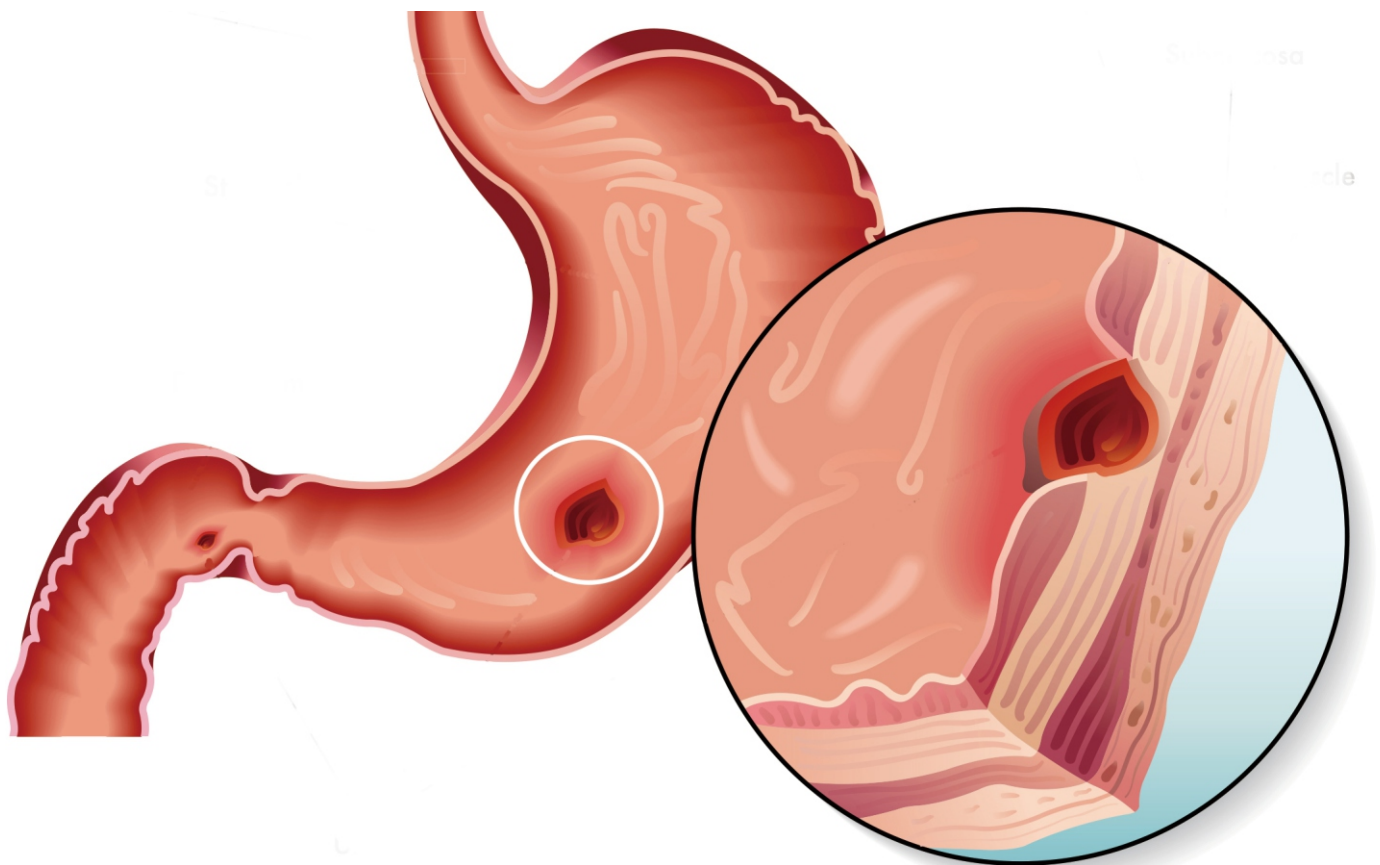


# Open Journal of Gastroenterology



ISSN: 2163-9450



<https://www.scirp.org/journal/ojgas>

# Journal Editorial Board

ISSN: 2163-9450 (Print)      ISSN: 2163-9469 (Online)

<https://www.scirp.org/journal/ojgas>

---

## Editor-in-Chief

**Prof. Weizhen Zhang**      Peking University, China

## Editorial Board

**Prof. Alireza Heidari**      California South University, USA  
**Dr. Sukhotnik Igor**      Bnai Zion Medical Center, Israel  
**Prof. Chang H. Kim**      Purdue University, USA  
**Prof. Rupert Leong**      The University of New South Wales, Australia  
**Dr. Grigorios Leontiadis**      McMaster University, Canada  
**Dr. Andrea Lisotti**      University of Bologna, Italy  
**Dr. Tsutomu Nishida**      Osaka University Hospital, Japan  
**Dr. Robert J. Richards**      Stony Brook University, USA  
**Prof. Basil Rigas**      Stony Brook University, USA  
**Prof. Enrico Roda**      Villa Maria Hospital Group, Italy  
**Prof. Omar I. Saadah**      King Abdulaziz University, Saudi Arabia  
**Prof. Fazlul H. Sarkar**      Wayne State University, USA  
**Dr. Emidio Scarpellini**      San Benedetto General Hospital, Italy  
**Dr. Christian Philipp Selinger**      Leeds Teaching Hospitals NHS Trust, UK  
**Dr. Zhongjie Shi**      Temple University, USA  
**Prof. Yu-Wen Tien**      National Taiwan University, Chinese Taipei  
**Prof. Dan Xie**      Sun Yat-sen University, China  
**Dr. Fang Yan**      Vanderbilt University Medical Center, USA

# Table of Contents

**Volume 12    Number 7**

**July 2022**

**Unusual Case of Miliary Tuberculosis with Hepatic Involvement**

M. A. Adu-Darko.....153

**Clinical Efficacy of Prolonged First-Line Treatment against *Helicobacter pylori* in Ouagadougou**

N. I. Compaore, C. C. Some, N. A. Guingane, T. R. Compaore, M. N. Compaore, R. Sombie, A. Bougouma.....161

**Ileo-Ileal Intussusception Caused by an Inflammatory Fibroid Polyp: A Case Report**

N. Elbahaoui, O. Lahnaoui, N. Boubkri, I. Yassine, L. Yasmine, M. Ouanani, A. Errougani.....170

# Open Journal of Gastroenterology (OJGas)

## Journal Information

### SUBSCRIPTIONS

The *Open Journal of Gastroenterology* (Online at Scientific Research Publishing, <https://www.scirp.org/>) is published monthly by Scientific Research Publishing, Inc., USA.

#### **Subscription rates:**

Print: \$79 per issue.

To subscribe, please contact Journals Subscriptions Department, E-mail: [sub@scirp.org](mailto:sub@scirp.org)

### SERVICES

#### **Advertisements**

Advertisement Sales Department, E-mail: [service@scirp.org](mailto:service@scirp.org)

#### **Reprints (minimum quantity 100 copies)**

Reprints Co-ordinator, Scientific Research Publishing, Inc., USA.

E-mail: [sub@scirp.org](mailto:sub@scirp.org)

### COPYRIGHT

#### **Copyright and reuse rights for the front matter of the journal:**

Copyright © 2022 by Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY).

<http://creativecommons.org/licenses/by/4.0/>

#### **Copyright for individual papers of the journal:**

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

#### **Reuse rights for individual papers:**

Note: At SCIRP authors can choose between CC BY and CC BY-NC. Please consult each paper for its reuse rights.

#### **Disclaimer of liability**

Statements and opinions expressed in the articles and communications are those of the individual contributors and not the statements and opinion of Scientific Research Publishing, Inc. We assume no responsibility or liability for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained herein. We expressly disclaim any implied warranties of merchantability or fitness for a particular purpose. If expert assistance is required, the services of a competent professional person should be sought.

### PRODUCTION INFORMATION

For manuscripts that have been accepted for publication, please contact:

E-mail: [ojgas@scirp.org](mailto:ojgas@scirp.org)

# Unusual Case of Miliary Tuberculosis with Hepatic Involvement

Michael Agyekum Adu-Darko

Department of Acute Internal Medicine, Milton Keynes University Hospital, Milton Keynes, United Kingdom

Email: agyekum64@gmail.com

**How to cite this paper:** Adu-Darko, M.A. (2022) Unusual Case of Miliary Tuberculosis with Hepatic Involvement. *Open Journal of Gastroenterology*, 12, 153-160. <https://doi.org/10.4236/ojgas.2022.127015>

**Received:** June 18, 2022

**Accepted:** July 23, 2022

**Published:** July 26, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution-NonCommercial International License (CC BY-NC 4.0).

<http://creativecommons.org/licenses/by-nc/4.0/>



Open Access

## Abstract

*Miliary tuberculosis (MTB)* of the liver can present non-specifically, which often leads to a diagnostic delay. The objective of this clinical case report is to highlight an unusual presentation of miliary TB in a young female patient, who was admitted to hospital with right upper quadrant tenderness and constitutional symptoms. Most of her investigations yielded little to support the diagnosis until a subsequent positive TB Elispot test and CT chest, abdomen and pelvis with contrast were done. Features of this case are discussed, together with anti-tubercular treatment (ATT) strategy utilized for miliary TB with hepatic involvement.

## Keywords

Miliary TB, Constitutional Symptoms, Anti-Tubercular Treatment (ATT)

## 1. Introduction

*Mycobacterium tuberculosis* (TB) infection of the liver, known as hepatic TB, is an extrapulmonary manifestation of TB. The first recorded case of hepatic TB was reported in 1858 by Dr. John Syer Bristowe, an English physician [1]. In 1905, more than 20 years after Koch's discovery of the TB bacillus, Drs. Rolleston and McNee had classified hepatic TB into miliary (disseminated) and local (isolated) forms [2]. Among reported hepatic TB cases, miliary form accounted for 79% of cases, while local hepatic TB accounted for 21% of cases [3]. If left untreated, miliary TB has a mortality approaching nearly 100% [4], reducing to 7.1% - 30% with treatment [5]. Clinical features of hepatic TB are nonspecific, which often leads to a delay in diagnosis with high morbidity and mortality [6]. The objective of this case report is to emphasize how unusual miliary TB can present and the importance of considering it early as a differential diagnosis.

Hepatic TB has become more prevalent, believed to be due to the immuno-

suppression caused by HIV leading to a reactivation of latent TB [7]. Over 50% of HIV and TB co-infected people present with extrapulmonary involvement, which includes hepatic TB [8].

