted in the left iliac fossa (Figure 2).

We established the diagnosis of situs inversus totalis. Our attempting to mobilize the parietal–sigmoid inflammatory block was unsuccessful, because of the tissue friability and the risk of colic effraction during laparoscopic dissection. Lavage and drainage of the peritoneal cavity were performed.

Postoperative evolution was favorable, with the resumption of the intestinal transit and suppression of peritoneal drainage. We performed an abdominal computed tomography (CT) scan which revealed abdominal situs inversus with dextrocardia.

The cardiac evaluation and the heart ultrasound (US) confirmed the dextrocardia without revealing any other cardiac changes (Figures 3–5). The patient was discharged three days after submission. Postoperative follow-up appointments at three, six and 12 months did not reveal any problems.
situs inversus, also known as situs oppositus, is a congenital condition in which major organs are reversed. It is found in 1:10 000 people. The normal placement of internal organs is known as situs solitus. It was first described by Aristotle in animals, and it was considered as a sign from gods [1, 3]. Complete transposition from right to left of intrathoracic and intraabdominal organs is called situs inversus totalis and is rarer than situs inversus. Usually, this condition involves no medical problems compared with situs ambiguous when structures are duplicated or absent.

Situs inversus totalis is an autosomal recessive genetic condition. Primary ciliary dyskinesia is found in 25% of these patients. Dysfunction of the cilia is associated with 50% chances of situs inversus development. The triad of situs inversus accompanied by chronic sinusitis and bronchiectasis is known as Kartagener syndrome [4–6].

During the embryonic development, there is a 180° rotation around the transverse axis of the body, which brings heart-ang itsa thoracic region. During the second rotation around the sagittal and longitudinal axis, it results the heart being correctly positioned in the mediastium.

The exact cause of situs inversus is not known. It was suggested that rotation of the heart tube causes all other changes to follow. Any mechanical disturbance that occurs in any of the two rotational movements can lead to an abnormal positioning of the heart or dextrocardia. Also, it was described a bowel rotation determining factor, which is usually located on the left side of the body. It was thought that the disturbance of this factor in determining the bowel rotation during ontogenesis may be the sole responsible for situs inversus. A previous study described the positive role of the paired-like homeodomain 2 (PITX2) gene in the heart and gut loop mechanism [7–9].

One of the theories underlying the malrotation states that it occurs by inactivating heterozygous mutations in the forkhead box F1 (FOXF1) transcriptional end, patients with this mutation frequently associate alveolar capillary dysplasia, which implies the misalignment of the pulmonary veins which causes defective development of intrinsic pulmonary vascularization [10].

The congenital absence of the appendix was first described in 1718 by Morgagni. This condition occurs in 1:100 000 surgeries for acute appendicitis [11].

Embryologically, the vermiform appendix is formed around the 10th week of pregnancy from the caecum as a tubular end-capped structure. Appendicular atresia known causes can be an intrauterine vascular accident or auto-amputations due to an intrauterine fibrous band [12]. Also, a developmental defect called the apple peel jejunal atresia (autosomal recessive transmission) and associated with short midgut syndrome can cause appendicular atresia.

Agenesis of the vermiform appendix may be isolated or may be part of a complex of ileo-cecal malformations. Collins studied this aspect and made the following classification: type I – absence of appendix and cecum; type II – rudimentary cecum and absence of appendix; type III – normal cecum and absence of appendix; type IV – normal cecum and rudimentary appendix; type V – giant cecum and absence of appendix [12–14]. The presented case is a type III.

The existence of sigmoid diverticulitis at this age is not very frequent (5% at the age of 40 or in younger patients). The diagnostic process of sigmoid diverticulitis, even in complicated forms, is difficult in the absence of a proper imaging examination or without a history of diverticulosis. The presence of an abdominal situs inversus will raise even greater problems of differential diagnosis.

The occurrence of alagic symptoms of both left and right iliac fossae frequently guide the clinician to either acute appendicitis or sigmoid diverticulitis. Signs of acute abdomen in the left iliac fossa (through acute appendicitis) and signs of peritoneal irritation in the right iliac fossa as a manifestation of sigmoid diverticulitis may be related to abnormal length and location of the appendix and sigmoid (long appendix, with pelvic location, megasigmoid, dolicho-sigmoid). Nevertheless, this situation is even more rarely associated with situs inversus totalis.

The rarity of situs inversus cases, the non-specific clinical manifestations, the diagnostic difficulties, and the technical challenges that involves surgery on a mirroring anatomy compared to the surgical routine have led us to review the literature for the last 30 years, analyzing different surgical ways of approachment, such as laparoscopic approach, the single port or robotic approach.

Performing a search in the PubMed® database between 1990–2020 and using the term situs inversus totalis, 817 results were obtained. Adding acute appendicitis after excluding the articles that presented pediatric cases and those that could not be accessed, we obtained 13 results. Nine articles were selected. Using the same search data and the same exclusion criteria, 20 articles were selected from the Google Scholar® database [15–42].

