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Romanian Journal of Military Medicine

REVISTA DE MEDICINĂ MILITARĂ

- *Benchmarks of the evolution and revolution of military medicine in the XXI century – Tradition, Trust, Professionalism*
- *Management of Helicobacter pylori infection – new insights*
- *The use of low-intensity ultrasound system in Orthopedics for treatment of fractures*
- *A new global threat for the public safety: Zika virus*
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EDITORIAL

Benchmarks of the evolution and revolution of military medicine in the XXI century – Tradition, Trust, Professionalism

Florentina Ioniță Radu

Brig. Gen. FLORENTINA IONIȚĂ RADU

Commander, Central Emergency Military Hospital, Ministry ofNational Defence, Romania
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There is no secret to anyone that we live in a society marked by uncertainty and unpredictability, a society in which information flows through all communication channels, both in cyberspace and in mass media. Therefore, it is increasingly difficult for the „modern man" to decide upon the veracity and value of the informational content so that, eventually, based on the latter, he can upgrade his knowledge in any area of interest.

In such a context, it is difficult for society to control its evolution and to identify valuable markers that would ensure a valid growth in time and space. Lacking history, hierarchy, elite, rules and order, one can talk neither about the development of an organization nor about the development of society as a whole.

I think we have all passed, in recent years, through a "period of resistance" to the wave of non-values that invaded us and created an organic need to protect and preserve the values our parents and grandparents taught us. Despite the appearance of resignation, the accumulation of such energy has made us stronger, more aware of our role and this made us persistent and gave us the power and the chance to change our future and our children's future.

Returning to the reason that brought us together, by means of this page, you – the reader and me – the author, I can say without any doubt that every cell of my being has reacted with emotion at the course and unrest of the last years of military medicine. It was only when I became the Commander (General Manager) of the "Dr. Carol Davila" Central Clinical Emergency Military Hospital (SUUMC), that I fully understood the huge potential of this noble profession – military doctor – potential generated by the excitement of the trust and respect offered each day by the public opinion in general and especially by citizens.

I have always considered that medicine is a field in which evolution ignores borders, bureaucratic rules, customs and paradigms, because trying to rescue somenone's life is such a pure and noble approach that no sacrifice for this purpose can ever be considered too big.

This year the "Dr. Carol Davila" Central Clinical Emergency Military Hospital, a symbol for the history of Romanian society, celebrates the honorable age of 185 years of tradition, trust and professionalism, dedicated to research, development and innovation in medicine. 185 years in the service of life, without

any deviation from the fulfillment of the two oaths: the military oath and Hipocrate's oath.

We should always keep, in our minds and hearts, the memory of those who, on the battlefield of the two World Wars, nursed their fellows and some of them even lost their lives trying to rescue the latter, the persistence of the struggle with their own limits taking care of the victims of the earthquake that shook Bucharest in March 1977; the emotion lived when faced with the young soldiers, victims of the construction of Transfăgărăşan and of the Danube – Black Sea Canal. Recently, the victims of the tragic fire at Club Colectiv were a challenge for the doctors and nurses in our hospital. All the departments of the hospital worked as a real efficient and dedicated team having only one purpose: to save the lives of the victims who were our patients.

During 185 years, together with the Romanian Army, we have been in the service of the country and of the population, doing our best in our duty with modesty, professionalism, ethics and team spirit. We did not pose as mentors, although here, in this area of health, the foundations of medicine, pharmacy and education in this field in Romania were laid. Medical and surgical specialties were also born here, specialties that today are spoken of as a fact, not as a gift from our ancestors, military doctors – thoracic surgery, urology, epidemiology etc.

The only thing military medicine was deprived of until now, is "a single voice of professionals" in this field, segment considered by most of our civil colleagues relatively narrow as area of specialty and therefore lacking the capital injection necessary to ensure its technical and cutting-edge technology, which apparently decreased our competitiveness in the market of medical services provided. Not true! In the absence of facilities, the human resource of this system accepted the professional challenge and approached a sphere of increasingly complex pathology, and on the other hand, the interdisciplinary collaboration has strengthened human links and increased our performance as professionals. It is true that until three years ago, we may not have had the latest surgical technologies but we beat cancer through the physician's sharp spirit, the surgeon's, the pathologist's and oncologist's experience.

Three years do not mean anything for a hospital, but for someone diagnosed with a relentless disease they mean everything... This was one of my thoughts that motivated me to develop centers of excellence – assigned and equipped to the highest standards – capable of providing prevention, treatment and monitoring of disease in the oncologic pathology, strokes, cardiovascular diseases and digestive diseases; lung transplant – a medical and surgical activity of high human and professional performance, which also involves a great responsibility assumed by SUUMC, on medium and long term, for patient's life quality, service which is not available at this time, in any other public hospital in Romania; neurological and neuromotor rehabilitation center for the veterans from the operation theaters.

Romania's geopolitical and geostrategic situation, as a state located at the EU and NATO border, obliges me, at the same time, to analyze the development of the operational medicine component in the Central Military Clinical Emergency Hospital "Dr. Carol Davila", so that, in wartime, we can be prepared to face the specific challenges related to the pathology and casuistry of a military confrontation.

Both as a doctor, and especially as the manager of the Central Military University Emergency Hospital "Dr. Carol Davila", I understand that the expectations of the whole society towards military medicine are very high, whether we speak of peace or war. People expect us to be a performant regional hospital, which provides at safe and high standards, a medical act comparable to that granted by a specialty hospital from abroad, while in wartime the hospital should become an elite military medical facility, ROL 4, able to provide medical care to the standards required by our NATO allies.

With a background of 185 years, the Central Military Clinical Emergency Hospital "Dr. Carol Davila", returns in force, as an important player on the market of medical services in Romania and elsewhere, proving that to the three qualities that have pierced the veil of history – TRADITION, TRUST, PROFESSIONALISM –

we should add the key to success in order to ensure the evolution of this type of institution, within the criteria imposed by the information society, consisting of flexibility, predictability, resilience and responsiveness in the case of a crisis or disaster.

As arguments in support of the above, I would point out some key milestones of the work of the last three years, namely, that SUUMC is the only institution in the medical network of the Ministry of Defence running projects from European funds for research, development and innovation in the medical field. It is connected to military medical centers in the Balkans, by means of the collaboration platform of telemedicine type, IMIHO. The hospital has developed collaboration agreements with major centers in the field, in the country and abroad (Belgium, Austria, Turkey and Serbia) to conduct training programs for medical staff and it is a serious instruction and training institution for students and residents, as a consequence of the extension of academic and university partnerships.

At the beginning of a new stage of life, I hope that The Romanian Journal of Military Medicine, in this new format, supported by a high scientific editorial board, will fulfill its objective to disseminate knowledge, to bring added value to the market of specialized publications in this field, from Romania and from abroad, to support the research activity and to motivate young people who make their first steps on the road to a career dedicated to the most precious thing that we all receive: health.

As a team player who strongly believes in the power of military medicine elite, in the interdisciplinary dialogue of this discipline, I assure you that I will support this approach, as I have already done it so far, in order to increase its quality every year and to borrow from the brilliance of the historic celebration of 185 years from the signing of the birth certificate of the Army Hospital.

REVIEW ARTICLE

Article received on November 26, 2015 and accepted for publishing on January 21, 2016.

Management of Helicobacter pylori infection – new insights

Andrei Gavrilă[1],Andrada Popescu[1], Petruț Nuță[1], Raluca S. Costache[1,2], Mariana Jinga[1,2], Săndica Bucurică[1,2], Bogdan Macadon[1], Mihăiță Pătrășescu[1], Florentina Ioniță Radu[1,3]

Abstract: *Introduction: Our objective is to review current international guidelines for Helicobacter Pylori treatment and our department`s experience in this field.*

Materials and methods: Helicobacter pylori is a Gram-negative, microaerophilic bacterium that can be found mainly in the gastric mucus or on the inner surface of the gastric epithelium, infecting up to 50% of the population. Colonization with this bacterium is not a disease in itself, but can cause chronic gastritis, peptic ulcer, gastric cancer and MALToma. Because of this, infection with H. pylori continues to be a major healthcare burden, especially in less-developed countries.

A multitude of non-invasive tests are available for the diagnosis of Helicobacter pylori infection (blood antibody, stool antigen or urea breath test), but the most reliable method of diagnosis is histological examination from two sites after endoscopic biopsy, combined with either a microbial culture or rapid urease test.

Treatment of Helicobacter pylori infection is becoming a challenge, as eradication following standard triple therapy is decreasing worldwide due to increased bacterial resistance against antibiotics, which has led to the development of newer therapies such as the sequential treatment in which a PPI and amoxicillin is given for 5 days followed by a PPI, clarithromycin and metronidazole for another 5 days, or the quadruple therapy based on a PPI, bismuth subcitrate, metronidazole and tetracycline for 10 days.

Results and conclusion: H. pylori infection remains one of the most challenging infectious diseases, causing high morbidity and mortality, mainly because none of the actual antibiotic therapies can provide successful eradication.

Keywords: Helicobacter pylori, ulcer, adenocarcinoma, antibiotics, PPI

INTRODUCTION

Helicobacter pylori (Hp) is a helix shaped, Gram-negative, microaerophilic bacterium that can be found mainly in the gastric mucus or on the inner surface of the gastric epithelium[1]. Hp infection is the most common chronic infection in humans, but colonization with this bacterium is not a disease in itself. Although most infected individuals remain asymptomatic for life, Hp is responsible for a number of pathological manifestations including chronic gastritis, gastric or duodenal ulcer, adenocarcinoma

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of the stomach or gastric mucosa–associated lymphoid tissue (MALT) lymphoma[2].

THE DISCOVERY OF HELICOBACTER PYLORI

The Helicobacter pylori bacterium was discovered by two Australian researchers by the name of Barry Marshall and Robin Warren, who also deciphered its role in gastritis and peptic ulcer disease (PUD)[3]. Their discovery was published in 1982, at a time when it was a long-standing belief that stress and lifestyle factors were the major causes of PUD. The scientific community of the time met their findings with skepticism and a lot of criticism, refusing to belief that any life-form can survive in the acid medium of the stomach. This is why it took a very long time and effort for their discovery to become widely accepted[4].

Marshall`s 1985 “self-help” experiment rebutted the “stress and life-factors” dogma. He first underwent gastric biopsy to show the absence of the bacterium, then, to the horror of his assistant, ingested a turbid, foul-tasting solution of Hp. Soon he developed a number of symptoms including nausea and vomiting and an endoscopy with biopsy was performed, which revealed signs of gastritis and the presence of Helicobacter Pylori[3].

EPIDEMIOLOGY

Transmission of Hp is believed to be by gastro-oral or fecal-oral routes as the bacterium can be cultured from vomitus or diarrhea stools. Therefore, the overall prevalence of infection can be influenced by lack of proper sanitation and basic hygiene, of safe drinking water, as well as overcrowding, making it a public-health issue in developing countries[1].

One of the most important risk factors is childhood socioeconomic status, meaning that infection is acquired at an early age, especially in developing countries. It is common for spontaneous clearance to occur during early childhood, but the chance of reinfection is greater in developing countries compared to developed ones – where it is estimated to occur in less than 0.5% of cases per year[5].

Due to these factors, prevalence of infection can reach up to 80 % by the age of 20-30 in developing areas, whereas in developed countries prevalence is less than 20 % in individuals younger than 30 years, but can reach up to 40-50 % in those 60 of age or older[2].

PATHOPHYSIOLOGY

Clinical outcome of Hp infection is dependent on sophisticated interactions between the bacterial, host and environmental factors. In order to promote chronic infection, H. pylori first has to survive in the harsh acidic environment of the gastric medium[6]. One of the most important bacterium survival technique is the “acid acclimation mechanism” that adjusts periplasmic pH by regulating activity of urease. Another factor on which successful colonizationof the gastric epithelium depends is bacterial motility provided by the presence of 4 to 6 functional unipolar flagella. Recent studies show that peptidoglycan-degrading enzymes are necesary for the proper assembly ofthese flagella[7]. After colonization, adherence to gastric epithelial cells is necessary and this is done thanks to a variety of outer membrane proteins (OMPs), several of which can serve as adhesins, the most important being BabA and SabA. H. pylori employs genetic diversification to adapt to the host immune response and promote persistent infection[8].

This pathogen possesses various virulence factors known to be significant in the induction of disease during infection. One of the most studied effector molecule is cytotoxin-associated gene A (CagA) which is injected into the host cell upon contact via the cag pathogenicity island (cagPAI)-encoded typeIV secretion system. Once intracellular, CagA localizes on the inner surface of the celular membrane and is subjected to a tyrosine-phosphorylation process by Src family kinases. The phosphorylated CagA subsequently induces a signaling cascade, causing proinflammatory responses in epithelial cells[9]. While the literature is contradictory, some studies, including those of Kang et al. and Papadakos et al., sugest that inflamation is induced via the nuclear factor (NF)-kB signaling pathway and subsequent interleukin (IL)-8 secretion[7]. Taking this into

consideration, and also the fact that CagA translocation and phosphorylation are mediated by cholesterol-rich microdomains of the plasma membrane, Lin et al. found that methylantcinate B, a triterpenoid extracted from the Antrodia camphorata mushroom, attenuates CagA translocation and phosphorylation and inhibits CagA functions, including NF-kB pathway activation and IL-8 secretion; but further in vitro research is needed to assess the possibility of a new, antibiotic-free regimen[9].

