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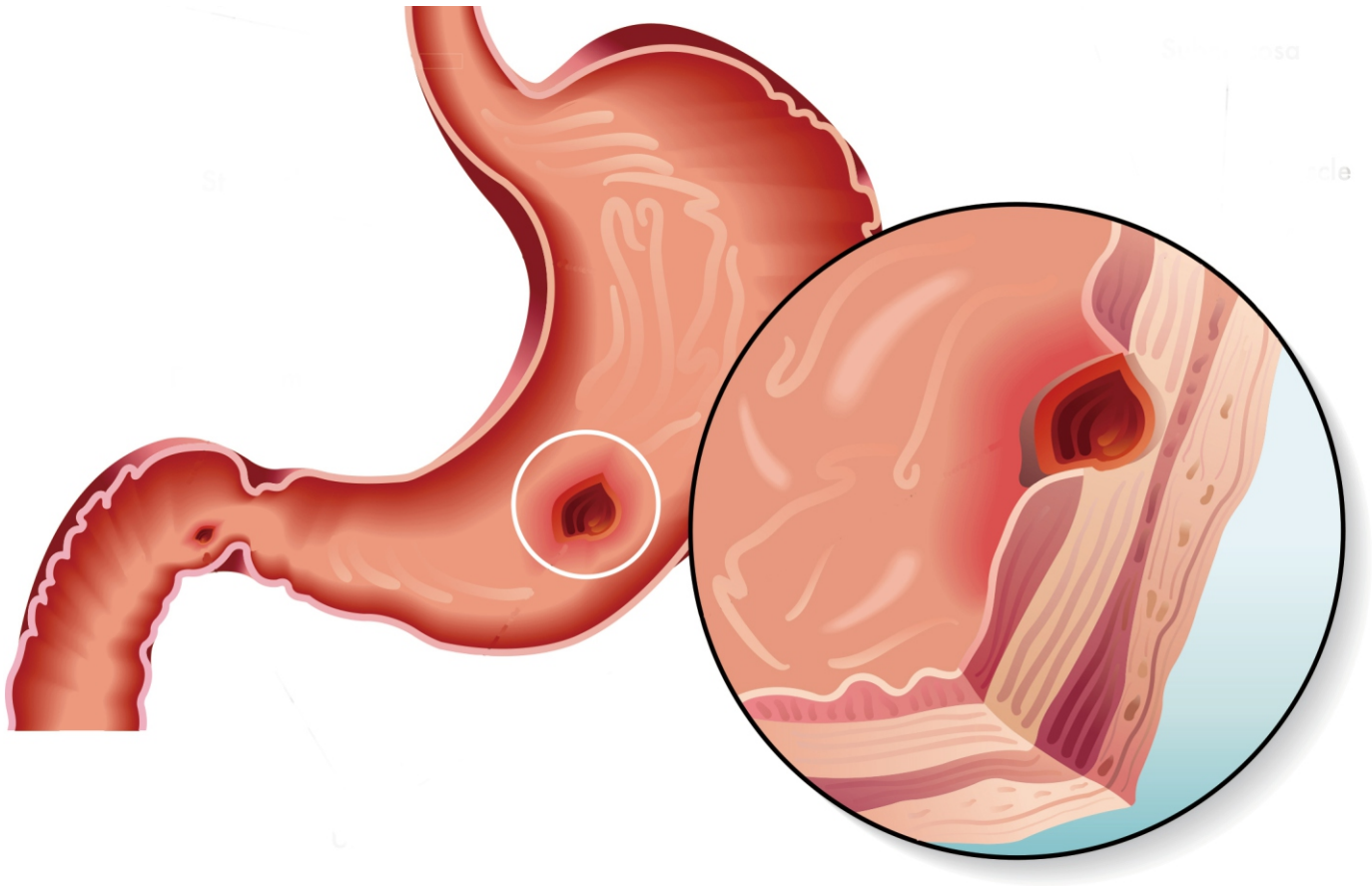

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A Case of Hepatocellular Carcinoma Diagnosed with Resistant Hypoglycemia

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Abstract

Background: There are many causes of the etiology of hypoglycemia. Hypoglycemia is very rare in individuals without diabetes. Although it can accompany islet cell malignancies such as insulinoma, it is much less common in solid organ tumors such as hepatocellular carcinoma as a component of paraneoplastic syndrome. **Case Presentation:** We present a 58-year-old male patient with no additional disease, who was examined for resistant hypoglycemia and was diagnosed as having hepatocellular carcinoma radiologically for the first time. Insulin level measured when serum glucose was 44 mg/dl: 0.4 μU/mL, c-peptide level: 0.355 ng/mL detected. Viral serology was found to be positive for HbsAg. In dynamic magnetic resonance imaging, showing continuity in segments 6 - 7 and 8 in the right lobe, and also partially towards 5, heterogeneous hyperintense in T2 A's, diffusion-limiting, heterogeneous contrast enhancement in postcontrast series, cystic-necrotic in the center. The alpha-fetoprotein level was 60,500 ng/mL. **Conclusion:** Paraneoplastic hypoglycemia due to underlying malignancies should be considered in patients presenting with hypoglycemia.

Keywords

Hepatocellular Carcinoma, Resistant Hypoglycemia

1. Introduction

There are many causes of the etiology of hypoglycemia. It is often seen as a side effect of the treatment of diabetes. The most common cause of hypoglycemia is sulfonylurea or exogenous insulin usage as a treatment of diabetes. However, organ failure, sepsis, alcoholism, and gastric bypass are also common etiologies. Hypoglycemia is very rare in individuals without diabetes. Although it can ac-

company islet cell malignancies such as insulinoma, it is much less common in solid organ tumors such as hepatocellular carcinoma as a component of paraneoplastic syndrome. It constitutes approximately half paraneoplastic hypoglycemia due to non-islet cell tumors, whereas HCC constitutes only one-fourth of hypoglycemia. Islet tumors of the pancreas cause hypoglycemia with excessive insulin production. Extra pancreatic (non-islet) tumors have hypoglycemia with concurrent low insulin levels. Proposed mechanisms for hypoglycemia of extrapancreatic tumors include increased and preferential glucose utilization by tumors, failure of glycogenolysis, and decreased gluconeogenesis [1]. Hepatocellular cancer (HCC) is the most common primary tumor of the liver and accounts for 80% - 90% of primary liver cancers. Diagnosis of HCC is a difficult case, generally; serum markers, one or more imaging modalities, and histological confirmation are required. Delays in diagnosis can occur because of the absence of pathognomonic symptoms for HCC and the large functional reserve of the liver. The paraneoplastic syndrome can be observed especially in HCC cases with large diameters and high alpha-fetoprotein (AFP) values and it has been associated with poor prognosis [2] [3]. It has been reported that hypoglycemia occurs in approximately 4% - 27% of patients with a diagnosis of HCC. HCC usually presents with complaints of right upper quadrant pain, distention, icterus, and weight loss. Hypoglycemia is a rare clinical presentation [4]. Non-islet cell tumor hypoglycemia (NICTH) presents as recurrent or constant hypoglycaemic episodes and mostly affects elderly patients with advanced tumors [5]. Occasionally, these hypoglycaemic episodes can predate the diagnosis of the underlying tumor [6]. A 58-year-old male patient diagnosed as having hepatocellular carcinoma with resistant hypoglycemia was reported in this paper. Written informed consent was obtained from the patient participating in this study.

2. Case Presentation

A 58-year-old male patient was admitted to the psychiatry clinic with the prediagnoses of dissociative disorder and conversion disorder due to headache, dizziness, and disorganized behavior for 2 months. It was discovered that the patient had hypoglycemia in the follow-ups. Due to persistent hypoglycemia despitedextrose infusion, further investigations were conducted. He had no previous history of systemic disease and no history of drug use. Upon physical examination, his general condition was moderate, conscious, oriented, and cooperative. His blood pressure was 140/90 mmHg, heart rate was 85/minute and body temperature was 36.2˚C. The liver was palpated 4 cm below the right rib. In laboratory examinations, complete urinalysis was normal. In the complete blood count, white blood cell count was 6.910/mm^3, hemoglobin 14.6 g/dL, and platelet count was 251.000/mm^3. Alanine aminotransferase: 83 U/L (N: 0 - 40 U/L) Calcium: 8.3 mg/dL, albumin was 4.74 g/dL. Serum electrolytes were normal. Prothrombin time and activated partial thromboplastin time were normal. C-reactive protein was 10 mg/dL, sedimentation was 19 mm/hour. Fingertip

glucose was 29 mg/dL. Insulin, c-peptide, cortisol, and serum glucose were studied at the time of hypoglycemia. Insulin level measured when serum glucose was 44 mg/dl: 0.4 μU/mL (N: 1.9 - 23 μU/mL), c-peptide level: 0.355 ng/mL (N: 1.1 - 4.4 ng/mL), cortisol: 12.2 ug/dL detected (Table 1). An Adrenocorticotropic hormone (ACTH) stimulation test was performed to rule out the diagnosis of adrenal insufficiency. Any cortisol level was found to be >18 ug/dL. Adrenal insufficiency was ruled out.