Of the 29 articles, 23 were case reports and six were reviews associated with case reports. Thirty patients were selected observing an equal number in terms of gender distribution (Table 1).

It was observed that the average age at the time of diagnosis was 35.9 years. The main symptom was pain in the left iliac fossa or lower abdomen followed by fever and nausea. The imaging investigation of choice was abdominal tomography – 20 (66.66%) cases, followed by abdominal US nine (30%) cases, one case was diagnosed intraoperatively and in one case the diagnosis of situs inversus was previously established.
Table 1 – Data search retrieved literature case reports on situs inversus totalis, acute appendicitis, in the databases (PubMed® and Google Scholar®)

| No. | Year  | Author(s) [Ref. #] | Age [years] | Sex | Main symptoms | Imaging diagnosis | Intraoperative findings | Surgical approach | Evolution  |
|-----|-------|--------------------|-------------|-----|---------------|-------------------|------------------------|------------------|------------|
| 1.  | 2020  | Di Buono et al. [15]| 23 M        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Laparoscopic, appendectomy | Uneventful |
| 2.  | 2010  | Karagülle et al. [16]| 54 F        |     | Left lower quadrant pain | Abdominal US, CT scan | Acute appendicitis    | Open appendectomy | Uneventful |
| 3.  | 2008  | Huang et al. [17]  | 60 F        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Open appendectomy | Uneventful |
| 4.  | 2010  | Seifmanesh et al. [18]| 24 F        |     | Left lower quadrant pain | Abdominal US      | Acute appendicitis, peritonitis | Laparotomy | Uneventful |
| 5.  | 2010  | Petrou et al. [19] | 59 M        |     | Left lower quadrant pain | CT scan           | Acute appendicitis, gangrenous appendicitis | Open appendectomy | Uneventful |
| 6.  | 2000  | Djo han et al. [20]| 20 F        |     | Left lower quadrant pain | CT scan           | Appendiceal mucinous adenocarcinoma | Open appendectomy | Uneventful |
| 7.  | 2009  | Uludag et al. [21] | 29 M        |     | Left lower quadrant pain, nausea | Abdominal US      | No appendix             | Laparoscopic appendectomy and cholecystectomy | Uneventful |
| 8.  | 2010  | Akbulut et al. [22]| 25 F        |     | Left lower quadrant pain after blunt abdominal trauma, fever | CT scan           | Acute appendicitis, bowel perforation | Laparotomy, appendectomy, bowel resection | Uneventful |
| 9.  | 2005  | Hou et al. [23]   | 48 M        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Conservative treatment | Prolonged hospitalization |
| 10. | 2012  | Oh et al. [24]    | 86 F        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 11. | 2006  | Golash [25]       | 40 M        |     | Left lower quadrant pain, fever | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 12. | 2010  | Perera & Hennessy [26]| 46 M        |     | Left lower quadrant pain, fever | CT scan           | Acute appendicitis, peritonitis | Laparoscopic appendectomy | Uneventful |
| 13. | 2013  | Channabasappa et al. [27]| 35 F        |     | Left lower quadrant pain, CT scan | Abdominal US      | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 14. | 2004  | Song et al. [28]  | 32 F        |     | Left lower quadrant pain | None              | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 15. | 2001  | Franklin et al. [29]| 25 F        |     | Right upper quadrant pain | Abdominal US      | No appendix             | Laparoscopic appendectomy and cholecystectomy | Uneventful |
| 16. | 2016  | Koç et al. [30]   | 46 F        |     | Lower abdominal pain | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 17. | 2010  | Cissé et al. [31]| 20 F        |     | Lower abdominal pain | CT scan           | Acute appendicitis, peritonitis | Open appendectomy | Uneventful |
| 18. | 2008  | Hassan et al. [32]| 37 M        |     | Lower abdominal pain, fever | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 19. | 2013  | Patel et al. [33]| 28 M        |     | Lower abdominal pain | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 20. | 2010  | Akbulut et al. [34]| 16 M        |     | Lower abdominal pain | Abdominal US      | Acute appendicitis    | Open appendectomy | Uneventful |
| 21. | 2014  | Versluis & Suliman [35]| 18 F        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 22. | 2020  | Arid [36]         | 28 M        |     | Left lower quadrant pain | Abdominal US      | Acute appendicitis    | Laparoscopic appendectomy | Uneventful |
| 23. | 2016  | Rajkumar et al. [37]| 22 M        |     | Left lower quadrant pain | Previous knowledge of situs inversus. Abdominal US | Acute appendicitis    | Single port appendectomy | Uneventful |
| 24. | 2012  | Yang et al. [38]  | 50 M        |     | Left lower quadrant pain | CT scan           | Acute appendicitis    | Conservative treatment | Relapse and laparotomy after 5 months |
| 25. | 2019  | Yeni et al. [39]  | 48 F        |     | Lower abdominal pain | CT scan           | Acute appendicitis    | Open appendectomy | Uneventful |
| 26. | 2013  | Chuang et al. [40]| 50 M        |     | Lower abdominal pain | CT scan           | Acute appendicitis, peritonitis | Laparoscopic appendectomy | Uneventful |
Intraoperatively, in 20 (66.66%) cases the diagnosis was acute appendicitis, four (13.33%) cases were associated with peritonitis, one case (3.33%) had gangrenous appendicitis, one case (3.33%) was represented by an appendicular mucinous adenocarcinoma. In two cases, a noninflammatory appendix was detected, the appendectomy being prophylactically performed.

