CLINICAL CHARACTERISTICS OF PATIENTS WITH FITZ-HUGH-CURTIS SYNDROME: A REPORT IN VIETNAM AND A LITERATURE REVIEW

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ABSTRACT

Objective: To review the characteristics in a series of clinical cases of patients with Fitz-Hugh-Curtis (FHC) syndrome and to review the literature. **Research Subjects and Methods:** Descriptive Study, Report on Clinical Case Series, and Literature Review. The study involved 3 clinical cases with FHC. **Results:** The 3 clinical cases of FHC shared common characteristics of a silent disease progression. Patients sought medical attention due to abdominal pain (epigastric pain, right lower rib pain, and right iliac fossa pain). Atypical infection and inflammation syndromes were present with no fever, slight or no increase in white blood cell count, and a slight increase in CRP. Symptoms of vomiting and bowel disturbances were not pronounced. The characteristic symptom of the patient's discharge is very distinct, which is thin, white vaginal discharge, and when using a duckbill speculum, it can be seen flowing from the cervical os. Abdominal ultrasound, if thoroughly examined, could detect the condition. Computed tomography (CT) imaging with intravenous contrast injection was highly valuable for definitive diagnosis. Early detection, specific antibiotic treatment following a protocol, and early multidrug therapy resulted in effective treatment outcomes, reduced hospitalization time, and decreased risk of complications. **Conclusion:** FHC syndrome can occur not only in patients seeking gynecological care but can also be encountered in various clinical settings in internal medicine and surgery specialties. Atypical infection and inflammation syndromes with vaginal discharge are very characteristic. Abdominal CT with contrast injection is valuable for diagnosis. The disease can be effectively treated in internal medicine with specific antibiotics and multidrug therapy.

Keywords: Characteristics, Fitz-Hugh-Curtis Syndrome, Literature review.

INTRODUCTION

Fitz-Hugh-Curtis (FHC) Syndrome is a rare complication of pelvic inflammatory disease, named after the two physicians, Thomas Fitz-Hugh and Arthur Hale Curtis, who first reported it in 1930 and 1934 [1], [2], [3], [4], [5]. It is a condition of perihepatitis associated with genital tract infections, occurring in approximately a quarter of patients with pelvic inflammatory disease [3], [5], [6], but it can also occur in women without pelvic inflammatory disease and in men [4], [6], [7], [8], [9]. There have been some clinical case reports and studies on this condition worldwide, but the research is still limited [10], [11], [12], [13], [14], especially in the context of an increasingly complex and diverse field of pathology and modern diagnostic applications in today's disease management [15], [16]. Recently, at Hai Phong – Vinh Bao International Gerneral Hospital, Vietnam, we encountered three cases of FHC Syndrome in the context of examinations in the fields of internal medicine and surgery. Therefore, we report the clinical characteristics of these patients to provide new insights and a global literature review.

CLINICAL CASE INTRODUCTION

CASE 1

A 63-year-old female patient was admitted in September 2023 with a complaint of abdominal pain on the left side of her lower ribcage. Patient's medical history included hypertension, type 2 diabetes, lipid disorders, chronic venous insufficiency of both lower limbs, and gastritis. Patient history: PARA: 3003 (3 normal deliveries), menopausal for 13 years. The patient presented with abdominal pain for one week prior to admission, with increased left lower ribcage pain, excessive vaginal discharge, and no fever. The pain intensified on the day of the visit to the internal medicine department. Her condition on arrival: Awake, responsive, normal skin and mucous membranes, no edema, no subcutaneous bleeding. Heart and lung examinations were normal. The abdomen was soft, not distended, and there was tenderness when palpating the left lower quadrant. Consultation with the Obstetrics and Gynecology department revealed a normal vulva and perineum examination. There was thin, white vaginal discharge. The cervix was intact, the uterus was small in size, and the adnexa on both sides had no palpable masses and elicited pain on pressure.

