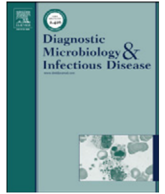
Diagnostic Microbiology and Infectious Disease 83 (2015) 395–399

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



Clinical Studies

Is procalcitonin increased in cases of invasive amoebiasis? A retrospective, observational study

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ARTICLE INFO

Article history:
Received 19 May 2015
Received in revised form 19 August 2015
Accepted 20 August 2015
Available online 28 August 2015

Keywords:
Amoebiasis
Procalcitonin
C-reactive protein
Entamoeba histolytica
Liver abscesses

ABSTRACT

Procalcitonin (PCT) levels are commonly used for diagnostic guidance in routine bacterial infections. By contrast, little data are currently available regarding PCT in parasitic diseases, and its role in cases of invasive amoebiasis has not yet been described. For this purpose, 35 adult patients with a proven diagnosis of invasive or digestive amoebiasis were included in a 4-year study period. Serum PCT was retrospectively assessed. Results were analysed with regard to the usual inflammatory biomarkers, like C-reactive protein (CRP). PCT was significantly higher in patients with proven invasive amoebiasis than in digestive amoebiasis (mean value: 4.03 μg/L versus 0.07 μg/L, respectively; $P < 0.001$), but the SD was greater than with CRP, and the effect was less than that demonstrated in bacterial infections. By contrast, PCT was not shown to be elevated during digestive amoebiasis.
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1. Introduction

Procalcitonin (PCT) is the precursor peptide of calcitonin, a hormone involved in calcium homeostasis. Several cell types can produce PCT in response to proinflammatory stimuli. A high PCT level is usually compatible with serious bacterial infections and sepsis (Van den Bruel et al., 2011; de Azevedo et al., 2012; Domínguez-Comesaña and Ballinas-Miranda, 2014) and plays a prognostic role in evaluating their clinical outcome (Van den Bruel et al., 2011; de Azevedo et al., 2012; Ugajin et al., 2014; de Azevedo et al., 2015). Thus, PCT measurement has been implemented into routine clinical practice for diagnostic guidance in bacterial infections (Long et al., 2011; Prkno et al., 2013; Wacker et al., 2013). In addition, substantial elevations in PCT levels have been reported as being correlated with high levels of parasitaemia during malaria attacks (Chiwakata et al., 2001; Diez-Padrisa et al., 2011). The role of PCT has also been widely discussed in invasive fungal infections (Dou et al., 2013; Marková et al., 2013; Cortegiani et al., 2014). Overall, it is considered that low levels (<0.50 μg/L) (Al-Dorzi et al., 2014) usually rule out all of the above-mentioned infections and point towards virus (Piacentini et al., 2011) or nonspecific inflammatory diseases (Tsalik et al., 2012; Anand et al., 2015).

Amoebiasis is a parasitic infection caused by the digestive protozoan *Entamoeba histolytica*, which has recently been differentiated from its morphologically similar species *Entamoeba dispar* (Stanley, 2003). The intestinal clinical forms range from asymptomatic colonisation to amoebic dysentery. *E. histolytica* can, however, disseminate from gut mucosae to other organs such as the liver. Here it generates abscesses (Stanley, 2003; Oku et al., 2012; Petri and Haque, 2013), which define invasive amoebiasis. This condition is a medical emergency and may lead to death (up to 70,000 deaths per year worldwide (Stanley, 2003)), in the absence of a rapid and reliable diagnosis. Nowadays, amoebic serology represents the gold standard for this purpose, but this requires time and a seasoned laboratory. Very few alternative biomarkers are currently available for predicting the invasiveness of amoebiasis, and those that are in use are not specific. For instance, hyperneutrophilia is inconsistent; there is no hypereosinophilia in invasive amoebiasis (Stanley, 2003; Wuerz et al., 2012); and liver enzymes show variable blood levels, with no major increase (Wuerz et al., 2012). These limitations may delay the initiation of effective treatment; hence, additional biomarkers that indicate invasive amoebiasis are needed.

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http://dx.doi.org/10.1016/j.diagmicrobio.2015.08.014
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Since no study concerning the association of PCT with *E. histolytica* infection has been reported thus far, the main purpose of this retrospective, observational study was to investigate whether there is an increase in PCT in cases of invasive amoebiasis.

2. Materials and methods

2.1. Inclusion criteria

The study was carried out retrospectively using automated, computerised extraction of clinical data from our laboratory software. The search engine was programmed to find all the recorded cases of invasive amoebiasis (January 2010–September 2014), which had been confirmed by at least 1 positive specific anti–*E. histolytica* serological test, either indirect immunofluorescence assay (IFA by Amoeba Spot-IF®; BioMérieux, Marcy-L'Etoile, France) or indirect haemagglutination (IHA by Amibiase HAI FUMOUZE®; Fumouze Diagnostics, Levallois-Perret, France) in 1 of the 3 teaching hospitals involved in the study (Tours, Nantes, and Angers, France). Titres above 1:100 for IFA and/or above 1:160 for IHA were defined as positive (Hartmann et al., 1980).