Considering that the patient may have paraneoplastic hypoglycemia, thorax and abdomen imaging were performed for solid tumors. Thorax computed tomography was unremarkable. In dynamic magnetic resonance imaging, the liver was approximately 132 × 124 × 120 mm in size in its widest part, showing continuity in segments 6 - 7 and 8 in the right lobe, and also partially towards 5, heterogeneous hyperintense in T2 A's, diffusion-limiting, heterogeneous contrast enhancement in postcontrast series, cystic-necrotic in the center (Figure 1). A

Table 1. Patient's laboratory values.

White blood cell	6.910/mm^3	Alanine aminotransferase	83 U/L
Hemoglobin	14.6 g/dL	Calcium	8.3 mg/dL
Thrombocyte	251.000/mm^3	Albumin	4.74 gr/dL
C reactive protein	10 mg/dL	Sedimentation rate	19 mm/saat
Glucose	44 mg/dL	Cortisol	12.2 ug/dL
İnsulin	0.4 μU/mL	C-peptide	0.355 ng/mL
HbsAg*	Positive (3762 S/Co)	Alpha-fetoprotein	60,500 ng/mL

*HbsAg: hepatitis B surface antigen.

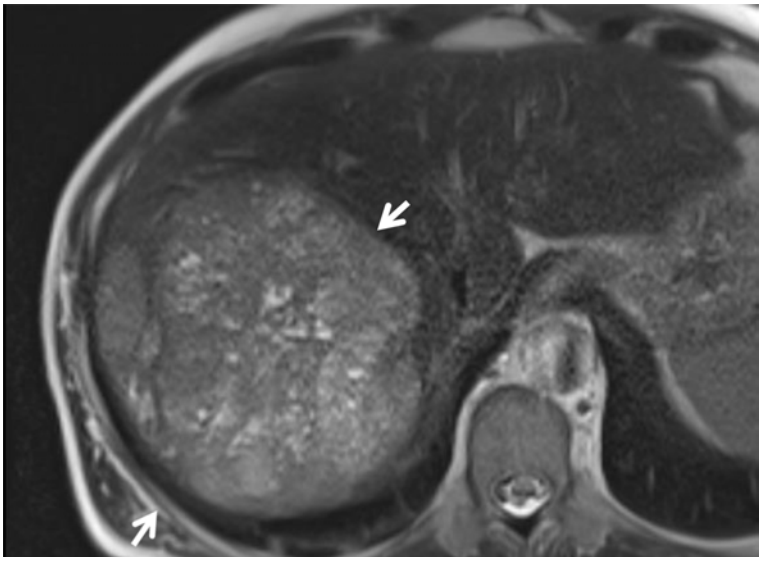

Figure 1. The mass lesion in the liver compatible with HCC.

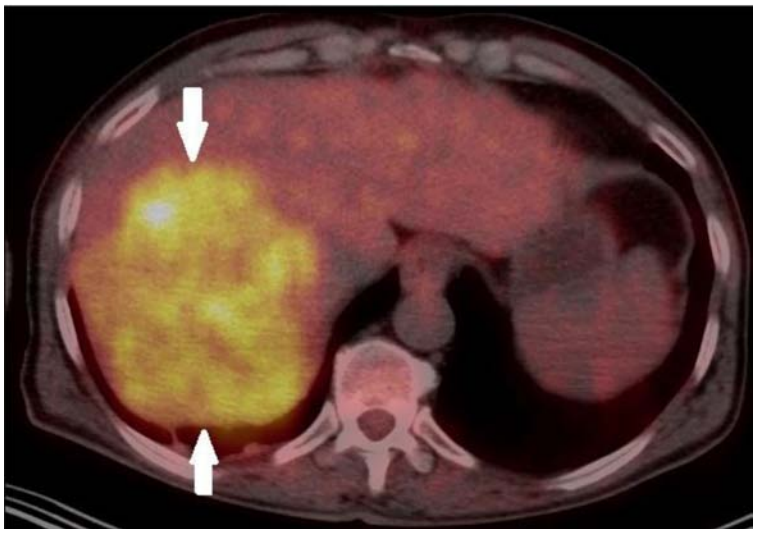

Figure 2. A hypermetabolic lesion with heterogeneous increased FDG uptake was observed in the liver.

space-occupying lesion image with components was observed. The pancreas is of normal size and normal localization; its internal structure is smooth and its outer contours are lobulated. A positron emission tomography (PET/CT) with fluorine-18-fluorodeoxyglucose (18-FDG) was performed. A hypermetabolic lesion with heterogeneous increased FDG uptake was observed in the liver (**Figure 2**). The alpha-fetoprotein level was 60,500 ng/mL (N: 0 - 5.8 ng/mL). Biopsy was not performed on the patient since the patient's current imaging methods and high AFP level were compatible with HCC. Viral serology was found to be positive for HbsAg. HBV DNA was 2556 IU/mL and entecavir 1 mg/day was started. IGF-II measurement was attempted, but the assay is not available in Turkey. The patient required treatment with dextrose in continuous infusion to achieve normal blood glucose and to remain symptom-free. The patient was started on 2 × 20 mg methylprednisolone treatment. Then, the dose was gradually reduced and steroid treatment was implemented at the physiological dose. It was accepted as inoperable by the surgical oncology council. The patient underwent transarterial chemoembolization. Octreotide was given to the patient whose hypoglycemia attacks continued after transarterial chemoembolization. There was no improvement in blood sugars with octreotide treatment either. The patient underwent chemoembolization with antineoplastic drug together with lipiodol, twice in total, by preserving the hepatic artery branches feeding the normal liver parenchyma. In control films, it was observed that the vascularization of the mass decreased significantly and intra-mass stagnation developed. No complications were observed after the procedures. Lastly, 400 mg/day sorafenib treatment was started in the patient with resistant hypoglycemia. The patient is still receiving sorafenib and physiological doses of prednisolone. Dextrose infusion is given to achieve normal blood sugar. Response to treatment will be evaluated 2 months later by control PET-CT and whether there is a decrease in hypoglycemia attacks.

3. Discussion

High glucose use in patients with decreased gluconeogenesis plays an important role in the pathophysiology of hypoglycemia in non-islet cell malignancies such as HCC. This type of NICTH (type A) is observed in late-stage HCC when the tumoral burden is high and hepatic destruction is extensive [7]. In such cases, insulin and C-peptide levels are found to be low [8]. While glucose level was low in our case, insulin and C-peptide levels measured were significantly low. Another cause of paraneoplastic hypoglycemia is increased glucose utilization due to stimulation of insulin receptors and excessive production of tumoral insulin-like growth factor-2 (IGF-2). In type B NICTH, there is increased tumor secretion of incompletely processed IGF-2 (pro-IGF-2), which is poorly metabolized due to defective hepatocytes in cirrhosis. This defective pro-IGF-2 is smaller, crosses the capillary membranes easier, and stimulates more insulin receptors throughout the body than normal IGF-2. This occurs early in liver disease and is characterized by overwhelming tissue glucose uptake and severe, persistent hypoglycemia [9] [10]. In our patient, clinically due to persistent hypoglycemia, it was thought to be Type B in the foreground. However, high tumor burden, low insulin, and c-peptide levels were observed to be compatible with Type-A.