Clinical laboratory results showed a C-reactive protein (CRP) of 8.1 mg/L, White blood cells of 12.0 G/L, and Neutrophil (NEU) of 7.6 G/L. Results of Ultrasound: Mildly dilated small bowel loops with fluid stasis, increased peristalsis, thickened walls, and mild peritoneal fat infiltration, with some fluid between the loops. The appendix measured 3.8mm in diameter and contained air, with no signs of fat infiltration. Conclusion: Monitoring images of small intestine inflammation or FHC syndrome

CT imaging with intravenous contrast showed a normal-sized liver with smooth borders and no focal lesions before and after contrast injection. The intrahepatic fluid was about 8.7 mm. There was significant fluid accumulation in the Douglas pouch, measuring approximately 29.2 mm, with free fluid around both ovaries. Free fluid was also present between the bowel loops. The appendix appeared thin, with a diameter of about 5.1 mm, and showed no signs of fat infiltration. No abnormalities were seen after contrast injection. Conclusion: Images showed fluid in the liver capsule, inflammatory bowel disease, fluid in the Douglas pouch, and fluid around both ovaries (suggestive of Fitz-Hugh-Curtis Syndrome). The patient was jointly consulted by internal medicine and obstetrics specialists and diagnosed with adnexitis -FHC Syndrome.

Treatment: The patient was admitted and treated with a combination of antibiotics (Metronidazole 500 mg twice daily for 5 days, Doxycycline 100 mg orally twice daily starting on day 5, and daily intravaginal medication). After 7 days of combined antibiotic treatment, her condition stabilized, and she was no longer experiencing abdominal pain. Examination: The patient was alert and had abdominal pain. The abdomen was soft and there was no guarding. Internal examination revealed a normal vulva and perineum, and there was no vaginal discharge. The cervix was undamaged, the uterus was smaller than normal, and both adnexa appeared normal, with no palpable masses and no pain on pressure. Blood test results showed a CRP of 3mg/L, White blood cells of 8.7 G/L, and NEU of 3.3 G/L. Ultrasonography of the uterus and ovaries: Anterior-posterior diameter of the uterus was 27.9 mm, and the endometrial lining measured 5.5mm. The structure and muscle tissue in the cervix and uterine fundus were homogeneous, with no abnormal masses. Both ovaries were smaller for the patient's age, with the right ovarian cyst measuring 14.6 x 10.2 mm. Douglas pouch: No fluid was present. Abdominal ultrasound: No free fluid was observed in the abdominal cavity. No abnormalities were detected. The patient was discharged in stable condition after one week of treatment.

CASE 2

A 34-year-old female patient was admitted to the internal medicine department in September 2023 with complaints of right lower ribcage pain. Medical history: On admission, the patient reported dull right lower ribcage pain, occasionally cramping, with intermittent nausea, but no vomiting. She had no fever, and her temperature was not measured. Urination and bowel movements were normal. On examination, the patient was alert and cooperative, had no signs of anemia, had signs of infection (+), had no meningeal signs, no focal neurological deficits, regular heart rhythm, clear lung sounds bilaterally, and a soft abdomen. There was tenderness upon palpation in the lower right abdomen and a sharp pain at the gallbladder point. The liver was not enlarged. Blood pressure was 126/62 mmHg, heart rate was 101 beats per minute, and SpO2 was 98%. No abnormalities were observed in other organs.