DIAGNOSIS

The diagnostic procedure of Hp infection can be difficult due to the fact that up to 80-85% of infected individuals are asymptomatic, while the rest develop a series of non-specific symptoms, such as nausea, vomiting, abdominal pain, heartburn, halitosis or diarrhea[1]. This is why specific indications for testing were stipulated. These include active or documented history of peptic-ulcer disease, early-stage gastric MALToma, early gastric cancer, or uninvestigated dyspepsia in high prevalence areas[4]. Testing for the primary prevention of gastric cancer can be performed in individuals with high risk, such as those with family history of gastric cancer, or first-generation immigrants from a region with high-incidence for this malignancy. Some physicians recommend testing prior to starting long-term non steroidal anti-inflammatory drugs or proton pump inhibitors (PPI)[10].

There is also clear evidence that Hp can be involved in the pathogenesis of some extra digestive diseases, with a clear indication to test for infection in individuals with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura (ITP) and vitamin B12 deficiency[11]. Other studies have tried to find a link between Hp infection and some cardiovascular, lung, hepatobiliary or neurological disorders, but failed to produce an unequivocal causative association thus far[12].

Several methods are currently available for detecting Hp infection. Unfortunately, there is no gold-standard diagnostic test due to the fact that every method has it`s limitations and disadvantages [13] (as seen in table 1).

Table 1: Diagnostic tests for Helicobacter pylori infection [14]

Endoscopic Testing	Advantages	Disadvantages
A) Histology	Excellent sensitivity and specificity	Expensive. Requires infrastructure and trained personnel
B) Rapid urease testing	Inexpensive. Provides rapid results. Excellent specificity and very good sensitivity.	Posttreatment sensitivity significantly reduced
C) Culture	Excellent specificity. Allows antibiotic sensitivities determination	Expensive. Difficult to perform. Not widely available.
D) Polymerase chain reaction (PCR)	Excellent sensitivity and specificity. Allows antibiotic sensitivities determination	Not standardized across laboratories. Not widely available
Nonendoscopic Testing	**Advantages**	**Disadvantages**
A) Antibody testing (quantitative and/or qualitative)	Inexpensive. Widely available Very good NPV	PPV dependent upon background Hp prevalence. Not recommended after Hp therapy
B) Urea breath tests (^{13}C and/or ^{14}C)	Identifies active Hp infection. Excellent PPV and NPV regardless of Hp prevalence. Useful before and after Hp therapy	Reimbursement and availability remain inconsistent
C) Fecal antigen test	Identifies active Hp infection. Excellent NPV and PPV, regardless of Hp prevalence. Useful before and after Hp therapy	Polyclonal test less well validated compared to the UBT in posttreatment settings. Monoclonal test appears reliable before and after Hp therapy.

The sensitivity of all tests (endoscopic and nonendoscopic) that identify active Hpi infection is reduced by the recent use of PPIs, bismuth, or antibiotics
PPI = proton pump inhibitor; NPV = negative predictive value; PPV = positive predictive value; UBT = urea breath test.

Table 2: Possible reasons for Helicobacter pylori treatment failure.

1	resistance acquired by mutations
2	the low gastric pH limits antibiotic efficacy
3	antibiotic concentration can be insufficient if there is a high bacterial load
4	existence of sanctuaries to which antibiotics do not diffuse
5	existence of viable bacteria in dormant forms not accessible to antibiotics
6	impaired host mucosal immunity
7	risk of re-infection
8	lack of patient compliance (due to adverse effects or poor understanding of complex antibiotic regimen)

TREATMENT

Historically, various combinations of antibiotics have been used to eradicate the infection, however, no optimal treatment has yet been defined, as there is not a single drug regimen that can eradicate it. There are many factors that have increasingly compromised the effectiveness of most commonly used therapies (as seen in table 2)[1].

These factors have reduced the eradication rates to unacceptable levels (< 80% in some geographic areas). As a response, new treatment strategies have been studied and recently been validated to replace the standard ones[15].

Eradication therapies should be guided ideally by individual susceptibility testing. As this is not cost-effective, local antibiotic resistance patterns should dictate the regimen. Another factor that influences the treatment strategy is drug availability in different countries[16]. These regimens can be divided into first-line treatment and second-line or rescue treatment and are summarized in table 3[1].

Table 3: Treatment regimens for Helicobacter pylori infection

First-line therapies		
Regimen name	*General characteristics*	*Duration*
"Standard triple treatment"	simultaneous PPI + clarithromycin + amoxicillin (each twice daily)	7 days
10 or 14 days triple	simultaneous PPI + clarithromycin + amoxicillin (each twice daily)	10 or 14 days
Sequential therapy	5 or 7 days simultaneous PPI + amoxicillin, followed by 5 or 7 days simultaneous PPI + clarithromycin + 5-nitroimidazole (each twice daily)	10 or 14 days
Quadruple therapy	Simultaneous PPI (twice daily) + bismuth subsalicylate, metronidazole and tetracycline (each 4 times daily)	10 or 14 days
Second-line and rescue therapies		
Regimen name	*General characteristics*	*Duration*
Concomitant therapy	Simultaneous PPI + 3 antibiotics (often amoxicillin, clarithromycin, and 5-nitroimidazole) (each twice daily)	7, 10 or 14 days
Levofloxacin therapies	Levofloxacin will replace clarithromycin in triple, sequential or concomitant regimens	7, 10, 14 days
Hybrid therapy	7 days simultaneous PPI + amoxicillin, followed by 7 days simultaneous PPI + amoxicillin + clarithromycin + 5-nitroimidazole (each twice daily)	14 days
Rifabutin triple therapy	PPI + amoxicillin + rifabutin (each twice daily)	14 days

PPIs are mandatory compounds in every regimen and are administered twice daily at standard doses: omeprazole 20 mg, esomeprazole 40 mg, lanso-prazole 30 mg or pantoprazole 40 mg (with studies showing higher eradication rates for the more potent second-generation PPIs – namely esomeprazole). Standard antibiotic dosages are used in all treatment regimens: amoxicillin 1 g, clarithromycin 500 mg,

metronidazole 500 mg, tinidazole 500 mg, bismuth subsalicylate 524 mg or bismuth subcitrate 420 mg, tetracycline 500 mg, levofloxacin 500 mg, and rifabutin 300 mg[17].

A recently published meta-analysis by Li et al. has compared many of the available regimens for efficacy and tolerance. In terms of efficacy, the standard triple therapy was outranked by all other regimens, with the best eradication rates for the sequential therapy amongst first-line treatments and for the concomitant therapy amongst rescue treatments. The same study has shown that increased treatment duration improves eradication rates, but at the same time enhances the likelihood of adverse effects, lowering patient compliance – almost all rescue regimens were poorly ranked in terms of tolerance[18]. Because of the fact that none of these regimens is ideal, eradication should always be assessed, preferably using a non-invasive test (eg: urea breath test or stool antigen test). Confirmation of eradication can also provide an early image on the pattern of antibiotic resistance in a specific population[15].

All this effort in treating Hp infection is justified by the many benefits of eradication for patience with PUD, but also some malignant conditions. For example a cured individual has better ulcer remission rates for both gastric and duodenal ulcer and does not need maintenance acid suppression therapy after eradication and ulcer healing[10]. It is also more cost-effective and superior compared to maintenance acid suppressive therapy in preventing duodenal ulcer[1]. As for malignant pathologies, early stage low-grade MALT lymphoma can be cured by Hp eradication up to 80% of cases and there is also the possibility of regression or decrease in progression of precancerous gastric lesions (atrophic gastritis and intestinal metaplasia) after eradication[15].

Other studies have shown inverse associations between Hp infection and the prevalence of certain diseases. A recent study published by Rubenstein et al. confirmed prior studies that showed a strong negative association between Hp infection (particularly the cagA strain) and erosive esophagitis, Barrett's esophagus or adenocarcinoma of the esophagus. However, contrary to the prevalent hypothesis explaining this association, they were unable to detect a negative association between Hp infection and gastroesophageal reflux disease symptoms[19]. Lebwohl et al. found a strong inverse relationship between Hp presence and celiac disease (CD), but failed to establish the mechanism by which Hp might be protective against CD[20]. Other studies have postulated that Hp is protective against some extradigestive conditions, especialy asthma and other allergic pathologies in children[21].

THE ROLE OF PROBIOTICS IN HP MANAGEMENT

Probiotics are defined by the World Health Organization (WHO) as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". Most commonly used in clinical practice are lactic-acid-producing micro-organisms (Lactobacillus spp. or Bifidobacterium spp.). Lactic acid produced by these probiotics can have a direct antimicrobial effect by lowering the pH, but can also inhibit the Hp urease. There is also increasing evidence in animal models that some strains of probiotics can inhibit H. pylori growth by competing with different adhesion sites in the gastric mucosae. Another mechanism being stipulated is that some probiotics can increase the expression of the MUC2 and MUC3 genes, which can subsequently lead to an increase of mucus thickness in both antrum and corpus after long-term probiotic intake.

Many studies have been conducted in this field and by analyzing some of them Enzo et al. have reached the conclusion that the use of probiotics as an adjuvant to PPI–antibiotic treatment could improve eradication rates, but the main benefit of this association is the prevention of side-effects, leading to better patient compliance[22].

FUTURE THERAPIES

Efforts to develop a vaccine against H. pylori began in early 1990`s with initial attempts to promote a localized mucosal immune response in the stomach via oral vaccines. Recently, an intramuscularly trivalent vaccine (recombinant Cag-A, Vac-A, and neutrophil-activating protein) was developed, but

failed to induce immunity, despite the fact that these antigens were recognized by the host's humoral and cellular immune systems. Although considerable progress has been made in understanding the innate and adaptive immune response against Hp infection, it is still uncertain how to promote the development of host immunity with the final goal of creating a successful vaccine[23].

DISCUSSIONS AND CONCLUSIONS

Despite the constant progress made in the management of Helicobacter pylori infection, it is still considered a major public health issue due to it`s high prevalence (especially in developing countries) and various conditions that can arise from it (even though 80-85% of infected individuals are asymptomatic). The main reasons for treatment failure is resistance acquired by mutations and lack of patient compliance and recent studies are showing that the standard triple therapy is out-performed in effectiveness by most other treatments. Probiotic adjuvant therapy appears to have a clear effect in reducing side effects, but insufficient data exists to conclude that their use improves eradication rates. Knowing that there is no "gold-standard" in Hp eradication therapy and falling short of the individual susceptibility testing goal, the regimen should be dictated by local antibiotic resistance patterns.

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REVIEW ARTICLE

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The use of low-intensity ultrasound system in Orthopedics for treatment of fractures

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INTRODUCTION

The treatment of non-union or delayed union of fractures includes a growing number of approaches and techniques, one of which is bone growth stimulation using low-intensity ultrasound (LIUS). The treatment is effective, painless and safe. Currently, Exogen is the only device marketed worldwide that uses LIUS to influence the fracture healing process.

THE HEALING PROCESS OF THE FRACTURED BONES

All the fractured bones have to go through a healing process. This is true in cases of surgery or injury. The process of bone healing has three stages. The first stage is inflammation. This starts when the bone has been fractured. Bleeding always takes place in the area of the fracture. This leads to clotting of blood and inflammation in the area. This provides the framework of a new bone. The second stage is bone production. With time, the clotted blood formed in the inflammation stage is replaced by cartilage and fibrous tissues. As the healing continues, the hard callus replaces the soft callus. This can be seen by x-rays some days after the fracture [1, p 20]. The last stage is bone remodeling. This stage goes on for months. In this stage, the bone continues to become compact and returns to its original shape and structure. The blood circulation in the area of the fracture improves. Once some bone healing has taken place, weight bearing encourages the bone remodeling stage [2, p 99].

THE EXOGEN ULTRASOUND BONE HEALING SYSTEM

This is an approved and clinically tested system for treatment of bone fractures. Exogen makes use of the painless ultrasound waves in order to activate the cells that are near the site of the fracture. This speeds up the natural repair process [3, p 1999].

Clinical studies have shown that the system accelerates the healing process of the fractured bones by 38 % in acute fractures [4, p 655] and 86% in non-union or delayed union. It has been shown that Exogen can improve the fracture healing process of older people, those who take tobacco and those who are obese, cases in which the healing process might be delayed. Exogen system can accelerate the process of healing as much as 50 % for the patients who smoke [6, p 254].

The picture below offers a basic explanation of how Exogen works at the cellular level.

To enhance bone healing, Exogen releases low intensity pulsed ultrasound waves at the point of the fractured bone. This jump-starts the natural healing process of the body. The waves move through the skin and the soft tissues to stimulate the critical cells

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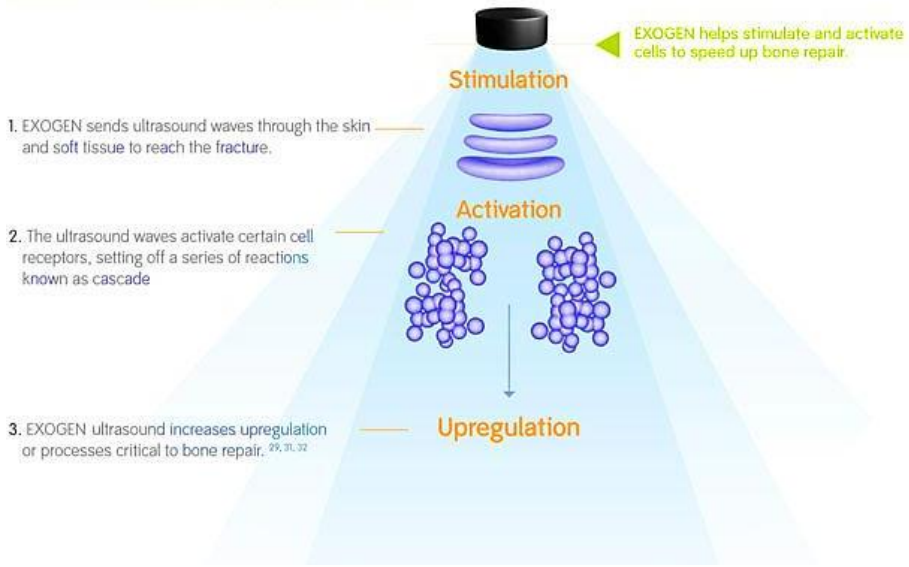
involved in bone healing.