About 90% of patients with HCC have cirrhosis, usually due to chronic alcohol use and chronic viral hepatitis B and C. HCC may occur before cirrhosis develops in some cases of chronic hepatitis B [11]. The emergence of hepatocellular carcinoma before the development of cirrhosis in our patient is another important feature of the case. Treatment options such as frequent nutrition, parenteral dextrose infusion, corticosteroids, glucagon, and growth hormone are used successfully in the treatment of hypoglycemia [12]. Dietary advice regarding frequent intake of complex carbohydrates is beneficial. Steroids are the most used drug to treat HCC-associated hypoglycemia. The therapeutic effect is based on hepatic gluconeogenesis stimulation and peripheral glucose intake inhibition. Furthermore, steroids can reduce "big" IGF-2 levels, whether it is through a reduction of production or promoting a maturation process of pro-IGF-2 and normal complex formation [13]. The beneficial effects of corticosteroids are reversible when treatment is withdrawn or when the dose declines below a critical threshold [5]. The combination of corticosteroids and GH has also been proposed as a palliative treatment option [14]. GH stimulates hepatic gluconeogenesis and glycogenolysis as well as the production of IGF-binding protein-3 and acid-labile subunit [15]. Somatostatin analogs such as octreotide generally do not restore blood glucose levels to normal in non-islet cell tumor hypoglycemia. In our patient, blood glucose levels did not return to normal after octreotide treatment. We administered parenteral dextrose infusion and corticosteroid treatment to the patient. Thus, we prevented complications that may arise from hypoglycemia in the period until the initiation of the underlying HCC treatment. The main treatment for hypoglycemia due to paraneoplastic syndrome is to treat the underlying malignancy and appropriate surgical resection is the most effec-

tive treatment option. Chemotherapy, embolization, and radiotherapy are other treatment methods [16]. Since our patient was considered inoperable, transarterial chemoembolization was performed and sorafenib treatment was started. Consequently, paraneoplastic hypoglycemia due to underlying malignancies should be considered in patients presenting with hypoglycemia.

Conflicts of Interest

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

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Autoimmune Hepatitis as a Hepatic Manifestation of Common Variable Immunodeficiency: A Case Report

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Abstract

Common variable immunodeficiency (CVID) is one of the most prevalent primary immunodeficiency disorders, characterized by an alteration in the maturation of B lymphocytes. Patients with this condition are redisposed to a higher risk of infections. Despite being an immune deficiency disorder, the prevalence of autoimmune disorders is reported in more than 20% of patients. The likelihood of patients' gastrointestinal tract being affected is relatively low, close to 6%. We present the case of a 22-year-old man with a history of CVID without medical treatment, who presented with upper gastrointestinal bleeding secondary to esophageal varices due to cirrhotic portal hypertension. Infectious and toxic causes of cirrhosis were ruled out. Histological changes compatible with autoimmune hepatitis (AIH) were documented by liver biopsy. The diagnosis of autoimmune diseases is a challenge in the presence of IDCV, we highlight the importance of establishing a timely diagnosis and an intentional search for these conditions to offer timely treatment and avoid late complications.

Keywords

Immunodeficiency, Hepatitis, Liver, Autoimmune

1. Introduction

Common variable immunodeficiency (CVID) is characterized by a disorder in the differentiation of B lymphocytes that creates a predisposition to hypogammaglobulinemia, these conditions lead to an increased risk of recurrent bacterial infections, particularly intestinal and pulmonary in up to 95% of patients affected with this entity [1]. The approximate prevalence of this disorder varies between 1:50,000 - 100,000 of the world population, with a male-female ratio of

1:2. Its diagnosis is usually made in the first decade of life; however, there are case reports of patients diagnosed in the third decade of life [2]. The pathogenesis of CVID has not been delineated clearly; however, mutations in several genes associated with B-cell development, including autosomal-recessive mutations in BAFF-R, CD20, CD19, CD81, CD21, and inducible costimulator, have been found in a small subset of patients [3]. Survival 20 years after the diagnosis of CVID was 64% for males and 67% for females, compared to the expected 92% population survival for males and 94% for females [4]. It is estimated that 25% of patients with CVID have associated autoimmune disorders such as thyroiditis, rheumatoid arthritis, and celiac disease. Liver disorders are rare in the medical literature [5]. Liver disease, including primary biliary cirrhosis and autoimmune hepatitis, which may lead to persistently increased liver enzyme levels, also occurs in CVID. The cause remains unknown, with liver biopsy specimens showing mild periportal changes or granulomas. In one cohort study, 43% of patients had abnormal liver function tests, predominantly increased alkaline phosphatase. Nodular regenerative hyperplasia leading to portal hypertension and cholestasis was found in 14 of 40 subjects in a cohort of subjects who had these abnormalities in liver function tests [6]. Due to the decrease in serum immunoglobulins, the diagnosis of autoimmune diseases is a challenge, since the expression of antibodies is altered and their serum values are normal or decreased, leading to false-negative laboratory reports. We present the case of a 22-year-old Caucasian male patient with liver cirrhosis secondary to autoimmune hepatitis (AIH) with a history of CVID.

2. Case Presentation

A 22-year-old man presented to the emergency department of our hospital with a history of haematemesis. His medical history highlights the history of autoimmune thrombocytopenia diagnosed 12 years ago without treatment or medical follow-up and the diagnosis of IDCV 6 years ago, without treatment for 3 years. He denied a family history of liver disease or immune disorders, drug, alcohol, or tobacco use, or risk exposures for HIV, HBV, or HCV infection. The patient reported that 4 weeks beforehand he had undergone a surgical extraction of fourth molars, later he presented swelling, redness and heat in the left submandibular region, associated with fever not quantified by thermometer for which he received antibiotic treatment (ciprofloxacin*) and non-steroidal anti-inflammatory drugs (ketorolac and diclofenac 2 - 3 tablets per day) with partial improvement of symptoms. Twelve hours before consultation, he started with haematemesis in 3 episodes and hematochezia in 1 occasion. On admission, a blood pressure of 80/50 mmHg and a heart rate of 140 beats per minute stand out, so resuscitation with crystalloids was started, the physical examination revealed the presence of sclera with jaundice, a swollen, erythematous area and local heat in the left submandibular region, flat, symmetrical abdomen, absence of collateral circulation, non-painful hepatomegaly, without changing dullness, and

rectal examination with an examining glove showed traces of bright red blood.

3. Diagnostic Support

Anemia, thrombocytopenia, altered liver biochemistry with mild hypertransaminasemia, a cholestatic pattern, and a prolonged INR were documented in the admission laboratories. The endoscopic study showed the presence of large esophageal varices according to the Baveno classification (Figure 1(A)) and mild portal hypertensive gastropathy, for which he received endoscopic therapy with the collation of 3 ligature bands. As part of the diagnostic approach, hepatoportal Doppler ultrasound was performed, reporting data of diffuse cirrhosis-type liver disease, portal hypertension, splenomegaly, and ascites (Figure 1(B) and Figure 1(C)). Chronic viral infectious processes were ruled out. ANA was documented at 1:1200 and the rest of the antibodies were negative (Table 1). Due to the association with autoimmune diseases and because the rest of the studies performed were negative, a percutaneous liver biopsy was performed, which reported F2-3 fibrosis on the Metavir scale, interface hepatitis, associated with lymphoplasmacytic infiltrate, integrating a diagnosis of AIH (Figure 1(D) and Figure 1(F)).

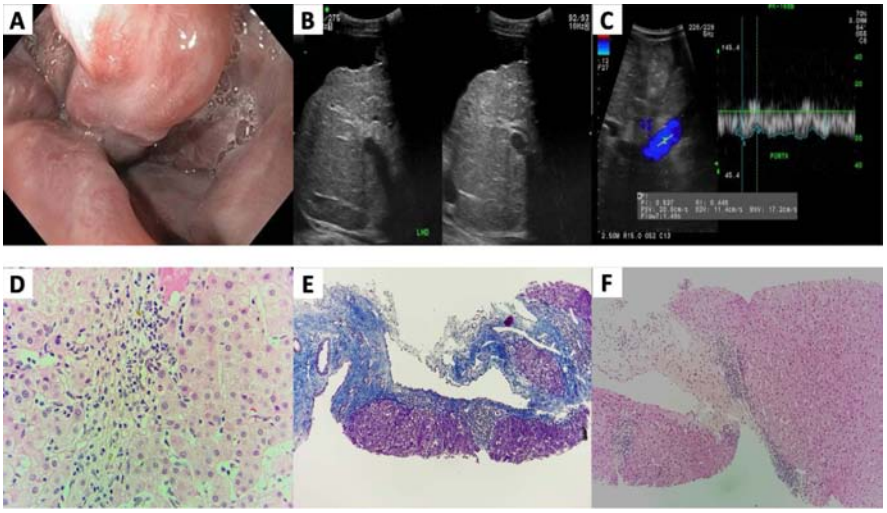

Figure 1. (A) Esophagogastroduodenoscopy shows the presence of at least 3 venous vascular pathways greater than 5 mm, in the esophagus with the presence of hematocystic points that run to the esophagogastric junction. (B) Liver ultrasound image showing the right lobe with lobulated and defined contours, with a heterogeneous parenchyma at the expense of a generalized and diffuse increase in its echogenicity with a pseudonodular pattern and perihepatic free fluid. (C) Doppler ultrasound image showing a portal vein with an inspiration caliber of 14 mm, with hepatopetal flow, maximum peak velocity of 20.6 centimeters per second and calculated congestive index of 0.08. (D) H&E 40× showing the hepatic parenchyma with pseudoacinar transformation. (E) 10× with Masson's trichrome showing expansion of the portal spaces by fibroconnective tissue that binds them together and forms a nodular pattern with evidence of fibrosis bridges from one portal space to another. (F) 20× with H&E shows interface area between portal space and hepatic lobule with increased lymphoplasmacytic cells which focally infiltrate hepatocytes.