Tuberculous bacilli can reach the liver via hematogenous dissemination, from the lungs, or by local spread from the gastrointestinal tract [9]. In miliary hepatic TB, bacilli reach the liver via the hepatic artery [10]. Miliary hepatic TB is characterized by diffuse seeding of the liver with tubercles ranging from 0.6 to 2.0 mm in diameter situated in the lobules of the liver [11].

Symptoms include abdominal/flank pain, decreased appetite, fever and chills, malaise and weight loss. Patients often have leukocytosis, elevated inflammatory & liver markers and creatinine. Local hepatic TB and miliary TB may differ in presentation. Local hepatic TB may present primarily as diffuse abdominal pain, while patients with miliary hepatic TB may present with acuterespiratory symptoms such as a cough, with or without sputum production [12].

Liver biopsy with mycobacterial culture is considered the most specific diagnostic test for hepatic TB [11] [12]. Ultrasound guided liver biopsy is generally preferred to improve the sampling and increase the diagnostic accuracy [13].

A clearer understanding of hepatic TB will help clinicians with diagnostic and management decisions to improve patient outcomes.

The World Health Organization (WHO) recommendation for the treatment of drug susceptible pulmonary TB (rifampin, isoniazid, ethambutol, and pyrazinamide for two months, followed by 4 months of rifampin and isoniazid) has been applied to hepatic TB with positive outcomes [14].

Although the optimal duration of treatment of hepatic TB is controversial, usually a duration of 6 - 12 months appears to be effective for most patients [14].

## 2. Clinical Presentation

A 19-year-old female university student originally from Nigeria, West Africa, presented to hospital with intermittent chills, headaches, vomiting, epigastric pain of 7 day duration. She denied cough or weight loss. Physical examination was positive for right upper quadrant tenderness, pyrexia 38 degrees Celsius, hypotension and tachycardia. Murphy's sign was negative and she did not have any palpable lymphadenopathy. The patient was awake and oriented, however, ill-appearing, and complaining of marked photophobia. Her body mass index (BMI) was 18. She denied exposure to immunosuppressant drugs and was HIV negative. **Table 1** shows the lab tests done, which demonstrated liver function derangement (both hepatic and cholestatic picture) and lymphocytosis. Procalcitonin level was elevated at 0.89 nanogram/ml (reference < 0.1 nanogram/ml), suggesting likely bacterial infection. Haemoglobin, white cell count, neutrophil count, lymphocyte count, prothrombin time, partial thromboplastin time and international normalized ratio were within the normal range. At this point, she was commenced on broad-spectrum intravenous antibiotic and acyclovir to cover for possible meningoencephalitis. She had a normal brain CT scan, and

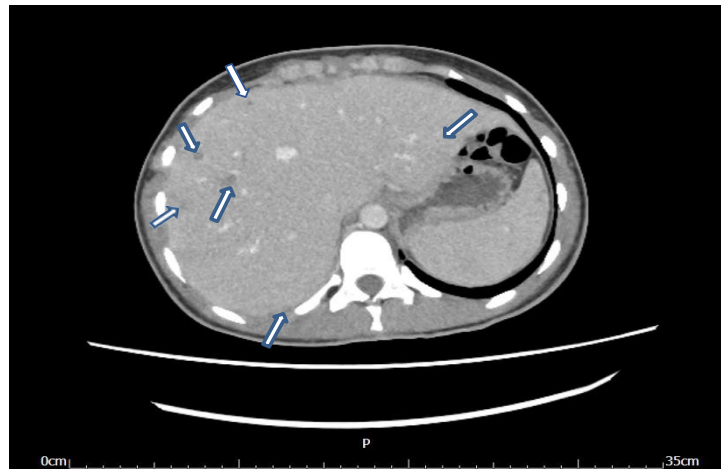
subsequent MRI brain with whole spine scan was reported as normal with no leptomeningeal enhancement or abnormal lesions. The patient had a lumbar puncture, which demonstrated normal opening cerebrospinal fluid (CSF) pressure of 16 mm Hg. Patient's CSF results are summarised in **Table 2**. The CSF microbiology indicated negative cultures, negative gram film, marked lymphocytosis (90%), in the context of low glucose levels and normal protein count. No fungal isolates were detected on the CSF. Her TB culture specimen and TB PCR (GeneXpert) were both negative. TB Elispot test came back positive after 10days. Subsequently, a CT thorax, abdomen and pelvis with contrast revealed numerous tiny nodules in both lungs, liver, spleen and right kidney with no collections (**Figure 1** and **Figure 2**). She was diagnosed as a case of *miliary tuberculosis infection*, immediately commenced on anti-tubercular therapy (ATT) and transferred to a tertiary hospital for more specialist care input as well as a liver biopsy via interventional radiology. The histology of the liver biopsy did not demonstrate granuloma, but her TB culture on the specimen was positive for Acid Fast Bacillus (AFB) confirmed to be *Mycobacterium tuberculosis*. On starting ATT,

**Table 1.** Laboratory exams.

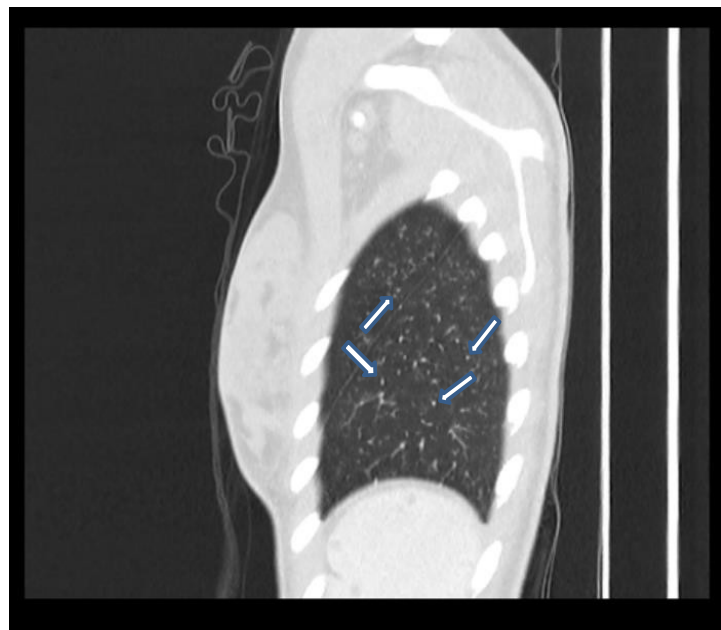
| PARAMETERS       | Value               | Reference Range              |
|------------------|---------------------|------------------------------|
| Hb               | 132 g/L             | (123 - 145 g/L)              |
| WBC count        | $4.5 \times 10^9/L$ | $(4.0 - 11.0 \times 10^9/L)$ |
| Neutrophil count | $2.8 \times 10^9/L$ | $(1.5 - 8.0 \times 10^9/L)$  |
| Lymphocyte count | $1.0 \times 10^9/L$ | $(1.0 - 4.0 \times 10^9/L)$  |
| AST              | 88 IU/L             | (10 - 35 IU/L)               |
| GGT              | 660 IU/L            | (6 - 42 IU/L)                |
| ALP              | 317 IU/L            | (30 - 130 IU/L)              |
| Bilirubin        | 14 umol/L           | (<21 umol/L)                 |
| CRP              | 48 mg/L             | (<10 mg/L)                   |

**Table 2.** Cerebrospinal fluid (CSF) exam.

| PARAMETERS      |                   |                        |
|-----------------|-------------------|------------------------|
| Appearance      | Colourless, clear |                        |
|                 | Value             | Reference Range        |
| pH              | 7.30              | 7.35 - 7.45            |
| Glucose         | 1.8 mmol/L        | 1.6 - 2.5 mmol/L       |
| Protein         | 0.25 g/L          | 0.1 - 0.5 g/L          |
| WBC             | $2 \times 10^6/L$ | 0 - 5 cells/uL         |
| Neutrophils     | -                 | -                      |
| Lymphocytes     | >10 cells/uL      | 0 - 5 cells/uL         |
| Red blood cells | 1/mm <sup>3</sup> | 0 - 10/mm <sup>3</sup> |



**Figure 1.** CT abdomen showing multiple miliary nodules (tubercules) indicated by the white arrows.



**Figure 2.** CT thorax (lateral view) showing multiple miliary nodules (tubercules) indicated by the white arrows.

her high-grade fevers improved in the next 24 hours, and she had initial visual assessment and daily liver function tests (LFTs) to monitor for side effects of ATT. Although she initially had worsening of her GGT and ALP, they remained stable over 72 hours of initiation therapy. Patient stayed in hospital for another 7 days before discharge with planned follow-up with the community TB nurse and Infectious Diseases outpatient reviews. She remained compliant with ATT and returned to her studies successfully.

### 3. Discussion

Tuberculosis (TB) is a leading cause of preventable morbidity and mortality



worldwide. The latest World Health Organization (WHO) figures indicate that total of 1.5 million people died from TB in 2020 (including 214,000 people with HIV) [15]. Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS) [15]. In 2020, an estimated 10 million people fell ill with tuberculosis (TB) worldwide [15]. The disease is characterized by high mortality, reported to be between 18% and 30% [15]. The epidemiology of military TB has been altered by the emergence of the human immunodeficiency virus (HIV) infection and widespread use of immunosuppressive drugs [15]. A TB liver abscess commonly arises from local hepatic TB but may also occur following military hepatic TB [16]. Local hepatic TB tends to cause more hepatocellular damage than military hepatic TB [17]. In contrast to military hepatic TB, those with local hepatic TB do not generally have evidence of active pulmonary disease [18].

Miliary TB is diagnosed by the presence of a diffuse miliary infiltrate on chest radiograph or high-resolution computed tomography (HRCT) scan, or evidence of miliary tubercles in multiple organs at laparoscopy, open surgery, or autopsy [19]. Liver biopsy with mycobacterial culture remains the most specific diagnostic test for hepatic TB [12]. The characteristic histological feature of both miliary and local forms of hepatic TB is the granuloma [11]. Hepatic granulomas are due to cell-mediated immunological responses to TB antigens and consist of focal aggregates of macrophages, including Kupffer cells that may coalesce to form Langerhans giant cells with surrounding lymphocytes and fibroblasts [17]. The clinical and morbid anatomic picture needs to be confirmed by bacteriology, histopathology, and/or a dramatic chemotherapeutic response [12]. Early risk stratification with a high index of suspicion in patients with potential risk factors, early anti-tubercular treatment, and nutritional support are key to better outcomes.

