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Amebic Liver Abscess: A New Perspective on the Prognosis of Patients in an Endemic Area Regional Referral Center

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Abstract

Introduction: The study aims to describe the actual clinical findings, diagnostic methods, treatment, and prognosis of patients with Amebic Liver Abscess (ALA). Two decades ago, the estimated prevalence of anti-ameba antibodies with asymptomatic presentation varied from 6% to 14% in the general population of developing countries. The prevalence of symptomatic amebiasis in any form was even higher.The invasive disease was a highly morbid and common complication, with an associated mortality that varied between 1 to 26%.

Material and methods: All patients diagnosed with ALA between January 2006 and March 2012 in the regional referral center was included in the study. The diagnosis was based on: 1) clinical findings; 2) ultrasound evidence of an abscess; 3) abscess fluid with an "anchovy paste-like" appearance, negative on culture and Gram stain; and 4) response to medical treatment to metronidazole.

Results: Ultrasound of the hepatobiliary tree revealed a mean maximum diameter of 9.5 cm (range 1.4 to 28 cm). Thirty-eight (76%) patients had one abscess and 12 patients (24%) had multiple abscesses. Intravenous metronidazole were administered to all patients. Percutaneous abscess drainage (PAD) followed by ceftriaxone to prevent secondary infection was performed on 48% of patients (n=24). The abscess fluid of all patients who received PAD had an "anchovy paste-like" appearance, negative on Gram stain and culture. In this series, 100% of patients responded to metronidazole and percutaneous drainage as indicated. No patient experienced serious complications such as abscess drainage to the pleural cavity, peritoneum, pericardium or elsewhere. Average hospital stay time was 9 days (range 3 to 37 days). No patient died during or after treatment.

Discussion: The prognosis of patients with ALA has significantly improved in the last two decades. The improvement demonstrated by this study may be attributed to earlier diagnosis and earlier intervention.

Keywords: Early diagnosis; Liver abscess; Amebic prognosis

Introduction

Amebic infection is an endemic disease caused by the *Entamoeba histolytica* protozoa and it is the third most lethal parasitic infection worldwide. The global annual incidence of amebic invasive infection is estimated by the World Health Organization (WHO) to be 50 million, with 40,000 to 100,000 attributable deaths during the same period. Endemic regions are considered to be the African tropical areas, Brazil, India, and Mexico [1]. In developed countries, immigrants from endemic countries, travelers to the tropics, institutionalized mental health patients, homosexual males who have sex with males, and immune depressed individuals have an increased risk of ALA [2]. Two decades ago, the estimated prevalence of anti-ameba antibodies with asymptomatic presentation varied from 6% to 14% in the general population of developing countries [3,4]. The prevalence of symptomatic amebiasis in any form was even higher. Consequently, the invasive form of the disease was a commonplace and highly morbid complication with and estimated mortality between 1% and 26% that was correlated with the series demographics, such as age- children were the most vulnerable [5]. The most frequent causes of death were due to complications of either the abscess itself, or the treatment thereof, notably surgery [6,7]. ALA occurs when *E. histolytica* trophozoites penetrate the intestinal mucosa and invade other organs via the cardiovascular circulation. In the liver, trophozoites may form one or more abscesses of different sizes. The risk of death due to a ruptured ALA is significant [8]. The ruptured amebic abscess triggers a systemic inflammatory response and a wide range of complications. The fluid can drain into the pleural cavity, the peritoneum, the gastric camera, the pericardium, the lungs, the biliary tree, the vasculature and the sub phrenic area. In these cases, the mortality varies from 25 to 75% [8-11]. The three most frequently used diagnostic methods are direct microscopy, antigen detection and antibodies haemagglutination. Serologic tests of choice include Indirect Fluorescent Antibody Test (IFAT), Counter- Immunoelectrophoresis (CIEP), or Enzyme Linked Immunosorbent Assay (ELISA). Positive serologic tests occur concurrently with the clinical presentation of amebiasis in 60-90% of cases, while in endemic areas, positive serology is seen in 5-10% of the overall population- illustrating the issues of both false positive and false negative results [12,13]. Diagnosis of *E. histolytica* by Polymerase Chain Reaction (PCR) tests started in the early 1990s. Today, PCR-based approaches are not only endorsed by the WHO but also are regularly applied in clinical and epidemiological studies in the developed world. PCR identification of *E. histolytica* can be accomplished from clinical specimens such as stool, tissue, and liver abscess aspirate. Although 18S rDNA PCR testing is expensive, it is as sensitive as ELISA techniques