Table 1. Main findings laboratory investigations.

TEST NAME	RESULT	REFERENCE RANGE
Hemoglobin	7 gr/dL	14 - 16 gr/dL
Hematocrit	21.6%	40% - 48%
Mean corpuscular volume	85 fL	75 - 100 fL
Platelet count	56,000/mm^3	150,000 - 400,000/mm^3
Leukocytes - Total	7230/mm^3	3500 - 10,000/mm^3
Alkaline phosphatase |	237 UI/L	40 - 160 UI/L
Gama-glutamyltransferase	160 UI/L	8 - 60 UI/L
Transaminase ALT	48 UI/L	29 - 33 UI/L
Transaminase AST	37 UI/L	29 - 33 UI/L
Bilirrubin - Total	2.0 mg/dL	0.3 - 1.2 mg/dL
Albumin	3.1	3.5 - 5 gr/dL
INR	1.45	0.9 - 1.1
Serum creatinine	0.74 mg/dL	0.7 - 1.2 mg/dL
IgG	146 mg/dL	800 - 1500 mg/dL
IgM	18.1 mg/dL	45 - 150 mg/dL
Antinuclear antibodies	1:1200	<1:40
Anti-smooth muscle antibodies	1:40	<1:80
Antimitochondrial antibodies	<1:40	<1:40
HIV	Negative	Negative
HBsAg	Negative	Negative
HCV antibodies	Negative	Negative

4. Treatment and Follow-Up

Upon admission, the patient was initially treated with intravenous omeprazole and terlipressin in accordance with the international management guidelines for gastrointestinal bleeding of non-variceal and variceal origin for 5 days [7] [8]. An upper endoscopy was performed that revealed large esophageal varices, which were treated with ligation. Secondary prophylaxis was started with non-selective beta-blockers and endoscopic follow-up at 8 weeks for the second ligation session [7]. After 7 days of hospitalisation, the patient was feeling better. There were no further episodes of haematemesis. On discharge, it was decided to start treatment with prednisone 40 mg/day and after 2 weeks azathioprine was added at 2.5 mg per kilo without presenting hematological side effects [9]. Currently with prednisone 5 mg/day and azathioprine 150 mg/day, in his follow-up he has not presented elevated transaminases and does not present cholestasis. He will receive a liver ulltrasound every 6 months to assess for hepatocellular carci-

noma and continues to receive intravenous immunoglobulin once a month.

5. Discussion

IDCV is a rare disorder, and its pathophysiology is complex and poorly understood. Its main characteristic is hypogammaglobulinemia resulting from alterations in the differentiation of B lymphocytes. It has been established that gastrointestinal disorders are found in 6% - 20% of patients with this entity, the most common being celiac disease and liver disorders that range from nodular regenerative hyperplasia to cirrhosis [10] [11].

It has been described that patients with CVID and hypertransaminasemia may have characteristics of AIH, since despite being an immunodeficiency disorder, up to 25% of patients have autoimmune diseases [6]. Previous studies have established a prevalence of episodes of non-B and non-C hepatitis in patients with CVID of approximately 41%, generally in patients older than 30 years [4] [12]. The diagnosis of HAI in this context is complex, because the criteria for its diagnosis require high levels of IgG, which are decreased in patients with IDCV [13] [14]. Antibody expression is usually altered, giving false negative results, so in the appropriate clinical context, histological findings and the presence of hypertransaminasemia should lead to suspicion of AIH [10]. In our case, the decision to perform a liver biopsy was based on the absence of a cause of advanced liver disease. The most common liver involvement in patients with CVID includes elevated levels of transaminases and alkaline phosphatase, nodular regenerative hyperplasia (NRH) or liver cirrhosis. NRH is defined as hepatocellular nodules less than 3 mm in diameter, not surrounded by marked fibrosis, however, histological findings on biopsy are consistent with AIH due to the presence of interface hepatitis and lymphoplasmacytic infiltrate [14].

Despite this, there are reports in which, after the administration of intravenous immunoglobulins for the treatment of IDCV, patients recover their immune response, raising IgG and serum antibody figures [1]. The use of steroids increases the risk of developing infectious processes, however, given the HAI activity data, they should be initiated for its management [10].

Patients with CVID paradoxically experience a higher risk of developing autoimmune disorders, because they share a pathophysiological basis that involves alterations in the function of B lymphocytes [5]. Given the vast array of pathology these patients can suffer from, a broad differential diagnosis is necessary when approaching a patient with CVID. A deliberate search should be made in order to offer treatment, prompt medical care and avoid late complications.

Conflicts of Interest

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

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Post-Endoscopy Self-Limited Unspecified Fever: Rare or Common Adverse Event after Endoscopy?—An Observational, Cross-Sectional Study

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Abstract

Background: Although post-endoscopy fever (PEF) without colon perforation or haemorrhage is believed to be rare, incidence, risk factors and causes in the adult population have not been fully investigated. The purpose of the present study was to investigate the incidence of PEF and identify the risk factors associated with the development of PEF and its outcomes. **Material and Methods:** Over a three-month period, 1054 non-hospitalised patients who had an endoscopic procedure at Cleveland Clinic Abu Dhabi received a post-procedure phone call within the first 24 hours. After identifying patients with fever and obtaining verbal consent, patients were enrolled in the study using a standardised telephone interview. **Results:** Thirty-four patients with PEF were identified. The highest temperature measured was 39.8 degrees Celsius. Oesophagogastroduodenoscopy, as a single procedure, was the most commonly performed (41.2%). Logistic regression revealed that no significant group differences across procedure types existed in terms of adjusted odds of fever. However, results also indicated that age has a significant negative relationship with fever—higher age is associated with lower odds of fever ($b = -0.033$, $p = 0.024$). **Conclusion:** PEF is an unpleasant side effect and it is associated with patient discomfort, dissatisfaction and fear during post-endoscopy recovery. Although our findings do not fully explain the possible mechanisms underlying post-endoscopy fever, this study data should increase awareness about PEF as a common side effect related to endoscopy.

Keywords

Post Endoscopy Fever, Drug-Induced Fever, Bacteria Translocation

1. Background

Gastrointestinal (GI) endoscopy is a common procedure performed for the evaluation and treatment of various GI tract disorders. Unfortunately, the increased use of these procedures for diagnostic and therapeutic reasons has been accompanied by a corresponding increase in the incidence of post-endoscopy complications.

In our clinical practice, we have encountered patients who experienced fever after the endoscopy procedure without peritoneal signs or definitive fever foci. As a result, patients were often referred to the emergency department or admitted to the hospital to receive other unanticipated evaluations for further assessment.

The term "fever" is used liberally in clinical publications due to the lack of agreement on a universally accepted definition [1]. In 1868, Carl Wunderlich, professor of medicine in Leipzig, suggested for the first time that fever is not a disease but rather a sign of disease and is credited with proposing one of the earliest evidence-based definitions of fever [2]. Currently, according to Harrison's Principles of Internal Medicine [3], fever is defined as a core temperature >37.5˚C (99.5˚F), a morning oral temperature >37.2˚C (>99˚F), or late afternoon oral temperature >37.7˚C (>99.9˚F). Given the many factors influencing the results of temperature measurements, there can never be a single, universally accepted, value defining a fever [1]. A fever rarely presents without other symptoms. It is often accompanied by specific complaints like chills, fatigue, joint or muscle ache among others.

Although post-endoscopy fever (PEF) without colon perforation or haemorrhage is believed to be rare, its incidence and risk factors in the adult population have not been investigated completely. PEF is a relatively common adverse event following endoscopy in children, with a greater risk following interventional procedures, causing concern for perforation and/or significant infection as a complication from endoscopy [4] [5]. In a study published by Kramer and colleagues [5], fever represented 21.6% of all perioperative events with an incidence of 0.55% across all pediatric endoscopic procedures [6]. Similar results are published by Coser and colleagues for adult population where fever represented 21.5% of all post-colonoscopy emergency department visits [7].

The reasons for PEF have not yet been fully investigated. Endogenous immune response, bacteria translocation, contaminated endoscopes, or drug-induced fever is all potential reasons that can lead to post-procedural elevated temperature.