Blood test results showed: White blood cells 9.5 G/L, NEU: 64.2%, Platelets: 333 G/L, CRP: 20.6mg/l, Beta Human Chorionic Gonadotropin (Beta HCG) (-), Test Dengue: NS1 (+). The ultrasound revealed that the uterus was not enlarged, and the endometrial lining was thin. The cervix was in the correct position, and there was a hypoechoic nodule in front of the cervix measuring 15.2x12.1mm in size. Both ovaries had cysts, with the right cyst measuring 34.8x34.8mm and the left cyst measuring 35x30mm. No free fluid is seen in the abdomen. CT imaging showed a normal-sized liver with smooth borders and no focal lesions before and after contrast injection. The fluid in the hepatic capsule was about 4.5mm thick. Imaging showed a thickened ascending colon wall with mild inflammation in the ileocecal area. The Douglas pouch had thickened fluid measuring approximately 26.2mm, and there was fluid in the areas around both ovaries and fallopian tubes. The right ovarian cyst measured about 44.7 x 40.6mm. Diagnostic conclusion: The complex pattern of damage from the small pelvis to the liver capsule is consistent with Fitz-Hugh-Curtis Syndrome.

The patient was examined by the Obstetrics department with the following findings: A 34-year-old female patient with a history of PARA 3003 (3 vaginal deliveries and a 7-year-old child). Irregular menstrual periods, with a last menstrual period 15 days ago. Currently, the menstrual flow has been clean for 7 days. On examination, the patient was alert and cooperative, with a heart rate of 70 beats per minute, blood pressure of 130/80 mmHg, and a temperature of 36.8 C. Her abdomen was soft, with pain in the right lower ribcage and right lower quadrant. There was no guarding. Pelvic examination showed a normal vulva and perineum, white vaginal discharge, undamaged cervix with a cervical string, retroverted uterus, normal uterine size, and tenderness on both adnexal areas.

Diagnosis: Adnexitis - Fitz-Hugh-Curtis Syndrome/Dengue Fever. The patient was admitted for inpatient treatment and received combined antibiotic therapy: Metronidazole 500mg twice daily for 3 days, Doxycycline 100mg orally twice daily starting on day 3, and daily vaginal suppositories.

After 7 days of combined antibiotic treatment, her condition stabilized, and she was no longer experiencing abdominal pain. Examination: The patient was alert and had abdominal pain. The abdomen was soft and there was no guarding. Internal examination reveals normal vulva, normal perineum, and vagina with no discharge. The cervix shows inflammation of the glands around the external orifice, with a loop, uterus of normal size, 2 unclear masses in the adnexa, no fullness, and no pain. The re-evaluated test results showed CRP of 1.6mg/l; Leukocytes of 6.4 G/L, and NEU of 2.6 G/L. Ultrasound of the uterus and ovaries: Anteroposterior diameter: 52.2 mm, Endometrial thickness: 8.9 mm, Cervical fluid in the correct position. Both ovaries have cysts measuring 36.6 x 29.5 mm. Douglas pouch: No fluid was present. The patient was discharged after one week of stable inpatient treatment and prescribed a one-week course of combination antibiotics after discharge.

CASE 3

A 37-year-old female patient, with a history of PARA 2002 cesarean section with the youngest child being 8 years old. She had irregular menstrual cycles and was admitted for an internal medicine examination in August 2023 with complaints of abdominal pain and fever. Medical history: The patient had been admitted to another medical facility one week prior to hospitalization at our hospital. She had experienced symptoms of abdominal pain around the umbilical region, loose stools, and fever, which had initially been diagnosed as a suspected bloodstream infection. She was treated with intravenous antibiotics (Ciprofloxacin + Cefoperazone) for seven days but did not improve. She continued to experience abdominal pain in the right lower quadrant and right lower ribcage, as well as watery diarrhea and requested transfer to our hospital. She continued to experience lower abdominal cramps and right lower quadrant pain, without bowel movements or urination. Examination at admission: The patient was awake and alert, with good contact. Blood pressure: 118/68 mmHg, Heart rate: 125 beats per minute. No signs of anemia, infection, or meningeal syndrome. No focal neurological signs. Regular heart rate, clear lung sounds bilaterally, mildly distended abdomen, tenderness in the epigastric and right lower quadrant, the liver and spleen were not enlarged, and no abnormalities in other organs were observed.

