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EDITORIAL

Magnetic resonance diffusion tensor imaging and fiber-tracking diffusion tensor tractography in the management of spinal astrocytomas

Alessandro Landi, Valeria Palmarini, Alessandro D'Elia, Nicola Marotta, Maurizio Salvati, Antonio Santoro, Roberto Delfini

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Abstract

Some specially imaging of magnetic resonance imaging, the diffusion-weighted imaging (DWI), the diffusion tensor imaging and fractional anisotropy (FA), are useful to described, detect, and map the extent of spinal cord lesions. FA measurements may are used to predicting the outcome of patients who have spinal cord lesions. Fiber tracking enable to visualizing the integrity of white matter tracts surrounding some lesions, and this information could be used to formulating a differential diagnosis and planning biopsies or resection. In this article, we will describe the current uses for DWI and fiber tracking and speculate on others in which we believe these techniques will be useful in the future.

Key words: Fiber tracking diffusion tensor imaging; Surgery; Magnetic resonance diffusion tensor imaging; Intramedullary astrocytomas; Spinal cord tumors; Radiology

Core tip: Intramedullary high grade astocytomas are rare tumors of spinal cord. Current surgical treatment involves loss of neurological function. The possibility to visualize directly the white matter tracts in the spine, with the applications of specific sequences of magnetic resonance imaging (diffusion-weighted imaging, diffusion tensor imaging and fractional anisotropy) allows neurosurgeons to better guide the surgical approach and resection, with the goal of neurological function preservation.

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INTRODUCTION

Some specially imaging of magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and fractional anisotropy (FA), are useful to described, detect, and map the extent of spinal cord lesions[1-3]. FA measurements may are used to predicting the outcome of patients who have spinal cord lesions. Fiber tracking enable to visualizing the integrity of white matter tracts surrounding some lesions, and this information could be used to formulating a differential diagnosis and planning biopsies or resection. In this article, we describe the current use for DWI and fiber tracking and speculate on others in which we believe these techniques will be useful in the future.

Intrinsic tumors of the spinal cord are more or less 10% of all central nervous system tumors[4,5], are rare neoplasms, and astrocytomas are the most frequent type[6,7]. MRI techniques provide only anatomical information while DTI, a form of diffusion-weighted MRI, gave us information about assesses of physiological water directionality and motion, providing images of white matter tracts of the central nervous system[8-10]. The possibility to visualize white matter tracts in the spine enables neurosurgeons to better guide their surgical approach and resection. Intramedullary high grade astrocytoma has a minor incidence compared to all other tumor and its outcome is burdened with important consequences for the patients[11]. Certainly many of the neurological consequences depend on the early diagnosis; for this reason operation is recommended as soon as possible. Actually DTI is used for the design of surgical excision of brain tumors, but the capability of the DTI to display faithfully secondary alterations to the white matter tracts caused by the lesion current studies, allow us to hypothesize that (whit literature supporting)[12-14] use of DTI is also possible for spinal surgery to prepare preoperative planning for tumor resection, preoperative diagnosis, and postoperative outcomes and this is one of the key point of the future therapy of intrinsic tumors of the spinal cord[15-17], however further studies are needed about this technique to understand and more studies are necessary for this technology to establish standardized protocols.

TECHNIQUE DESCRIPTION AND USE OF DTI-DWI-FT

In organized tissues, water diffusion is anisotropic and the quantitative description of this anisotropy is possible with DTI, that is a modification of diffusion imaging which can display vectors corresponding to the direction of water molecular movement, which has become a useful tool in the clinic trial of spinal pathologies, including tumors[18-20]. DTI sequences with computation of FA are more sensitive in determining the presence of intrinsic abnormalities in spinal cord compression due to the presence, for example, of a tumor[21,22]. Can be used in different ways both the study of the directional anisotropy, using DTI, or the removal of this anisotropy, that can be measured by tensor trace, all this information are used to compile mapping of the fibers through an algorithms[23,24]. Anyhow these techniques are affected by artifacts that depend on the movement, the noise and this make it difficult to diagnose with exactness the extension and moreover the quality of the DWI, in term of resolution, is poor to image structures as small the spinal cord and its internal features, DTI have a better characterization of white fibers and their possible displacement by the tumor and the reconstruction of 3D images of white matter tracts use new tracking algorithms. So as to employ the indicated encouraging technology, it is necessary to understand the basis of the anisotropy contrast in DTI and the restrictions imposed by using a macroscopic technique to visualize restrictions. In our opinion, also based on the review of the recent literature in the field, DTI and fiber tracking (FT) are used to describe tumors and to detect their limbs. Is also possible to envisage a histological diagnosis if you know that FA values are similar for astrocytomas, ependymomas and metastases but are different for hemangioblastomas[25-27]; in particular the lowest FA values are seen in metastases, and the highest are seen in hemangioblastomas. Unfortunately the algorithm alone is unable to distinguish between extracellular edema and destroyed white matter tracts by tumor cell involvement. Based on these observations using FA maps, the edema that surrounding lesion may be separated from the tumor due to lower values in the former. FT may show fibers that are destroyed or displaced by the tumor. This could be important to estimate highly infiltrative tumors and to identify their margins before surgery resection[2,28,29].