This case had risk factors including reduced BMI and possible exposure given her ethnic background. Interestingly, she did not have a BCG scar on inspection of her shoulders. She presented with non-specific systemic symptoms with markedly deranged liver function tests (LFTs), in the context of features suggestive of meningitis. Of note, majority of miliary TB cases reported were associated with immunosuppression secondary to diabetes, underlying malignancy or coinfection with HIV/AIDS, which was not seen in our case. The patient's TB Elispot test result arrived 10 days into her admission, as it was usually performed by an off-site laboratory out of area of the admitting hospital. While liver biopsy may not always be necessary, microbiological and histological findings can allow for a more accurate diagnosis [11]. Occasional elevation of ALT (typical range: 0 - 200 U/L) and aspartate transaminase (AST) is often seen (typical range: 0 - 200 U/L) [19] [20]. Higher levels of ALT and AST were observed in jaundiced patients [21]. According to a systematic review by Hickey AJ *et al.* [22], the most common abnormalities associated with hepatic TB include ALP (typical range: 200 - 750 U/L) and GGT (typical range: 100 - 400 U/L). In this case report, patient did not develop jaundice. Mild hyperbilirubinemia has been reported in both miliary

and local hepatic TB cases [12], with similar trend seen in this case report's elevated bilirubin. A liver biopsy is indicated in any person with a constellation of clinical, laboratory, and radiographic suspicion of hepatic TB [19], all of which were seen in this patient. Ultrasound (US) guided liver biopsy is generally preferred to improve the sampling and increase the diagnostic accuracy [19]. Liver biopsies, when taken, should be sent for both microbiological and histological evaluation [19]. In a hepatic TB case series, AFB smear had a median sensitivity of 25% (range: 0% - 59%) [20], and unsurprisingly, this patient's AFB smear was negative. She had US guided liver biopsy subsequently, and TB culture was positive.

The duration of treatment was based on the recommendation by The National Institute for Health and Clinical Excellence (NICE) [3] guidelines from UK, American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA) [8]; all endorsing six (6) months of treatment (2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin, followed by a 4-month continuation phase with isoniazid and rifampicin).

In conclusion, miliary TB with hepatic involvement can easily be missed due to their insidious onset and presentation, typically with vague symptoms and signs. In this case, the patient kept on deteriorating even with appropriate broad-spectrum antibiotic treatment and timely CT chest, abdomen and pelvis was key to confirming the diagnosis and starting treatment early. Prompt commencement of ATT will achieve good clinical response should the diagnosis be correct, which can be lifesaving in the setting of risk factors such as low BMI. Patients with definitive or clinically suggestive hepatic TB should be promptly initiated on 4-drug anti-TB therapy, and clinicians should observe closely for drug toxicity and complications, such as Drug Induced Liver Injury (DILI) and TB-Immune Reconstitution Inflammatory Syndrome (IRIS) [21]. Co-infection with HIV can complicate the management of hepatic TB, and clinicians must be knowledgeable of differences in pathophysiology, treatment, and disease management [22]. A high index of suspicion for hepatic TB is important if clinicians are to make an early diagnosis and initiate prompt treatment to improve clinical outcomes [22].

#### **4. Learning Points**

- A high index of suspicion should be considered in patients with risk factors for miliary TB.
- Early diagnosis with TB specimen cultures, abdominal CT is crucial to preventing long term sequelae.
- Early commencement of ATT demonstrates good rapid clinical response, should the diagnosis of TB be accurate.

#### **Authors and Affiliations**

MAD is the sole contributor in writing the manuscript, including history taking,

examination, laboratory investigations and follow up. DK was involved in the care of this patient and so was AC. JR assisted in radiology analysis and interpretation.

### Ethics approval and Consent to Participate

Consent for publication was obtained from the patient.

### Financial Support/Conflict of Interests

There was no funding supporting this work. The author has no relevant affiliation or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter discussed in the manuscript.

### Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

### References

- [1] Bristowe, J.S. (1858) On the Connection between Abscess of the Liver and Gastrointestinal Ulceration. *Transactions of the Pathological Society of London*, **9**, 241-252.
- [2] Chien, R.N., Lin, P.Y. and Liaw, Y.F. (1995) Hepatic Tuberculosis: Comparison of Miliary and Local Form. *Infection*, **23**, 5-8. <https://doi.org/10.1007/BF01710049>
- [3] National Institute for Health and Clinical Excellence, National Collaborating Centre for Chronic Conditions (2006) Management of Non-Respiratory Tuberculosis. In: *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and control*, Royal College of Physicians, London, 63-76.
- [4] Falk, A. (1965) U.S. Veterans Administration-Armed Forces Cooperative Study on the Chemotherapy of Tuberculosis. Tuberculous Meningitis in Adults, with Special Reference to Survival, Neurologic Residuals, and Work Status. *American Review of Respiratory Disease*, **91**, 823-831. <https://doi.org/10.1164/arrd.1965.91.1.6>
- [5] Venkatraman, N., King, T., Bell, D., Woltmann, G., Wiselka, M., Abubakar, I., et al. (2016) High Levels of Neurological Involvement But Low Mortality in Miliary Tuberculosis: A 6-Year Case-Series from the UK. *European Respiratory Journal*, **47**, 1578-1581. <https://doi.org/10.1183/13993003.01958-2015>
- [6] Muray, C.J. and Lopez, A.D. (1997) Global Mortality, Disability, and the Contribution of Risk Factors: Global Burden of Disease Study. *Lancet*, **349**, 1436-1442. [https://doi.org/10.1016/S0140-6736\(96\)07495-8](https://doi.org/10.1016/S0140-6736(96)07495-8)
- [7] Sharma, S.K. and Mohan, A. (2009) Disseminated and Miliary Tuberculosis. In: Sharma, S.K. and Mohan, A., Eds., *Tuberculosis*, 2nd Edition, Jaypee Brothers, New Delhi, 493-518. [https://doi.org/10.5005/jp/books/10992\\_34](https://doi.org/10.5005/jp/books/10992_34)
- [8] Blumberg, H.M., Burman, W.J., Chaisson, R.E., Daley, C.L., Etkind, S.C., Friedman, L.N., et al. (2003) American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, **167**, 603-662. <https://doi.org/10.1164/rccm.167.4.603>
- [9] Wang, J.Y., Hsueh, P.R., Wang, S.K., Jan, I.S., Lee, L.N., Liaw, Y.S., et al. (2007)

- Disseminated Tuberculosis: A 10-Year Experience in a Medical Center. *Medicine*, **86**, 39-46. <https://doi.org/10.1097/MD.0b013e318030b605>
- [10] Chong, V.H. and Lim, K.S. (2010) Hepatobiliary Tuberculosis. *Singapore Medical Journal*, **51**, 744-750
- [11] Purl, A.S., Nayyar, A.K. and Vij, J.C. (1994) Hepatic Tuberculosis. *Indian Journal of Tuberculosis*, **41**, 131-134.
- [12] Hersch, C. (1964) Tuberculosis of the Liver: A Study of 200 Cases. *South African Medical Journal*, **38**, 857-863.
- [13] Grant, A. and Neuberger, J. (1999) Guidelines on the Use of Liver Biopsy in Clinical Practice. *Gut*, **45**, IV1-IV11. <https://doi.org/10.1136/gut.45.2008.iv1>
- [14] Alvarez, S.Z. (1998) Hepatobiliary Tuberculosis. *Journal of Gastroenterology and Hepatology*, **13**, 833-839. <https://doi.org/10.1111/j.1440-1746.1998.tb00743.x>
- [15] World Health Organization (2020) WHO Report: Global Tuberculosis Control. World Health Organization, Geneva.
- [16] Essop, A.R., Posen, J.A., Hodgkinson, J.H. and Segal, I. (1984) Tuberculosis Hepatitis: A Clinical Review of 96 Cases. *QJM*, **53**, 465-477.
- [17] Huang, W.T., Wang, C.C., Chen, W., Cheng, Y.F. and Eng, H.L. (2003) The Nodular Form of Hepatic Tuberculosis: A Review with Five Additional New Cases. *Journal of Clinical Pathology*, **56**, 835-839. <https://doi.org/10.1136/jcp.56.11.835>
- [18] Nawaz, A., Malik, K., Alvi, A. and Ali, B. (2016) Hepatic Tuberculosis in an Immunocompetent Patient—A Diagnostic Challenge. *American Journal of Gastroenterology*, **111**, S949.
- [19] Mert, A., Ozaras, R., Tabak, F. and Ozturk, B.M. (2003) Localized Hepatic Tuberculosis. *European Journal of Internal Medicine*, **14**, 511-512. <https://doi.org/10.1016/j.ejim.2003.09.007>
- [20] Ferrari, T.C.A., Couto, C.M., Vilaca, T.S. and Xavier, M.A.P. (2006) Localized Hepatic Tuberculosis Presenting as Fever of Unknown Origin. *Brazilian Journal of Infectious Diseases*, **10**, 364-367. <https://doi.org/10.1590/S1413-86702006000500013>
- [21] Alvarez, S.Z. and Carpio, R. (1983) Hepatobiliary Tuberculosis. *Digestive Diseases and Sciences*, **28**, 193-200. <https://doi.org/10.1007/BF01295113>
- [22] Hickey, A.J., Gounder, L., Moosa, M.Y. and Drain, P.K. (2015) A systematic Review of Hepatic Tuberculosis with Considerations in Human Immunodeficiency Virus Co-Infection. *BMC Infectious Diseases*, **15**, Article No. 209. <https://doi.org/10.1186/s12879-015-0944-6>

# Clinical Efficacy of Prolonged First-Line Treatment against *Helicobacter pylori* in Ouagadougou

Nômawendé Inès Compaore<sup>1</sup>, COUNA Christiane Some<sup>2</sup>, Nanelin Alice Guingane<sup>3</sup>, Tegwinde Rebeca Compaore<sup>4</sup>, Marie Nina Compaore<sup>5</sup>, Roger Sombie<sup>2</sup>, Alain Bougouma<sup>2</sup>

<sup>1</sup>Service of Medicine and Medical Specialties, Medical Center with Surgical Antenna El Fateh-Suka, Ouagadougou, Burkina Faso

<sup>2</sup>Service of Hepato-Gastroenterology of Yalgado Ouedraogo University Hospital Center, Ouagadougou, Burkina Faso

<sup>3</sup>Service of Hepato-Gastroenterology of the University Hospital Center of Bogodogo, Ouagadougou, Burkina Faso

<sup>4</sup>LABIOGENE, Laboratory of Molecular Biology and Genetic, University of Ouagadougou, Ouagadougou, Burkina Faso