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[13]. Compared to conventional PCR, laboratory diagnosis by real-time qualitative PCR (qPCR) methodology is faster and more sensitive, cheaper due to lower reagent costs, and more reliable due to a lower risk of amplicon contamination from the laboratory environment [12,14-16]. Ahmad et al. [17] state that the detection of E.histolytica by PCR is more sensitive than amebic antigen detection and that PCR assay can be successfully used to confirm the diagnosis of ALA. Other authors have previously mentioned that percutaneous drainage is the most accurate diagnostic method for ALA. Percutaneous drainage is applied when criteria are met, due to the risk of complications [18-20]. At the present time, ALA does not only affect developing countries. The incidence and prevalence of ALA in the developed world is also increasing and is possibly explained by modern international travel, migration, and the consequences of immunosuppression of varying etiology. In this study, the following questions were posed: how are patients diagnosed and treated? How has the prognosis of these patients evolved? To answer these questions, this study examined a sample of patients diagnosed with ALA in a regional referral center from the West of Mexico.

Material and Methods

This study was approved by the Ethics Committee of the Hospital Civil de Guadalajara, and it conforms to the provisions of the Declaration of Helsinki, (as revised in Edinburgh 2000) and all patients gave written informed consent, including the patient whose ultrasound is shown in Figure 3. Only adult patients were included in this study. Inclusion criteria were: 1) Patients from any race or gender, 2) Diagnosis of ALA, 3) Patients who accepted to participate and signed an informed consent. A total of 50 patients diagnosed with ALA from January 2008 to March 2012 were prospectively included. The diagnosis was based on: 1) clinical findings (right upper quadrant pain, fever, malaise or fatigue, vomiting, weight loss, hepatomegaly, and/or dehydration signs) 2) sonographic evidence of an abscess (hypoechogenic or anechoic lesion with central echoes, cell debris, fibrin or thick pus, with an irregular or virtual wall [20,21] 3) "anchovy paste-like" appearance of the abscess fluid and negative culture and Gram stain, and 4) response to medical treatment with metronidazole. The metronidazole response criterion was met when symptoms improved and the total white blood cell count decreased, in less than 72 hours. Exclusion criteria were: 1) suspicion or confirmation of a mixed bacterial and amebic abscess 2) patient consent was not given and 3) presence of a pyogenic abscess. The following procedures were performed on all patients: 1) a complete clinical history done by an experienced gastroenterologist and a gastroenterology fellow; 2) blood tests on hospital admission, 48 hours after treatment was initiated, and prior to hospital discharge: cytometry, glucose, creatinine, urea, liver function tests (alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, direct and indirect bilirubin), serum electrolytes (sodium, potassium, calcium), and coagulation tests (prothrombin time, partial thromboplastin time and INR). The following devices were used: 1) ACL™ 7000 (Instrumentation Laboratory©), 2) CELL-DYN Ruby™(Abbott Laboratories), 3) UniCel®DxC 800Synchron® Clinical System (Beckman Coulter, Inc.), and 4) Abbot Axsym® (Abbott Laboratories). A hepatobiliary ultrasound was performed by an experienced radiologist and a radiology fellow. ALAs were drained when at any one of the following criteria was met: 1) no response to medical treatment between five to seven days; 2) high risk of abscess rupture, quantified as an abscess cavity larger than 5 cm, and 3) presence of lesions in the left lobe [22].

Characteristic	Number
Total patients	50
Male:female	40:10
Mean age (range)	mean 42 (18 to 80)
Hispanic	100%
Urban area	mean 27 (54%)
Domestic utilities (clean water, sewage, electricity)	mean 42 (84%)
Smoking	31 (62%)
Alcohol consumption	29 (58%)
Tattooes	13 (29%)
Incarceration > 2 days	8 (16%)
Rehabilitation center	7 (14%)
Age at first sexual intercourse mean (range)	17 (range 12 to 30)
Total number of sexual partners	7 (range 1 to 50)

Table 1: Baseline characteristics.