FT showed the main posterior white matter tracts, such as posterior lemniscal tracts and posterolateral corticospinal tracts. In patients with spinal neoplasms, 3D FT reconstructions of the spinal cord involvement, showed the tumor limbs matching those seen on the MRI T2-weighted imaging if are solid tumors with dislocated or wrecked spinal cord fibers tumors unlike metastases that are localized and tend not to infiltrate[21,30,31]. Regrettably FT does not consider these margins in patients with cystic tumors. FT algorithm is based on the principal diffusion direction method, because in the spinal cord the white matter fibers have a craniocaudal orientation and are anisotropic. This algorithm is used to reconstruct fiber tracts by using FA values; where there is no interruption (linear diffusion), FA values are fixed at certain value. In this case the FT algorithm is unable to link voxels inside the same tract

due to the increased isotropic diffusivity of extracellular water; This aspect is contrary to solid-state lesions, in which the FA values are different (usually elevated). The decrease of the FA thresholding value identifies tracts among edema or tumor cells and it seems to be unrelated to the multidirectionality of the tracts[32,33]. The increase of the FA thresholding value reduced the regular anatomic tracts that were seen on normal white matter anatomy. Totally of these information reccomend that FT could be applied to visualize the bent white matter tracts in the solid state astrocytomas, but absence of sensitivity in cases of presence of cystic and/or vasogenic edema. Further studies are mandatory to establish these conclusions.

USE IN SPINAL NEURONAVIGATION

The possibility to combination of anatomical data, contained in MRI T_1-weighted images, and the trajecztories of the pyramidal tract, allowed the demonstration of its position related to the lesion, both during operation planning and surgery[13]. Based on the reconstructed pyramidal tract, surgeon may compares to various alternatives in surgical approaches, permitting to perform a surgical plan reducing pyramidal tract damages. In fact neuronavigation should be use in two different ways: (1) to understand the extention of an intrinsic spinal lesions that must be remove; and (2) to help in estimating tumor removal limits during surgery.

In the future, to permit the routinary use of FT system in neurosurgical and neuro-radiological procedure, the workflow could be change. The DTI sequence could be acquired together with all already existing MRI protocols. For this reasons is mandatory that a neuro-radiologist or a computer scientist always perform FT, and the images combined by anatomical data and fiber tract trajectories, were sent back to the picture achieving and communication systems (PACS) central archive or directly to neurosurgical planning and navigation systems. Also is essential that the MR imaging protocol is executed at least few day before the surgical procedure in order to have a more recent radiological status of the lesion; the average time necessary to process the images for neuro-planning/neuro-navigation is not a inaccessible costituent and the FT system could be, beyond all expectation, included in routinary clinical use without any delays in the clinical-therapeutic timing.

CONCLUSION

DTI-based fiber tracking can certainly detects: (1) white matter fibers tracts; (2) presence of anatomo-pathological alterations; and (3) deviations and involvement of white matter tracts by spinal tumors. Moreover it gives to a minimally invasive neurosurgery. DTI sequences that can visualize the white matter tracks *in vivo* and under normal clinical conditions, are useful for fiber tracking if the tracking algorithm is strong and can solve ambiguities[10]. Advancement of near-tumoral anisotropy contrast acquisition is another significant issue to permit a increasingly faithful identification of white matter tracts in this crucial area and to discriminate among edematous reaction that might resolve successive surgical operation. Moreover it is useful to detect white matter tumor occupation or destruction, which has significant implications on neurosurgical strategies. Further investigation is still necessary and an available integrated FT software tool may be included into the PACS infrastructure of a clinic and medical staff trained to use it. Thus because the diffusion of this technology is still very limited and users could be also trained and motivated to export the resulting data to the neuronavigation and neurosurgical planning systems and use them in their routine[9,11].