The purpose of the present study was to investigate the incidence of PEF and

possibly identify the risk factors associated with the development of PEF and its outcomes.

2. Material and Methods

Authors performed a single-center, observational, prospective study. Ethics approval for this study was provided by the Institutional Review Board (IRB) of Cleveland Clinic, Abu Dhabi, UAE, under Study Registration No. A-2019-046, on 9th September 2019.

Over a three-month period, 1054 non-hospitalized patients who had an endoscopic outpatient procedure at Cleveland Clinic Abu Dhabi were interviewed by telephone within the first 24 hours after the procedure as routine post-procedure practice. Endoscopic outpatient procedure was defined as any endoscopic procedure in which the purpose was to inspect the mucosa and/or obtain biopsies for histologic analysis or minor procedures that will not require hospitalisation and will be performed under monitored anaesthesia care (e.g. Endoscopic ultrasound (EUS), Banding, Dilatation). An inclusion criterion for the identification of patients with fever was the existence of subjective symptoms (chills, fatigue, joint or muscle ache) that are confirmed by an elevated body temperature. Due to the lack of universally accepted value for fever and the existence of numerous factors that may affect the same, the authors included in the febrile group all patients with confirmed values above 37.5 degrees Celsius, regardless of the type of thermometer used or the site from which the temperature was measured.

After identifying 34 patients with fever and obtaining verbal consent, we enrolled all 34 patients in the study performing standardized telephone interviews. The standardized telephone interview consisted of five questions related to the presence of fever like symptoms and self-initiated measured temperature at home, the values obtained during the measurement, the use of antipyretics and antibiotics, as well as visits to doctors or emergency departments. Data from the remaining 1020 patients with no fever were retained and served as the comparison group in inferential analyses. Individual consent for the remaining 1020 patients with no fever for retrospective data analysis was waived by same study registration number.

All endoscopic procedures were performed in the Department of Gastroenterology, using standard gastroscopes (GIF-H190 or GIF-HQ190; Olympus Optical Co., Ltd., Tokyo, Japan), and adult or pediatric colonoscopes (CF-HQ190 or PCF-H190; Olympus Optical Co., Ltd., Tokyo, Japan). The choice of endoscope was selected at the discretion of the proceduralist.

Monitored anaesthesia care (MAC) was used in all patients. Sedation for the procedures was provided by propofol (by continuous infusion or intermittent bolus doses). Standard American Society of Anesthesiologists recommendation monitoring (electrocardiography, pulse oximetry, non-invasive blood pressure monitoring and continuous monitoring of end-tidal CO_2) were applied.

This study followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement guidelines for observational studies [8].

3. Statistical Methodology

Statistical data are presented through descriptive statistics. Discrete variables are presented as absolute number (n) and percentage (%) and normally distributed data are shown as mean with standard deviation (SD).

Unadjusted group comparisons were made using independent samples t-test and Fisher's exact tests for continuous and categorical variables respectively. Adjusted endoscopy group differences (colonoscopy, oesophagogastroduodenoscopy, oesophagogastroduodenoscopy & colonoscopy) in terms of odds of fever were calculated and compared using logistic regression. Group odds of fever were adjusted via inclusion of the following covariates: age (years), BMI, endoscopy duration (minutes), and propofol (mg).

All analyses were performed using Microsoft R Open 4.0.2.

4. Results

Demographic and clinical data of all included patients were collected and documented from electronic medical records. Patients' confidentiality was protected by assigning a de-identified patient code.

After evaluating 1054 non-hospitalized patients who had an endoscopic procedure, thirty-four patients with PEF were identified. Identification of febrile patients takes place in the pre-COVID period, which is important given the frequency and importance of fever during the pandemic. Flow chart of study process is presented in **Figure 1**. Demographic information on sex, age, ASA status, BMI and type of endoscopy procedure are presented in **Table 1**. None of the 34 patients identified during the study had a fever prior to endoscopy nor were they under the influence of antipyretics or antibiotics prior or immediately after endoscopy for any reason. The frequency of fever was similarly present in both sexes (Male-44%: Female-56%), with a slightly higher percentage in the female population without statistical significance. Frequency by age was more prevalent in the younger adult population (Mean [SD]-39.2[11.5]).

Logistic regression revealed that no significant group differences existed in terms of adjusted odds of fever. However, results also indicated that age has a significant negative relationship with fever – higher age is associated with lower odds of fever ($b = -0.033$, $p = 0.024$) (**Table 2**).

For patients with fever, the highest temperature measured was 39.8 degrees Celsius. The temperature range was in between 37.6 and 39.8 degrees Celsius, with fever-like symptoms as chills, weakness, body and joint pain with shivering. Only one patient visited the emergency department due to the presence of fever and existing accompanying symptoms, while 80% of patients took antipyretic medications to alleviate the existing discomfort and temperature.

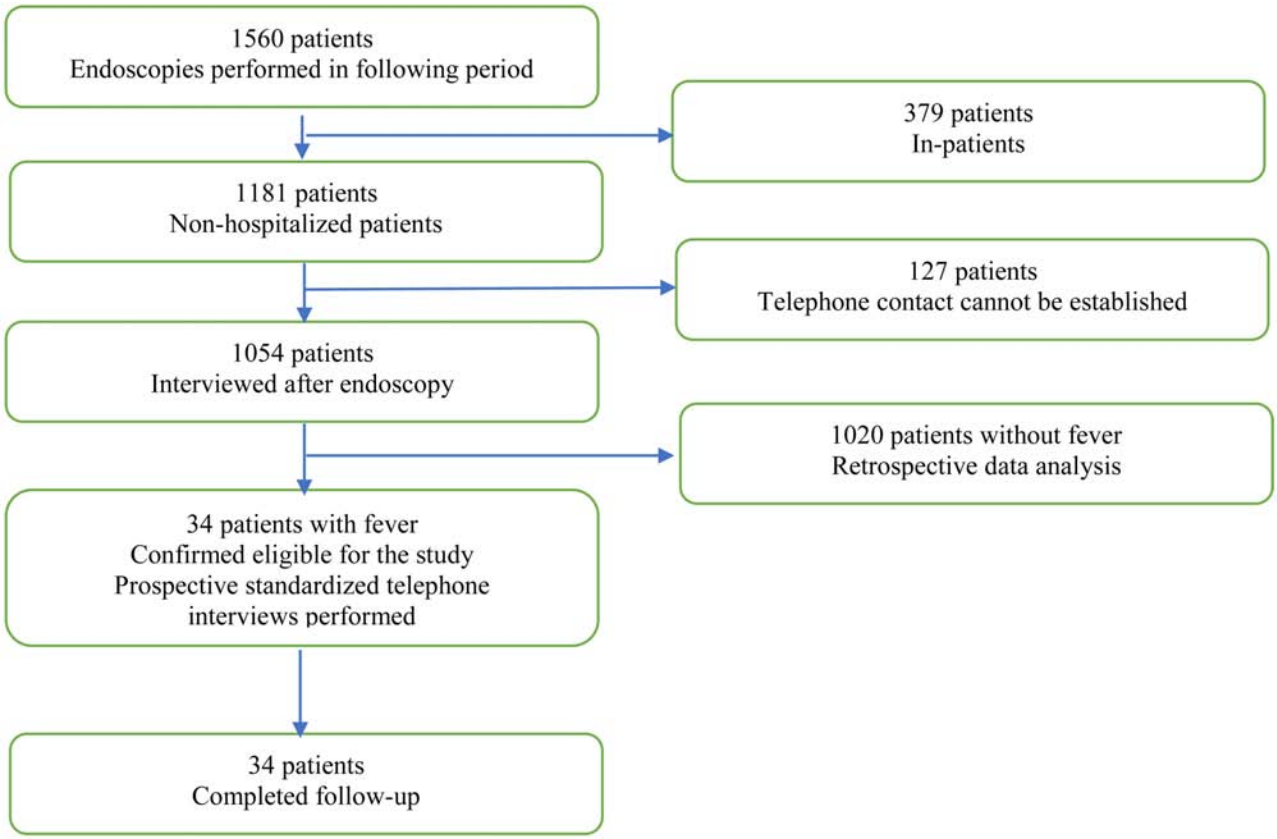

Figure 1. Flow chart of study process.

Table 1. Patient demographics and sample description (ASA—American Society of Anesthesiologists physical status classification; BMI—Body Mass Index; EUS-Endoscopic ultrasound).