<sup>5</sup>Epidemiology/Health Science Center of Houston, Houston, United States of America

Email: noomadoc@gmail.com

**How to cite this paper:** Compaore, N.I., Some, C.C., Guingane, N.A., Compaore, T.R., Compaore, M.N., Sombie, R. and Bougouma, A. (2022) Clinical Efficacy of Prolonged First-Line Treatment against *Helicobacter pylori* in Ouagadougou. *Open Journal of Gastroenterology*, 12, 161-169. <https://doi.org/10.4236/ojgas.2022.127016>

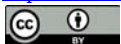
**Received:** June 5, 2022

**Accepted:** July 24, 2022

**Published:** July 27, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

**Background:** *Helicobacter pylori* (*H. pylori*) infection is a public health concern. In fact, due to bacterial resistance, treatment strategy is a challenge. It is then more recommended to prolong first-line treatment. In order to be acceptable, the clinical efficacy of treatment must be higher than 90%. **Aim:** We aimed to assess the outcome of prolonged first-line treatment among adults. **Patients and Methods:** The study was cross-sectional among adults and patients were treated for *H. pylori* eradication for the first time during 10 to 14 days. Recruitment was made from March 2019 in six private polyclinics and two hospitals of the city of Ouagadougou. We used monoclonal antigen (Ag) test on the stool samples for diagnostic and for the patients follow up. Chi squared ( $X^2$ ) tests and ANOVA for the comparison of percentages and means were determined using with STATA<sup>®</sup> software program in the bilateral 95% confidence interval for the statistical analysis. **Results:** In the different medical centers for 19 months, 365 patients were compiled. The sex-ratio was 0.64. The average age was 43.55 years. The treatment efficacy was 92.88%. Treatment efficacy was better with p-value  $<10^{-3}$  depending on prescriber: gastroenterologist (94.07%), general practitioner (75%); compliance before treatment: excellent (95.88%) or bad (50%); number of consultations:  $\geq$ four (94.35%), three (96.32%), two (78.85%). Triple therapies efficacy was 90.81%; p = 0.19. Quadritherapy efficacy was 95%; p = 0.5. **Conclusion:** This research is a contribution to the advent of national or African recommendations.

---

## Keywords

*Helicobacter pylori*, Treatment Efficacy, Triple Therapies, Quadritherapy

---

### 1. Introduction

*Helicobacter pylori* (*H. pylori*) infection is a public health concern. In Burkina Faso and other developing countries, the prevalence of this infection remains high (80%) [1] [2] [3] [4]. However, it's tending to fall (less than 50%) in many countries [5] [6] [7].

It's necessary to follow up after treatment in order to confirm its efficacy when the eradication rate is over ( $\geq$ ) 80% [5]. To be acceptable, clinical efficacy of treatment must be higher than 90% [8] [9]. *H. pylori* treatment follow up can be done with a urea breath test or monoclonal antigen test on stool sample [5] [8] [9].

*H. pylori* eradication leads to gastric cancer prevention, patients' clinical well-being and reduced health costs [4] [5]. However, bacterial resistance is growing, and treatment strategy is a challenge [5] [8] [10]. And it is more recommended to prolong first-line treatment [5].

In Burkina Faso there are several publications on *H. pylori* epidemiology [1] [2] [3]. We found neither national nor African recommendations on treatment [11]. Local antimicrobial resistance is the determinant of successful *H. pylori* treatment [12]. A prospective molecular study attested a low-level primary clarithromycin resistance of *H. pylori* on 2018 [3]. *H. pylori* eradication rate after seven days triple therapy was poor (22.3%) in a neighboring country [13]. Western countries currently use sequential quadruple therapy or bismuth-based [13]. This study was done to assess the outcome of prolonged first-line treatment (10 to 14 days) among adults. We compared different regimens implemented in current practice and the aim was to select the best first line treatment.

### 2. Methodology

The study was cross-sectional in cohort of Burkinabe patients from March 2019 to September 2020 in the city of Ouagadougou. Patients' recruitment was made in six (6) private polyclinics (El-Fateh Suka, Nina, Notre Dame de la Paix, SANDOF, Yati and Cercle d'or medical Center) and two hospitals (Yalgado Ouedraogo University Hospital Center and Saint Camille Hospital of Ouagadougou). Patients were at least 18 years old and treated for *H. pylori* eradication for the first time during 10 to 14 days.

The minimum size calculated using the OpenEpi<sup>®</sup> software was 356 based on the Fleiss<sup>®</sup> method with continuity correction. We set the power at 80%; the sparrow size ratio, unexposed/exposed to 1; the percentage of the unexposed with results at 80% and that of the exposed at 91%. Patients were grouped according to their level of education into several occupational groups: no high

school diploma, middle manager; senior manager and others (students and retirees). The terms middle and senior managers referred respectively to less than 3 years and over 3 years in college.

We used monoclonal antigen (Ag) test on patients stool samples for *H. pylori* infection's diagnostic. The test was also used for following up after treatment: follow up for at least four weeks and not more than 12 weeks after the end of treatment (beyond possible reinfection). To be valid, it had to have been done remotely from taking proton pump inhibitors (PPIs) more than 2 weeks and/or an antibiotic and/or bismuth more than 4 weeks.

The PPIs used were prescribed as a single daily or twice-daily dose: omeprazole 20 mg, lansoprazole 30 mg, esomeprazole 20 and 40 mg or pantoprazole 20 and 40 mg. The different therapeutic regimens according to the associated antibiotic therapy applied were:

Triple therapies:

- three lines of standard: amoxicillin 1000 mg 2 times daily ± clarithromycin 500 mg 2 times daily or metronidazole 500 mg 2 times daily
- high doses: amoxicillin 750 mg 3 times daily + metronidazole 500 mg 3 times daily;
- sequential: amoxicillin for the first 5 to 7 days and the following days clarithromycin + metronidazole;

Quadritherapy:

- concomitant: amoxicillin + clarithromycin + metronidazole;
- bismuth: 3 capsules (bismuth potassium sub citrate 140 mg + tetracycline hydrochloride 125 mg + metronidazole 125 mg and potassium 32 mg) × 4 times daily;
- high doses + clarithromycin;
- with Cefixime (replaced of amoxicillin): Cefixime 200 mg 2 times daily + metronidazole + clarithromycin.

The parameters used to assess treatment were: compliance before treatment (excellent, good, acceptable, bad and very bad), treatment tolerance (excellent, good, acceptable, bad and very bad), duration of treatment (10 days, 11 to 13 days and 14 days), prescriber (gastroenterologist or general practitioner), delay before control (4 to 6 weeks, 7 to 8 weeks, 9 to 10 weeks, 11 weeks) and Number of consultations (2, 3, ≥4).

Clinical efficacy of the prolonged first-line treatment was attest by a negative Ag test control after treatment.

The data was collected in anonymous evaluation form for each patient and then compiled in STATA<sup>®</sup> (College Station, TX) software program.

Chi squared ( $X^2$ ) tests and ANOVA for the comparison of percentages and means were carried out in the bilateral 95% confidence interval for the statistical analysis.

Our study includes all those who gave their informed consent, completed their treatment for the first time during 10 to 14 days and who have been seen at least

twice. Our objective was to collect anonymously the data's of at least 178 patients in each group. Triple therapies or quadritherapy were randomly assigned by prescribers.

### 3. Results

From June 09, 2019, to August 06, 2020, 365 patients were compiled for the study.

Extended first line therapy failed in 26 patients (7.12%). Treatment efficacy was 92.88%.

The results of the post-therapeutic control were summarized according to the socio-demographic risk factors in "Table 1", treatment risk factors in "Table 2" and other therapeutics risk factors in "Table 3".

The average age was 43.55 years.

The sex-ratio was 0.64 in favor of women (p-value not significant).

The residency was mix for four patients. Those residing in urban areas were 57.89%.

The higher the level of education, the longer the treatment was prolonged, and it was associated to better result of treatment.

Treatment efficacy was better (p-value <  $10^{-3}$ ) depending on compliance before treatment: excellent (95.88%) or bad (50%). Good tolerance was associated to better results but a ratio could not be established among our patients.

Treatment efficacy was better (p-value <  $10^{-3}$ ) depending on prescriber (gastroenterologist) and higher number of consultations.

**Table 1.** Treatment outcomes by socio-demographic risk factors.

| Socio-demographic risk factors (%) | Ag <i>H. pylori</i> control test |        | p-value | X <sup>2</sup> |
|------------------------------------|----------------------------------|--------|---------|----------------|
|                                    | Ag - N (%)                       | Ag + N |         |                |
| <b>Age</b>                         |                                  |        |         |                |
| 22 to 40 years old (46.30)         | 159                              | 10     | 0.91    | 0.15           |
| 41 to 60 years old (40.55)         | 132                              | 15     |         |                |
| 61 to 90 years old (13.15)         | 47                               | 1      |         |                |
| <b>Gender</b>                      |                                  |        |         |                |
| Male (38.9)                        | 135                              | 7      | 0.19    | 0.14           |
| Female (61.1)                      | 204                              | 19     |         |                |
| <b>Residency</b>                   |                                  |        |         |                |
| urban (57.89)                      | 196                              | 13     | 0.70    | 0.43           |
| Rural (42.11)                      | 141                              | 11     |         |                |
| <b>Profession</b>                  |                                  |        |         |                |
| No High school diploma (42.46)     | 139 (89.68)                      | 16     | 0.02    | 0.21           |
| Middle manager (34.79)             | 120 (93.70)                      | 7      |         |                |
| Senior Manager (13.5)              | 46 (95.83)                       | 2      |         |                |
| Others (9.59)                      | 34 (97.14)                       | 1      |         |                |



**Table 2.** Treatment outcomes by treatment risk factors.

| Treatment risk factors (%)             | Ag <i>H. pylori</i> control test |        | p-value          | X <sup>2</sup>   |
|--|----------------------------------|--------|------------------|------------------|
|  | Ag – N (%)                       | Ag + N |                  |                  |
| <b>Compliance before treatment</b>     |                                  |        |                  |                  |
| Excellent                              | 186 (95.88)                      | 8      | 10 <sup>-4</sup> | 10 <sup>-4</sup> |
| Good                                   | 118 (92.91)                      | 9      |                  |                  |
| Acceptable                             | 23 (82.14)                       | 5      |                  |                  |
| Bad                                    | 4 (50)                           | 4      |                  |                  |
| Very bad                               | 8 (100)                          | 0      |                  |                  |
| <b>Treatment tolerance<sup>a</sup></b> |                                  |        |                  |                  |
| Excellent                              | 134 (97.10)                      | 4      | 0.17             | 10 <sup>-3</sup> |
| Good                                   | 104 (90.43)                      | 11     |                  |                  |
| Acceptable                             | 61 (84.72)                       | 11     |                  |                  |
| Bad                                    | 28 (100)                         | 0      |                  |                  |
| Very bad                               | 12 (100)                         | 0      |                  |                  |
| <b>Duration of treatment</b>           |                                  |        |                  |                  |
| 10 days                                | 122 (89.71)                      | 14     | 0.048            | 0.29             |
| 11 to 13 days                          | 9 (100)                          | 0      |                  |                  |
| 14 days                                | 208 (94.55)                      | 12     |                  |                  |

<sup>a</sup>The reported reasons for poor tolerance were: the high number of tablets to swallow (28 patients); insomnia (4 patients); constipation (4 patients); polyarthralgia (4 patients) and discomfort (4 patients). There was intolerance to metronidazole for 8 patients and to clarithromycin for 4 patients.