Figure 1: The way Exogen Accelerates the Healing Process of a Fractured Bone [14]



In order to understand the role that the ultrasound plays in healing of the fractured bones, there is a need to understand what it is and how it works. It uses transcutaneous acoustic energy. The piezoelectric crystal produces sound waves which are transmitted through the various body tissues to make a number of changes which are implicated in the tissue healing [8, p 1098]. The density of the tissue is directly proportional to the sound waves that the tissue absorbs. The bone possess high density which makes the ultrasound waves to target the areas which may be affected or have bony abnormalities.

Low intensity pulse ultrasound (LIPUS) specifically works as a potential noninvasive therapeutic in healing of fractures. The waves which are produced by LIPUS introduce micromechanical stress in the area that has been fractured. This stimulates the cellular and molecular responses that are involved in the normal fracture healing. The osteogenic and angiogenic effects caused by the administration of LIPUS are non-thermal. The effects are mechanical in nature with a temperature variation of less than 10C [9, p 802].

The optimum parameters used to archive the maximum benefits of LIPUS are: a pulse width of 200us, an intensity of 30 Mw/cm2 and a 1.5 MHz frequency repeated at 1 kHz every day for 20 minutes [6, p 254].

HOW ULTRASOUND EXERTS MECHANICAL STRESS

There are two mechanisms by which LIPUS induces the mechanical stress in tissues. First it achieves it by displacement of the ends that are fractured and secondly by cavitation.

Research shows that displacement of the fractured ends occurs in at Nano metric scale [9, p 802]. This then stimulates the cellular and the molecular pathways which are involved in the bone healing process [10, p 1022]. It has been shown that LIPUS causes micro motion at the hard and soft tissues interface also. This action produces a mechanical stimulus that is more salient to the integrin mechanoreceptors which take part in osteogenic differentiation and cellular signaling. However it is not yet clear through the available research which displacement mechanism is dominant [11, p 703].

The second mechanism involves the acoustic streaming and cavitation. This mechanism promotes the idea that the sound waves that are emitted from LIPUS allow the accumulation of gas bubbles in the tissues and the cells [12, p 411]. This creates a cavity

which gives room for the acoustic streaming. The streaming leads to turbulence or circular flow in the fluids from the tissues as the sound waves move around the bubble of gases. The acoustic streaming produced increased cell permeability. Once this has happened, the blood pressure rises in the area where the fracture has occurred. The increase in the blood pressure leads to the acceleration of healing by ensuring that there is sufficient gas exchange and the delivery of nutrients to the site. When the cavitation is not stable, the bubbles burst and the resultant energy stimulates the surrounding tissues [13, p 2642].

THE EFFECT OF LIPUS ON CELLS AND MOLECULES

There have been studies that have demonstrated the ability of LIPUS to promote fracture healing through the alteration of molecular and cellular mechanisms which are involved in the process of healing. Integrins are crucial in signaling modulation involved in fracture healing [14, p 345].

They act as mechanoreceptors and are also reactive to pressure changes and vibration caused by LIPUS in the cells environment. The mechanical stimuli increase the clusters of integrin on the fibroblasts. They also up regulate the mRNA expression of the integrin in osteoblasts [15, p 284]. The changes that occur enhance the sensitivity of the respective cells to motion and increase the cells intercellular signaling capacity. An important outcome associated with the intercellular signaling induced in the osteoblasts is the increased activation of ocyclooxygenase-2 enzyme.

This increases the production of prostaglandin which is critical in the mineralization during the process of endochondral ossification especially on the soft callus [16, p 660]. The endochondral ossification which is enhanced by LIPUS leads to formation of the bony callus by the process of augmented mineral deposition [17, p 77].

LIPUS also stimulates the differentiation of the cells which are involved in the process of fracture healing, chondroblasts, fibroblasts, mesenchymal and osteoblasts. Additionally, it increases the way aggrecan expresses itself [18, p 1957]. Aggrecan is a stimulator of chondrogenesis. Presence of aggrecan accelerates the differentiation of chondroblasts into chondrocytes. The production of chondroitin sulfate at the site of injury is accelerated by the presence of more chondrocytes.

Chondroitin sulfates are essential components in supporting bonny and cartilaginous structures. Because of the cavitation process aforementioned, LIPUS increases pressure at the site of injury due to the increase in the vascular permeability [19, p 727]. The increase in pressure has been associated with mesenchymal stem cells differentiation which enhances the development of fibro cartilaginous callous.

LIPUS increases the expression of the early osteogenic genes which include osteonectin, the insulin growth factor and osteopontin. These genes have an important role in making sure that proper osteoblast differentiation takes place [20, p 3190]. The osteoprogenitor cells from the bone marrow may also differentiate into the osteoblasts at a high rate when LIPUS is used. This will enhance the bone healing process and remodeling.

CONCLUSION

The use of low-intensity ultrasound system is a relatively new technology that has been proven to be safe and efficient in the treatment of acute fractures or in cases of non-union or delayed union. The effects at the cellular and molecular level demonstrate its efficacy.

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REVIEW ARTICLE

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A new global threat for the public safety: Zika virus

Simona Bicheru[1], Ion Ștefan[2], Marius Necșulescu[1], Diana Popescu[1], Lucia Ionescu[1], Gabriela Dumitrescu[1], Viorel Ordeanu[1,3]

Abstract: *Zika virus, the etiological agent of Zika fever, is transmitted by mosquitoes and has been affecting the South American continent starting with 2015. It was reported in several European countries, carried by the people who returned from Latin America, as reported by the health authorities in those countries. Today, according to the World Health Organization (WHO), the virus suspected to cause serious birth defects in the fetus has also been confirmed in 21 of the 55 countries of South America, but also in other states from Europe and North America. Zika virus is a single stranded positive sense RNA virus belonging to Flavivirus genus (family Flaviviridae) and was first identified in 1947 in Uganda rainforest Zika. The increased number of cases of microcephaly, in children from northern Brazil, suggested a connection with Zika virus, but it has not yet been proven. Also, the virus can be transmitted sexually and through blood or blood products. Diagnosis of the infection is made using Polymerase Chain Reaction (PCR). So far, there is no specific antiviral treatment or vaccine against the infection with Zika virus. The best form of prevention is to avoid mosquito bites. WHO has estimated that the spread of Zika virus, transmitted through mosquito bite, is "a global public health emergency". The priority is to protect pregnant women and to control the mosquitoes.*

Keywords: *Zika virus, Flaviviruses, microcephaly, Aedes aegypti, mosquitoes*

INTRODUCTION

Zika virus, the etiological agent of Zika fever, is transmitted by mosquitoes and has been affecting the South American continent starting 2015. It was reported in several European countries, carried by the people who returned from Latin America, as stated by the health authorities in those countries. Today, according to the World Health Organization (WHO), the virus suspected to cause serious birth defects in the fetus has also been confirmed in several countries from Europe: Great Britain, Italy, Netherlands, Portugal, Denmark and Switzerland.

Zika virus has been reported sporadically in Africa and Asia for several decades. Zika fever outbreaks were reported for the first time in 2007 (Yap island found in the Pacific Ocean), then in 2013 (French Polynesia). In 2015, outbreaks occurred in Africa (Cape Verde Islands) and South America (Brazil and Colombia). From here, Zika virus quickly spread to several countries in South and Central America and was finally reported in 21 countries of the region in early 2016. [1][2][3] On January 28, the World Health Organization announced that 3-4 million people in

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America could be infected with Zika virus in 2016. [4] On February 1, 2016, the WHO has estimated that the spread of Zika virus, transmitted through the bite of *Aedes aegypti* mosquito, is "a global public health emergency".

THE ETIOLOGICAL AGENT

Zika virus is a single stranded positive sense RNA virus belonging to *Flavivirus* genus (family *Flaviviridae*) and was first identified in 1947 in Uganda rainforest Zika. It is the etiological agent of Zika fever, a viral infectious disease transmitted by infected mosquitoes. [1][2][3]

SYMPTOMATOLOGY

The incubation period is 3-12 days after an infected mosquito bite. Most infections caused by Zika virus are asymptomatic (60-80%). Symptoms are usually mild and disappear within 2-7 days without severe complications or death. The main symptoms are rash (macular or a papular exanthema that initially appears on the face and then spreads throughout the body), moderate fever, arthralgia, myalgia, headache, non-purulent conjunctivitis with conjunctival hyperemia. Vertical transmission can occur during labor (in the viremic stage) or transplacentar. The increased number of microcephaly cases in children from northern Brazil suggested a connection with Zika virus, but it has not yet been proven. Also, the virus can be transmitted sexually and through blood or blood products. [1][2][3]

TRANSMISSION

Zika virus is transmitted by mosquitoes and was isolated from species of the genus *Aedes*, such as *A. aegypti* (Figure1), *A. africanus*, *A. apico argenteus*, *A. furcifer*, *A. hensilli*, *A. luciocephalus* and *A. vitattus*. Studies showed that the incubation period in mosquitoes is approximately 10 days [22]. Zika virus can be transmitted through interpersonal sexual contact and can cross the placenta, affecting the unborn fetus. An infected mother (in the viremic stage) can transmit the virus to the newborn at the time of labor. [24][25][26]

The vertebrate hosts of the virus are the monkeys.

Figure 1: Aedes aegypti (http://www.cdc.gov)

Before the current pandemic, which began in 2007, Zika virus rarely generated collateral infections in humans, even in areas recognized as highly enzootic [7]. In 2009, Brian Foy, a biologist at Colorado State University, reported the sexual transmission of the Zika virus. [13][14]. In 2015, the Zika virus was detected in the amniotic fluid of two pregnant women, indicating that it is possible to cross the placenta and cause infections in newborns. [4][34][4][5][35][36]

DISEASE

Zika virus infection symptoms normally include mild headache, maculopapular rash, fever, malaise, conjunctivitis and arthralgia. [33] The first thoroughly documented cases of Zika virus infections were described in 1964, being characterized by mild headache, progressing through maculopapular rash, fever and back pain. Within two or three days, the initial symptoms remitted, but the rash persisted. Patients with Zika fever are advised to rest and are prescribed fluids and acetaminophen, while aspirin and nonsteroidal anti-inflammatory drugs should be used only after Denga fever was ruled out, in order to reduce the risk of bleeding. [38]

COMPLICATIONS

Microcephaly. In December 2015, it was suspected that an infection of the fetus with Zika virus, transmitted transplacental, may cause microcephaly and brain damage. [5][34] Consequently, the European Centre for Disease Prevention and Control issued a comprehensive update on the possible association of the Zika virus with congenital microcephaly. [35] (Figure 2)

According to CDC Atlanta (Centers for Disease Control and PreventionUSA), "were reported cases of

microcephaly defects in children of mothers who were infected with the Zika virus during pregnancy."

Figure 2. Comparison between a child with microcephaly (left) and a normal child (http://www.cdc.gov)

Zika viral infections were confirmed in several newborns with microcephaly; the number of microcephaly cases associated to Zika virus infection is unknown. [8][10][34]

On January 17, 2016 the Pan American Health Organization (PAHO), the Regional Office of the WHO, has recommended that its member states "establish and maintain the ability to detect and confirm cases of infection with Zika virus, given the increased number of congenital anomalies, Guillain-Barré syndrome and other neurological or autoimmune syndromes recorded in areas affected by Zika, to prepare healthcare facilities to respond to a possible increasing demand for specialized care for neurological syndromes and to strengthen prenatal care." [28][29]

DIAGNOSTIC

Zika virus is detected through PCR (gene amplification by Polymerase Chain Reaction). [15] [16] Since the viremic stage may be short, the WHO recommends that the RT-PCR testing should be done on the sera collected within 1 to 3 days after symptom onset or on the saliva or urine samples collected during the first 3 to 5 days after onset. [20][21][22][23]. Serological diagnosis can also be used by detection of specific IgM antibodies. Those appear towards the end of the first week of illness. [18]

Serological diagnosis can be difficult, given possible cross-reactions with other flaviviruses, for example the *Dengue* virus, *West Nile* virus or *Yellow Fever* virus. Zika commercial diagnostic tests are available at Euroimmun (www.euroimmun.com).

TREATMENT

Until present time, there is no specific antiviral treatment or vaccine available against Zika virus infection. The best form of prevention is to avoid mosquito bites.

Prophylaxis

The existence of mosquitoes and larval nests is an important risk factor for the infection with Zika virus. Disease prevention consists in decreasing the number of mosquitoes at source (elimination or modification of larval nests) and reducing contacts between these insects and humans. Those traveling to endemic areas should be informed on methods of protection against mosquito bites. These involve avoiding outdoor exposure at dusk and dawn, wearing clothes that cover as much exposed skin, using repellents, nets for beds impregnated with insecticide, accommodation in rooms with air conditioning and mosquito nets. It is also recommended emptying, cleaning and covering all containers that can collect water such as buckets, flower vases and tires in order to eliminate the places where mosquitoes can reproduce. During outbreak, health authorities can proceed to spray insecticide.