Patient demographics and sample description				
		Fever	**w/o Fever**	**p**
Total No. Patients		34	1020	
Age—Mean (SD)		39.2 (11.5)	45.2 (14.4)	0.016
BMI—Mean (SD)		28.4 (6.4)	29 (6.5)	0.548
Sex – No. (%)	Male:	15 (44.1%)	491 (48.1%)	0.728
	Female:	19 (55.9%)	529 (51.9%)	
ASA – No. (%)	I	4 (11.8%)		
	II	24 (70.6%)		
	III	6 (17.6%)		
Esophagogastroduodenoscopy – No. (%)		14 (41.2%)	306 (30%)	
Colonoscopy – No. (%)		6 (17.6%)	305 (29.9%)	0.212
Esophagogastroduodenoscopy and colonoscopy– No. (%)		14 (41.2%)	409 (40.1%)	
Intervention (EUS, Banding, Dilatation) – No. (%)		2 (5.9%)	23 (2.25%)	0.171

Table 2. Logistic regression results (BMI—Body Mass Index).

Logistic Regression Results							
	b	Std. Error	z	p	OR	95% CI of OR	
						min	max
Age (years)	−0.033	0.014	−2.263	**0.024**	0.968	0.941	0.996
BMI	−0.004	0.027	−0.169	0.866	0.996	0.945	1.049
(Intercept) Endoscopy Colonoscopy	−2.917	0.970	−3.008	0.003	0.054	0.008	0.362
Esophagogastroduodenoscopy	0.965	0.537	1.796	0.072	2.625	0.916	7.525
Esophagogastroduodenoscopy and Colonoscopy	0.390	0.507	0.770	0.442	1.478	0.547	3.994
Duration (minute)	0.021	0.017	1.241	0.215	1.021	0.988	1.056
Propofol (mg)	0.000	0.001	0.312	0.755	1.000	0.999	1.001

Oesophagogastroduodenoscopy, as single procedure, was the most commonly performed (41.2%). Colonoscopy was performed as a single procedure in 17.6% and double (oesophagogastroduodenoscopy and colonoscopy) in 41.2% of our patients. Polypectomy was performed in only 5 patients (14.7%). Multiple biopsies were performed in 26 of the 34 patients (76.5%). Data analysis suggest that both oesophagogastroduodenoscopy and oesophagogastroduodenoscopy with colonoscopy have higher probability of fever relative to colonoscopy, but these relationships aren't statistically significant at the 0.05 level.

Data recording length of the procedure and the total amount of propofol that was used during the procedure are presented in Table 3. Propofol was used in almost all of the endoscopy procedures in our institution. The dose was directly related to the duration of the procedure. Related to fever, both amount of propofol and duration of procedure aren't statistically significant at the .05 level.

Co-administered medications Fentanyl (50 - 100 mcg) and Lidocaine (50 - 100 mg) are very often used as a part of MAC protocol. Other medications like Glycopyrrolate, Ondansetron, or Metoclopramide were rarely used and based on our limited data it is not possible to determine a cause-effect relationship.

Co-morbidities related to patients with fever are presented in Table 4. The most common co-morbidity was hypertension (20.6%) followed by diabetes mellitus (14.6%).

During the study, the authors also monitored the relationship between fever and the type of scope used during the procedure. Each case of fever was associated with a different scope, which excludes the possibility that the scope itself could be a potential source of infection and fever due to the existence of possible damage in the endoscope channel. Also, a cause-effect relationship between fever and a specific technique by the endoscopist or anaesthetist has not been observed.

Bearing in mind that the subject of the study were non-hospitalized patients and that we conducted a phone questionnaire that was conducted 24 hours after the endoscopic procedure, we were not able to perform laboratory analysis in

Table 3. Data are presented as mean ± SD for length of procedure and amount of Propofol that is used during procedure.

Data recording length of the procedure and the total amount of propofol				
		Fever	w/o Fever	p
Length of procedure (min)	Esophagogastroduodenoscopy	14.5 ± 15.3	9.1 ± 8.5	0.026
	Colonoscopy	24 ± 18.2	21.4 ± 10.8	0.556
	Esophagogastroduodenoscopy and colonoscopy	25.3 ± 5.3	28.2 ± 10.3	0.287
Propofol mg	Esophagogastroduodenoscopy	339.3 ± 208.6	271.2 ± 130.2	0.065
	Colonoscopy	467 ± 186	438.4 ± 406	0.866
	Esophagogastroduodenoscopy and colonoscopy	489 ± 167.7	489 ± 271	0.997

Table 4. Co-morbidities, presented as absolute number (n) and percentage (%).

Co-morbidities	
Hypertension (HTA)	7/34 (20.6%)
Diabetes Mellitus (DM)	5/34 (14.7%)
Asthma	3/34 (8.8%)
Hypothyroidism	3/34 (8.8%)
Cirrhosis	3/34 (8.8%)
Chronic Kidney Disease	3/34 (8.8%)
Arthritis	3/34 (8.8%)
Coronary artery Disease (CAD)	2/34 (5.9%)
Cerebrovascular Accident (CVA)	1/34 (2.9%)

patients positive for fever. Pro-inflammatory markers were not measured. Based on auto-anamnestic data in all patients, the temperature occurred in the first 24 hours in the form of a self-limiting episode with all of the accompanying symptoms, after which it completely resolved spontaneously or after a single dose of paracetamol. Repeated episodes of fever were not reported.

5. Discussion

Published literature on post-endoscopy fever is limited. Most studies that analysed post-endoscopic fever were analysed after polypectomy and in most cases only in hospitalised patients. Lee and colleagues [9] reported a case-control study of patients who experienced post-polypectomy fever (PPF), defined as elevated temperature after polypectomy without evidence of other explainable fever foci. Although their findings do not explain the possible mechanisms underlying PPF, risk factors are defined as hypertension and large polyps. In our study, we monitored PEF incidence in a non-hospitalised, predominantly healthy population in which screening endoscopic procedures were performed. Polypectomy was performed in only five PEF patients (14.7%) and the most common single was oesophagogastroduodenoscopy (41.2%).

The relationship between age and fever in our study contradicts previously published papers. A study published by Coser and colleagues [7] did not find a statistically significant correlation between age and fever, however, our results indicate that age has a significant negative relationship—higher age is associated with lower odds of fever.

The mechanisms of PEF are complex and it is not yet fully explained. While its outcome is generally favorable, PEF can generate patient discomfort, fear and unnecessary diagnostic procedures as well as possible hospitalisations.

Endogenous immune response has not been sufficiently examined for gastro-colonic endoscopic procedures, but it has been for bronchoscopy procedures [10]. Fever following a bronchoscopy, particularly bronchoalveolar lavage (BAL), can be associated with an endogenous immune response. A systemic inflammatory response is characterized by an increase in circulating cytokine levels such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 beta, and IL-6 [11] [12] [13] [14]. During polypectomy, adenomatous polyps have an inflammatory stromal microenvironment, rich in macrophages, neutrophils, and T helper cells [15] that can be a trigger for endogenous immune response.

Alternatively, endoscopic examinations may be the gateway through which bacteria invade the body. Transient bacteremia after colonoscopy, with or without polypectomy, occurs in approximately 4% of procedures, with a range of 0% to 25% [16] [17] The reported incidence of bacteremia after diagnostic upper GI endoscopy, with or without biopsies, was less than 8% comparing bacteremia after colonoscopy, with or without biopsies and polypectomies, which ranges from 0% to 25% [10].

Post-polypectomy coagulation syndrome (PPCS) is an uncommon complication (incidence 0.003% to 0.1%) after colonoscopy as described in the literature. This syndrome is the result of an electrocoagulation injury to the colonic wall that induces a transmural burn and localised peritoneal inflammation without evidence of perforation on radiographic studies. PPCS has typical symptoms such as abdominal pain, fever, leukocytosis and peritoneal tenderness [18]. Factors associated with an increased risk include large polyp size, non-polypoid shape of lesion, caecum or ascending colon location, and patient history of hypertension.

Contaminated endoscopes can also potentially be associated with endoscopy healthcare-associated infections and possible PEF. Flexible endoscopes may become heavily contaminated with blood, secretions and microorganisms during use. They are difficult to clean and disinfect, and easy to damage because of their complex design with narrow lumens and multiple internal channels. In addition, the ability of bacteria to form biofilms in the endoscope channels, especially when these become damaged, can contribute to the failure of the decontamination process [10] [19]. In a study published by Gorse and Messner, the authors reported that endoscopy-related infections, usually bacterial, occurred at 6% of institutions that participated in a national survey [20]. Our data is inconsistent

with the above study as we could not establish a causal relationship between fever and gastro or colonoscopes used in clinical practice.