**Table 3.** Treatment outcomes by others therapeutics risk factors.

| Others therapeutics treatment risk factors (%) | Ag <i>H. pylori</i> control test |        | p-value          | X <sup>2</sup>    |
|--|----------------------------------|--------|------------------|-------------------|
|  | Ag – N (%)                       | Ag + N |                  |                   |
| <b>Prescriber</b>                              |                                  |        |                  |                   |
| Gastroenterologist                             | 318 (94.07)                      | 19     | 10 <sup>-4</sup> | <10 <sup>-4</sup> |
| General Practitioner                           | 21 (75)                          | 7      |                  |                   |
| <b>Delay before control</b>                    |                                  |        |                  |                   |
| 4 to 6 weeks                                   | 234                              | 19     | 0.91             | 0.26              |
| 7 to 8 weeks                                   | 52                               | 0      |                  |                   |
| 9 to 10 weeks                                  | 45                               | 7      |                  |                   |
| 11 weeks                                       | 8                                | 0      |                  |                   |
| <b>Number of consultations</b>                 |                                  |        |                  |                   |
| 2  | 41 (78.85)                       | 11     | 10 <sup>-3</sup> | 10 <sup>-3</sup>  |
| 3  | 131 (96.32)                      | 5      |                  |                   |
| ≥4   | 167 (94.35)                      | 10     |                  |                   |

The results of the post-therapeutic control have been summarized according to antibiotics regimens and or anti-secretory regimens in “**Table 4**”.

Treatment efficacy was not related to antibiotics regimens, antisecretory type or dosage. A single dose of Omeprazole (20 mg) twice daily was 91.37% therapeutically efficient (p-value not significant).

**Table 4.** Treatment outcomes by antibiotics regimens.

| Treatment regimens (%)   | Ag <i>H. pylori</i> control test |        | p-value | X <sup>2</sup> |
|--|----------------------------------|--------|---------|----------------|
|  | Ag - N (%)                       | Ag + N |         |                |
| <b>Antibiotics regimens</b>                                      |                                  |        |         |                |
| <b>Triple therapies</b>  | <b>168 (90.81)</b>               | 17     | 0.6     | 0.9            |
| Amoxicillin/clarithromycin                                       | 110 (93.22)                      | 8      |         |                |
| Metronidazole/clarithromycin                                     | 1 (100)                          | 0      |         |                |
| Amoxicillin/metronidazole  | 26 (81.25)                       | 6      |         |                |
| High dose  | 27 (90)                          | 3      |         |                |
| Sequential   | 4 (100)                          | 0      |         |                |
| <b>Quadritherapy</b>   | <b>171 (95)</b>                  | 9      | 0.27    | 0.50           |
| Bismuth  | 33 (91.67)                       | 3      |         |                |
| Concomitant  | 112 (96.55)                      | 4      |         |                |
| High dose  | 22 (91.66)                       | 2      |         |                |
| With Cefixime  | 4 (100)                          | 0      |         |                |
| <b>Anti-secretory regimens</b>                                   |                                  |        |         |                |
| <b>Type of anti-secretory</b>                                    |                                  |        |         |                |
| Omeprazole   | 233 (91.37)                      | 22     | 0.13    | 0.12           |
| Pantoprazole   | 34 (100)                         | 0      |         |                |
| Lanzoprazole   | 44 (91.67)                       | 4      |         |                |
| Oesomeprazole  | 28 (100)                         | 0      |         |                |
| <b>Anti-secretory Dosage</b>                                     |                                  |        |         |                |
| Double unique (Pantoprazole et Oesomeprazole)                    | 8 (100)                          | 0      | 0.93    | 1              |
| Simple twice daily (Omeprazole and others)                       | 295 (92.48)                      | 24     |         |                |
| Double twice daily (Pantoprazole/Lanzoprazole and Oesomeprazole) | 36 (94.74)                       | 2      |         |                |

#### 4. Discussion

In that Burkina Faso, *H. pylori* prevalence is over 80% in various populations [1] [2] [3] [14] [15] [16], while in Europeans' and many developed countries it is less than 50% [5] [15]. It is accepted nowadays that geographic and socio-economics differences between populations is the main reason of these variations [4] [11]. Inadequate health-care system, lack of treatment guidelines, lack of standardized diagnosis and lack of data are several challenges encountered in Africa [11].

Middle-aged women, residing in urban areas were the most represented among our patients. In similar studies, no gender difference is established to this bacterium [4] [5] [13] [15]. In developing countries, *H. pylori* infection rate is more predominant in young adults [1] [2] [13]. Alcohol and tobacco seem to have no epidemiological effect [13].

The higher the level of education, the longer the treatment was prolonged, and it was associated to better result of treatment (p-value not significant) in this study.

The choice of the identification methods depends on the performance, the availability, the cost and other factors [17]. The pathological examination of gastric biopsies has high specificity and sensitivity [4] [5]. Breath test with urea la-

beled with carbon-13 or 14 is still the reference as a non-invasive test for checking the efficiency of *H. pylori* eradicating treatments [5] [13]. However its cost remains high and it is scarcely available in our country. Fecal antigen assays especially those based on ELISA have excellent sensitivity and specificity [5] [12]. Some serology tests have high sensitivity and specificity but need locally validated [5].

Prolonged first line treatment revealed an excellent clinical efficacy at 92.88% among our study population.

Concomitant quadritherapy (96.55%) was the best treatment regiment, followed by the triple therapy combining amoxicillin with clarithromycin (93.22%). Increasing doses of amoxicillin and metronidazole appeared to improve outcomes in triple therapy (from 81.25% to 90%) but not in quadritherapy (from 96.55% to 91.66%). Rates of 100% were observed but in very small numbers (<5 patients) with sequential triple therapy, which combined clarithromycin with metronidazole and quadritherapy with cefixime. The probable explanation is the low primary resistance of clarithromycin already mentioned in several studies [3] [5] [18] [19].

This study attests (p-value < 10<sup>-3</sup>) that the treatment efficacy is better if the prescriber is a gastroenterologist, compliance before treatment is excellent and the number of consultations is over three (≥3). Tolerance was also associated with treatment efficacy, but the ratio could not be established among our patients. Among treatment failure risk factors there are antibiotics resistance to *H. pylori*, older age, low therapeutic compliance, the onset of treatment side effects [18] [20] [21] [22].

Treatment efficacy was not related to age, sex, residence, time before control, or antisecretory type. A single dose of Omeprazole (20 mg) twice daily, seems to have an excellent therapeutic efficacy (91.37%). Future studies are required.

Our study has selection bias due to its place in real life with expenses borne by patients. We have not assessed financial constraints. However, this may also be an advantage allowing us to describe the real challenges of managing *H. pylori* in a hospital setting in Ouagadougou.

## 5. Conclusion

International recommendations on *H. pylori*, particularly American, European and Asian are constantly updated. This research could contribute to the advent of national or African recommendations [5] [6] [8].

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] Sermé, A.K., Compaoré, N.I., Compaoré, R., Djigma, F., Somda, K.S., Diarra, B.,

- Coulibaly, A., Zohoncon, T., Obiri-Yeboah, D., Sombie, A.R., Bougouma, A. and Simporé, J. (2016) *Helicobacter pylori* and Upper Digestive Diseases—Diagnosis through Real Time PCR. *Nigerian Journal of Gastroenterology and Hepatology*, **8**, 71-80.
- [2] Cataldo, F., Simporé, J., Greco, P., Ilboudo, D. and Musumeci, S. (2004) *Helicobacter pylori* Infection in Burkina Faso: An Enigma within an Enigma. *Digestive and Liver Disease*, **36**, 589-593. <https://doi.org/10.1016/j.dld.2004.05.005>
- [3] Sia, R., Plouzeau, C., Godonou, H.S.M., Guingané, A., Coulibaly, A., Somda, S., Sermé, A.K. and Burucoa, C. (2019) Low-Level Primary Clarithromycin Resistance of *Helicobacter pylori* in Burkina Faso: A Prospective Molecular Study. *Helicobacter*, **24**, Article ID: e12551. <https://doi.org/10.1111/hel.12551>
- [4] Diakité, M., Koné, A., Aké, A.F., Koffi, K.O.C., Okon, A.J.B. and Diallo, K. (2022) *Helicobacter pylori* Infection and Gastroduodenal Lesions: Prevalence and Associated Factors in Cote d'Ivoire. *Open Journal of Gastroenterology*, **12**, 27-35. <https://doi.org/10.4236/ojgas.2022.122003>
- [5] Malfertheiner, P., Megraud, F., O'Morain, C.A., Gisbert, J.P., Kuipers, E.J., Axon, A.T., Bazzoli, F., Gasbarrini, A., Atherton, J., Graham, D.Y., Hunt, R., Moayyedi, P., Rokkas, T., Rugge, M., Selgrad, M., Suerbaum, S., Sugano, K., El-Omar, E.M., on behalf of the European *Helicobacter* and Microbiota Study Group and Consensus panel (2017) Management of *Helicobacter pylori* Infection—The Maastricht V/Florence Consensus Report. *Gut*, **66**, 6-30. <https://doi.org/10.1136/gutjnl-2016-312288>
- [6] Smith, S., Fowora, M. and Pellicano, R. (2019) Infections with *Helicobacter pylori* and Challenges Encountered in Africa. *World Journal of Gastroenterology*, **25**, 3183-3195. <https://doi.org/10.3748/wjg.v25.i25.3183>
- [7] Jaka, H., Rhee, J.A., Östlundh, L., Smart, L., Peck, R., Mueller, A., Kasang, C. and Mshana, S.E. (2018) The Magnitude of Antibiotic Resistance to *Helicobacter pylori* in Africa and Identified Mutations Which Confer Resistance to Antibiotics: Systematic Review and Meta-Analysis. *BMC Infectious Diseases*, **18**, Article No. 193. <https://doi.org/10.1186/s12879-018-3099-4>
- [8] Sugano, K., Tack, J., Kuipers, E.J., Graham, D.Y., El-Omar, E.M., Miura, S., Haruma, K., Asaka, M., Uemura, N., Malfertheiner, P., on Behalf of Faculty Members of Kyoto Global Consensus Conference (2015) Kyoto Global Consensus Report on *Helicobacter pylori* Gastritis. *Gut*, **64**, 1353-1367. <https://doi.org/10.1136/gutjnl-2015-309252>
- [9] Huang, C.C., Tsai, K.W., Tsai, T.J. and Hsu, P.I. (2017) Update on the First-Line Treatment for *Helicobacter pylori* Infection—A Continuing Challenge from an Old Enemy. *Biomarker Research*, **5**, Article No. 23. <https://doi.org/10.1186/s40364-017-0103-x>
- [10] Benajaha, D.A., Lahbabia, M., Alaoui, S., El Rhazi, K., El Abkari, M., Nejari, C., Amarti, A., Bennani, B., Mahmoudi, M. and Ibrahim, S.A. (2013) Prevalence of *Helicobacter pylori* and Its Recurrence after Successful Eradication in a Developing Nation (Morocco). *Clinics and Research in Hepatology and Gastroenterology*, **37**, 519-526. <https://doi.org/10.1016/j.clinre.2013.02.003>
- [11] Smith, S.I., Ajayia, A., Jolaiya, T., Onyekwere, C., Setshedi, M., Schulz, C., Otegbayo J.A., Ndiph, R., Dieye, Y., Alboraie, M., Ally, R., Gunturul, R., Hyasinta, J., Ugiagbe, R., Ndububa, D., Arigbabu, A., on Behalf of the African *Helicobacter* and Microbiota Study Group (2022) *Helicobacter pylori* Infection in Africa: Update of the Current Situation and Challenges. *Digestive Diseases*, **40**, 535-544. <https://doi.org/10.1159/000518959>