Vaccination

There are effective vaccines against several *Flaviviruses*. Vaccines against the *Yellow Fever* virus (antiamarilic), *Japanese encephalitis* and *Tick-Borneencephalitis* have been introduced from 1930, while the dengue fever vaccine just became available for use. [37]

According to Anthony Fauci, of the National Institute of Allergy and Infectious Diseases, attempts are made in order to obtain a Zika virus vaccine. [38] Researchers at the Research Center for Vaccines have extensive experience in obtaining vaccines against other viruses such as the Chikungunya and the Dengue fever virus. [38] Nikos Vasilakis, from the Center for Biodefense and Emerging Infectious Diseasesappreciated that getting the vaccine could take up to two years, but an effective vaccine for

public use, approved by regulatory authorities, could be obtained in 10 – 12 years. [38][39][40][41]

EPIDEMIOLOGY

In 1947, scientists researching Yellow Fever revealed the onset of fever in a *Macaccus Rhesus* monkey located in a cage in the Zika Forest (Zika meaning "too high", in the Luganda language), near the Research Institute of Virology East Africa, in Entebbe, Uganda. The researchers have isolated from the monkey's serum a transmissible agent, which was first described in 1952 as the Zika virus [17] and was subsequently isolated in 1954 from a person in Nigeria. Since its discovery until 2007, rare cases of Zika virus infection were recorded in Africa and Southeast Asia. [40] In April 2007, the first outbreak outside Africa and Asia was declared on the island of Yap, in the Federated States of Micronesia; the cases were characterized by skin rash, conjunctivitis and pain, initially associated with Dengue, Chikungunya or Ross River disease. [41] However, the serum samples analyzed from patients in the acute phase of infection confirmed Zika virus infection. There have been 49 confirmed cases and 59 cases were disproved. There was no need for hospitalization and no deaths were reported. [42] Subsequently, outbreaks have appeared in Polynesia, Easter Island, the Cook Islands and New Caledonia. [5]

Starting April 2015, an epidemic broke out in Brazil with Zika virus (Figure 3) and has spread to South and Central America, the Caribbean, having a trend of global spread. In January 2016, CDC issued a level 2 travel alert for people traveling to affected areas (Table 1, Figure 4).

Figure 3: Zika virus epidemic map at 01.22.2016 (www.cdc.gov)

Figure 4: The geographical distribution of the Zika virus(www.cdc.gov)

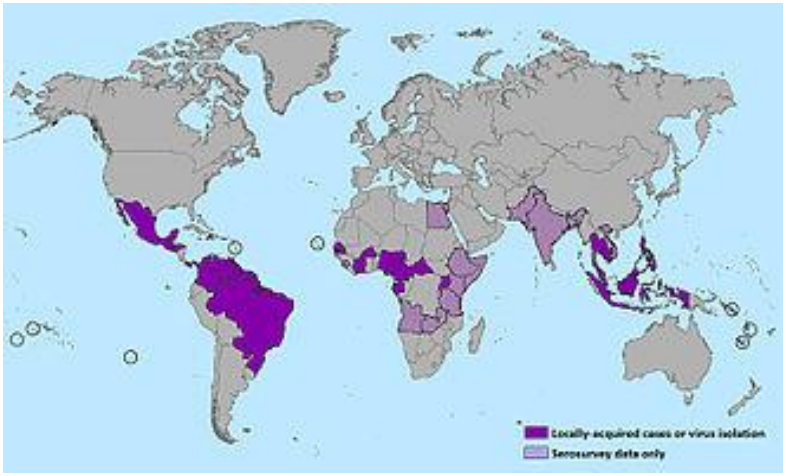

Table 1: Number of cases diagnosed with Zika virus (April 2015-present) (www.cdc.gov)

Country	Confirmed cases	Update
Australia	2	2 Feb 2016
Barbados	3	20 Jan 2016
Bolivia	1	20 Jan 2016
Brazilia	est. 1,5 mil	30 Jan 2016
Canada	4	30 Jan 2016
Chile	3	2 Feb 2016
Colombia	est. 20.000	30 Jan 2016
Curaçao	1	31 Jan 2016
Dominican Republic	8	27 Jan 2016
Ecuador	6	20 Jan 2016
El Salvador	est. 2.500	31 Jan 2016
French Guiana	2	8 Jan 2016
Guadeloupe	1	21 Jan 2016
Guatemala	1	27 Nov 2015
Guyana	1	21 Jan 2016
Haiti	5	21 Dec 2015
Honduras	3.649	1 Feb 2016
Jamaica	1	30 Jan 2016
Martinique	2	8 Jan 2016
Mexico]	18	31 Jan 2016
Nicaragua	3	31 Jan 2016
Panama]	50	28 Jan 2016
Paraguay	6	3 Dec 2015
Puerto Rico	22	26 Jan 2016
Saint Martin]	1	21 Jan 2016
Suriname	3	24 Jan 2016
United States	40	2 Feb 2016
Venezuela	3.700	28 Jan 2016
Total	**Est. 1.5 mil**	**up to 30.01.2016**

IMPLICATIONS FOR THE PUBLIC HEALTH

The WHO recommends that women planning to become pregnant should consult their physician before traveling to regions affected by the disease. [9][44] Governments and health agencies in the European Union, including UK and Ireland, as well as those in New Zealand, Canada, Colombia, Ecuador, El Salvador and Jamaica have issued similar travel warnings. Specific plans and measures were announced by authorities in Rio de Janeiro, Brazil, to prevent the spread of the Zika virus during the Olympic Games, taking place in this city, in 2016. [11][45][46]

According to CDC, Brazilian health authorities have reported more than 3,500 cases of microcephaly between October 2015 and January 2016. Some affected infants had a severe type of microcephaly, while others died.

These manifestations may be associated with Zika infection, occurred during pregnancy. Several studies are planned to assess the risks of the Zika virus infection during pregnancy. [45] In the worst affected regions in Brazil, about 1% of newborns are at risk for microcephaly. [46]

COMMENT

In humans, Zika virus causes an infectious disease called Zika fever, characterized by fever, headache, maculopapular rash, malaise, conjunctivitis, arthralgia etc.

The WHO has warned that the spread of Zika virus, transmitted by mosquitoes, is ''a global public health emergency'' and can be correlated with an increased number of newborns with congenital malformation recorded in Brazil last year.

WHO warns that Zika virus, transmitted mainly by mosquitoes, "explosively" spreads in South America, where in 2016 could be millions of cases. The priority is to protect pregnant women and to control the mosquito populations.

Medical experts are concerned about the very rapid transmission, over long distances of the virus with devastating consequences. From the confirmation of the presence of Zika virus, in May 2015, the virus has spread so far in 23 countries, including Brazil, Bolivia, Paraguay, Mexico, Venezuela and the epidemic continues to spread.

CONCLUSIONS

The World Health Organization has warned that the spread of Zika virus, transmitted by mosquitoes, is a

”global public health emergency”, which can be correlated with the increased number of newborns with congenital malformation recorded in Brazil last year and that the virus "explosively" spreads in South America, where in 2016 could be millions of cases.

Experts are concerned about the very rapid transmission, over long distances of the virus; the consequences can be devastating, and the priority is to protect pregnant women and to control the mosquito populations.

National health authorities are requested to take necessary measures for the prevention, diagnosis and treatment of Zika fever cases and to isolate import cases, in order to impede the spread of the disease.

Also, scientific research is needed in order to obtain an effective vaccine against Zika virus.

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SYSTEMATIC REVIEW

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Morphopatological and histochemical highlights in normal and varicose vein wall

Alina Condor[1], Caius Solovan[2], Liliana Vasile[2]

Abstract: *The nutrition of the venous wall appears to be an important factor in the vascular-fibrillar trophicity and in the dynamic of the extracellular matrix formation for the normal veins and, for the chronic venous ulcers of legs, on period of healing. Sequential biopsies were taken at various levels of venous wall of external and internal saphena in 16 cases presenting a chronic condition of legs venous system (35-58 years old patients, both sexes). 8 vein fragments with normal macroscopic appearance were also taken, in necropsy.*

These samples were analyzed using regular morphological methods and some histochemical reactions to reveal the glycogen, glycoproteins, and glycosaminoglycans substrates. There were been used the Gomori silver impregnation and orcein to expose some specific substrates like reticulin or elastin. Other staining methods, like Gomori trichrome, were used to differentiate the specific structures of the vein wall, were used to differentiate the specific structures of the vein wall.

A rich vascularization of normal and dilated vein wall could be remarked.Angiogenesis in vein wall and vasa vasorum changes as well as alcianophilic of vascular intima seem to be reactive and protective factors, depending on the applied therapeutic modalities. The veins are weak structures whose integrity depends on the thickness of the media and the support of neighboring structures.

INTRODUCTION

The emergence of varicosities it is supposed to be a consequence of defective development of venous wall and appears to be inherited. The proper nourishment of the venous walls appears to be an important factor in their trophicity. The incidence of varicose veins is about 1% of the adult population [5]. Both obesity and aging are involved as risk factors for emergence of defects in venous wall tissue support. The etiology and pathophysiology of varicose disease remains controversial. We emphasize the involvement of the following lesional links amid stasis hypoxia:

- Redistribution of microcirculation with arrangement in lobular aggregate of vessels in the superficial dermis;

- Areas of floride proliferation mimicking Kaposi's sarcoma (acro-angio-dermatitis), reticular dermis fibrosis and massive deposits of hemosiderin, degeneration of dermal fibroblasts (senescent fibroblasts converted by modulation into myofibroblasts having a role in periulceros tegument retraction) to extended tissue matrix lysis;

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-Outbreaks of fat necrosis concomitant with a proliferative-alternative response of adjacent epidermal, hyper parakeratosis and orthokeratosis and pseudoepitheliomatous hyperplasia.

The presence of lytic degradative tisular factors (metalloproteinase) and activation of monocito-macrofagic system induced degradation of the basal membrane and chronic venous ulcers.

Morpho-histochemical current study aims to deepen the importance of veins wall nutrition in normal and dilated veins. It also envisages the re-active participation of supra-adjacent dermo-epidermal tissue, the possible influence on vessel permeability and vasoprotective or anticoagulant medication used in selected cases in the study.

MATERIALS AND METHODS

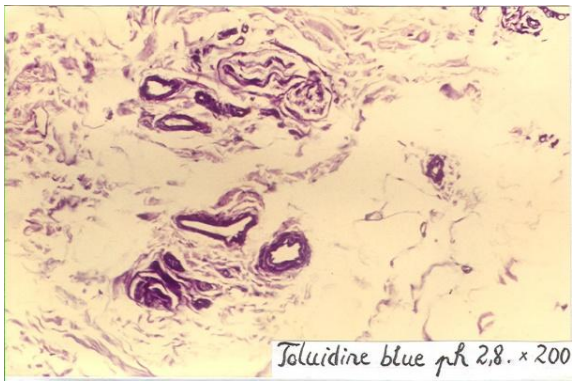
16 biopsies were taken sequentially from the varicose saphenous in areas of dilated vein (12 cases) and in the vicinity of shank chronic venous ulcer (4 cases); Saphenous fragments from normal vein were collected at necropsy (8 cases). Cases have included both sexes. The selected cases were with at least 5 years of disease duration and the type of treatment was also considered.

Patients in the study were selected from the inmates in Department of Surgery of Military Emergency Hospital and University Clinic of Dermatology in Timisoara.

Processing of samples was performed at the Department of Histology of Medicine and Pharmacy University in Timisoara by usual histological techniques: all samples were fixed in 10% formalin, buffered formalin, AFA fixator (Alcohol - Formaline - Acetic acid), paraffin inclusionated, sectioned at 5 µm, then colored by hematoxylin-eosin. For histochemical study, there were been applied reactions PAS (blue Alcian (BA)) and salivary amylase-PAS (Alcian blue used at pH 2.8 and pH 0.5); blue toluidine (BT) at pH 5 and pH 2.8; it was used Gomori silver impregnation for reticulin and it was also used trichrome Gomori reaction.

Orcein staining method was used to expose elastin.

Figure 1: Lipodermatosclerosis (*toluidine blue, pH 2,8, ×200*)

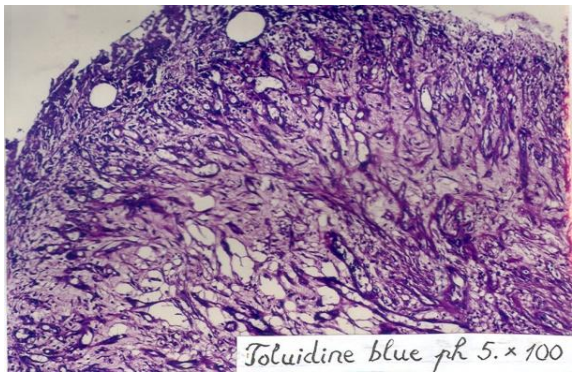


RESULTS

In all examined cases, the wall of external and internal saphenous veins was well vascularized, containing arterioles, venules, capillaries in musculo-fiber media. Constant, parietal capillaries from vasa vasorum were not flattened. In varicose veins adventitia, in small and medium vessels, were frequently found leukocytic marginations and acidophilic deposits and PAS positive, weak metachromatic fibrin (Figure 1).

Fibrin sleeves were also observed in the wall vessels of varicose veins in which angiogenesis is very marked. For AT, were remarked weak metachromatic perivascular sheaths, at pH 5 and chromophobe tissue matrix of dilated veins sheaths, at pH 2.8. Orthochromatic of nuclei allows observing the phenomenon of leukocytes margination (mostly lymphocytes) in the parietal small and medium vessels up next to intima, for both pH used (Figure 2).

