Elevated carbohydrate antigen 19-9 following *Helicobacter suis* gastritis and normalisation after eradication: first case report and review of the literature

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Abstract

Carbohydrate antigen 19-9 (CA 19-9) is a biological marker used to diagnose and monitor the progression of various cancers. Elevated CA 19-9 has also been sporadically observed in Helicobacter pylori infected patients. Similar to H. pylori, animal-hosted non-H. pylori Helicobacter (NHPH) species can induce gastroduodenal lesions in humans. We report the first case of CA 19-9 elevation related to H. suis gastritis and its normalisation after eradication.

A CA 19-9 screening prescribed as part of a regular check up by the general practitioner was found elevated in a 68-year-old man presenting chronic dyspeptic symptoms. Medical investigations were negative for presence of neoplasia or biliary obstruction. Upper gastrointestinal endoscopy confirmed the presence of chronic gastritis and H. suis was identified in gastric biopsies. The standard treatment for H. pylori successfully eradicated H. suis with normalisation of CA 19-9 levels.

In addition to H. pylori, infection with NHPH species should be considered as an additional cause of elevated CA19-9. (Acta gastroenterol. belg., **2022,** 85, **403-405**).

Keywords: *Helicobacter pylori,* non-*Helicobacter pylori Helicobacter*, chronic dyspeptic symptoms, gastritis.

Introduction

Carbohydrate antigen 19-9 (CA 19-9) is a biological tumour marker used as a diagnostic tool, prognosis indicator and follow-up parameter in various cancers (1). Although very high levels are strongly suggestive for the diagnosis of pancreatic cancer, CA 19-9 can be mildly elevated in different benign diseases affecting the gastrointestinal tract, including infections (1,2,3).

Elevation of CA 19-9 levels has been sporadically reported in *Helicobacter pylori* infected human (3). Apart from *H. pylori*, there are many other non-*H. pylori Helicobacter* (NHPH) species which naturally colonise the stomach of a wide range of animals. Some NHPH species have zoonotic potential (4,5) and infections have been associated with a large spectrum of clinical manifestations in humans (4). NHPH infections impose a diagnostic challenge owing to their low prevalence in human patients, their low colonisation density in the human stomach and their fastidious nature hampering cultivation and subsequent species identification (5,6,7). *Helicobacter suis* is the most prevalent gastric NHPH species in humans (4). It has been hypothesised that this bacterium is transmitted via direct or indirect contact with infected pigs (4,5,7).

We report the first case of elevated CA 19-9 levels associated with *H. suis* gastritis that completely normalised after *H. suis* eradication.

Case report

In March 2019, during a routine laboratory check-up in a 68-year-old man, a CA19-9 screening was performed without appropriate indication by his family doctor and showed elevated levels at 121 U/mL (normal range <37 U/mL). This abnormal value resulted in a gastroenterological outpatient visit where we confirmed an elevated level at 164 U/mL. The other laboratory parameters were normal, including glycaemia, bilirubin, hepatic and pancreatic enzymes, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and prostate-specific antigen (PSA).

The patient's only complaint was chronic mild dyspeptic symptoms whereas the physical examination was unremarkable. The patient had no relevant medical history and denied alcohol and tobacco use. He had had animal contact in his spare time during horseback riding and wild boar hunting for several years. Two years earlier, an upper gastrointestinal endoscopy was performed for dyspeptic complains. The exam revealed gastritis and the presence of *Helicobacter*-like organisms. However, because of the negative culture for *H. pylori* and in the context of the mild symptoms, this finding was trivialized and the patient was left untreated. No dosage of CA19-9 levels was noted at that time.