- [12] Kabakambira, J.D., Hategeka, C., Page, C., Ntirenganya, C., Dusabejambo, V., Ndo-li, J., Ngabonziza, F., Hale, D., Bayingana, C. and Walker, T. (2018) Efficacy of *Helicobacter pylori* Eradication Regimens in Rwanda: A Randomized Controlled Trial. *BMC Gastroenterology*, **18**, Article No. 134. <https://doi.org/10.1186/s12876-018-0863-2>
- [13] Doffou, A.S., Attia, K.A., Fulgence, M., Bathaix, Y., Bangoura, A.D., Kissy-Anzouan, Y.H., Kouamé, H.D., Mahassadi, K.A., N'Da, K.J., Kouyaté, M., Assi, C. and N'dri-Yoman, A.T. (2015) The *Helicobacter pylori* Eradication Rate in a High Prevalence Area (West Africa): Three Triple Therapy Comparative Study. *Open Journal of Gastroenterology*, **5**, 200-206. <https://doi.org/10.4236/ojgas.2015.512030>
- [14] Andoulo, F.A., Noah, D., Tagni-Sartre, M., Ndjitoyap, E.C. and Ngu Blackett, K. (2013) Epidémiologie de l'infection à *Helicobacter pylori* à Yaoundé: de la particularité à l'énigme Africaine. *The Pan African Medical Journal*, **16**, Article No. 115. <https://doi.org/10.11604/pamj.2013.16.115.3007>
- [15] Joutei, H.A.H., Hilali, A., Fechtali, T., Rhallabi, N. and Benomar, H. (2010) *Helicobacter pylori* Infection in 755 Patients with Digestive Complaints: Pasteur Institute, Morocco, 1998-2007. *Eastern Mediterranean Health Journal*, **16**, 778-782. <https://doi.org/10.26719/2010.16.7.778>
- [16] Vale, F.F. and Vitor, J.M.B. (2010) Transmission Pathway of *Helicobacter pylori*: Does Food Play a Role in Rural and Urban Areas? *International Journal of Food Microbiology*, **138**, 1-12. <https://doi.org/10.1016/j.ijfoodmicro.2010.01.016>
- [17] Itoua-Ngaporo, N.A., Ikobo, L.C.A.I.O., Mongo-Onkouo, A., Monamou, J.F.M., Apendi, C.P.A., Ngami, R.S., Mouakosso, M.N., Gassaye, D., Ibara, B.I.A. and Ibara, J.-R. (2019) *Helicobacter pylori* Infection in Brazzaville: Comparative Study of Two Identification Tests. *Open Journal of Gastroenterology*, **9**, 223-227. <https://doi.org/10.4236/ojgas.2019.911025>
- [18] Jaka, H., Mueller, A., Kasang, C. and Mshana, S.E. (2019) Predictors of Triple Therapy Treatment Failure among *H. pylori* Infected Patients Attending at a Tertiary Hospital in Northwest Tanzania: A Prospective Study. *BMC Infectious Diseases*, **19**, Article No. 447. <https://doi.org/10.1186/s12879-019-4085-1>
- [19] Miftahussurur, M., Modesto Cruz, M., Subsomwong, P., Abreu, J.A.J., Hosking, C., Nagashima, H., Akada, J. and Yamaoka, Y. (2017) Clarithromycin-Based Triple Therapy Is Still Useful as an Initial Treatment for *Helicobacter pylori* Infection in the Dominican Republic. *The American Journal of Tropical Medicine and Hygiene*, **96**, 1050-1059. <https://doi.org/10.4269/ajtmh.16-0729>
- [20] Lamarque, D., Burucoa, C., Courillon-Mallet, A., de Korwin, J.-D., Delchier, J.-C., Megraud, F., Heluwaert, F., Lehours, P., Megraud, F., Moussata, D., A miot, A., Breurec, S. and Raymond, J. (2017) Recommandations sur le traitement de l'infection à *Helicobacter pylori* chez l'adulte. *Hépatogastro & Oncologie Digestive*, **24**, 157-170.
- [21] Megraud F. (2004) Basis for the Management of Drug-Resistant *Helicobacter pylori* Infection. *Drugs*, **64**, 1893-1904. <https://doi.org/10.2165/00003495-200464170-00003>
- [22] Huang, J.-Q. and Hunt, R.H. (1999) Treatment after Failure: The Problem of "Non-Responders". *Gut*, **45**, I40-I44. <https://doi.org/10.1136/gut.45.2008.i40>

# Ileo-Ileal Intussusception Caused by an Inflammatory Fibroid Polyp: A Case Report

Nezha Elbahaoui<sup>1\*</sup>, Oumayma Lahnaoui<sup>1</sup>, Nisrine Boubkri<sup>1</sup>, Ilyass Yassine<sup>1</sup>, Laraqui Yasmine<sup>2</sup>, Mohamd Ouanani<sup>1</sup>, Abdelkader Errougani<sup>1</sup>

<sup>1</sup>Emergency Surgical Department, “UCV”, Ibn Sina University Hospital, Rabat, Morocco

<sup>2</sup>Anatomopathology Laboratory, Ibn Sina University Hospital, Rabat, Morocco

Email: \*nezhaelbahaoui@gmail.com

**How to cite this paper:** Elbahaoui, N., Lahnaoui, O., Boubkri, N., Yassine, I., Yasmine, L., Ouanani, M. and Errougani, A. (2022) Ileo-Ileal Intussusception Caused by an Inflammatory Fibroid Polyp: A Case Report. *Open Journal of Gastroenterology*, 12, 170-177.

<https://doi.org/10.4236/ojgas.2022.127017>

**Received:** June 29, 2022

**Accepted:** July 26, 2022

**Published:** July 29, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution-NonCommercial International License (CC BY-NC 4.0). <http://creativecommons.org/licenses/by-nc/4.0/>



Open Access

## Abstract

Inflammatory fibroid polyps (IFP) are a rare benign entity that arises from the submucosa of the gastrointestinal tract and protrudes into the lumen. The clinical presentation depends on the size and localization. They are particularly found in the ileum, where they are frequently present as an ileal intussusception. We report the case of a 56-year-old female patient who presented with periumbilical pain along with multiple episodes of vomiting and chronic constipation. An abdominal CT scan revealed an ileo-ileal intussusception of an endoluminal hypodense lesion with mesenteric lymphadenopathy. Surgical treatment consisted of segmental ileal resection with primary anastomosis. The histopathological analysis revealed an inflammatory fibroid polyp in the ileum. Although these tumors have no malignant potential, surgery is always indicated in ileo-ileal intussusception to ascertain the histological nature of the lesion.

## Keywords

Intussusception, Inflammatory Fibroid Polyp, Surgical Resection

## 1. Introduction

Inflammatory fibroid polyps are a rare entity among the benign pathologies of the submucosa of the digestive tract. They are mainly observed in adults and occasionally in children.

The symptomatology depends on the location of the polyp. In the case of intestinal location, invagination is often the mode of revelation reported in adults [1].

Intestinal intussusception, or invagination, is a condition in which a segment of the bowel slides into an immediately adjacent segment.

We report a case of a patient who was admitted to the emergency department with a bowel obstruction attributed to intestinal invagination.

## 2. Clinical Case

### 2.1. Patient History

B.D. was a female patient, age 56, with a medical history of hypertension treated with calcium channel blockers as a monotherapy, and she was admitted to the emergency department for acute bowel obstruction evolving for 5 days.

### 2.2. Clinical Finding

A physical exam revealed a distended abdomen with tenderness in the periumbilical region, without any palpable mass or organomegaly. Examination of hernial orifices revealed no abnormality.

A digital rectal examination found an empty rectum.

The rest of the physical exam was without abnormalities, and the patient was hemodynamically stable.

The patient's blood tests revealed hyponatremia at 130 mEq/l, potassium level at 4.20 mEq/l, and chloride level at 100 mEq/l. The rest of her biochemical parameters as well as her hemogram were within normal limits.

The abdominal X-ray showed no abnormalities.

A CT scan of the abdomen showed an ileo-ileal intussusception, an endoluminal hypodense lesion as a lead point, and mesenteric lymphadenopathy.

After medical preparation and resuscitative measures, the patient underwent surgery under general anesthesia.

A midline abdominal laparotomy was performed. Operative exploration found an ileo-ileal intussusception at 100 cm from the ileocecal valve without any signs of necrosis (**Figure 1**).