The preferred surgical approach was laparoscopic appendectomy in 50% of patients, in two (6.66%) patients were being associated with cholecystectomy. One case was solved by laparoscopic single port approach and two cases were treated conservatively, but the evolution was with prolonged hospitalization and in one case with reintervention at five months. Open surgery approach was preferred in nine (30%) cases, including the case with generalized peritonitis and the one with intestinal perforation, preferring laparotomy with ileum resection and anastomosis in abdominal trauma case. The patient whose histopathological diagnosis was mucinous adenocarcinoma required a surgical second look after neoadjuvant chemotherapy, performing right colectomy. No robotic surgery approach was found (Table 1).

These six reviews highlighted results similar to ours, in terms of symptoms, diagnostic suspicion, imaging diagnosis and predilection for laparoscopic surgery. Akbulut et al. analyzed the largest group of cases and highlighted similar data comparing to our study in terms of therapeutic option and histopathological diagnosis, as well as in terms of preoperative diagnosis. This study mentioned that 14.7% of cases of situs inversus totalis were diagnosed at the time of hospital admittance and 20% were diagnosed intraoperatively [22].

Searching for cases in which situs inversus totalis and sigmoid diverticulitis were associated returned two articles that presented two cases with situs inversus totalis and sigmoid diverticulitis, surgical intervention being the elective treatment [43, 44].

Consultation of the two databases returned no cases of appendicular agenesis with sigmoid diverticulitis in patients with situs inversus totalis.

Typically, the diagnosis of acute appendicitis is susceptible and clinically associated with inflammatory syndrome. This includes the exclusion of other pathologies with zonal localization: typhilitis, epiploic necrosis, or omental torsion, ureterolithiasis and renal colic, urinary tract infection, acute mesenteric adenitis (especially in children) biliary colic and cholecystitis (for subhepatic appendicular localizations, sometimes associated with jaundice), enterocolitis, perforated duodenal ulcer, Crohn’s disease, and right colon diverticulosis or cancer [2, 44].

In women, additionally, cystic ovaries or torsion, inflammatory pelvic disease, endometriosis, tubo-ovarian abscesses should be excluded.

However, appendicular agenesis cannot be clinically or imagistically appreciated (except for CT).

We consider it is useful to perform an abdominal US exam in any acute abdomen, even if the clinical examination is suggestive for a particular pathology, additional data being welcomed when trying to establish the diagnosis. CT is the most precise imaging method for exploring the pathology of the vermiform appendix, but it is not standard in all emergency rooms.

The association of sigmoid diverticulitis with situs inversus is rare and in opposition to the presented case, the differential diagnosis with acute appendicitis is not usually required to be done. In the absence of additional imaging data, laparoscopy is preferred over the classical approach.

The limitations of an open surgery approach are obvious in this case, due to the particular anatomical changes, the existence of the parietal–sigmoid block and the risk of colic effraction with consecutive colostomy [5].

We can say that laparoscopy was salutary, replacing the lack of imaging data and incomplete clinical examination, as well as preventing the surgeon from predictable organic lesions, due to particular anatomy. We also recommend the laparoscopic approach to be performed in any case in which acute appendicitis is suspected, especially in women, not just for a diagnostic exclusion but also because of its benefits in terms of postoperative complications, duration of surgical intervention, hospitalization, and recovery period [45, 46].

More and more studies recommend the laparoscopic approach in uncertain cases of acute abdomen. Gradually, laparoscopy has become the “golden standard” for this type of pathology [45, 47].

Conclusions

Situs inversus totalis with sigmoid diverticulitis and appendicular agenesis is a rare association in the surgical practice to our knowledge, this case being the first published case in which this triple association was found. The diagnosis can be oriented through imaging and determined after a surgical approach, especially in laparoscopic form, which allows the proper visualization of the abdominal cavity, with minimal parietal sacrifices.

Conflict of interests

The authors declare no conflict of interests.

Patient consent

The patient agreed in writing that medical data and images of his case could be used for possible publication in a medical article.

The approval of the Ethics Commission of the Hospital was also obtained, in the meeting of November 2019.

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