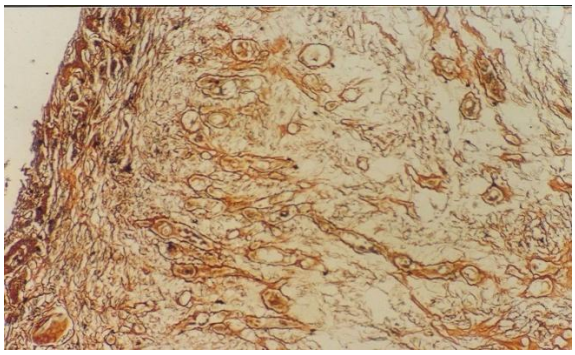
Figure 2: Perivascular sheaths and parietal leucocytes margination in small and medium sized vessels, close to venous intima (*toluidine blue, pH 5, ×100*)



In all methods used in this study, the average media of varicose veins appears thickened through a rich smooth muscle proliferation (HE col., Gomori trichrome col.), with weak orceinic material fragmented through the wall layers (Orcein col.). There were observed fake elastic limitations, fragmented, disorganized (orcein, Gomori trichrome). In one case of all cases examined, using combined staining AA-PAS, which stands under anticoagulant therapy, an edemic intima and hyperplasia were observed, with fundamental alcianophilic substance (FS) and somewhere with deposits PAS positive as a rich interstitial material PAS positive all that pushing aside and cleaving muscle layers of the vascular media. Other intimal changes reported in our study are notches and extensive fibrosis, miointima hyperplasia of saphenous varicose veins.

Alcianophilic fibrillar material with reticular disposition is perivascular distinguished in the neo-capillaries that invade from adventitia media. Silver impregnation for reticulin (Figure 3) shows neo-formation basic membrane by budding vasa vasorum from adventitia to media to decline to extinction the reticulin network of media muscular interstice and vasa vasorum walls.

Figure 3. Reactive angiogenesis in variceal venous wall (*silver impregnation, ×200*)



The phenomenon seems to affect 2/3 of external walls of the dilated veins. In neighboring dermal and epidermal tissue and in the perivascular support appear lesions like: lipodermatosclerosis, fibrosis and perivascular fibrin deposits and interstitial fragmentation of elastic fibers in the deep of dermis, tinctorial variations of epidermal cells cytoplasm for which an accumulation of PAS positive material could be noted and cemented SF was PAS reactive. For silver impregnation, the dermal epidermal limit appears fibrillary fine, thinner than the normal appearance.

DISCUSSIONS

The changes of vein wall tissue architectural pattern take place simultaneously with the progression of venous distension in varicose vein disease. It is noticed an important reaction of vessels in vasa vasorum which angiomatosic proliferate, invading media, almost to intima, leading to muscular media hypertrophy [5]. Vascular proliferation can be reactive to miointima hyperplasia and to varicose wall media. Chronic shank venous ulcer it is possible to occur, in time.

Thus, as a reaction to increased venous pressure in a vein much thickened, on account of media and intima and hence to the shank edema, fibrin sleeves occur, those may inhibit the angiogenesis [4]. However, it is created a protection against increased venous additional pressure with a possible role in causing tisular ischemia [6][8].

Fibrin sleeves were found around the capillaries of the dermis in lipodermatosclerosis. Massive deposits of fibrin are involved in elastin fragmentation of the deep dermis and in elastic limitations of vascular walls. Vasa vasorum angiomatosis proliferate in invading varicose vein media. Since 1992, "leukocyte sleeve" was reported as a response to chronic stasis. White blood cells can accumulate in the lumen of capillary and venular, increasing perivascular resistance.

Activated endothelium becomes thrombogenic surface (via tissue factor secreted by endotheliocyte: factor VIIa, factor X-Xa). Simultaneously, activated endotheliocyte was involved in angiogenic peptide synthesis, stimulating neovascularization of dermis and ectasiated venous walls. Tissue anoxia and ulceration is installed.

Consistent with the cited literature, we found also an increased number of capillaries in the skin of patients with venous hypertension in the lower limbs.

Wall vessels are the only ones bringing oxygenated blood, draining interstitial fluid and extravasated colloidal material [7][1][3]. This explains the rapid drainage and metastasis of tumor cells via veins and lymphatics with rich vascularity, having intraparietal capillaries opened.

Adventitial enriched positive PAS material, periadventitial and intraparietal, is represented by fibrin, and also by a macromolecular glycoprotein substrate containing laminin, fibronectin, tenascin detected by immunocytochemical investigations by some cited authors [2][5].

So we can correlate the "leukocytic margination" phenomenon in vasa vasorum and intraparietal vessels with depolymerization of SF tissue more evident in the 2/3 of external portion of the varicose venous wall.

The histochemical reactions used in our study, draw attention to the changes in the three fibrillar component. In varicose veins (dilated segments thereof) we found a quantitative increase of mature collagen fibers and reticulin, morpho-histochemical revealed, with a decrease and fragmentation of elastic fibers in the dilated walls. Together with the degradation of elastin, reticulin network growth can be an important factor in the parietal frailty in shank venous insufficiency evolution.

Marked alcianophilia of intima (AA pH 2.8) calls attention to presence at this level of complex carbohydrates with carboxyl groups and hydroxyl radicals in position of vic-glycol (sialic acid and hyaluronic acid) which act as intima hydrator, but may decrease macromolecular complexes stability of glycoproteins (with increase of sialic acid amount).

Sialic acid carboxyl groups and other substances not yet identified are responsible for basophilia and metacromazia of certain reticulin networks and basement membranes. The enriched PAS positive interstitial material in dilated vessels media is favorable to reticulin collagenization (gradual multiplication of preexistent collagen fibers in a glycoprotein matrix apparently unchanged).

Reticulin collagenization occurs when the hydroxyl group probably belonging to hydroxyproline and hydroxylysine achieve the appropriate concentration [9].

In the cases we investigated, collagenization is conducted in a glycoprotein reticulin dominant matrix (in the external 2/3 dilated vein wall), progressively decreasing toward intima, simultaneously decreasing nourishment intake by vessels of the vein wall fibrosing.

CONCLUSIONS

Morpho-histochemical methods draw attention to the complex of walls reshuffles of venous leg during chronic venous insufficiency. There are being considered the three coats of veins in that appear to be successive lesional patterns: mio-intimal hyperplasia, medial muscle hypertrophy, reactive angiogenesis, lipodermatosclerosis, collagenization of medial muscle.

The chronic venous stasis can be quantified by morphological parameters: mio-intimal hyperplasia, medial muscle hypertrophy, reactive angiogenesis, lipodermatosclerosis, collagenization of medial muscle. The prolonged venous hypertension modifies both the local microcirculation conditions and selecting of fibril-forming cells, triggering the evolution of chronic venous ulcers.

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ORIGINAL ARTICLES

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Expandable stents in digestive pathology – present use in an emergency hospital

Mădălina Ilie[1], Vasile Șandru[1], Cristian Nedelcu[1], Bogdan Popa[1], Gabriel Constantinescu[1]

Abstract: *Introduction: Self expandable metal stents (SEMS) are developed lately, as an effective and safe, less invasive alternative of surgery for the treatment of malignant intestinal/biliary obstruction. Recently, SEMS are also introduced in benign pathology.*
Aim: The aim of this presentation is to report a retrospective analysis of the total number of SEMS placed for esophageal, enteral, colorectal and biliary obstruction during the last 3 years in Clinical Emergency Hospital Bucharest, as well to review the literature published on this issue.
Methods: Between 2013-2015 in Clinical Emergency Hospital Bucharest, we have placed: 232 esophageal stents, 23 enteral stents, 5 colonic stents and 75 biliary stents under radiologic guidance. The main parameters followed were represented by: sex, age, grades of obstruction, stent diameter and type, immediate and late complications and survival rate.
Results: Regarding the esophageal stenting, most of the indications were malignant obstruction (155 cases of esophageal cancer and 30 cases of extrinsic compression), but also for esophageal fistula, peptic stenosis and even traumatic esophageal rupture. The majority of the enteral and colonic stents were inserted for malignant obstructions, having only 2 cases with benign obstructions. This is also the case for biliary stenting, were most of the indications were represented by pancreatic cancer. Technical and clinical success rates were approximately 92% and 80%, respectively. There were no major complications of perforation, bleeding, or death.
Conclusions: SEMS insertion can be performed safely, with minimal complications and hospitalization allowing the restart of oral feeding and improvement of nutritional status for the digestive obstruction or jaundice disappearance in case of biliary obstruction. It represents the first option for unresectable digestive/biliary malignant obstruction.

Keywords: *expandable stents, malignant obstruction, fistula, stenosis*.

INTRODUCTION

Over the past decades, the endoscopic approach for palliation of malignant obstruction has overcome the use of percutaneous approach. The options for endoscopic stenting are either self-expandable metal stents (SEMS) or plastic stents (PS). PSs are composed of polyethylene, polyurethane, or Teflon,whereas SEMSs are made of various metal alloys that are constructed to achieve adequate radial expandable force without sacrificing flexibility and conformability to the duct [1].SEMSs can be either uncovered or covered with material to prevent tumour ingrowths. Recently, uncovered self-expandable biodegradable stents were added to this portfolio [2].

The ideal stent have to be pliable, atraumatic but also forceful to maintain patency and position in the

[1] Clinical Emergency Hospital Bucharest

lumen. However, stents should also be easily removable and without any risk for benign hyperplastic or malignant tumor ingrowths or overgrowth.

The current guidelines from the American Society for Gastrointestinal Endoscopyfor distal malignant biliary obstruction recommend either SEMSs or PSs, with PSs preferred in cases of distant metastasis and short life expectancy. However, studies have shown that although PSs are less expensive, metal stents have better drainage and longer patency,with recent data showing they are more cost-effective [3][4].

METHODS

We have done a retrospective, non-randomized study between 2013-2015 in Clinical Emergency Hospital Bucharest. We have placed: 232 esophageal stents, 23 enteral stents, 5 colonic stents and 75 biliary stents under radiologic guidance. The main parameters followed were represented by: sex, age, grades of obstruction, stent diameter and type, immediate and late complications and survival rate. We had exclusion criteria: an INR more than 3 and an estimated survival time less than 3 weeks. Regarding the dysphagia we have used Mellow and Pinkas's scale.

0 = able to eat normal diet / no dysphagia.
1 = able to swallow some solid foods
2 = able to swallow only semi solid foods
3 = able to swallow liquids only
4 = unable to swallow anything / total dysphagia

We have used most the nitinol stents (alloy of nickel and titanium), because of their ability to conform to anatomical angulations and the latter for their removability.

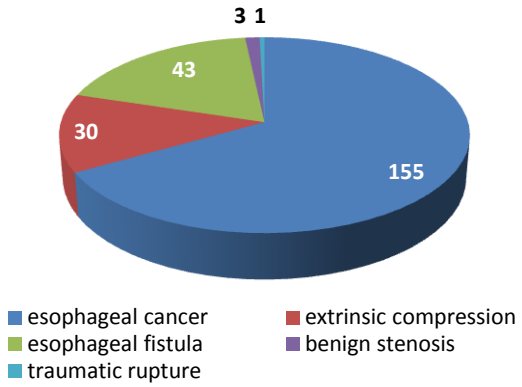
RESULTS

More than 65% of the patients were male with age varying between 49 and 83 years old.

Regarding the esophageal stenting we have placed in Clinical Emergency Hospital Bucharest, 232 oesophageal stents for the following indications (Figure 1):

-155 cases of esophageal cancer
-30 cases of extrinsic compression
-43 cases of esophageal fistula
- 3 cases of benign stenosis
- 1 case of traumatic rupture of the esophageal wall

Figure 1: Graphic representation of esophageal stenting indications



The majority of the cases (> 50 %) have unresectable disease at the time of diagnosis, either because of distant metastases or unsuitable candidates for surgical resection.

The aims of palliative therapy are to ameliorate symptoms of dysphagia, treat complications, maintain oral intake, minimize hospital stay, relieve pain and ultimately improve their quality of life.

We have used: totally covered SEMS or partially covered SEMS. Fully covered stents are more prone to stent migration; removable and theoretically may be more suitable for benign strictures/fistula whereas partially covered stents have a small portion of exposed bare metal in both proximal and distal ends to allow embedding into the oesophageal wall, which helps to decrease stent migration. The uncovered portion of the partially covered stents allows embedding and anchoring. No differences in survival rates were observed between these two types [5].

The techniques used for inserting the stent were: OTG – over the guidewire (most of the cases) or TTS (through the stent) both under radiologic view. At the beginning the lesion is visualized under endoscopy (Figure 2A – oesophageal fistula) and upper end is marked by injection of contrast agent into the

submucosa (Figure 2B).

It is very important for the marking to be done internally and not to put external marks that may move during the procedure. The stents are mounted in a preloaded constrained position on a delivery catheter.

A guide wire is passed through the lumen of the catheter (Figure 2C), and when the wire has been advanced beyond the obstruction, the stent is passed over it and positioned across the stricture with the upper end at the position of the internal contrast mark (Figure 2 D, E, F).

Figure 2A: Esophageal fistula

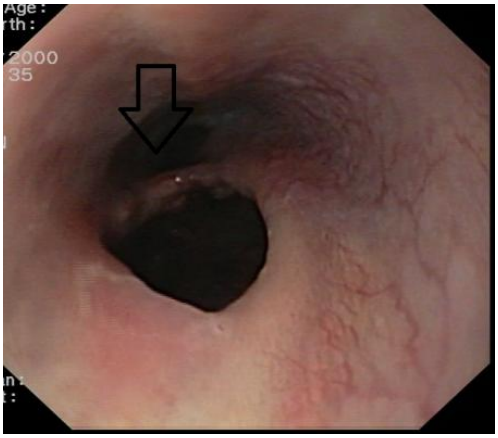
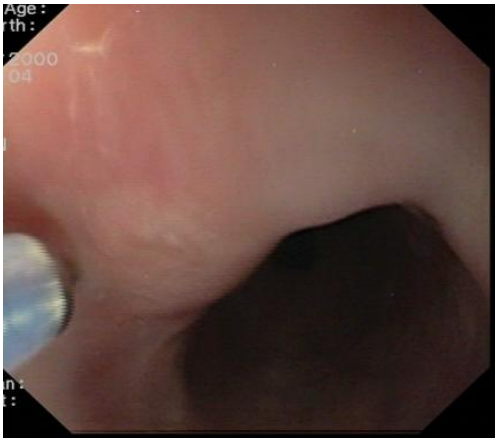


Figure 2B: Contrast injection



The immediate complications encountered were: retrosternal pain (60%), alleviated after antalgics, stent migration while as late complications we had: food impactation (7%),fibrous tissue invasion (4%), tumoral invasion (5%),uncovered fistula and upper GI bleeding.