Blood test results with Leukocyte index: 2.2 G/L, NEU: 87.3%, Platelets: 109 G/L, CRP: 4.3, Lipase: 80.5, ALT (Alanin transaminase): 84.1 U/L, Aspart transaminase (AST): 380.8 U/L, K: 3.0 mEq/L. Abdominal ultrasound showed no free fluid in the abdomen, with slight dilation of the appendix. The bowel loops contained fluid and exhibited increased motility, mild fat infiltration around the bowel loops in the right lower pelvis, and some fluid. The right ovarian cyst was monitored, as well as fluid in the Douglas pouch, with suspicion of FHC Syndrome or appendicitis.

CT scans showed the appendix located in the pelvic cavity, extending downwards and thickening with a diameter of about 8.4mm, containing fluid and gas. Light infiltration was around the appendix. After the medicine injection, the appendix strongly absorbed it. The liver was normal in size, with smooth edges, uniform parenchyma, and no pre- or post-injection contrast agent accumulation. Pelvis: No abnormal masses detected. No free fluid is seen in the abdomen.

Subclinical gynecological examination showed the patient was awake, afebrile, with a soft abdomen, no tenderness, and right lower abdominal pain. The transverse cesarean section scar was not painful. Vagina - Perineum was normal. Vaginal discharge with thin white mucus was coming from the cervix orifice. Cervical hypertrophy with slight inflammation of the upper lip. The uterus had a normal size, with a thick and soft (right) adnexal region, tender to touch. The (left) adnexal region appeared normal.

The patient was been monitored in collaboration with the Gastroenterology department to rule out acute appendicitis. The abdominal examination showed no signs of appendicitis. The patient received one week of antibiotic treatment without any signs of appendiceal inflammation, ruling out acute appendicitis.

Diagnosis and treatment: The patient was consulted by the General Surgery department to rule out acute appendicitis, and by the Obstetrics and Gynecology department, agreeing on the diagnosis of adnexitis and suspected FHC. On the first day, Ceftriaxone was administered slowly intravenously at a dose of 2g/one time/day; Combination antibiotic therapy was initiated, including intravenous Metronidazole 500mg twice daily for 5 days, oral Doxycycline 100mg twice daily for 5 days, and daily vaginal suppositories.

After 5 days of combined antibiotic treatment, her condition stabilized, and she was no longer experiencing abdominal pain. Upon re-examination: The patient was

awake, with a diffuse rash on the body, no abdominal pain, soft abdomen, and a non-tender abdomen. Pelvic examination: Normal perineum and vagina with no discharge. The cervix was mildly inflamed, and the uterus was of normal size and mobility. Both adnexal regions appeared normal with no palpable masses or tenderness. Laboratory retest after 1 week of treatment showed CRP: 7.6mg/l; White blood cells: 3.3 G/L, NEU: 28.3%. Ultrasonography of the uterus and ovaries: Anterior-posterior diameter of the uterus was 45.9mm, and the endometrial lining measured 18.3 mm. The structure and muscle tissue in the cervix and uterine fundus were homogeneous, with no abnormal masses. Right ovary showed a mixed structure with a size of 21.4x17.9mm and peripheral vascularity (indicative of a corpus luteum). Left ovary showed no abnormalities. Douglas pouch contained fluid (25.8mm thick). The patient was discharged in stable condition after more than 1 week of hospitalization and continued to receive an extended course of combined antibiotics to completely resolve the condition.