To investigate the elevated CA19-9, we performed whole body 18-fluorodeoxyglucose positron-emission computed tomography, a lower gastrointestinal (GI) endoscopy and an upper GI endoscopic ultrasonography, which all excluded neoplastic lesions and biliary obstruction. An upper GI endoscopy showed no macro-

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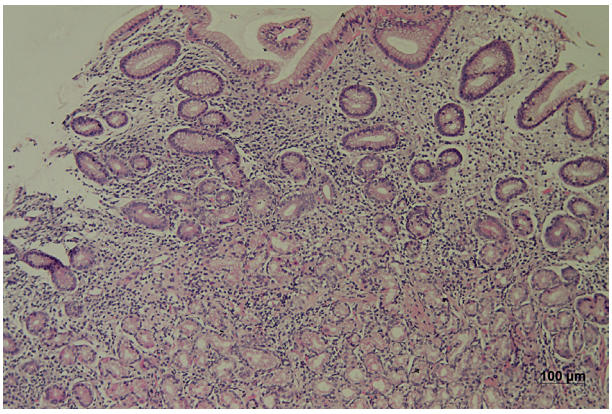

Fig. 1. — HE 10x: Haematoxylin and eosin staining showing moderate chronic inflammation of the gastric mucosae.

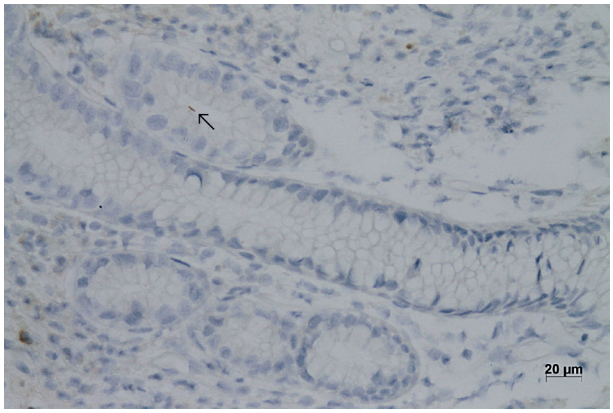

Fig. 2. — HP 40x: Immunohistochemical staining of the gastric mucosae, using anti-Helicobacter pylori antibody, revealing rare spiral-shaped microorganisms arrowed.

scopic abnormalities but histopathological analysis revealed the presence of mild chronic gastritis without intestinal metaplasia, predominantly in the antrum (Fig. 1) with the presence of spiral-shaped organisms (Fig. 2). Both antrum and fundus biopsies tested negative for the presence of *H. pylori* by polymerase chain reaction (PCR) and by culture. Samples were sent to a veterinarian microbiology laboratory (Merelbeke, Belgium) where spiral-shaped organisms were identified by PCR method and amplicon sequencing as *H. suis*.

The patient was treated with a 14-day eradication regime including 20 mg pantoprazole, 1 g amoxicillin and 500 mg metronidazole twice daily. The patient's condition improved and the symptoms resolved. The biological follow-up at 6- and 12-month post-eradication showed normalisation of the CA 19-9 levels. Upper gastrointestinal endoscopy performed six months later while the patient was asymptomatic revealed very mild histological chronic gastritis and no detection of *H. pylori* nor *H. suis* by PCR.

Discussion

The discovery of an elevated CA 19-9 marker is a source of anxiety for patients and physicians since it often indicates the presence of various digestive or extra-digestive cancers with higher specificity for pancreatic cancer at a cut-off above 90 U/ml (1). However, this marker lacks specificity, especially for mildly elevated values in asymptomatic patients (1) and for that reason, it should definitely not be used as a screening test. Besides malignancies (1), its elevation has also been described in non-malignant conditions such as interstitial pulmonary disease, collagen vascular disease or diabetes mellitus (2). Furthermore, CA 19-9 can potentially be elevated in any disorder affecting the gastrointestinal tract, such as benign obstructive jaundice, pancreatitis, ascites (1,2) and various gastrointestinal infections (1,3). An association between *H. pylori* infection and elevated CA 19-9 (3,8) has been rarely reported with normalisation after *H. pylori* eradication. First described in 1983, *H. pylori* and its implications as a globally spread human pathogen is well-known (4). Infection with *H. pylori* may be accountable for different conditions such as gastritis and peptic ulcer disease. Its implication in carcinogenesis is also patent (8). Although more evidence is required to confirm a direct causal link, this elevation of CA 19-9 is thought to be related to increased proliferation of gastric epithelial cells and inflammatory cytokines owing to *H. pylori* aggression (3).