Although high blood pressure was marked as contributing factor that promotes post polypectomy fever in a previously published study [9], the mechanism is still unclear. Possibly, blood pressure-regulatory systems, such as the renin-angiotensin system and sympathetic nervous system, interact with the proinflammatory cytokines, such as IL-6 and TNF-α as a possible potentional source of PEF [18] [21].

Propofol-induced drug fever during endoscopy is not new [22] [23], however it is not well known. In 2007, the U.S. Food and Drug Administration (FDA) released a safety alert concerning reports of cases of fever, chills, and body aches in patients shortly after the administration of propofol. New episodes of fever have been associated with patients following gastrointestinal procedures. Although the propofol emulsion is capable of supporting microbial growth in the event of contamination during administration, the tests performed by the FDA did not identify any units contaminated with bacteria or endotoxins [24]. Study published by Bennett and colleagues [25] investigated an unusual outbreak of bloodstream infections, surgical-site infections, and acute febrile episodes after surgical procedures between June 1990 and February 1993. Exposure to propofol was the only significant variable associated with postoperative complications. Although cultures of unopened containers of propofol were negative, cultures of propofol from syringes were positive at two hospitals. It was found that the contamination did not occur as inadequate sterility of propofol emulsion but to accidental extrinsic contamination. After this event, the product has been reformulated to contain disodium edetate 0.005%, to inhibit the growth of microorganisms in the event of accidental contamination. However, propofol can still support the growth of microorganisms, as it is not an antimicrobial preserved product under the United States Pharmacopeia standards and aseptic precautions needs to be maintained during administration.

Several limitations in this study should be noted. First, we cannot provide information on microbiological workup for patients who developed a post-endoscopy fever. The number of patients with PEF was too small to identify the risk factors for this condition. The time frame in which the study was performed (first 24 hours) is also a limiting factor since it is not in line with A lexicon for endoscopic adverse events: report of an ASGE workshop, 2010 [26]. Another limiting factor to consider is that neither the type of thermometer used nor the site from which the temperature was taken was consistent across all patients. Finally, this study was performed as a single-center study, and a larger multicenter study would give better insight into this problem. Further investigation on these limitations is recommended.

6. Conclusion

Our findings do not fully explain the possible mechanisms underlying PEF, but

our study should increase awareness regarding PEF as a common side effect after endoscopy. PEF is an unpleasant event and it is associated with patient discomfort, dissatisfaction and fear during their post-endoscopy recovery, with the possibility of causing unnecessary investigations as well as possible hospitalizations.

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Ethics Approval and Consent to Participate

Ethics approval for study was provided by the Institutional Review Board (IRB) of Cleveland Clinic, Abu Dhabi, UAE, under Study Registration No. A-2019-046, on 9th September 2019. For 34 patients with fever verbal, telephone consent was obtained. Consent for the remaining 1020 patients with no fever for retrospective data analysis was waived by same study registration number.

Availability of Data and Materials

The data that support the findings of this study are available from Cleveland Clinic Abu Dhabi, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of REC of Cleveland Clinic Abu Dhabi.

Authors' Contributions

Author contributes to the study and manuscript preparations include the following: Conception and design: Boris Tufegdzic; Drafting the article: Boris Tufegdzic; Critically revising the article: all authors; Reviewed submitted version of manuscript: all authors; Approved the final version of the manuscript on behalf of all authors: Boris Tufegdzic; Study supervision: Boris Tufegdzic.

Competing Interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Eosinophilic Gastroenteritis in Tropical Area: about 6 Cases from Senegal

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Abstract

The aetiologies of hypereosinophilia are dominated by digestive parasitosis and drug intake. In the tropics, because of the frequency of parasitosis, eosinophilic digestive pathologies of primary origin, which are rare, may be overlooked. We report 6 cases of eosinophilic gastroenteritis with polymorphic digestive manifestations testifying to the different locations of eosinophilic infiltration in the digestive parietal layer. Three patients had ascites rich in eosinophils, indicative of serous involvement, while the other two had a muscular form, and the last a mucosal involvement. The evolution was favourable in all cases with corticosteroid therapy, but a recurrence was noted in 4 cases when treatment was stopped.

Keywords

Eosinophilic Gastroenteritis, Ascites, Digestive Eosinophilic Infiltration, Senegal

1. Introduction

Eosinophilic gastroenteritis (EGE) is a rare pathology characterized by an inappropriate infiltration of one or more components of the digestive wall by polymorphonuclear eosinophils. Its etiology is poorly known even if a food allergy is incriminated. It is probably underdiagnosed because of its nonspecific manifestations, the eosinophilic infiltration being able to interest the mucosa, the muscular or the serosa of the digestive wall. EGE is rarely reported in sub-Saharan Africa where parasitosis remains the first cause of hypereosinophilia. We report 6 cases of eosinophilic gastroenteritis reflecting these different impairments.

2. Patients and Methods

This is a retrospective study, including patients hospitalized in the internal medicine and gastroenterology departments of the Principal Hospital of Dakar, between January 1, 2015 and December 31, 2021. We consulted hospitalization registers of the two departments during this period, and we included all the patients with a complete data, and discharged from hospital with the diagnosis of EGE. The diagnosis of EGE was retained after excluding other causes of tissue hypereosinophilia, when there was:

- clinical signs of gastroenteritis (vomiting, diarrhoea, abdominal pain) associated with endoscopic digestive parietal lesions with mucosal eosinophilic infiltration, or blood hypereosinophilia.
- abdominal pain associated with thickening of the colonic wall and blood hypereosinophilia.
- ascites rich in eosinophils.

The data studied were epidemiological (age, sex, terrain, food allergy), clinical (abdominal pain, diarrhea, vomiting, ascites), biological (complete blood count, CRP, liver function tests, parasitological stool examination), endoscopic (upper digestive endoscopy, colonoscopy), histological (biopsies performed during endoscopy), radiological (abdominal scan), therapeutic, and outcome.

Response to treatment was defined by an improvement in clinical signs and disappearance of peripheral eosinophilia. Recurrence was defined by a resumption of symptoms when corticosteroid treatment was reduced or stopped. A patient who remained more than 6 months without attending the follow-up consultation was considered lost to follow-up.

3. Results

During this period, 6 patients were hospitalized with the discharge diagnosis of eosinophilic gastroenteritis. They were 2 men and 4 women with an average age of 39.5 years [21 - 56 years]. None of the patients had a particular medical history, nor atopy or food allergies.

The revealing clinical signs were diarrhoea and vomiting associated with ascites in 2 cases, chronic diarrhoea isolated in 1 case, or associated with abdominal pain in 1 patient, isolated ascites in one patient and an occlusive syndrome without obstruction in one patient. At examination, ascites was found in three patients.

Blood hypereosinophilia was present in 5 patients with an average of 12,640 eosinophils per mm^3 [3530 - 20,470]. Blood eosinophils count was normal in one patient. There was no anemia, nor thrombocytopenia or thrombocytosis. The other biological parameters (hepatic functional explorations, renal function, blood ionogram, calcemia, serum protein electrophoresis and thyroid hormones) were normal in all patients.

There was no inflammatory syndrome. The parasitology stool examination was negative in all cases, as was the retroviral serology. Abdominal paracentesis

in 3 patients brought back a citrine yellow liquid, rich in proteins (respectively 47, 60.5 and 54 g/l) and eosinophils (350, 7520 and more than 7000 eosinophils per mm^3, respectively).

Upper digestive endoscopy was normal in 5 cases, and found duodenal ulceration in one case. Colonoscopy showed erythematous, ulcerated or granite rectocolitis in 3 patients, and was normal in 2 cases. All patients had colonic biopsies except one who had a normal colonoscopy. Biopsies were performed both on pathological mucosa and on normal mucosa, and showed an aspect of interstitial or oedematous colitis without eosinophilic infiltrate in 3 patients, and one case of ulcerative colitis of moderate intensity, with a diffuse polymorphic infiltrate, rich in eosinophils (more than 20 per field). Abdominal CT scan showed colonic wall thickening in 3 cases, ascites in 3 patients, and was normal in one case.

The diagnosis of eosinophilic gastroenteritis was retained in all patients, in its serous form in 3 cases, muscular in 2 cases and mucous in 1 case. All patients benefited from systematic deworming with albendazole. Corticosteroid therapy with prednisone 40 mg per day was initiated in all patients, with a favourable evolution marked by a rapid regression of symptoms. For the three patients with ascites, this had disappeared between 7 and 15 days of treatment. In the case of the occlusive syndrome, transit was normal after 48 hours of treatment, with disappearance of abdominal pain and cessation of vomiting. In the other two cases, the diarrhoea had improved after 3 to 5 days, as had the abdominal pain. Blood eosinophilic count was normal after one month except in the patient who had a very high rate, in whom it went from 17140/mm^3 to 1420/mm^3 in 30 days.