The intramedullary high grade astocytomas have got an infiltrating nature, that make a total surgical removed impossible without an important loss of neurological function. The application of DTI-based fiber tracking, for diagnosis and neuronavigation, should be used in the clinical routine for the management of intramedullary high grade astrocytomas. Thus because in this way the surgical intervention could be performed to obtain a more safer hystological diagnosis and tumor resection, without worsening of neurological function.

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REVIEW

Treatment of *Helicobacter pylori* infection: Current and future insights

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Abstract

Helicobacter pylori (*H. pylori*) is an important major cause of peptic ulcer disease and gastric malignancies such as mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma worldwide. *H. pylori* treatment still remains a challenge, since many determinants for successful therapy are involved such as individual primary or secondary antibiotics resistance, mucosal drug concentration, patient compliance, side-effect profile and cost. While no new drug has been developed, current therapy still relies on different mixture of known antibiotics and anti-secretory agents. A standard triple therapy consisting of two antibiotics and a proton-pump inhibitor proposed as the first-line regimen. Bismuth-containing quadruple treatment, sequential treatment or a non-bismuth quadruple treatment (concomitant) are also an alternative therapy. Levofloxacin containing triple treatment are recommended as rescue treatment for infection of *H. pylori* after defeat of first-line therapy. The rapid acquisition of antibiotic resistance reduces the effectiveness of any regimens involving these remedies. Therefore, adding probiotic to the medications, developing anti-*H. pylori* photodynamic or phytomedicine therapy, and achieving a successful *H. pylori* vaccine may have the promising to present synergistic or additive consequence against *H. pylori*, because each of them exert different effects.

Key words: *Helicobacter pylori*; Therapeutic regimens; Probiotics; Photodynamic; Phytomedicine

Core tip: This article aimed to provides a review of

current therapeutic options and the efficacy of some recent regiments. Also, essential need to new therapeutic agents such as probiotics, phytomedicine, photodynamic therapy and protective vaccine are described.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is spiral in shape with a flagellum, gram-negative, micro aerophilic bacterium which colonizes in the human gastric mucosa, and the infection may last for decades. It is thought *H. pylori* infection to be the most common bacterial infection, and influence approximately 50%-75% of the population all over the world[1]. *H. pylori* is the main reason for the upper gastrointestinal diseases, including peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric cancer and gastric mucosal-associated lymphoid tissue lymphoma[2].

Along with upper gastrointestinal tract problems, *H. pylori* caused chronic and low-grade inflammation in the gastric mucosa that could lead to some metabolic disorders. *H. pylori* infection may be correlated with insulin resistance, increased total and low density lipoprotein cholesterol and decrease of high density lipoprotein in infected peoples[3]. Also, *H. pylori* has a critical role in the other extragastric diseases such as chronic urticaria[4].

Although a variety of treatment regimens have been proposed for the eradication of *H. pylori* in order to achieve more effective eradication resistance[5]. In recent years, regimens that utilize proton-pump inhibitors (PPIs) in combination with several antibiotics such as amoxicillin plus clarithromycin or metronidazole have been considered as the first-line treatment for *H. pylori* infection[6]. PPI-based triple therapy has been described to be losing its efficacy for *H. pylori*, with eradication cure rates as low as 50% to 70%, due to high rates of antibiotic resistance, high rates of antibiotic-associated side effects and low compliance[5]. Decreased eradication rate has led to the development and use of new first-line treatment[4,7]. In some countries, new first-line treatments are not accepted because of a lack of national validation studies and a lack of studies of clarithromycin resistance[7].

The Maastricht Ⅳ/Florence Consensus Report recommended the bismuth-containing quadruple therapy as an alternative for first-line empirical treatment in areas with the clarithromycin resistance over 15%-20%. If this regimen is not available sequential therapy or a non-bismuth quadruple therapy (the so-called "concomitant" treatment) is recommended[8]. After failure of a PPI-clarithromycin-containing treatment for *H. pylori* infection, either a bismuth-containing quadruple therapy or levofloxacin-based triple therapy is recommended as second-line treatment or rescue therapy[8,9].