DISCUSSION

Regarding Fitz-Hugh-Curtis Syndrome (FHC): In 1930, Thomas Fitz-Hugh and Arthur Curtis described adhesions between the liver surface and the anterior abdominal wall in patients with a history of salpingitis and pelvic inflammatory disease. Fitz-Hugh believed that the gonorrhea bacterium was the cause of this inflammatory condition, and he found Neisseria gonorrhoeae on cell smears from the patient's hepatic area [1], [2], [3], [4]. In 1978, Mueller-Shoop found evidence of Chlamydia Trachomatis infection in 9 out of 11 patients diagnosed with PID and perihepatitis, which was confirmed by laparoscopy, with Chlamydia also detected in cervical mucus, fallopian tubes, and some liver capsule samples. Chlamydia was found to be more prevalent than Neisseria Gonorrhoeae, establishing it as a sexually transmitted disease [5]. The main causative agents of FHC, in order of frequency, are Chlamydia Trachomatis, Neisseria Gonorrhoeae, Mycoplasma, and some Gram-negative bacteria [4], [5]. The prevalence varies from 4-14%, starting with vaginitis, cervicitis, and pelvic inflammatory disease, eventually leading to FHC Syndrome [5], [7], [8], [9]. Clinical symptoms are often atypical, occurring when genital infections are not treated promptly. Perihepatitis can cause right lower rib pain and may be confused with other conditions such as cholecystitis, appendicitis, or pleuritis. Cases of right lower rib pain tend to have more pronounced symptoms than cases of pelvic pain, and a delayed diagnosis and treatment can lead to chronic pain, adhesive small bowel obstructions, infertility in cases of salpingitis, ectopic pregnancy, and more. The pathogenesis of FHC syndrome is not yet fully understood; it may be a result of direct infection, bloodstream infection, or lymphatic infection. The classic route in women is through sexual transmission, followed by retrograde invasion causing inflammation in the fallopian tubes and urinary tract. Untreated acute inflammation can lead to chronic pelvic inflammation. Then, from the urinary tract, it ascends along the colon's groove to the right greater omentum. On the left, perhaps due to the presence of the cecum's appendage, the cecum itself becomes a natural partition. Additionally, the habit of sleeping on the right side can also facilitate the movement of fluid from the pelvis [5], [9].

A common clinical characteristic in cases of HFC in this study is the presence of abdominal pain, with specific features of right lower rib pain, right pelvic pain, upper abdominal pain, and lower abdominal pain. The pain is often deep and aching, and may worsen with breathing. There may not be clear abdominal guarding. The pain can radiate to the back, up to the right shoulder or down the right arm. Symptoms of fever are intermittent, and the patient may experience chills, fatigue, and night sweats. Nausea and hiccups are present. All patients have symptoms of vaginal discharge with thin, white fluid characteristics, upon examination with a duckbill instrument, there is a discharge through the cervical opening to the vagina. Pelvic examination reveals that the adnexa is narrow, and patients experience pain when the uterus is manipulated.

For the clinical examination of these three cases, they share the following characteristics: Blood tests for all three cases show slight or no increase in white blood cell count, a mild increase in CRP, and a slight elevation in liver enzymes. Transvaginal ultrasound examinations of the adnexa in all three cases do not show typical findings, and there is no free fluid in the pelvis.

However, contrast-enhanced computed tomography (CT) results for all three cases are as follows:

Case 1: The liver was normal in size, with smooth edges, uniform parenchyma, and no pre-injection or post-injection contrast agent accumulation. There is approximately 8.7mm of fluid within the liver capsule. There was significant fluid accumulation in the Douglas pouch, measuring approximately 29.2mm, with free fluid around both ovaries. Free fluid was also present between the bowel loops. The appendix appeared thin, with a diameter of about 5.1mm, and showed no signs of fat infiltration. No abnormalities were seen after contrast injection.

Case 2: The liver was normal in size, with smooth edges, uniform parenchyma, and no pre-injection or post-

injection contrast agent accumulation. The fluid in the hepatic capsule was about 4.5mm thick. Imaging showed a thickened ascending colon wall with mild inflammation in the ileocecal area. The Douglas pouch had thickened fluid measuring approximately 26.2 mm, and there was fluid in the areas around both ovaries and fallopian tubes. The right ovarian cyst measured about 44.7 x 40.6 mm.