Figure 2C: Guidewire insertion

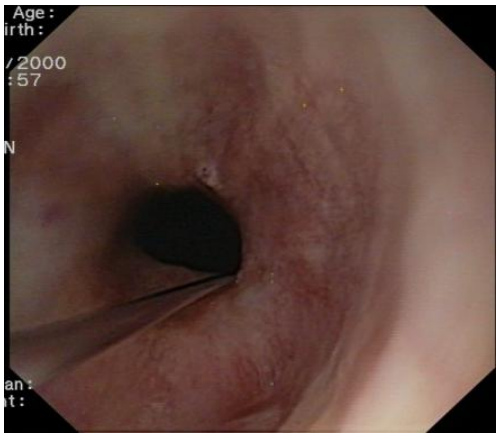


Figure 2D: Stent deployment

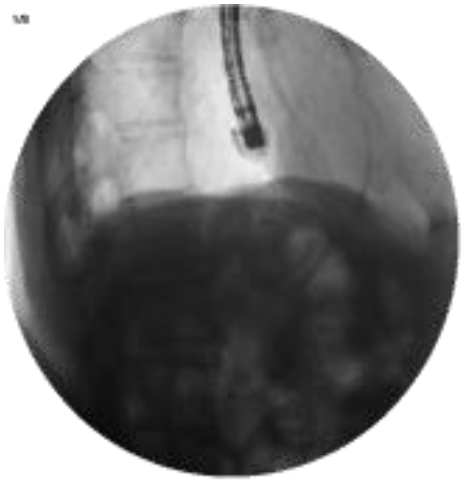
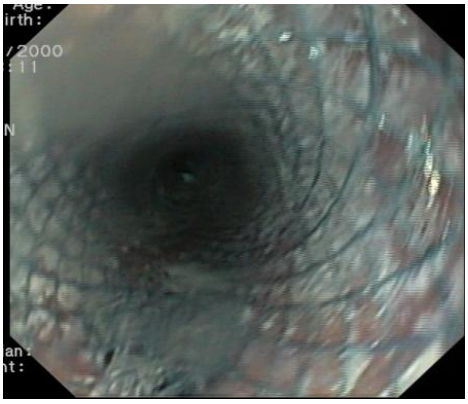


Figure 2E: Stent view on RX

Regarding the enteral stenting we had 23 total cases: 21 for malignant extrinsic compression and 2 cases

for benign stenosis. The technique used was TTS (through the scope) with low rate of complications.

Figure 2F: Stent under endoscopy view



A specific situation was double stenting, both enteral and biliary (Figure 3 A, B), especially in pancreatic head malignancies with obstructive components.

Figure 3A: Double stenting (enteral+biliary)

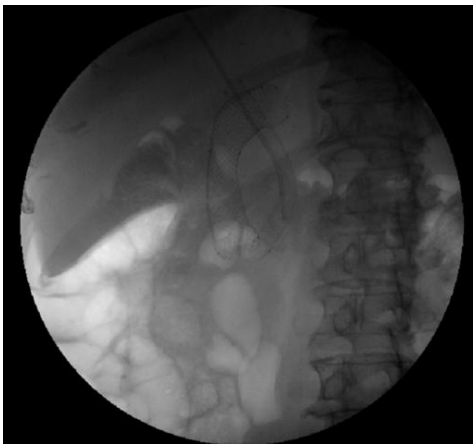
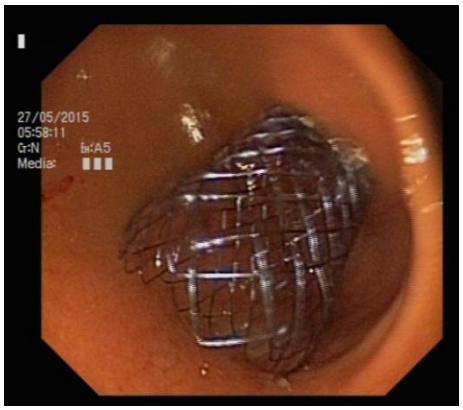


Figure 3B: Enteral stent-endoscopic view



Colonic SEMS placement is recommended as the preferred treatment for palliation of malignant colonic obstruction, except in patients treated or considered for treatment with antiangiogenic drugs [6]. Stent insertion may be considered as an alternative to emergency surgery in those who have an increased risk of postoperative mortality. We have placed only 5 colonic stents (Figure 4), mainly because of ease of accessibility to the surgical service in our hospital.

Figure 4: Colonic stent

In case of biliary stenting we have inserted 73 stents for malignant obstruction (approx. 60% pancreatic cancer) and only 2 for benign obstruction (chronic pancreatitis). SEMSs range from 4 to 12 cm in length with diameters when expanded ranging from 6 to 10 mm.

Self-expanding metal stents (SEMSs) are built from different metal alloys, mainly nitinol, that are used to achieve adequate radial expansive force leading to increased patency duration and reduced recurrent obstruction.

SEMSs are preloaded in an outer sheath with a diameter of 8.5F or smaller, allowing use with a therapeutic duodenoscope. After placement in the duct, the outer sheath is withdrawn, allowing the stent to expand (Figures 5A, B, C).

SEMSs can be covered, partially covered, or uncovered.

Partially or totally covered SEMSs can be repositioned or fully removed, reduce the rate of stent occlusion but they have risk of cholecystitis because of involvement of the cystic duct orifice). Acute cho-

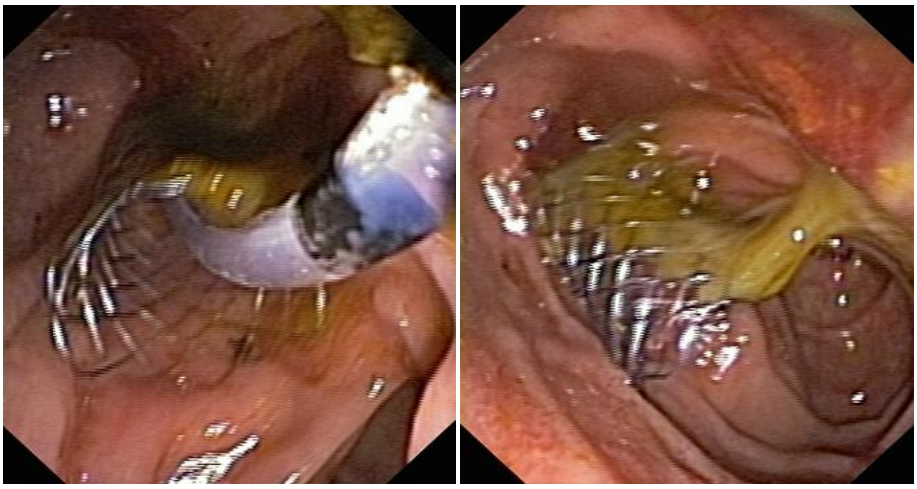
lecystitis may occur in as many as 10% of patients with intact gallbladders after placement of a covered SEMS across the cystic duct. In opposition, uncovered SEMS migrate less but have risk of tumor ingrowths [3].

SEMS insertion at patients with malignant biliary obstruction palliate jaundice, anorexia and most important help the initiation of chemotherapy that otherwise would be contraindicated.

Initial insertion of a plastic stent is most cost-effective if patient life expectancy is shorter than 4 months; if it is longer than 4 months then initial insertion of a SEMS is more cost-effective.

Figure 5A: Distal biliary obstruction; stent insertion radiologic view

Figures 5B, 5C: Endoscopic views



CONCLUSIONS

SEMS represents a very useful alterative, with minimal complications to classic surgery for palliation of unresectable digestive/biliary malignant obstruction. With the current development and applications of new materials and technologies, the future of stenting is evolving.

New trends include drug-eluting stents, biodegradable biliary/esophageal stent and the use of biodegradable polymers for local drug delivery, having also curative aim [7] . Radiation therapy, a cornerstone of treatment for malignant disease of the esophagus, may also be administered in conjunction with placement of esophageal endoprosthetics [8].

Regarding the biliary malignant obstruction, we recommend that SEMSs should be the first option because they have better patency, a lower occlusion rate, less need for reintervention, and fewer adverse events than plastic stents.

In conclusion, expandable metal stent placement is a very effective way of re-establishing luminal patency with negligible complications for an expert endoscopist.

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EDUCATION AND IMAGING

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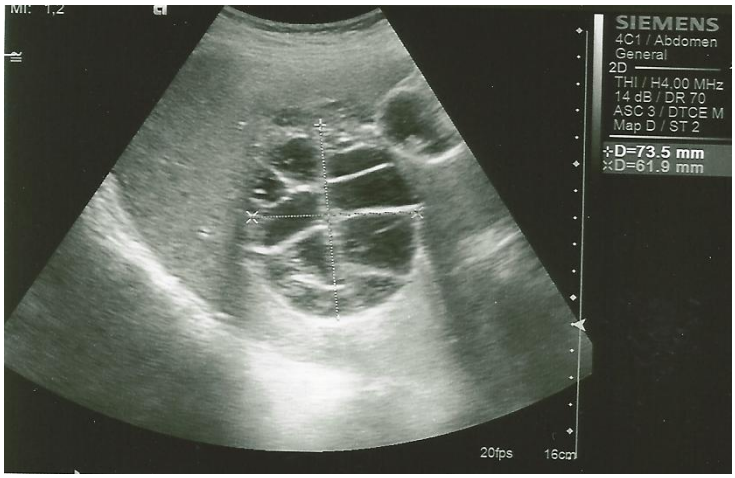
Hepatic hydatid cysts

Cătălina Diaconu[1], Mădălina Ilie[2,3], Alexandru L. Chiotoroiu[3], Laura Voicu[1], Daniel O. Costache[1], Raluca S. Costache[1,2]

43 years old man presented with recently installed abdominal pain localized in the hypocondrium and epigastrium associated with jaundice and pruritus.



The patient's history included operated bilateral inguinal hernia. Physical examination yielded jaundice, normal aspect of postoperative scars in the inguinal fossae (left and right), pain in the hypocondrium and epigastrium, no guarding, rebound or bruits were found.

Laboratory findings reveal leukocytosis with eosinophilia, hepatic cytolisis (alanine aminotransferase = 219 U/L), hyperbilirubinemia with a higher conjugated bilirubin (total bilirubin=6.01mg/dL, conjugated bilirubin=4.7mg/dL).

Ultrasonography reveals a round transonic image of 7/6cm localized in the IV and VIII segment, with septa that suggests liver hydatid cyst, hyperechoic image of 9mm (hydatid cyst) and a 9mm gallbladder polyp. Computed tomography shows hepatomegaly with a cystic multiseptate image in the IVth segment of 8.5 cm.

Under treatment against pain, proton pump inhibitor, hydratation and regime during hospitalization the symptoms disappear. However the hepatic cytolysis worsens with the progressive growth of alanine aminotransferase to values of 916 U/L, hence antihelminthic treatment is delayed.

Enchinococcal infection caused by the larval form of *Echinococcus granulosus* remains an important health issue worldwide. Hepatic hydatid cyst is the most frequently encountered form (50-93% of the cases) and left untreated these grow and lead to: developing fistulae in adjacent organs, rupture in the peritoneal cavity, produce daughter cysts or dye (rarely)[1]. Clinical manifestations appear after the cyst is larger than 10cm in diameter and only a third of the patients experience symptoms.

Even though biological finding are nonspecific, elevated bilirubin and alkaline phosphatase may appear. Leukocytosis may appear due to infection of the cyst and eosinophilia is present only in a quarter

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of patients [2].

Despite the fact that ultrasonography remains the main pillar in the diagnosis of the disease, computed tomography and serology help improve the accuracy of diagnosing liver hydatidosis. WHO Ultrasound classification of echinococcal cysts helps establish the treatment: 1 (unilocular, anechoic cyst with double line sign), 2 (multiseptate honey comb cyst), 3a (cyst with detached membranes), 3b (cyst with daughter cysts in solid matrix), 4 (heterogenous contents and no daughter cysts) and 5 (solid plus calcified wall). CE4 and 5 are inactive.

On the other hand Gharbi classification also divides in 5 types: type I cysts consist of pure fluid; type II has a fluid collection with a split wall; type III cysts contain daughter cysts (with or without degenerated solid material); type IV has a heterogeneous echo pattern; and type V has a calcified wall. Therefore our case presents a hepatic hydatid cyst stage CE2 after WHO classification and type III after Gharbi classification.

Uncomplicated and small lesions (under 5cm) CE1,2 and 3 can be treated with oral albendazole (10-15mg/kg/day) and close monitoring. However, large CE1 and CE3 cysts need treatment with both albendazole and PAIR (percutaneous aspiration, introduction of scolicide and reaspiration), performed after initiation of albendazole.

Primary surgical treatment has been replaced with less invasive methods since the relapse rate can reach 20%. In patients with complicated cysts, surgery is the treatment of choice. CE4 and 5 only need to be monitored [1][3].