In patients with penicillin allergy, for a first-line treatment, the bismuth containing quadruple therapy appear to be a better choice than a PPI-clarithromycin-metronidazole combination regimen[10]. As a rescue regimen, a levofloxacin containing regimen together with a clarithromycin and PPI represents a second-line treatment in the presence of penicillin allergy[8,10].

The Maastricht Ⅳ/Florence Consensus Report recommended the use of antimicrobial susceptibility testing (culture-guided therapy), after the failure of second-line treatment[8]. However, culture-guided third-line therapy has been advised, but if antimicrobial sensitivity data are not available, an empirical triple or quadruple therapy can be recommended as third-line regimens[11].

As such, during the last 30 years that the *H. pylori* was identified, there have been numerous therapeutic regimens suggested but a unique most effective and least harmful therapeutic regimen to cure *H. pylori* infection in all reported colonized individuals is still lacking[12].

THERAPEUTIC OPTIONS

Antimicrobial agents

Despite the number of studies, the optimal treatment for *H. pylori* infection has not been found and routine clinical treatments are usually triple or quadruple antibiotic therapies[13].

Prevalence of antibiotic resistance to various antimicrobials varies in different geographical regions, and is associated with the consumption of antibiotics in those areas[14]. The most commonly used antibiotics are imidazole (metronidazole or tinidazol), macrolide (clarithromycin or azithromycin), tetracycline, amoxicillin, rifabutin and furazolidon[9,15]. Bismuth, a heavy metal with anti-*H. pylori* activity is used in bismuth-based quadruple therapy and seems almost totally maintains high eradication rates, independent of antibiotic resistance[16,17].

A survey of antibiotic resistance to the four commonly used antibiotics against *H. pylori* in Vietnam from July 2012 to January 2014 showed that 42.4% were resistant to clarithromycin, 41.3% to levofloxacin, 76.1% to metronidazole, and 1.1% to amoxicillin[18].

A cross-sectional study with collection of gastric biopsies in the United States from 2009 through 2013 showed the prevalence of *H. pylori* resistance to levofloxacin was 31.3%, to metronidazole it was 20.3%, to clarithromycin it was 16.4%, and to tetracycline it was 0.8%. No isolate exhibited amoxicillin resistance, but clarithromycin resistance increased from 9.1% in 2009-2010 to 24.2% in 2011-2013[19].

Results on antibiotic resistance in two time, the first time period (2000) and the second period (2010)

in Greece revealed during the first time period 30% and 0% of patients were infected with clarithromycin or quinolone-resistant strains but, in the second time period (2010), the resistance rate to clarythromycin or quinolone increased to 42% and 5.3%, respectively[20].

A systematic review of literatures on *H. pylori* antibiotic resistance carried out in Iran within the time span of 1997 to 2013. The incidance of *H. pylori* resistance to various antibiotics, including metronidazole, clarithromycin, furazolidone, amoxicillin, tetracycline, ciprofloxacin, levofloxacin was 61.6%, 22.4%, 21.6%, 16.0%, 12.2%, 21.0% and 5.3%, respectively[21]. Compared the results from different countries showed prevalence of *H. pylori* resistance to various antibiotics is not the same and may be changed in time even in the same population.

Overwhelming evidence indicates that in order to determine an appropriate antibiotic in drug regimen against *H. pylori* infections, information on antibiotic susceptibility of the bacterium within different geographical areas of world is required.

Antisecretory agents-PPI

H. pylori treatment involves combination of antimicrobial and anti-secretory agents for 7 to 14 d. PPIs inhibit the parietal cell H^+/K^+ adenosine triphosphatase (ATPase), the enzyme of canalicular membrane of gastric parietal cells which is responsible for the last step in gastric acid secretion[22,23]. Inhibition of this enzyme is more efficient than H2-receptor antagonists in suppressing gastric acid secretion[24].

At low pH, gastric PPIs as acid-activated pro drug transform to a spiro intermediate of dihydrobenzimidazole, then undergoes aromatization to a sulfenic acid followed by dehydration to form a tetracyclic sulfonamide[25]. PPIs bind to different cysteines in the α subunit of the H^+/K^+ ATPase and inhibits the enzyme[26,27].

PPI with anti-secretory effect declines the acid production from stomach, which allows the tissues damaged by the infection to heal. PPI can also make acid-labile antibiotics more stable by elevation of the gastric pH, and also may alter luminal concentrations of antibiotics by transporting of antibiotics from plasma to gastric juices and elevating the success rate of eradication[28,29].