Food hygiene was stratified into three categories as follows: high hygiene when patients always drank purified water and food was always rinsed and washed at home, cooked by a member of the family with clean hands; medium hygiene patients always drank purified water and when food was sometimes rinsed or washed, cooked by a member of the family or consumed in a "clean" restaurant; and low hygiene when patients drank boiled water and/or food was never rinsed or washed, or was cooked by someone unsupervised.

Statistical analysis

Nominal variables (gender, urban area, housing conditions, smoking, alcohol consumption, tattoos, imprisonment, rehabilitation center, main area of food consumption and food hygiene) were expressed as proportions. A chi square or Fisher's exact test were used to compare the following discrete variables: hospitalization days, hematocrit, leucocytes, neutrophils, eosinophil, platelets, serum electrolytes (sodium, potassium, calcium), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, lactic dehydrogenase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, direct bilirubin, international normalized ratio, prothrombin time, and partial thromboplastin time at admission, at 48 hours of admission and before discharge. Statistical analyses were conducted using JMP software version 9.0.0. A P value less than 0.05 was considered statistically significant.

Results

Description

Baseline characteristics are described in Table 1. Fifty ALA patients were included. Eighty percent of the patients were male gender (n= 40). Mean age was 42 years (range 18 to 80). Fifty-four percent (n= 27) of patients lived in an urban area, 46% (n=23) lived in a rural location, and 84% (n=42) of patients had all domestic utilities (electricity, sewage, clean water). Social history was positive by report for smoking with 62% of patients (n=31) and positive by report for alcohol consumption in 58% (n=29) of patients. As for frequency, 48% of patients reported consuming alcohol two to three times per week (n= 14), 38% of patients (n=11) consumed more than three times per week, and 8% (n=4) reported only one drink per week. Tattoos were present in 26% (n=13) of patients. For different reasons, 16% (n=8) of patients were in prison for more than two days prior to the ALA diagnosis. Fourteen percent of patients (n=7) had previously been admitted to an addiction rehabilitation. Mean age of first sexual intercourse was 17 years old (range 12 to 30 years old) with a lifetime average of seven sexual partners (range 1 to 50). Heterosexual intercourse only was reported by

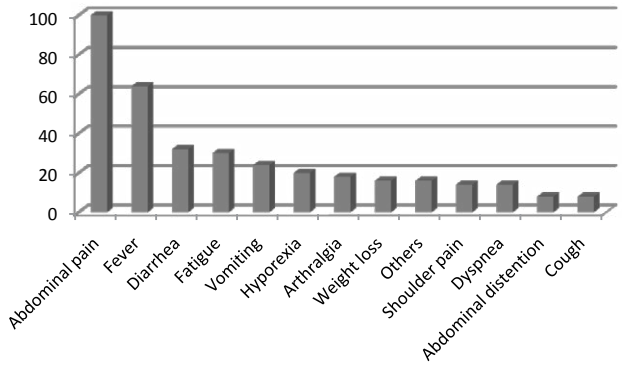
88% (n=44) of patients while 12% (n=6) reported previous homosexual intercourse. Sixty-two percent (n=31) of patients reported consuming the majority of their meals from street food vendors compared to 38% (n=19) of patients who reported eating most of their meals at home. With respect to patients´ food hygiene, 12% (n=6) were stratified as high,72% (n=36) as medium, and in 16% (n=8) as low.

Clinical Findings

Signs and symptoms

Abdominal pain was the most frequent symptom and was present in 100% (n=50) of patients. The next most frequent symptoms were: fever in 64% (n=32), previous diarrhea in 32% (n=16), unexplained fatigue in 30% (n=15), and previous vomiting in 24% (n=12) of patients. Weight loss was present in 16% (n=8) of patients with a mean loss of 8.5 kg (range 2 to 17 kg) over a mean time of 98 days (range 2 to 194 days). In patients with right upper quadrant pain, radiation to right shoulder was present in 14% (n=7). Other symptoms are reported in Figure 1.

The most frequent signs were abdominal pain during superficial palpation of the right upper quadrant (70%, n=35), followed by hepatomegaly (60% n=30), and dehydration (hypotension, dry mucosae) in 52% (n=26) of patients. On examination of the thorax, 52% (n=26) of patients presented signs suggestive of pleural effusion and were later confirmed by chest X-ray. In all patients the effusion occupied less than 20% of the pleural area and resolved before discharge. Following a suggestive chest X-ray, three patients receive



*Others- Malaise 6%, thoracic pain 6%, headache 4%

Figure 1: Symptoms referred by patients during the initial presentation of amebic liver abscess.