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CLINICAL PRACTICE

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More than simple hepatic cysts

Daniela Tabacelia[1], Mădălina Ilie[1], Alina Constantin[1], Anca Macovei Oprescu[2], Gabriel Constantinescu[1]

Abstract: *Caroli diseaseis a rare congenital disorder that classically causes saccular dilatation of the bile ducts. The complications of Caroli include choledochal cysts with recurrent cholangitis, abscess formation, septicaemia, intrahepatic lithiasis and amyloidosis.We report a rare case of a young female with Caroli disease pointing out the intrahepatic lithiasis as a rare complication of the disease.*

Learning points

- *Caroli disease is an uncommon condition that should be considered in the differential diagnosis of hepatic essential cysts.*
- *Clinically, it is characterized of recurrent episodes of fever and pain.*

The correct and early diagnostic is important because of the different complications and treatment unlike the essential hepatic cysts.

Keywords: *Caroli disease, intrahepatic lithiasis, endoscopic retrograde cholangiopancreatography*.

CASE REPORT

A 28 years old female presented to the emergency department with abdominal pain and fever after an ERCP procedure performed 2 weeks ago. From her disease history we retain an acute pancreatitis that was classified Balthazar B, one year ago, assumed to be caused by biliary main duct lithiasis; at that moment her initial biology showed ASAT 156U/L, ALAT 126U/L, lipase 2,398U/L, bilirubin 32 mmol/l and white cells 14,590/mmc; there was no sign of complication (acute cholangitis) that would have required a surgical treatment in emergency. Her family history was inconclusive for any specific digestive condition.

In our hospital, on physical examination her body temperature was reaching 38^0C, the heart rate 110 bpm, and blood pressure 110/70mmHg; on palpation she presented mild tenderness on epigastric and right quadrant; the usual blood tests showed white cell count with neutrophils raised, hepatic cytolysis and cholestasis until 5 times normal value. Next step was performing an abdominal ultrasound which revealed hepatic cysts (dilation of intrahepatic bile ducts) with liver hyperechoic images with acoustic shadow suggestive of intrahepatic lithiasis (Figures 1 A and B). A CT scan and a MRI were performed and revealed a normal pancreas without Wirsung dilatation, the biliary main duct with a 7 mm diameter without stones inside, and normal gall bladder without signs of cholecystitis but with beaded intrahepatic biliary duct dilatation until 18

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mm alternated with normal caliber ducts with numerous images of stones inside with a 12 mm maxim diameter. The dilated biliary canaliculi wall presented signs of cholangitis. All clinical and paraclinical data were typical for a Caroli disease with intrahepatic lithiasis and secondary cholangitis. The patient received treatment with urso-deoxy cholic acid (UDCA), antibiotics, anti-inflammatory drugs and pain medication followed by the resolution of the inflammatory episode.

Figure 1A

Figure 1B: Abdominal ultrasound revealing hepatic cysts with intrahepatic lithiasis

DISCUSSION

The hallmark of Caroli disease is intrahepatic duct dilatation [1]. Patients with Caroli disease are usually presenting to the hospital, when they develop complications as the result of biliary stasis, which leads to stone formation and infection. The stones are brown pigmented stones, composed of inspissated bile[1].

Caroli disease has two forms, one associated with congenital hepatic fibrosis and a simpler form occurring alone. The former, called Caroli's syndrome is associated with portal hypertension, and it's complications including splenomegaly, hematemesis and melena. Caroli disease is also associated with liver failure and polycystic kidney disease. The cause appears to be genetic; the simple form is an autosomal dominant trait while the complex form is an autosomal recessive trait.[2] Females are more prone to Caroli disease than males.[2] Family history may include kidney and liver disease due to the link between Caroli Disease and ARPKD (Autosomal recessive polycystic kidney disease). The symptoms include fever, intermittent abdominal pain, and hepatomegaly. Occasionally jaundice occurs.[3] Laboratory tests indicate cholestasis and hepatocytolysis associated with an inflammatory syndrome in the acute stages.

Caroli disease usually occurs in the presence of other diseases, such as autosomal recessive polycystic kidney disease, cholangitis, gallstones, biliary abscess, septicemia, liver cirrhosis, renal failure, and cholangiocarcinoma (7% affected).[2] People with Caroli disease are 100 times more at risk for cholangiocarcinoma than the general population.[3] Modern imaging techniques allow the diagnosis to be made more easily and without invasive imaging of the biliary tree.[4] Abdominal ultrasound can detect saccular or fusiform dilation of the bile ducts. Images taken by CT-scan or MRI will show enlarged intrahepatic (in the liver) bile ducts due to ectasia; cholangiography is the best approach to show the enlarged bile ducts as a result of Caroli disease.

The treatment of Caroli's disease depends on the clinical features and the location of the biliary abnormalities. Cholangitis is treated with appropriate antibiotics. In case of intrahepatic cholelithiasis litholytic therapy with urso-deoxy cholic acid (UDCA) is indicated[5]. When the ductal abnormalities are localized to one lobe, lobectomy relieves symptoms and appears to remove the risk of malignancy. In case of diffuse involvements of both lobes of liver, treatment options include conservative management, endoscopic therapy (sphincterotomy for clearance of intra-hepatic stone), internal biliary bypass procedures and in carefully selected cases liver transplantation[5].

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Nutritional approach in late gastric stenosis after gastric sleeve

Adina Mazilu[1]

INTRODUCTION

Laparoscopic gastric sleeve(LGS) is a very frequent used procedure nowadays in Romania, with more than 100,000 reported patients operated until now, the most part of patients being operated in private settings. It is a simple and efficient procedure, less expensive than gastric by-pass, with fewer complications, but can reduce obesity complications almost as well as gastric by-pass. Indications for this type of surgery are:

- Body Mass Index is greater than 40 kg/m^2 or between 35-40 kg/m^2 and patient has significant pathology that may benefit from weight loss-like diabetes, hypertension
- Severe co morbidities (cardiac, pulmonary, liver disease)
- Advanced age at time of operation
- Inflammatory bowel disease (Crohn's disease)
- Patient uses chronic medications (anti-inflammatory or immunosupressive)
- Need for continued surveillance of the stomach (that couldn't be evaluated after a gastric bypass)
- Severely enlarged liver found during the operation
- Severe adhesions or scarring to the bowel found during the operation
- Any combination of the above that significantly increases the patient's anesthetic or surgical risk

LGS may be used also combined with gastric by-pass done at 12-18 months after LGS, when anesthesia is less risky and liver has reduced diameters.

Acute complications are represented by hemorrhage reported in 1-6% of cases and gastric leaks in up to 5% in the immediate period after operation [1]. Gastric stenosis has a 0 to 4 % rate of appearance for this type of operation[4]. Most cases can be solved by endoscopic dilation with balloons;however some cases need to be converted to gastric by-pass.

In an article from 2014,in a study done on 565 patients, the incidence of complications was relatively low- the authors[2] reported in 7.79% of patients infarcts of the posterior pole of the spleen, 1.42% gastric fistulas in the His angle region, with 5 deaths among these patients – 3 due to septic complications in the course of fistula, 1 due to encephalopathy and 1 as a result of myocardial infarction.

Chronic complications include strictures, malnutrition and GERD. Chronic strictures usually require further intervention. Endoscopic dilatation is an useful tool used for short segment stenosis. Successive treatments in 4 to 6weeks interval are adequate to treat stricture and ameliorate patient symptoms. In contrast, long segment stenosis and failure of endoscopic management demands a surgical intervention – laparoscopic or open seromyotomy or conversion to Roux-en-Y gastric bypass. Parikh and colleagues reported an incidence of 3.5% of symptomatic stenosis following LGS in their series of

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230 patients; 2 patients required conversion to a Roux-en-Y gastric bypass owing to failure of endoscopic management.

In a recent study by Gehrer and colleagues[3], the prevalence of vitamin B12, vitamin D, folate, iron and zinc deficiency were reported to be 3%, 23%, 3%, 3% and 14%, respectively, after LGS In general, these investigators found micronutrient deficiencies to be less prevalent after LGS than Roux-en-Y gastric bypass; however, folate deficiency was slightly more common after LSG than Roux-en-Y gastric bypass (22% vs. 12%).

CLINICAL CASE

Our patient, a 25 years girl operated – LSG-1 year before, presented with severe malnutrition and dehydration, associating also hypokaliemia. She has been vomiting at least 4 times a day during the past 6 months and she lost almost 100 kg in 1 year (from 130 Kg, 167 cm to 37 Kg at admittance). She has done upper endoscopy 10 days ago and dilation of gastric stricture was not possible. She was told she needed surgical intervention after gaining 10 kg.

She was very pale, with brittle hair and dry skin, with Bichat's sign positive, hypotensive – 70/50 mmHg, tachycardic and refused admittance even if she was explained that she had a very high risk of death. She agreed to come and stay in hospital after solving the problems for her job. As she associated hypokaliemia we tried to correct it with 20 mEq of kalium in saline, but patient reported intense pain on peripheral i.v. infusion, so we used first 1,000mL of saline, and then Ringer and Kalium progressively.

Family reported repeated episodes of binge eating at home with ingestion of Coke and high amounts of food, after that unprovoked vomiting. Discussion with patient revealed also depression, this kind of food pattern was the patient's cry for help due to unresolved adolescence trauma, even if she had family and friends support now. We tried also to relieve the pressure from job.

Next day iv saline 500 ml, Ringer 1000 ml, Kabiven were introduced, with almost complete correction of hypokaliemia.As patient had urinary tract infection we added Gentamycin 320 mg/day and Ciprofloxacin 400 mg/day, for seven days, with good evolution.

Third day we introduced Fresubin – enteral formula – 500 ml/day, divided in 7-8 meals, no more than 100 ml/meal, associated with Osetron and Controloc on i.v. line. Patient stopped vomiting the third day and the next day we introduced small amounts of baby food – milk and egg, fruits puree, small amounts of soup with chopped meat.

By seventh day patient gained enough weight so we tried to reduce the amount of Fresubin and Kabiven and leave her on oral intake of mashed food, but this induced reappearance of vomiting. X-ray revealed no passage of barium due to complete gastric stenosis, so i.v. nutrition was resumed.

Laboratory 8 a.m. serum cortisol was more than 10 mcg/dl, so we excluded Addison disease.Patient had low TSH and low T3 levels – confirming sick euthyroid syndrome and hypotalamic amenorhhea with low Estradiol levels – 17 pg/ml.

In the last 3 days we introduced small amounts of rapid insulin – 10 U/day to improve anabolism.Patient reached 47 kg, with mild edema in the legs and was discharged in the 12^{th} day of admittance.She still has mild hypoproteinemimia – albumin 3.2 mg/dl, total proteins 5,6 g/dl and mild hypocalcemia – 8.8 mg/dl.She was discharged with proton pump blocker and prokinetic treatment, associated with buvable ferrum sulfate.

She repeated the endoscopy and was converted to gastric by-pass after 3 days without more complications.

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CLINICAL PRACTICE

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Fever and abdominal tumoral masses

Augustin C. Dima[1], Teodor Artenie[1], Daniel Florea[1], Florina Bold[1], Paul I. Oprea[1]

Abstract: *49 year-old man presented to our clinic for pain in the right hypochondrium, diarrhea, and fever. The clinical examination highlights a tumoral formation in the right side of the abdomen, with firm consistency, poorly defined margins, and present mobility in the deep structures. On biological exams, leukocytosis with neutrophilia, inflammatory syndrome, and hypoalbuminaemia were identified. The first computed tomography exam described parietal thickening of the ascending colon, with infiltrative aspect, and multiple local adenopathies, lomboaortic and interaortocave. Moreover, four nodular liver tumors, with hypodense image in native examination, were identified. The lab tests for infectious diseases were all inconclusives: three hemocultures, three stool samples, and three coproparasitological exams were all negatives. Interdisciplinary examinations, internal medicine and infectious diseases, sustained the diagnosis of colonic neoplasm with peritumoral abscess and liver pseudo-tumoral masses. The colonoscopy did not revealed any bowel lesions relevant for neoplasia. This result as well as the bio-clinical context imposed abstention from surgical intervention.*
Wide spectrum antibiotics and symptomatic treatment were initiated. But, ten days after hospitalization, the second computed tomography exam showed reduction of the ascending colon wall thickness associated with significant increases of the liver tumors is so revealed. The investigations for other possible etiologies were so continued.

Keywords: *colon tumor, intestinal amoebiasis, liver abscesses.*

INTRODUCTION

In current clinical approach of abdominal pathology one must not forgot the rare disorders whose clinical picture and imaging could mime neoplasia, pathology so frequent today.

The current diagnosis of colon tumors is made especially using imaging diagnostic methods, whose accuracy is high, facilitating anaccurate stage diagnosis, very important in determining therapeutic tactics. But it must not be forgotten also the importance of classical clinical features that could bring essential elements for the certainty diagnosis.

CASE REPORT

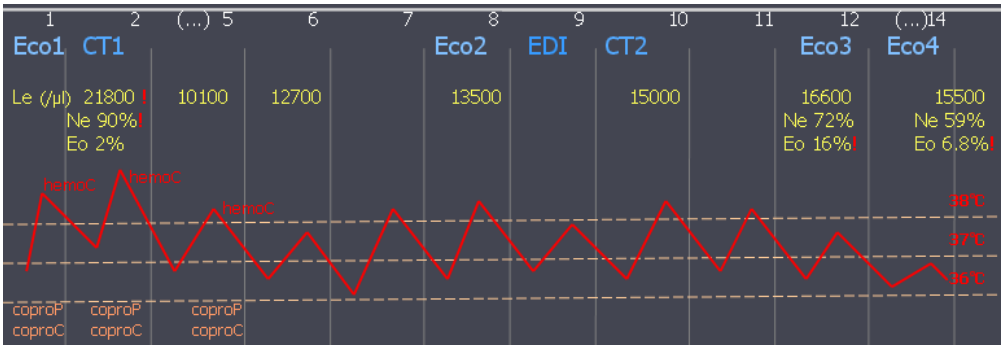
We present the case of a 50-years old patient, smoker, diabetic, hypertensive, who presented for right upper hypochondrium pain, diarrhea, nausea, febrile syndrome, with the onset of symptoms about 48 hours prior to presentation.