The differences in pharmacokinetics for example elimination half-life, bioavailability and metabolism of currently available PPIs may translate into differences in clinical outcomes[30]. All PPIs have good oral bioavailability and all PPIs except tenatoprazole undergo hepatic metabolism *via* the CYP isoforms CYP2C19 and CYP3A4, therefore with the elimination half-lives ranging from 1 to 1.5 h have the short elimination rate[31,22]. Genetic polymorphism in CYP2C19 plays an important role in the metabolism of individual PPIs to different amounts, thereby affecting therapeutic effectiveness[32].

Several studies have produced conflicting data on eradication rates of *H. pylori* among CYP2C19 genotypes taking PPI based regimens[33]. Some examples of the CYP2C19 pathway's relative impact on the PPI metabolism have been demonstrated. The lansoprazole-based or omeprazole-based triple therapies were affected by CYP2C19 genotype status, whereas esomeprazole-based or rabeprazole-based triple therapies were not[30,33,34]. The dosage and duration of treatment of PPIs for adults correspond to those that are able to suppress gastric acid secretion. Long-term omeprazole therapy in *H. pylori* positive patients induced changes in mucosal inflammation and glandular atrophy[35]. Hyper gastrinemia induced by PPI administration and corpus atrophic gastritis in patients with *H. pylori* infection might promote the development of gastric cancer[36].

THERAPEUTIC REGIMENS

Dual therapy

Dual treatments including a PPI with either clarithromycin or amoxicillin or metronidazole were popular during the previous decades. Dual therapy is now obsolete due to lack of efficacy of clarithromycin and metronidazole[37]. On the contrary, worldwide primary and secondary resistance to amoxicillin of *H. pylori* is generally low and rare respectively, although it is a usual medication in standard triple therapy and therefore it is suitable for use in the dual therapy of *H. pylori* infection[9].

Amoxicillin is effective at high (> 5.5) pH environments. According to some controversial data, PPI in standard doses wouldn't be able in rapid metabolizers to achieved enough pH inhibition for effective antibiotic activity in mucus of gastric, determining lower eradication rates after therapy with regimens containing standard dose of PPI[38,39].

Several studies assumed that there is direct and indirect demonstration which stated high-dose PPI, above the common standards, could ameliorate *H. pylori* treatment cure rates. The general idea in the back of high-dose PPI plus amoxicillin treatment is to overcoming resistance by altering the environment in which dormant *H. pylori* settled, thus inciting the bacteria to get in the replicative state and become sensitive to the antibiotics[40,41]. In spite of the advantage of the low resistance rate to amoxicillin and theoretical advantages of high-dose PPI, it has been shown that the efficacy of high dose dual treatment is vary in different reports[9].

A number of recently different regiments for the *H. pylori* treatments are described in Table 1.

An open-label, prospective, single-center pilot study evaluated the effectiveness of amoxicillin plus high-dose PPI dual therapy for *H. pylori* eradication. The intention-to-treat (ITT) cure was achieved in 72.2% and in per protocol (PP) 74.2%, respectively[42].

In an open-labelled and single-center prospective study, the overall success at eradication of *H. pylori* by two planned consecutive rescue therapies was tested.

Table 1 Numbers of different regimens for *Helicobacter pylori* infection treatments