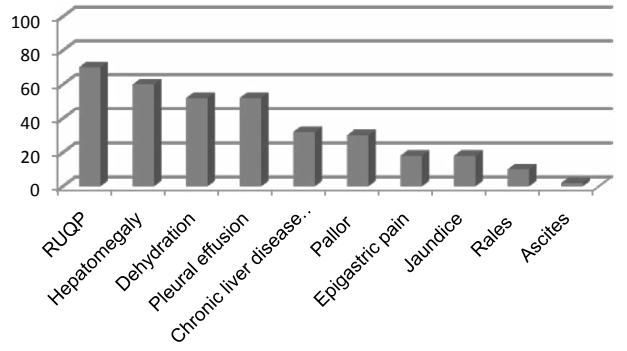


Figure 2: Positive signs at the initial physical examination.

treatment of pneumonia. Pallor was present in 30% (n=15) of patients while epigastric pain and jaundice were present in 18% (n=9). Thirty two percent (n=16) of patients were positive for at least two of the following chronic liver disease stigmata: temporal hypotrophy, parotid hypertrophy, and spider angiomas. No liver biopsies were performed and no patient had confirmed cirrhosis. Other signs are reported in Figure 2.

Laboratory findings

Only 4% (n=2) of the patients were positive for anti-HCV antibodies, one patient (2%) was positive for HBVsAg, and one patient (2%) was HIV-1 positive. Comparison of admission versus discharge blood tests revealed significant decreases in leucocytes (P=0.001), neutrophils (P=0.005), eosinophils (P=0.002), platelets (P=0.005), and INR (P=0.003). Other laboratory findings are shown in Table 2.

Imaging

Ultrasound of the hepatobiliary tree (Figure 3) revealed a mean maximum diameter of 9.5 cm (range 1.4 to 28 cm). Thirty-eight (76%) patients had a unique abscess (Table 3) and 12 (24%) patients had multiple abscesses. The average abscess volume by calculation was 305 cm^3 (19 cm^3- 990 cm^3). Abscesses affected a mean of two liver segments (range 1 to 8). However, in 92% (n=46) of patients, the abscess affected only one or two segments while in one patient, the abscess occupied all eight liver segments. This abscess resolved and this patient recovered with no sequellae following percutaneous drainage and metronidazole therapy. With respect to abscess location, 64% were on the right, 36% were on the left, and only 4% of abscesses occupied both lobes (Table 3).

Treatment and Outcome

Intravenous metronidazole was the elected treatment for all patients. Forty-eight percent of patients (n=24) required a percutaneous drainage and received ceftriaxone afterwards to avoid secondary infections. The abscess fluid of all patients an "anchovy paste-like" appearance and was negative for Gram stain and culture. In this series, 100% of patients responded to metronidazole and percutaneous drainage as indicated. No patient died during or after treatment. No patient had serious complications such as abscess drainage to pleural cavity, peritoneum, pericardium or elsewhere. The average stay at the hospital was 9 days (3 to 37 days). The patient who stayed for 37 days developed nosocomial pneumonia that resolved after antibiotic treatment. In three cases, nosocomial pneumonia was diagnosed and these patients received treatment for both conditions.

Discussion

This study included a group of 50 patients diagnosed with ALA in a regional referral center. Most of the patients were young males with a mean age of 42 years. Unsurprisingly, almost half of the patients inhabited rural areas. About 30% of Mexico´s population is rural and has limited access to basic utilities such as electricity, running water and sewage. Nonetheless, other factors appear to influence the development of ALA. Firstly, over half of patients reported chronic alcohol consumption and smoking habits. Chronic alcohol consumption has previously been associated with an increased risk of developing ALA, but to our knowledge, no prior studies reported an association between ALA and smoking. One previous study reported 70% of patients with ALA were alcoholics; these results are comparable to ours [23]. Secondly, one third of our sample patients had a tattoo and has used drugs. Sixteen percent of the patients reported a history of incarceration and 14% received medical care in rehabilitation clinics. A higher risk of