Case 3: CT scans showed the appendix located in the pelvic cavity, extending downwards and thickening with a diameter of about 8.4mm, containing fluid and gas. Light infiltration was around the appendix. After the medicine injection, the appendix strongly absorbed it. The liver was normal in size, with smooth edges, uniform parenchyma, and no pre- or post-injection contrast agent accumulation. Pelvis: No abnormal masses detected. No free fluid is seen in the abdomen.

For treatment and management: Due to the variety of causative agents initially unknown before treatment, the initial treatment drug may be a broad-spectrum antibiotic and used in multidrug therapy. However, after the diagnosis of HFC was determined, all three cases were treated with a combination of basic antibiotics, including Metronidazole 500mg twice daily and Doxycycline 100mg twice daily. Vaginal suppositories and medications for treating vaginal inflammation were also used. The patients stabilized and were discharged after about 1 week of hospitalization. To ensure complete recovery, they continued an outpatient treatment regimen for 1 week after discharge, still using the same basic antibiotics (Metronidazole 500mg and Doxycycline 100mg twice daily for 7 more days), in line with the recommended treatment protocol, which proved to be effective. The combination of medications and the treatment of vaginal inflammation helped the patients stabilize quickly and reduced their inpatient stay [5].

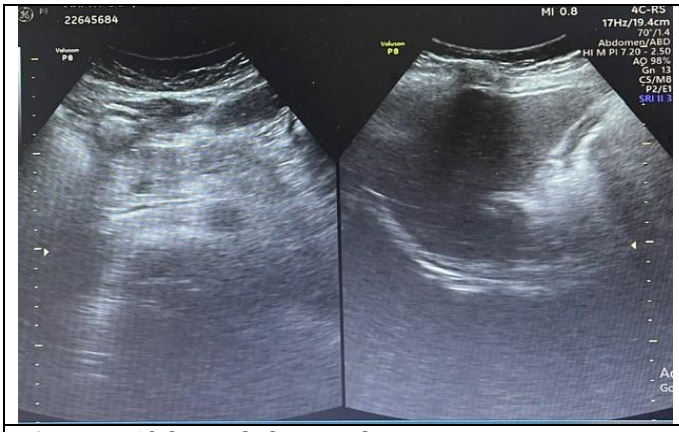

Figure 1: Abdominal ultrasound image

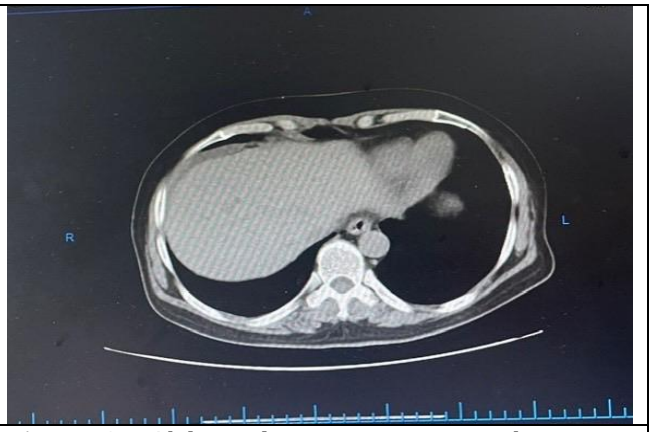

Figure 2: Abdominal scanner image with contrast injection

CONCLUSION

Fitz-Hugh-Curtis Syndrome (FHC) is associated with pelvic inflammatory diseases (PID), including inflammation of the pelvis, cervix, and fallopian tubes. The disease often starts silently, progressing without much attention until specific symptoms (such as upper abdominal pain, right lower rib pain, and right pelvic pain) prompt patients to seek medical care. Patients typically visit internal medicine or general surgery departments due to gastrointestinal symptoms.