Regimens	Patients (*n*)	Eradication rate	Conclusion	Ref.
High dose dual therapies				
Amoxicillin 750 mg and esomeprazole 40 mg every 8 h for 14 d	36	The ITT cure was achieved in 72.2% (95%CI: 56%-84%) and PP cure achieved in 74.2% (95%CI: 56%-87%)	However, the regimen was not sufficient to eradicate 90% *H. pylori* but, the result was positive in that dual therapy with the doses tested here was at least as successful as empiric triple therapy with a PPI, amoxicillin, and clarithromycin	[42]
Amoxicillin 1 g t.d.s. and rabeprazole 20 mg t.d.s. for 2 wk	149	Eradication success PP and ITT was 75.4% (95%CI: 68.3%-82.4%) and 71.8% (95%CI: 64.6%-79.0%), respectively.	Eradication success of 75% on PP analysis as a first rescue therapy including 2-wk high dose PPI-amoxicillin dual therapy was achieved. Following these patients by a second rescue therapy with PPI triple therapy were highly successful in achieving eradication rate (> 90%) in *H. pylori* treatment failures	[43]
Amoxicillin 1 g b.i.d. and omeprazole 20 mg q.i.d. for 14 d	74	Eradication rate of 81.1% in the dual therapy group *vs* 63.8% in the triple therapy group was achieved	Dual therapy is more effective, cost-effective and is less risky in terms of side effects compared to standard triple therapy in patients with dyspepsia	[44]
Amoxicillin 1 g and dexlansoprazole 120 mg each twice a day at approximately 12-h intervals for 14 d	13	PP and ITT treatment success were both 53.8% (95%CI: 25%-80%)	However compliance was 100% and reported side effects were mild and none interrupted therapy but dexlansoprazole, despite being administered at high dose, failed to achieve an intragastric milieu in treatment-native patients	[41]
Amoxicillin 750 mg and rabeprazole 20 mg, 4 times/d for 14 d	150	In the ITT analysis, *H. pylori* was eradicated in 95.3% of treatment-naïve patients (95%CI: 91.9-98.8%) and in 89.3% of treatment-experienced patients (95%CI: 80.9%-97.6%)	High-dose dual therapy is superior to standard regimens as empirical first-line or rescue therapy for *H. pylori* infection with similar safety profiles and tolerability	[45]
Triple therapies				
Amoxicillin 1 g and metronidazole 500 mg both three times a day plus esomeprazole 40 mg twice a day	136	Eradicationrates were 82.4% (95%CI: 74.7%-88.1%) by ITT analysis and 88.2% (95%CI: 81.2%-92.8) by PP analysis.	Cure rates of the combination of esomeprazole, amoxicillin and metronidazole are high and the treatment was well tolerated	[47]
Amoxicillin 1 g twice daily, levofloxacin, 500 mg, once daily and esomeprazole 20 mg twice daily for 7 d	345	ITT analysis eradication rates 78.1% (95%CI: 69.4%-85.3%), 78.3% (95%CI: 69.6%-85.4%), and 82.8% (95%CI: 74.6%-89.1%) for tripletherapy, standard sequential therapyand levofloxacin-containing sequential therapyre spectively and PP analysis eradication rates were 80.9% (95%CI: 72.3%-87.8%), 82.6% (95%CI: 74.1%-89.2%), and 86.5% (95%CI: 78.7%-92.2%), respectively, for the three therapies	Standard sequential therapy and 7-d levofloxacin triple therapy produced unacceptably therapeutic efficacy in China. Only levofloxacin-containing sequential therapy achieved borderline acceptable result	[48]
Amoxicillin 50 mg/kg per day, q.d.s., nifuratel 30 mg/kg per day, q.d.s. and bismuthsubcitrate 8 mg/kg per day, q.d.s. for 10 d	73	PP and ITT treatment success were both 86% (95%CI: 76.6%-93.2%)	The combination of nifuratel, bismuth subcitrate, and amoxicillin was a tolerable and effective regimen for *H. pylori* eradication	[49]
Amoxicillin 1 g, clarithromycin 500 mg and rabeprazole 20 mg all twice daily for 10 d in comparison with half dose	115	Eradication rates were 77.6% (95%CI: 66.9%-88.3%) in the standard dose *vs* half dose 77.2% (95%CI: 66.3%-88.1%) on ITT analysis. PP eradication rates were 78.9% (95%CI: 68.4%-85.9%) and 81.5% (95%CI: 71.1%-91.8%) respectively	A half-dose 10-d regimen is equally effective but cheaper and better tolerated than its standard-dose regimen	[50]
Amoxicillin 1 g, clarithromycin 500 mg plus either omeprazole 20 mg or esomeprazole 40 mg twice daily for 1 wk	200	For patients classified as homologous extensive metabolizers, the PP *H. pylori* eradication rate was significantly higher in the esomeprazole group than in the omeprazole group (93% *vs* 76%, $P < 0.05$)	Only for extensive metabolizers esomeprazole 40 mg twice daily for triple therapy improve the *H. pylori* eradication compared to omeprazole-based therapy	[51]
Amoxicillin 1 g, clarithromycin 500 mg and lansoprazole 30 mg, all taken twice a day for 14 d	1463	Comparing effectiveness of standard 14-d regimen of triple therapy with that of the four-drug regimens given concomitantly or sequentially therapy showed the eradication rate with standard therapy was 82.2%, and concomitant therapy (73.6%) and finally by sequential therapy (76.5%)	Neither four-drug regimen was significantly better than standard triple therapy in any of the seven sites of Latin America	[52]