Treatment with corticosteroids was gradually reduced after one month of treatment to reach minimum doses between 7.5 and 5 mg of prednisone per day, without recurrence of symptoms. One patient was lost to follow-up after 6 months without recurrence. In two cases, after one year of follow-up without treatment, there was no resumption of symptoms. In the 3 other patients, the evolution was marked by a relapse after stopping treatment at 1, 4 and 6 months respectively (two patients with a serous form, and one with a muscular form). However, as soon as the corticosteroid therapy was reintroduced, the symptoms improved.

The 6 observations are summarized in **Table 1**.

4. Discussion

Eosinophilic gastroenteritis (EGE) is defined by histological eosinophilic infiltration of more than 20 eosinophils per field of one or more components of the digestive wall, in one or more portions of the digestive tract without extraintestinal involvement, with the exclusion of another cause of gastrointestinal eosinophilia [1]. It is a rare pathology, first described by Kaijser in 1937 [2]. The prevalence is estimated between 5.1 and 8.4/100,000 inhabitants in large population cohorts in the United States, with a slight female predominance, and a more frequent involvement in Caucasians [3] [4]. This prevalence is difficult to assess

Table 1. Characteristics of patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	38	56	21	29	50	43
Sex	Male	Male	Female	Female	Female	Female
Evolution duration before diagnosis	1 month	1 week	Several years, accentuation since one week	3 months	6 years	2 weeks
Clinical presentation	Diarrhea Vomiting Ascites	Diarrhea Vomiting Ascites	Abdominal pain Occlusive syndrome Vomiting. Constipation	Diarrhea Abdominal pain	Chronic diarrhea	Ascites
Blood eosinophils count (/mm^3)	8500	13,560	3530	17,140	180	20,470
Ascites eosinophils count (/mm^3)	7520	+7000	-	-	-	350
Digestive endoscopy	Upper digestive endoscopy: duodenal ulcerations Colonoscopy: erythematous and ulcerated proctitis	Upper digestive endoscopy: normal Colonoscopy: normal	Upper digestive endoscopy: normal Colonoscopy: normal	Upper digestive endoscopy: normal Colonoscopy: erythematous and granitic rectosigmoiditis	Upper digestive endoscopy: normal Colonoscopy: erosive rectocolitis	Normal
Histology	Nonspecific interstitial colitis	Nonspecific edematous colitis	-	Exulcerated sigmoiditis without eosinophilic infiltrate	Ulcerative colitis with a polymorphic infiltrate rich in eosinophils	
Abdominal CT scan	Antro-pyloric wall thickening Ascites	Thickening of the left colonic wall Ascites	Diffuse thickening of the colonic wall	Thickening of the left colon and transverse colon	Normal	Ascites
Eosinophilic gastroenteritis type	Serous	Serous	Muscular	Muscular	Mucosa	Serous
Treatment	Prednisone	Prednisone	Prednisone	Prednisone	Prednisone	Prednisone
Outcome	Favourable without relapse	Favourable, but relapse 6 months after stopping treatment	Favourable, but relapse 4 months after stopping treatment	Favourable, but lost of follow-up after 6 months without relapse	Favourable without relapse	Favourable, but relapse 1 month after stopping treatment

in Africa where the disease is rarely reported in isolated cases [5]. We report 6 cases of EGE followed in our hospital over a period of 5 years, *i.e.* 0.24% of patients hospitalized in the hepato-gastroenterology and internal medicine departments during this period.

EGE is a pathology whose etiopathogenesis is not completely elucidated. However, atopy (rhinitis, eczema, asthma, food allergy) is found in more than half of the cases [6]. This had not been found in our patients, but allergy tests had not been carried out.

Due to the eosinophilic infiltration of the digestive wall that can affect all layers, EGE leads to polymorphic clinical presentations, depending on the parietal involvement. In 1970, Klein proposed an anatomical classification distinguishing three types of EGE according to the parietal layer affected: mucous membrane, muscularis and serous [7], responsible for diarrhoea, abdominal pain, nausea or vomiting, or ascites. In our 6 patients, the clinical symptomatology was various (**Table 1**).

Blood eosinophilia, present in 70% of cases [2] [8], is found in 5 of our patients. It has a strong orientation, but its absence should not prevent the realization of a digestive endoscopy when the diagnosis is suspected [9]. The level of blood eosinophils count also makes it possible to classify the disease as minimal, moderate or severe [2]. On the other hand, the severity of peripheral eosinophilia does not reflect the importance of the infiltration of the digestive layer by eosinophils [10], or the severity of the disease. Among our patients, 5 had very high levels of blood eosinophils count, suggesting a hypereosinophilic syndrome. However there were no symptoms suggestive of involvement of another organ, and the presentation was acute in all cases. Another suggestive biological element in this context is the increase of serum IgE levels above 100 IU/ml which is reported in 2/3 of patients [11]. In front of this symptomatology, it is essential to perform an upper digestive endoscopy, as well as an ileo-colonoscopy with staged biopsies. However, these examinations may be normal or show nonspecific lesions.

In our patients, digestive endoscopy examinations were normal or showed lesions such as erythema or ulcerations. The anatomo-pathological examination of the staged biopsies helps in the diagnosis in the case of mucosal involvement by highlighting more than 20 eosinophils per field. Only one patient presented an eosinophilic infiltrate in the colonic mucosa. In the other patients, the depth of the parietal involvement, as well as the discontinuous distribution of eosinophilic infiltration could explain the absence of eosinophils on the biopsies. On the other hand, the presence of a high number of eosinophils in the ascites fluid confirms the diagnosis of serous involvement, as is the case in our three patients with ascites. On CT scan, thickening of the colonic wall was noted in three patients, probably testifying the infiltration of the muscle layer.

The diagnosis of EGE can be difficult, the clinical presentation not being specific. Talley suggests 3 diagnostic criteria that are currently widely used: presence of gastrointestinal symptoms, histological signs of eosinophilic infiltration of the

digestive tract or an elevated level of eosinophils in the ascites fluid, and the exclusion of other causes of tissue hypereosinophilia (digestive parasites, frequent in tropical area, drugs, neoplasia and essential hypereosinophilic syndrome) [8].

Parasitological stool examinations were done in all our patients and were negative in all cases. However, given the tropical environment, they all benefited from systematic deworming with albendazole and ivermectin prior to treatment. An improvement in clinical symptoms or hypereosinophilia was not noted after this antiparasitic treatment. Thus, among our six patients, four met Talley's criteria, and the diagnosis of EEG was retained in the other two based on digestive signs, blood eosinophilia, and the aspect of colonic parietal thickening on CT scan, without any other cause found.

From a therapeutic point of view, we did not prescribe a diet to our patients because none of them reported food allergies. However, skin tests looking for an allergy have not been carried out. Indeed, diet can play an important role in the remission of symptoms, with clinical improvement reported in 75% of patients who had well respected it especially those with mucosal involvement [12]. Furthermore, EGE responds very well to corticosteroid therapy, with disappearance of symptoms, ascites, hypereosinophilia and eosinophilic tissue infiltration [13]. Prednisone is the molecule of choice with remission reported in over 90% of cases [2]. All our patients initially evolved well under prednisone-based treatment. A rapid disappearance of ascites was noted, as was the amendment of all digestive signs. However, recurrence is feared and causes low doses of corticosteroids to be maintained over time in these cases [9] [14].

This study has some limitations. Indeed, we performed a retrospective study on a small number of patients with a diagnosis of EEG. It is a disease less reported in sub-Saharan Africa. There is a significant number of patients with incomplete data or having undergone colonoscopy for chronic diarrhea of undetermined aetiology in whom the anatomopathological examinations of colonic biopsies were not contributory. The search for eosinophils on the samples and especially their count under the microscope are often lacking in the anatomopathological reports. Thus, a complementary prospective study would make it possible to better evaluate the incidence of the GEE in our countries.

5. Conclusion

In front of digestive symptomatology associated with eosinophilia in a tropical environment, parasitoses are evoked in the first place. However, after eliminating them, we must think of eosinophilic gastroenteritis, which is rare. The diagnosis is based on the demonstration of eosinophilic infiltration of the digestive wall on biopsies or on ascites fluid. Eosinophilic gastroenteritis responds very well to corticosteroid treatment, but relapse is frequent.

Data Availability Statement

All the files of the patients are at principal hospital of Dakar.

Conflicts of Interest

No conflict of interest for all authors.

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