In addition to *H. pylori*, there are many other spiral-shaped organisms initially described as "*Gastrospirillum hominis*". With the development of genomic sequencing, we can individualise different gastric NHPH species (4). Some of them are recognized as human pathogens (4), with a reported prevalence rate of 0.2% up to 6% in human patients with gastric complaints undergoing gastric biopsy (4), although this is probably an underestimation of their true prevalence (7). *Helicobacter suis* appears to be the most prevalent NHPH species in humans, found in 13.9% to 30.9% of human gastric NHPH infections (4). As such, *H. suis* has been recognized as a zoonotic pathogen (5). Primarily found in pig stomachs (4), it may also colonize the stomachs of non-human primates, although macaque-associated strains differ from porcine and human strains (9). The source of infection for our patient is unclear since he had no known contact with pigs. Since *H. suis* has been detected on pork carcasses and in minced pork (7) and since *Helicobacter* species are able to survive in water (10), consumption or contact with contaminated pork and water could be a possible transmission route. Since the patient hunted wild boar for years, contact with these animals could have been a possible source of infection, although *H. suis* have never been detected in the majority of the wild boar populations (9). A clear causal relationship between gastric colonisation with *H. suis*, other NHPH species in general and morbid gastrointestinal conditions has yet to be ascertained (4,11) owing to the wide spectrum of clinical manifestations that range from asymptomatic forms, aspecific mild manifestations such as dyspeptic symptoms to acute or chronic gastritis, antrum and

duodenal ulcers and MALT lymphoma (4). Surprisingly, NHPH infections are associated with a higher risk of developing MALT lymphoma than *H. pylori* infections (4).

The management of NHPH infections in humans remains difficult owing to the large variety of species recently discovered, difficult diagnosis and limited available information on treatment efficacy (4,7). Diagnosis is particularly difficult owing to the poor sensitivity of the rapid urease and urea breath tests (4,5,6,7), fastidious culture (5,7), patchy distribution of these microorganisms in the human stomach and relatively low colonisation density (6). Histopathology findings may show aspecific infiltration of the gastric mucosa with lymphocytes and macrophages, mucosal edema and sometimes the presence of nodular gastritis (5). Infection with NHPH species should be suspected in the presence of spiral-shaped organisms with repeated negative results by culture and PCR targeting *H. pylori* on gastric biopsies (11). Diagnosis is based on immunohistochemistry to confirm the presence of NHPH, but detection of DNA by PCR and amplicon sequencing is considered to be the gold standard for exact identification of the NHPH species (4). PCR is also useful to evaluate NHPH status after eradication therapy (5). Microbiological analyses should be considered in a specialised microbiology centre with experience in NHPH detection. Finally, treatment is still empirically based since antimicrobial susceptibility and acquired resistance are difficult to predict in the absence of a specific culture (4). In the absence of randomised controlled trials, treatment is currently based on the triple therapy used for *H. pylori* eradication by combining a proton pump inhibitor with appropriate dosages of amoxicillin and either clarithromycin or metronidazole (5,7).

In conclusion**,** although *H. suis* has been progressively recognised as a human pathogen, it should be noted that there have been very few cases reported in the literature. We report for the first time the association between *H. suis* infection and elevated CA 19-9 levels in a patient presenting mild dyspeptic manifestations and gastritis, and most importantly, normalisation of CA 19-9 levels following *H. suis* eradication. We therefore believe that infection with *H. suis* should be considered as an additional cause of elevated CA 19-9 particularly if gastritis is present. Further research (e.g. DNA sequencing) is needed to improve our knowledge of NHPH species, potentially leading to more accurate diagnosis and treatment. The indication for testing for NHPH species infection in patients with gastric disorders and tested negative for *H. pylori* warrants further studies.

Conflict of interest information

The authors declare that there is no conflict of interest in this case report and literature review.

Informed consent

Written informed consent was obtained from the patient for publication of clinical data, including all images in this case report.

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