Segmental ileal resection was performed without releasing the intussusception, followed by a termino-terminal anastomosis using the 3-0 absorbable monofilament suture.

The gross examination of the specimen showed an ovoid, white, light-obstructing mass with regular contours, measuring  $4 \times 3$  cm (**Figure 2**). The adjacent mucosal folds appeared normal.



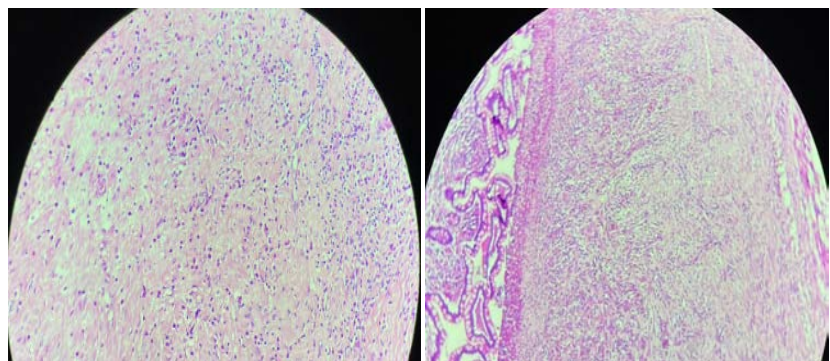
**Figure 1.** Per operative view of the intussusceptions.

Pathology showed a proliferation of spindle-shaped cells that were arranged in short bundles with no cytonuclear atypia. The stroma was fibromyxoid, highly vascularized, with an eosinophil-rich inflammatory infiltrate (**Figure 3**).

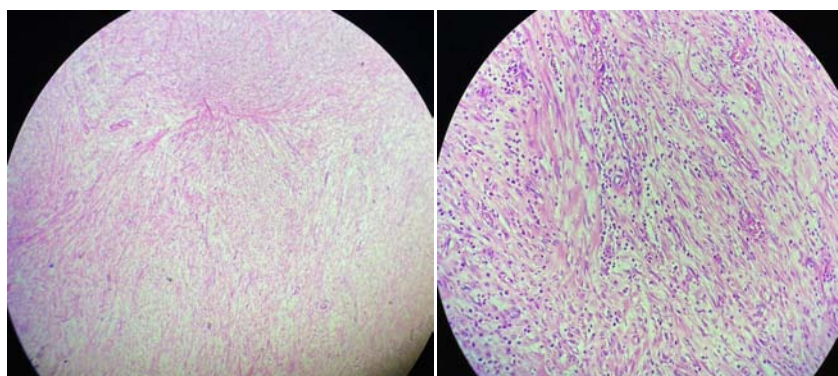
Immunohistochemistry analysis confirmed the diagnosis of inflammatory fibroid polyp (**Figure 4**).



**Figure 2.** Macroscopic appearance of the polyp as a whitish tumor.



**Figure 3.** Microscopic study with onion bulb appearance of our case report, Ibn Sina Rabat pathology laboratory.



**Figure 4.** Additional microscopic and immunohistochemical studies of our case report, Ibn Sina Rabat pathology laboratory.

### 2.3. Follow-Up and Outcome

The patient had an uneventful postoperative recovery with no specific complica-



tions.

Oral intake was authorized on the third postoperative day (POD) and the patient was discharged on POD 6.

There were no recurrences at the 10-month follow-up. A total colonoscopy and esophagogastroduodenoscopy showed no other locations or abnormalities.

### 3. Discussion

Inflammatory fibroid polyps (IFP) are a rare and benign anatomopathological entity of the gastrointestinal tract [1]. They were initially called “Vanek’s tumor” or “eosinophilic granuloma” by Vanek in 1949. The term “inflammatory fibroid polyps” was proposed by Helwing in 1953 [2] [3].

IFPs can occur anywhere in the gastrointestinal (GI) tract, but they are most common in gastric localization followed by the small intestines, especially the jejunum and colon [4] [5]. When located in the small intestines, IFP can manifest an intestinal obstruction attributed to intestinal invagination, which is the case in our patient [6].

These lesions arise from the submucosa of the GI tract and present as small nodules protruding into the lumen; they may be sessile or pedunculated.

The clinical presentation of PFAs is variable. Patients are usually asymptomatic, and polyps are discovered incidentally on prior radiologic or endoscopic examination.

When present, symptoms are polymorphic and vary according to the size, location, and the number of polyps. They may include generalized abdominal pain over several months with or without alteration of the general condition, upper or lower digestive bleeding, and a sub-occlusive or occlusive syndrome attributed to intestinal invagination when the localization is the small bowel, as in our patient [7].

The paraclinical diagnosis of intestinal obstruction is often radiological, allowing the diagnosis of intestinal invagination. Abdominal radiography without preparation shows images of hydro-aeros levels often localized topographically according to the site of the intussusception or sometimes a rounded opacity of hydric tone circumscribed on one side by a clear crescent and which may contain within it clear arciform images (a “coil spring” appearance) [8]. (**Figure 5**)

Abdominal CT with contrast injection or enteroscanner is an examination that allows a global study of the digestive tract. In the non-emergency context, the PFI appears as a regular protrusion in the digestive lumen without any thickening of the wall opposite.

In the case of intestinal invagination, as in the case of the observation described above, a cocooned tissue mass is visualized at the exact site of the occlusion, and the severity is assessed by looking for signs of complications, essentially digestive distress or perforation [9] [10].

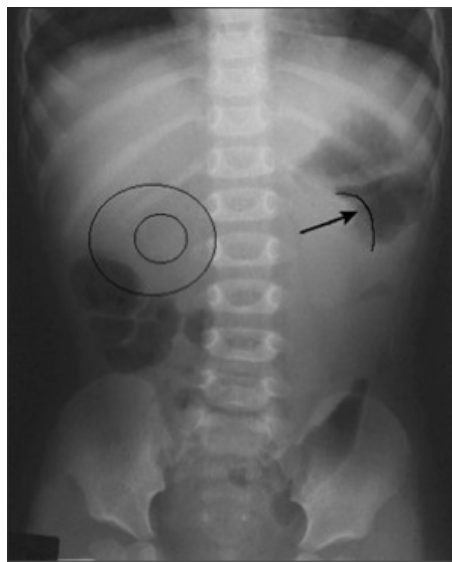
On the other hand, the CT scan in the diagnosis of PFI cannot determine which layer develops, hence the interest in performing an echo-endoscopy outside of the emergency context, which allows for making the exact topographic diagnosis.

Abdominal MRI or entero-MRI remains more efficient than CT in diagnosis

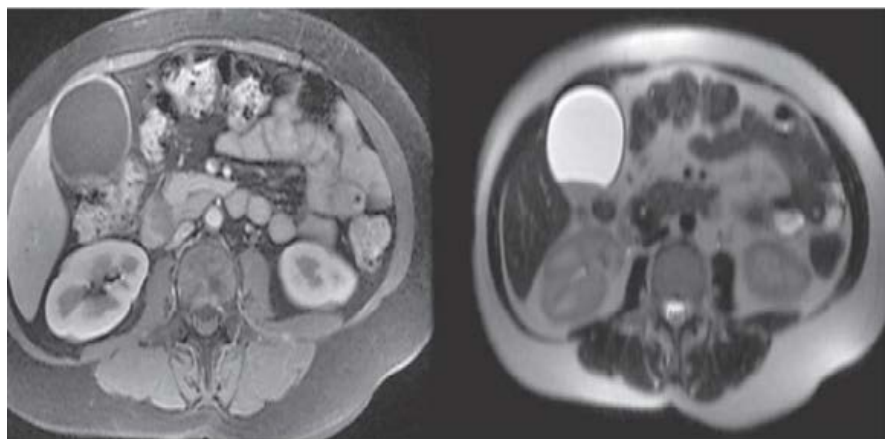
of PFI, which appears as a hypointense endoluminal tumor on the T1 sequence and intermediate on T2 [11]. (**Figure 6**)

Digestive endoscopy remains a reference examination in the diagnosis of these polyps, allowing us to visualize the site of the tumor, the size of the polyp, which can go from a few millimeters to several centimeters, and the macroscopic aspect (generally, the millimetric polyps are sessile whereas those that are voluminous are pedicled), and to take biopsies to confirm the histological diagnosis. Sometimes it also allows us to make a therapeutic gesture in exactly the right situations.

Macroscopically, the polyp develops from the submucosal layer, and it is manifested at high fibroscopy by an endoluminal expansion localized to the antral or pre-pyloric region, which is covered by normal mucosa with an ulcerated central depression for polyps that exceed 10 mm [14].



**Figure 5.** Unprepared abdomen showing an intussusception with an impression of the bladder [12].



**Figure 6.** Magnetic resonance imaging shows a hypointense 26 mm image on the T1 sequence (left), and intermediate intensity on the T2 sequence (right) in favor of the PFI of the duodenum [13].

Sometimes these tumors are covered with a whitish exudate on their surfaces, a feature described by Tanaka *et al.* [15].

Concerning the colonic setting, the polyp is in the form of a pedunculated tumor protruding into the lumen covered by healthy mucosa. [16]

An echo-endoscopic complement plays an important role in the characterization of submucosal polyps, particularly gastric or rectal polyps. The appearance is of a heterogeneous hypoechoic mass arising from the submucosa. This appearance can be confused with GIST or submucosal lipomas [17]

The biological workup is not very helpful in the diagnosis of PFI. In some cases, we note the presence of microcytic hypochromic anemia, motivating the realization of a digestive exploration, and finding a polyp with occult bleeding. Two cases reported in the literature by I. ED-DARRAZ *et al.* [18]

Anatomical-pathological examination remains the only means of confirming the diagnosis of Vaneck's polyp. It is performed on a biopsy specimen during endoscopy or on the surgical specimen. The macroscopic appearance of the polyp is in the form of a whitish, firm, and pale mass, sometimes myxoid, not encapsulated. In this section, the submucosal origin is confused, and sometimes it may protrude beyond the muscularis propria, giving an hourglass aspect [19].

Microscopic examination shows a vascularized fibroinflammatory tissue with 3 entities: fibroblastic, inflammatory, and vascular. The cells are made up of elongated or star-shaped monomorphic mesenchymatous elements with amphophilic cytoplasm; mitoses are rare, and the extracellular space contains mucoid material with collagenous and reticulin fibers dispersed between the cells. Spindle cells are often arranged in clusters or concentrically around the vessels, creating an "onion bulb" appearance [20] [21] [22].