Quadruple therapies				
Tetracycline 500 mg q.d.s., levofloxacin 500 mg o.d. esomeprazole 40 mg b.d and tripotassium dicitratobismuthate 120 mg q.d.s.	24	The eradication rates according to ITT and PP analysis were both 95.8% (95%CI: 87.8%-103.8%)	The 10-d quadruple therapy achieves a very high eradication rate for *H. pylori* infection after failure of sequential therapy	[56]
Amoxicillin 1 g b.d., esomeprazole 40 mg b.d., levofloxacin 500 mg o.d. and bismuth 240 mg b.d. for 14 d	200	PP and ITT eradication rates were 91.1% (95%CI: 87%-95%) and 90% (95%CI: 86%-94%)	14-d bismuth - and levofloxacin-containing quadruple therapy is effective second-line therapy in patients whose sequential or concomitant therapies have failed	[10]
lansoprazole (30 mg twice daily) and bismuth potassium citrate (220 mg twice daily), along with 500 mg tetracycline and 400 mg metronidazole 4 times daily (LBTM), 500 mg tetracycline and 100 mg furazolidone 3 times daily (LBTF), 1000 mg amoxicillin 3 times and 500 mg tetracycline 4 times daily (LBAT), or 1000 mg amoxicillin and 100 mg furazolidone 3 times daily (LBAF)	424	PP rates of eradication were greater than 90%for all regimens: 93.1% for LBTM (95%CI: 88.1%-98.0%), 96.1% for LBTF (95%CI: 92.4%-99.8%), 94.6% for LBAT (95%CI: 90.0%-99.2%), and 99.0% for LBAF (95%CI: 97.0%-100%). The ITT response rates were 87.9% for LBTM (95%CI: 81.7%-94.0%), 91.7% for LBTF (95%CI: 87.1%-96.3%), 83.8% for LBAT (95%CI: 76.8%-90.9%), and 95.2% for LBAF (95%CI: 91.1%-99.3%)	Four bismuth-containing quadruple therapies achieved greater than 90% eradication of *H. pylori* in patients who did not respond to previous treatment, including patients with metronidazole resistance	[57]
Amoxycillin 1000 mg, ranitidine 300 mg and bismuth subcitrate 240 mg b.d., with either furazolidone 200 mg b.d. (RABF), or metronidazole 500 mg b.d. (RABM) for 2 wk	106	ITT eradication rates were 75% and 55% (P = 0.03) and per protocol eradication rates were 82% and 56% (P = 0.006) in the RABF and RABM groups, respectively	Quadruple therapy containing furazolidone, instead of metronidazole, results in a significantly higher *H. pylori* eradication rate in Iranian duodenal ulcer patients	[60]
Tetracycline hydrochloride 375 mg, metronidazole 375 mg and bismuth subcitrate potassium 420 mg q.d.s., and omeprazole 20 mg b.d. for 10 d	64	Eradication rates ranged from 93.2% to 93.8% in the ITT population, and from 94.7% to 95.0% in the PP population	A quadruple regimen of bismuth, metronidazole and tetracycline plus omeprazole produces a high eradication rate in subjects previously failing *H. pylori* eradication regimens	[61]
Tetracycline 500 mg q.d.s., esomeprazole 40 mg b.d. and bismuth subcitrate 300 mg q.d.s. plus either levofloxacin 500 mg once daily or metronidazole 500 mg q.d.s. for 10 d	150	ITT analysis revealed that both groups showed similar eradication rates. levofloxacin group, 78.9% (95%CI: 69.7%-88.1%) and metronidazole group, 79.7% (95%CI: 70.5%-88.7%)	The 10-d bismuth quadruple therapies with high-dose metronidazole or levofloxacin were effective even in areas with high resistance. These two therapies were equally safe and tolerated	[62]
Amoxicillin 1 gram, clarithromycin 500 mg, metronidazole 500 mg esomeprazole 40 mg given twice a day for 10 d	232	ITT analysis demonstrated similar eradication rates for sequential 92.3%; (95%CI: 87.5%-97.1%) and concomitant therapy 93.0% (95%CI: 88.3%-97.7%). PP eradication results were similar for sequential 93.1%; (95%CI: 90.7%-95.5%) and concomitant therapy 93.0% (95%CI: 88.3%-97.7%)	Sequential or concomitant therapy with a PPI, amoxicillin, clarithromycin, and an imidazole agent are equally effective and safe for eradication of *H. pylori* infection. Concomitant therapy may be more suitable for patients with dual resistance to antibiotics.	[67]
Amoxicillin 1 g and omeprazole 40 mg twice daily for 14 d, clarithromycin 500 mg and nitroimidazole 500 mg twice daily (for the final 7 d) Concomitant therapy: Same 4 drugs taken concurrently, twice daily for 14 d	343	In PP analysis, rates of eradication for hybrid and concomitant therapies were 92% and 96.1%, respectively. In ITT analysis, rates were 90% and 91.7% respectively	Optimized non bismuth quadruple hybrid and concomitant therapies cured more than 90% of patients with *H. pylori* infections in areas of high clarithromycin and metronidazole resistance	[68]
Sequential therapy				
Amoxycillin 1 g b.d. plus omeprazole 20 mg b.d. for the first 5 d, followed by clarithromycin 500 mg b.d. tinidazole 500 mg b.d. and omeprazole 20 mg b.d., for the remaining 5 d	52	The eradication rate was 98% (95%CI: 94.3%-100%) with ITT analysis	The 5 plus 5 d therapy as sequential therapy achieved sufficient eradication rate	[70]
Amoxicillin plus omeprazole for 5 d, followed by omeprazole plus clarithromycin plus tinidazole for another 5 d	78	*H. pylori* eradication was achieved in 36 children receiving sequential treatment 97.3% (95%CI: 86.2%-99.5%) and 28 children receiving triple therapy 75.7% (95%CI: 59.8%-86.7%)	10-d sequential treatment achieves a higher eradication rate than standard triple therapy	[71]