Atypical infection and inflammation syndromes were present with no fever, slight or no increase in white blood cell count, and a slight increase in CRP. Their daily activities are largely unaffected. Symptoms of vomiting and bowel disturbances are not pronounced.

The characteristic symptom of the patient's discharge is very distinct, which is thin, white vaginal discharge, and when using a duckbill speculum, it can be seen flowing from the cervical os.

Even though abdominal ultrasound examinations can sometimes detect FHC, a detailed evaluation is essential to avoid missing the diagnosis. Abdominal CT with contrast injection is valuable for diagnosis.

Early and specific combination antibiotic treatment, along with multidrug therapy, results in effective treatment and a shorter hospital stay.

Effective interdisciplinary collaboration among medical specialties, including internal medicine, surgery, and gynecology, is crucial when encountering patients with vague abdominal pain. This can lead to early diagnosis and treatment of FHC, reducing the risk of salpingitis, pelvic inflammation, infertility, and ectopic pregnancies.

REFERENCE

1. Stajano C. La reaccion frenica en ginecologia. Semana Medica-Beunoa Airea 1920; 27: 243-248.
2. Curtis A. A cause of adhesions in the right upper quadrant. JAMA 1930; 94: 1221-1222.
3. Curtis A. Adhesions of the anterior surface of the liver. JAMA 1932; 99: 2010-2012.
4. Fitz-Hugh T Jr. Acute gonococcic peritonitis of the right upper quad-rant in women. JAMA 1934; 102: 2094-2096.
5. Peter NG, Clark LR, Jaeger JR. Fitz-Hugh-Curtis syndrome: A diagnosis to consider in women with right upper quadrant pain. Cleveland Clinic Journal of Medicine March 2004; 71 (3): 233-239.
6. Theofanakis CP, Kyriakidis AV. Fitz-Hugh-Curtis Syndrome. Gynecological Surgery 2011; 8: 129-134.
7. Ekabe CJ, Kenbila J, Njim T, et al. Chlamydia trachomatis-indoced Fitz-Hugh-Curtis Syndrome: a case report. BMC Research Notes 2017; 10: 10 (2017).
8. Takata K, Fukuda H, Umeda K, et al. Fitz-Hugh-Curtis syndrome in a man positive for Chlamydia trachomatis. Clin J Gastroenterol. 2018; 11 (4): 338-342.
9. Basil H, Pop A, Malik A, Sharma S. Fitz-Hugh-Curtis Syndrome. Treasure Island (FL): StatPeals Publishing; 2023 Jan.
10. Lee SC, Nah BG, Kim HS, et al. Two cases of Fitz-Hugh-Curtis syndrome in acure phase. Korean J Gastroenterol. 2005; 45 (2): 137-42.
11. Shimada N, Honda Y, Sugimoto M. Image diagnosis of abdominal infectious disease (infectious enterocolitis and Fitz-Hugh-Curtis Syndrome). Nihon Rinsho. 2007; 65 (Suppl 2. Pt. 1): 247-50.
12. Yang HW, Jung SH, Han HY, et al. Clinical feature of Fitz-Hugh-Curtis syndrome: analysis of 25 cases. Koean J Hepatol. 2008; 24 (2): 178-84.
13. Perricone G. Hepatology of Gastroenterology and Hepatology 2014; 29 (11): 1853-1853.
14. Ikusaka M, Shikino K. Fitz-Hugh-Curtis syndrome. BMJ Case. 2019; 12: e229326.
15. De Boer JP, Verpalen IM, Gabriëls, et al. Fitz-Hugh-Curtis syndrome resulting in nutmeg liver on computed comagraphy. Radio Case Rep. 2019; 14 (8): 930-933.
16. Sásnchez-Oro R, Jara-Díaz AM, Martínez-Sanz G. Fitz-Hugh-Curtis syndrome: A cause of right upper quadrant abdominal pain. Med Clin (Barc). 2020; 154 (11): 447-452.