The immunohistochemical study plays an important role in the diagnosis of Vaneck's polyp by studying these antibodies which are present in most cases: vimentin, cyclin D1, CD 34, smooth muscle actin, or HFF35, fascin, calponin, and Desmin [4] [8] [23].

Molecular biology shows a genetic abnormality with the existence of a mutation in exon 12 of the PDGFR alpha gene, which predominates in intestinal PFI, and a mutation in exon 18 of the same gene in gastric PFI [24].

The differential diagnosis is essential with gastrointestinal tumors or GIST, which are the most frequent tumors of the digestive tract, hence the interest of the immuno-histological study.

The curative treatment consists of the resection of the polyp either by the endoscopic technique of polypectomy or mucosectomy for small polyps; or resection by surgical means depending on the localization, the urgent symptomatology, or not of the polyp.

Generally, small polyps of incidental discovery or asymptomatic with small sizes do not require complete resection. This, as well as the potential for degeneration, has not been demonstrated, so there is no consensus on the pace of monitoring.

The surgical procedure is still being discussed as a curative option. The pro-

cedure depends on the location of the polyp. In symptomatic gastric forms that cannot be resected endoscopically, the procedure consists of partial gastric resection or wedge resection, depending on the location of the polyp. In the case of colonic or gastric forms, and especially in the case of occlusion, tumor resection is performed according to the affected segment with the restoration of digestive continuity during the same surgical procedure if the preoperative conditions allow it.

The evolution is marked by the absence in the majority of cases of recurrences or metastases after complete resection, confirming the benign nature of the polyp.

#### 4. Conclusion

The inflammatory fibroid polyp or Vanek's polyp is a benign lesion of the digestive tract with submucosal development. It is observed in adults and is usually a fortuitous discovery. The diagnosis is essentially histological on endoscopic resection or the surgical specimen after surgery for occlusion of intestinal intussusception as in the case described above.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

#### References

- [1] Rossi, P., Monturo, M., Balassone, B., Ricciardi, E., Anemona, L., Manzelli, A. and Petrella, G. (2012) Inflammatory Fibroid Polyp. A Case Report. *Annali Italiani di Chirurgia*, **83**, 347-351.
- [2] Vanek, J. (1949) Gastric Submucosal Granuloma with Eosinophilic Infiltration. *The American Journal of Pathology*, **25**, 397-411.
- [3] Helwig, E.B. and Ranier, A. (1953) Inflammatory Fibroid Polyps of the Stomach. *Surgery, Gynecology and Obstetrics*, **96**, 355-367.
- [4] De Haan, P.M., Martínez, Y.R. and Gutiérrez, F.R. (2014) Intususcepción intestinal debido a un pólipo fibroide inflamatório (tumor de Vanek). *Medicina Legal de Costa Rica*, **31**, 116-121.
- [5] Singhn, N.G., Kahvic, M., Mannan, R. and Enezi, A.A. (2011) Gastric Inflammatory Fibroid Polyp: Report of a Case. *Indian Journal of Pediatrics*, **6**, 42-45.
- [6] Savargaonkar, P., Morgenstern, N. and Bhuiya, T. (2003) Inflammatory Fibroid Polyp of the Ileum Causing Intussusception: Report of Two Cases with Emphasis on Cytologic Diagnosis. *Diagnostic Cytopathology*, **28**, 217-221. <https://doi.org/10.1002/dc.10258>
- [7] Nonose, R., Valenciano, J.S., Silva, C.M.G., Souza, C.A.F. and Martinez, C.A.R. (2011) Ileal Intussusception Caused by Vanek's Tumor: A Case Report. *Case Reports in Gastroenterology*, **5**, 110-116. <https://doi.org/10.1159/000326930>
- [8] Sargent, M.A., Alton, D.J. and Babyn, P. (1994) Plain Abdominal Radiography in Suspected Intussusception: A Reassessment. *Pediatric Radiology*, **24**, 17-20. <https://doi.org/10.1007/BF02017652>

- [9] Orjollet-Lecoanet, C., Ménard, Y., Martins, A., Crombé-Ternamian, A., Cotton, F. and Valette, P.J. (2000) L'entéroscanner: Une nouvelle méthode d'exploration du grêle. *Journal de Radiologie*, **81**, 618-627.
- [10] Klingbeil, K.D., Balaban, A., Fertig, R.M., Gamret, A.C., Gong, Y., Torres, C. and Satahoo, S.S. (2017) Inflammatory Fibroid Polyp of the Gastric Antrum Presenting as Hypovolemic Shock: Case Report and Literature Review. *Intractable & Rare Diseases Research*, **6**, 304-309. <https://doi.org/10.5582/irdr.2017.01060>
- [11] Paley, M.R. and Ros, P.R. (1997) MRI of the Gastrointestinal Tract. *European Radiology*, **7**, 1387-1397. <https://doi.org/10.1007/s003300050306>
- [12] <https://slideplayer.fr/slide/5423617/>
- [13] Wysocki, A.P., Taylor, G. and Windsor, J.A. (2007) Inflammatory Fibroid Polyps of the Duodenum: A Review of the Literature. *Digestive Surgery*, **24**, 162-168. <https://doi.org/10.1159/000102099>
- [14] Matsushita, M., Hajiro, K., Okazaki, K. and Takakuwa, H. (1996) Endoscopic Features of Gastric Inflammatory Fibroid Polyps. *American Journal of Gastroenterology*, **91**, 1595-1598.
- [15] Tanaka, K., Toyoda, H., Imoto, I., *et al.* (2008) Anemia Caused by a Gastric Inflammatory. *Gastrointestinal Endoscopy*, **67**, 345-346. <https://doi.org/10.1016/j.gie.2007.08.029>
- [16] Sadamoto, Y., Kubo, H., Tanaka, M., Szumilo, J., Cwik, G. and Wallner, G. (2001) Gastrointestinal-Gastric Inflammatory Fibroid Polyp. *Journal of Gastroenterology and Hepatology*, **16**, 1069. <https://doi.org/10.1046/j.1440-1746.2001.02591.x>
- [17] Tada, S., Iida, M., Yao, T., Miyagahara, T., Hasuda, S. and Fujishima, M. (1990) Granular Cell Tumor of the Esophagus: Endoscopic Ultrasonographic Demonstration and Endoscopic Removal. *American Journal of Gastroenterology*, **85**, 1507-1511.
- [18] <http://hdl.handle.net/123456789/17650>  
<http://ao.um5.ac.ma/xmlui/bitstream/handle/123456789/17650/M582019.pdf?sequence=1&isAllowed=y>
- [19] Assarian, G. and Sundaresan, A. (1985) Inflammatory Fibroid Polyp of the Ileum. *Human Pathology*, **16**, 311-312. [https://doi.org/10.1016/S0046-8177\(85\)80019-8](https://doi.org/10.1016/S0046-8177(85)80019-8)
- [20] Kim, Y.I. and Kim, W.H. (1988) Inflammatory Fibroid Polyps of Gastrointestinal Tract. Evolution of Histologic Patterns. *American Journal of Clinical Pathology*, **89**, 721-727. <https://doi.org/10.1093/ajcp/89.6.721>
- [21] Namba, T., Watanabe, H. and Enjoji, M. (1979) Inflammatory Fibroid Polyps of the Stomach. A Histological Study of 48 Cases. *Fukuoka Igaku Zasshi*, **70**, 721-731.
- [22] Blackshaw, A. and Levison, D. (1986) Eosinophilic Infiltrates of the Gastrointestinal Tract. *Journal of Clinical Pathology*, **39**, 1-7. <https://doi.org/10.1136/jcp.39.1.1>
- [23] Liu, T.C., Lin, M.T., Montgomery, E.A. and Singhi, A.D. (2013) Inflammatory Fibroid Polyps of the Gastrointestinal Tract Spectrum of Clinical, Morphologic, and Immunohistochemistry Features. *The American Journal of Surgical Pathology*, **37**, 586-592. <https://doi.org/10.1097/PAS.0b013e31827ae11e>
- [24] Huss, S., Wardelmann, E., Goltz, D., *et al.* (2012) Activating PDGFRA Mutations in Inflammatory Fibroid Polyps Occur in Exons 12, 14 and 18 and Are Associated with Tumour Localization. *Histopathology*, **61**, 59-68. <https://doi.org/10.1111/j.1365-2559.2012.04203.x>



# Open Journal of Gastroenterology

ISSN: 2163-9450 (Print)      ISSN: 2163-9469 (Online)  
<https://www.scirp.org/journal/ojgas>

**Open Journal of Gastroenterology (OJGas)** is an international journal dedicated to the latest advancement of Gastroenterology. The goal of this journal is to provide a platform for scientists and academicians all over the world to promote, share, and discuss various new issues and developments in different areas of Gastroenterology. All manuscripts must be prepared in English, and are subject to a rigorous and fair peer-review process. Accepted papers will immediately appear online followed by printed hard copy.

## Subject Coverage

The journal publishes original papers including but not limited to the following fields:

- Abdominal Gastroenterology
- Anorectal Disorders
- Bezoars & Foreign Bodies
- Diverticular Disease
- Esophageal Disorders
- Gastric & Peptic Disorders
- Gastroenteritis
- GI Bleeding
- GI Diagnostics
- Hepatic Disorders
- Inflammatory Bowel Disease
- Irritable Bowel Syndrome
- Lower GI Complaints
- Malabsorption Syndrome
- Nutrition
- Pancreatitis
- Tumors of the GI Tract
- Upper GI Complaints

We are also interested in short papers (letters) that clearly address a specific problem, and short survey or position papers that sketch the results or problems on a specific topic. Authors of selected short papers would be invited to write a regular paper on the same topic for future issues of the OJGas.

## Website and E-Mail

<https://www.scirp.org/journal/ojgas>

E-mail: [ojgas@scirp.org](mailto:ojgas@scirp.org)

## ***What is SCIRP?***

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

## ***What is Open Access?***

All original research papers published by SCIRP are made freely and permanently accessible online immediately upon publication. To be able to provide open access journals, SCIRP defrays operation costs from authors and subscription charges only for its printed version. Open access publishing allows an immediate, worldwide, barrier-free, open access to the full text of research papers, which is in the best interests of the scientific community.

- High visibility for maximum global exposure with open access publishing model
- Rigorous peer review of research papers
- Prompt faster publication with less cost
- Guaranteed targeted, multidisciplinary audience



**Scientific  
Research  
Publishing**

**Website: <https://www.scirp.org>**

**Subscription: [sub@scirp.org](mailto:sub@scirp.org)**

**Advertisement: [service@scirp.org](mailto:service@scirp.org)**