A second automated search was carried out to extract all the patients who had been detected with *Entamoeba* spp. in stool samples. Detection methods followed standard practice in the microbiological labs: direct examination of freshly emitted faeces, followed by Bailenger's technique of concentration and merthiolate–iodine–formaldehyde concentration (Lawson et al., 2004). Microscopic identification of *E. histolytica* was achieved by skilled microbiologist and/or by specific amplification of the 16S-like SSU rDNA by PCR. Briefly, the DNA was extracted using QIAmp DNA mini kit® spin columns (Qiagen SA, Courtaboeuf, France). The amplification reactions were performed using 5 μL of a DNA sample in a volume of 20 μL of a mixture that contained a TaqMan Fast Universal PCR Master Mix 2x® (Applied Biosystems™, Saint Aubin, France), internal positive control (Applied Biosystems™), and the oligonucleotide primers for *E. histolytica*: Eh-196F (5′-AAA TGG CCA ATT CAT TCA ATG A-3′) and Eh-294R (5′-CAT TGG TTA CTT GTT AAA CAC TGT GTG-3′) and the probe Eh-245 (6FAM)-AGG ATG CCA CGA CAA-(NFQ). The thermal cycling conditions consisted of 20 seconds at 95 °C, followed by 50 cycles of 3 seconds at 95 °C, and 30 seconds at 60 °C, using a TaqMan 7500® Fast Real-Time PCR System (Applied Biosystems™). The detection and the data analysis were performed with TaqMan Fast 7500® software version 1.4.0 (Applied Biosystems™) (Ben Ayed et al., 2008). If not done previously, an anti–*E. histolytica* serological test was performed retrospectively on these patients, according to the above-mentioned references (IFA and IHA tests), in order to rule out any subclinical invasive infection.

For both of these automated searches, the noninclusion criteria were age <18 years old, to avoid the expected physiological variations in biomarker levels during childhood, and lack of biological specimens in the serum collection (frozen at −80 °C). For each selected patient, demographic, biological, clinical, and radiological data were collected on the basis of a standardised survey. Evidence of one or more liver abscess(es), detected by abdominal ultrasound and/or computed tomodensitometry scan, was recorded. Potential undercurrent bacterial infections, malaria, and chronic or acute viral/nonviral hepatic diseases were also noted.

2.2. Biological assay

Serum PCT was measured by immunoassay using the B·R·A·H·M·S Kryptor compact® (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's instructions. The assay was retrospective and monocentric and was performed once. A normal PCT value was expected to be below 0.06 μg/L (Syvanen et al., 2014), whilst the cutoff for sepsis was established at 0.50 μg/mL (Al-Dorzi et al., 2014), according to the manufacturer's recommendations (http://www.procalcitonin.com/).

C-reactive protein (CRP) was measured using rabbit anti-CRP antibodies coated on latex particles (CRP Latex reagent® on the AU2700®; Beckman Coulter, Pasadena, CA, USA). Normal CRP values were taken to be those under 6 mg/L. Aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP) were assessed using the AU2700® (Beckman Coulter), according to the methodology recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (Schumann et al., 2002). Normal values of AST, ALT, and ALP were considered to be 0–40 U/L, 0–30 U/L, and 50–160 U/L, respectively (Siest et al., 2013). Normal values for GGT ranged from 8 to 61 U/L for males and from 5 to 36 U/L for females. α-2-macroglobulin was measured by immunonephelemetric methods using a BN ProSpec Analyser® (Siemens Diagnostics, Saint-Denis, France). Normal α-2-macroglobulin values were taken to be 1.50–3.50 g/L for males and 1.75–4.20 g/L for females (Siest et al., 2013).

2.3. Statistical analysis

Statistical analysis was performed using "The R Project for Statistical Computing version 3.1.2." software (http://www.r-project.org/). The Fisher test was used for the comparison of qualitative variables; and the Mann–Whitney test, for quantitative variables. The Student *t* test was used for comparison with theoretical values. The Spearman's rank correlation coefficient was used to assess the correlation of biomarkers. The alpha-risk was adjusted to 0.05.

2.4. Ethics

All personal data were anonymous. Approval was given by the ethics committee at our teaching hospital (Espace de Réflexion Ethique, Région Centre, France). The study registration number 2015_003 was issued by the Technology and Freedom Committee (Commission de l'Informatique et des Libertés) on January 10, 2015.

3. Results

3.1. Inclusion

Overall, 18 patients were identified as invasive amoebiasis cases. Two individuals had previously been excluded, the first because he was under 18 years old at the time of diagnosis and a second individual due to an unclear diagnosis. The latter patient had neither a history of foreign travel nor typical symptoms and showed discordant serology (IFA = 1:400; IHA = 0).

By means of the second automated extraction, 17 patients were included in the digestive amoebiasis group on the basis of at least 1 positive stool examination. Seven patients had previously been excluded because their respective ages were below 18 years old. None of the selected individuals had a positive anti–*E. histolytica* serological test, which ruled out any possibility of invasive amoebiasis (Fig. 1).

3.2. Demographics of the 2 populations

Mean age was 47.00 for the patients included in the invasive amoebiasis group and 48.29 for those in the digestive amoebiasis group ($P = 0.88$) (Table 1). The sex ratio displayed a majority of male subjects, 72.23% for the invasive amoebiasis group and 70.59% for the digestive amoebiasis group; however, there was no significant difference between these 2 groups ($P = 0.93$) (Table 1). In the former group, abscesses were mostly located in the liver (94.44%). African ethnics were significantly more prevalent in the digestive amoebiasis group than in the invasive group (41.18% versus 11.12%; $P = 0.03$). By contrast, Caucasian patients were more highly represented in the latter group (52.94% versus 88.88%; $P = 0.03$) (Table 1).

None of the included patients were reported to have acute malaria, and no individual experienced invasive bacterial infection at the time of the study. One patient in the invasive amoebiasis group had an uncomplicated lower urinary tract infection due to *Escherichia coli*,

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