Lab test	Admission mean (range)	At 48 hrs mean (range)	Discharge mean (range)	P value Admission vs 48 hrs	P value Admission vs discharge
Hematocrit	36.9 (18-47.1)	35.5 (25.6-48.3)	35.3 (11.7-48.9)	0.78	0.06
Leucocytes	21 (4.56-82.8)	16.4 (5.6-88.6)	9.2 (1-18)	0.31	0.001
Neutrophils	19.5 (2-85)	36.4 (3.2-84.3)	42.1 (2-87.1)	0.009	0.005
Eosinophils	0.2 (0-2)	0.7 (0-3)	1.4 (0-7)	0.015	0.002
Platelets	343,100 (22,000-943,000)	430,900 (142,000-872,000)	504,500 (236,500 904,000)	0.009	0.005
AST	104.4 (18-1076)	33.6 (17-63)	31.4 (12-55)	0.04	0.24
ALT	73.3 (12-315)	35.2 (10-68)	21.2 (9-35)	0.03	0.19
GGT	161 (24-449)	149.3 (43-356)	107.4 (38-350)	0.08	0.15
ALP	238.3 (17-1325)	166 (48-388)	141 (15-309)	0.02	0.13
TB	2 (0.1-15.4)	0.9 (0.4-2.1)	0.6 (0.2-1.9)	0.03	0.16
DB	0.97 (0.1-9.6)	0.5 (0.1-1.5)	0.4 (0.1-1)	0.28	0.13
INR	1.18 (0.85-1.57)	1.39 (0.92-1.97)	1.3 (1.1-1.7)	0.022	0.003
Cholesterol	93.5 (59-174)	79.6 (10.9-165)	114 (71-170)	ND	0.36

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; DB: Direct bilirubin; GGT: Gamma-glutamyltranspeptidase; INR: International normalized ratio; LDH: Lactic dehydrogenase; PT: Prothrombin time; PTT: Partial thromboplastin time; TB: Total bilirubin; WBC: White blood cells

Table 2: Laboratory tests results at admission, 48 hours post admission and before discharge.

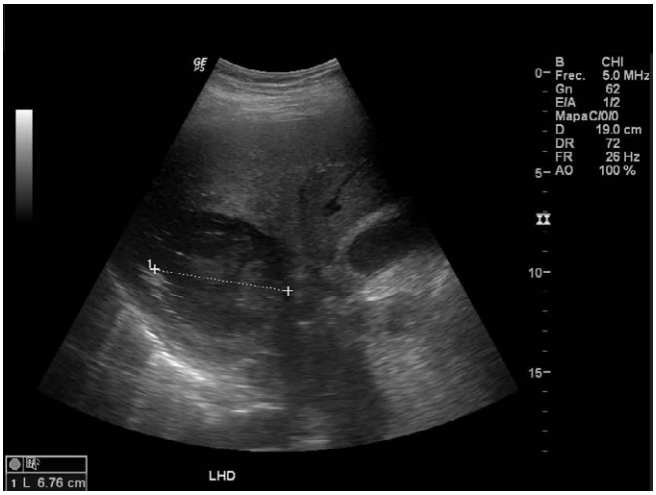


Figure 3: Amebic liver abscess ultrasound from the right lobe.

Sonographic finding	Measurements
Largest diameter, mean (range)	9.5 cm (1.4 to 28 cm)
One: multiple abscesses, mean (%)	38 (76%):12 (24%)
Calculated volume, mean (range)	305 cm^3 (19-990 cm^3)
Segments affected, mean (range)	2 (1-8)
Right: leftlobe, mean (%)	32(64%): 18 (36%)

Table 3: Sonographic findings of the amebic liver abscess.