Clinical examination revealed hypochondrium and right flank sensitive abdomen, tumor mass in the right flank, with firm consistency, imprecisely defined, relatively mobile on the deep plans, without signs of peritoneal irritation, fever (38.7˚C), shivering.

[1] Carol Davila Central Emergency Military Hospital, Bucharest

Biologically, neutrophilic leukocytosis, inflammatory syndrome, and hypoalbuminemia were noted. Plain chest and abdominal radiography were without pathological changes (Figure 1). Abdominal ultrasound identified hypoechogenic liver formations.

Figure 1: Biological evolution during diagnostic and after specific treatment



CT exam identifies hepatomegaly and four nodular liver formations: hypodense on native examination, irregularly shaped, with uneven structure, apparently separated from their dense walls (Figures2a, 3a, 4a). In addition, a parietal tumoral formation belonging to ascending colon, located toward liver angle, showing asymmetrical narrowing partially iodophile (with a maximum thickness of 2.1cm), infiltrating the cecum – ascendant digestive wall and the adjacent fatty abdominal tissue that adheres to the liver capsule. Perilesional, lumbar aortic and interaortocaval adenopathies, (with maximum dimensions of 1.3cm) (Figures5a, 6a, 7a) were also described.

Figure 2(a, b): Computer tomography exam: first two liver masses evolution under treatment

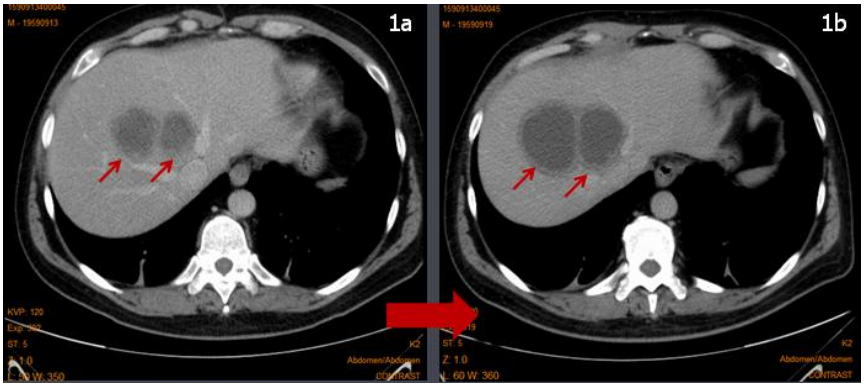


Figure 3(a, b): Computer tomography exam: liver masses evolution under treatment

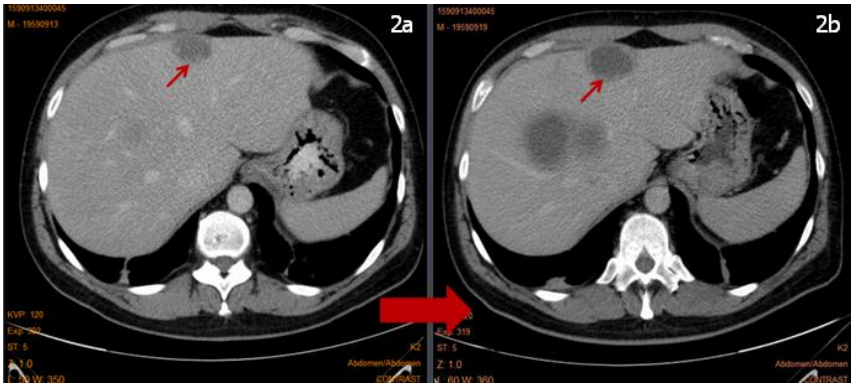


Figure 4(a, b): Computer tomography exam: liver masses evolution under treatment of the third tumoral mass

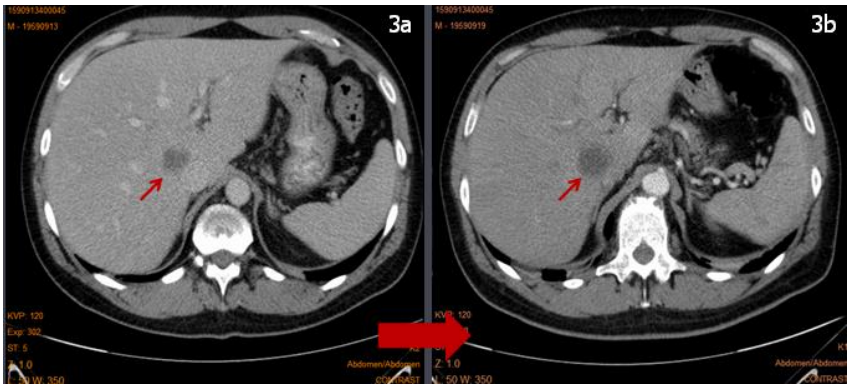


Figure 5(a, b): Computer tomography exam: colon tumor evolution under treatment

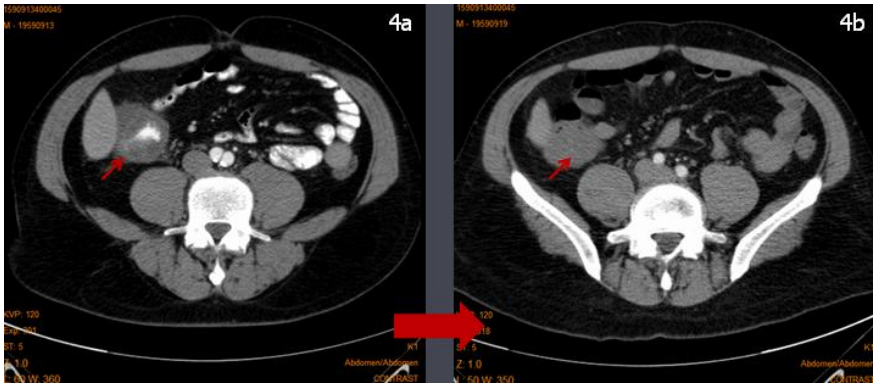


Figure 6(a, b): Computer tomography exam: colon tumor and local adenopathies evolution under treatment

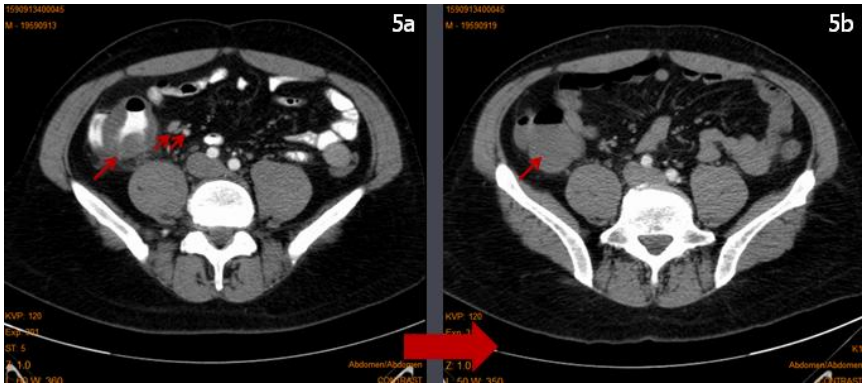
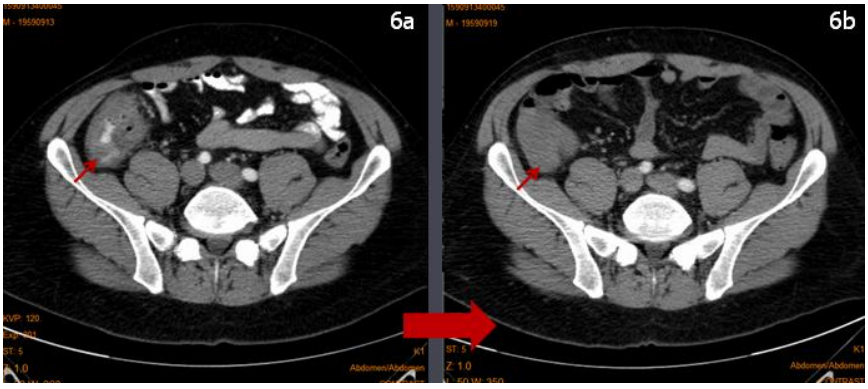


Figure 7(a, b): Computer tomography exam: colon tumor evolution



The paraclinical picture was completed with three negative blood cultures, three negative copro-parasitological exams, three negative coprocultures and tumor markers (carcinoembryonic antigen, CA 19-9, alpha-fetal protein) negative (Figure 1).

Internal medicine and infectious diseases examinations declines the eventuality of infectious or parasitic primary etiology of colony formation and supports the diagnosis of colon cancer with peritumoral abscess and septic liver determinations.

At this point, the imaging seems to support thediagnosis of ascending colon tumoral mass associated with secondary liver metastases or with local associated infection and liver abscesses.

Clinical arguments, however, given the relatively sudden symptoms onset, are pleading for diverticulitis or segmental colitis of the ascending colon with septic determinations in liver. Therefore, we consider it appropriate to postpone surgery and to make further investigations.

It was initiated treatment with broad antibiotic spectrum (imipenem – cilastatin 500 mg/ 500 mg, 4 times daily, linezolid 600 mg 2 times daily, both for 10 days and Moxifloxacin 400 mg daily for 5 days) associated with symptomatic treatment.

Lower digestive endoscopy describes in the rectum, at 4-5 cm from the anus, a 1 mm polyp covered by normal mucosa, at 10 cm from the anus a 2 mm sessile polyp, covered with congestive mucosal, biopsy was performed. In the sigmoid colon, to about 25 cm, a 10 mm semi pedunculated polyp, cylindrical, covered by the congestive mucosa, supple for biopsy. At the descending colon polyp plan, ovoid of 7-8 mm, covered with inflamed mucosa, supple for biopsy. Transverse and ascending colon without changes.

Caecum, opening of appendix and the ileocecal valve without modifications.

The morphopathologic diagnosis of colon polyps was of tubular adenoma. So, the endoscopic examination does not argue for tumor etiology.

The evolution under treatment was favorable: reducing the number of daily diarrheal stool (from 10 to 12 per day to 2-3 per day) and also fever – under vesperal fever and the overall condition has improved. Biologically, continuing with leukocytosis with neutrophilic, but at lower values and the increasing of cholestasis defining liver enzymes (Figure 1).

We repeat, on day 10 – from the admission – the CT examination and we see a significant increase in volume of liver formations, the largest with a diameter of about 7cm, with better separation than previously, clear evidence of the relatively thick walls and of clear fluid content (Figures2b, 3b, 4b). Also, the marked reduction in the ascending colon thickness and reduction in the size of abdominal adenopathy (Figures5b, 6b, 7b) were noted.

Diagnosis of infectious disease is gaining before a possible neoplastic etiology, se we ask forparasitology and infectious diseases check-up and serological determinations.

Positive diagnosis is supported by the presence of Ig G type anti-Entamoeba histolytica antibody (negative Entamoeba histolytica antigen, negative Echinococcus antibodies, negative Giardia duodenalis CoproAg and Cryprosporidium CoproAg) for which specific treatment is initiated.

Thus, the positive diagnosis was: liver amoeba disseminated abscesses in both lobes, in remission and intestinal amoebiasis affecting the ascending colon, submitted.

The patient's evolution after the initiation of the etiological treatment was favorable with improvement of the general condition, normalization of blood counts at two weeks of antiparasitic ambulatory treatment and marked reduction of liverabscesses dimension with their disappearance in a year.

DISCUSSIONS

Entamoeba histolytica is a protozoan that is an important health problem in tropical and subtropical countries [1]. Infection is fecal-oral, 90% of those affected remain asymptomatic, being determined by ingestion of food contaminated with parasite cysts [2]. It affects particularly the gastrointestinal tract

(more frequently the check and ascending colon) and liver [3].

The difficulty of diagnosis in this case was given by the initial CT imaging appearance of ascending colon tumor, accompanied by the negative coprocultures and coproparasitological exams.

Imaging appearance of colonic amoebiasis mimicking neoplastic pathology has been described in the literature, but this presentation as a colon tumor formation remains a rare occurrence[4][5]. Most frequently, the colonic amebiasis diagnosis is done by highlighting the parasite in the stool, the examination of three successive stools leading to a positive diagnosis in 70% of patients [6].

The correct diagnosis in the presented case was obtained only after achieving immunological determinations, serology for Entamoeba histolytica is positive in up to 90% of patients with amoebic colitis [7].

Also, another feature that hindered the diagnosis was the initial presence of neutrophilic leukocytosis, with no eosinophilia (Figure 1), which could be explained by possible plurimicrobial superinfection of the parasite gateway from ascending colon.

After starting antiparasitic treatment an increase in eosinophils in serum is observed, most likely secondary to parasitic destruction and thus the emergence of new antigenic elements.

Important in the proper management of this patient was refraining from any surgery and introduction of specific therapy (Metronidazol) despite the pressure brought by imaging and biological data. Surgery in Entamoeba histolytica infection is a must in cases of acute colitis with necrosis and perforation when it may be necessary even total colectomy [8][9] and could also be followed by many complications.

Another problem of therapeutic tactic was the discussion on the need for drainage of liver abscesses, their sizes being significant. The ultrasound tracking has shown that the effective antiparasitic treatment was enough, observing the gradual decrease of their sizes, with their disappearance one year after the initiation of antiparasitic treatment.

In general, the literature does not support the need of drainage for uncomplicated liver amoebian abscesses [10]. Could be drained big liver abscesses (>300 cm^3) or when there are questions about the etiology of liver abscess, like in the case of pyogenic liver abscess [11][12] when cultures from drainage samples could be informative on the etiology and further treatment.

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