ALA in people with these exposures has been reported. ALA has been associated to possible infectious vectors such as intravenous drug use or tattoo needles [24]. Thirdly, it has been reported that homosexuals have a higher risk of invasive amebic diseases, especially in HIV infected patients [25, 26]. In this study, 12% of the patients mentioned having homosexual contacts and one patient (2%) was HIV positive. In this regional referral center, all patients diagnosed with ALA are routinely analyzed for HIV. Thirty two percent of the patients had at least two positive stigmata of chronic liver disease (temporal hypotrophy, parotid hypertrophy and/or spider angiomas). All ALA patients in this facility are screened for HBV and HCV infection to exclude some of the most frequent causes of chronic liver disease besides alcohol. Most patients showed improved laboratory test results on discharge compared to admission. In particular, leucocytes, neutrophils, eosinophils and platelets showed a significant improvement in all patients (Table 2). Fourthly, a high number of patients were exposed to insufficient food hygiene. Poor food hygiene has been associated with an increased risk of ALA [27]. In summary, patients included in this study were exposed to multiple risk factors (inappropriate hygienic conditions, limited access to basic utilities, alcoholism, tattoos, smoking, homosexual intercourse, imprisonment) for developing ALA. In this study, neither serologic tests nor PCR were performed for the diagnosis of ALA for the following reasons. It has been previously reported that serum antibody levels in people from endemic areas remain positive for years after infection with *E. histolytica*. Although, stool sample qPCR is highly sensitive and specific, its high cost makes it unsuitable for financial

reasons. For these reasons, in endemic areas the diagnosis is based on clinical presentation and supported by ultrasound findings and liver abscess aspirate characteristics [12], while a negative culture and Gram stain excludes bacterial infection. Moreover, besides the high cost, in this tertiary care facility a PCR result takes over 72 hours. Often by this time, patients have already received treatment and are improving. Thus, in this country amebic liver abscesses are far more numerous than pyogenic abscess [28]. Based in this rationale, the determination of serologic tests and PCR were unsuitable for routine diagnostic use. ALA treatment is started immediately when the ALA is diagnosed by suggestive clinical features, ultrasound findings and the liver abscess aspirate characteristics as other authors have already mentioned. In this study, as in other reports, abdominal pain, fever and diarrhea, were the most frequently reported symptoms, while right upper quadrant pain, hepatomegaly and dehydration were the most commonly observed signs [29]. All patients were adequately and successfully treated with metronidazole. This scheme has been successfully used in this center for the last 20 years. There have been some reports of sporadic failure and rare reports of metronidazole resistance. Becker et al. [30] reported that metronidazole remained the most effective preventive and curative method for amebic infections. Some patients received ceftriaxone after the abscess puncture to prevent secondary infection and this proved useful. In recent years, the main change in therapeutic approaches to ALA is foregoing invasive procedures such as surgical drainage. Previous studies have also reported that the ultrasonography guided percutaneous drainage has replaced surgical intervention as the primary choice for reduction in abscess size [18]. The main cause of extended hospital stay was nosocomial pneumonia. The mean number of in-hospital days in this study was similar to other reports [31]. In this group of 50 patients with ALA, no patients had fatal complications. When compared to studies of ALA patients more than 20 years ago, the prognosis of patients today is remarkably better. In the eighties, the invasive disease was highly morbid and caused an estimated mortality from 1 to 26%. This study demonstrates that the prognosis of patients with ALA has changed dramatically. In this group of 50 patients with ALA, no patient died, and no patient developed serious complications - neither caused by the abscess itself nor caused by the treatment. The main reason for this improvement is ascribed to earlier detection and earlier treatment. A contributing factor is likely that patients were carefully selected for percutaneous drainage and furthermore that no patient underwent surgical drainage. When patients are misdiagnosed and wrongly treated, the prognosis is poor. Clinical methods used in this study are adequate to make an early diagnosis in order to initiate treatment immediately. Metronidazole remains an acceptable, affordable, and proven medical treatment of ALA in endemic areas. Even without serologic investigation, ALA patients who are treated under the supervision of an experienced clinician have a better prognosis of this fearsome complication of invasive amebiasis.

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Authors´ Contributions

Dr. Cernichiaro-Espinosa Linda A participated in acquisition of data, analysis and interpretation of data; drafting and critically reviewing the article for important intellectual content.Dr. Segura-Ortega Jorge E evaluated, diagnosed and treated the patients, follows up on the patients, participated in the study design, and participated in the analysis and interpretation of data.Dr. Arturo Panduro conceived and designed the study, carried out laboratory studies, and was the final reviewer published submission. Dr. Moreno-Luna Laura E diagnosed and clinically evaluated patients and their progress, conceived, designed, and coordinated the study, performed statistical analysis, and helped draft the manuscript. All authors read and approved the final manuscript.

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