Amoxicillin 1000 mg b.i.d. and pantoprazole 40 mg b.i.d. for the first 5 d, followed by pantoprazole 40 mg b.i.d., clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d. in the remaining 5 d	175	Comparison of standard triple therapy with a sequential schema represented two treatment groups did not differ with regard to *H. pylori* eradication rate for both ITT population (63.9% *vs* 71.4% for standard and sequential therapy respectively, $P = 0.278$) and per protocol population (65.9% *vs* 74.1% for standard and sequential therapy respectively, $P = 0.248$)	In the present study, the two treatments resulted in similar rates of eradication, and both treatments were relatively ineffective	[72]
Amoxicillin 1 g and lansoprazole 30 mg for the first 7 d or 5 d, followed by lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 500 mg for another 7 d or 5 d	900	The eradication rate was 90.7% (95%CI: 87.4%-94.0%) in the 14 d, 87.0% (95%CI: 83.2-90.8) in the 10 d group, and 82.3% (95%CI: 78.0-86.6) in the triple therapy 14-d group	This study support to the use of sequential treatment as the standard first-line treatment for *H. pylori* infection	[76]
Amoxicillin 1 g plus omeprazole 20 mg for the first 5 d, followed by 20 mg of omeprazole, 500 mg of clarithromycin, 500 mg of metronidazole, for the remaining 5 d	158	Comparing 10 d-sequential therapy with PPI-based triple therapy revealed eradication rate for 10 d-sequential therapy was 77.9% (60/77) by ITT and 85.7% (60/70) by PP analysis, but eradication rates in PPI-based triple therapy were 71.6% (58/81) and 76.6% (58/76) by ITT and PP analysis, respectively	The 10-d sequential therapy regimen failed to achieve significantly higher eradication rates than PPI-based triple therapy	[77]
Amoxicillin 1 g b.d. plus PPI b.d. for the first 5 d, followed by a PPI b.d. clarithromycin 500 mg b.d. and metronidazole 500 mg b.d. for the next 5 d	139	The ITT eradication rate was 84.2% (95%CI: 77%-90%) and the PP cure rate 90.7% (95%CI: 84%-95%)	Sequential treatment seems highly effective for eradicating *H. pylori*	[75]
Amoxicillin 1 g plus omeprazole 20 mg followed by 5 d omeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg or followed by 5 d omeprazole 20 mg, levofloxacin 250 mg and tinidazole 500 mg or followed by 5 d omeprazole 20 mg, levofloxacin 500 mg and tinidazole 500 mg twice daily	375	Eradication rates in the ITT analyses were 80.8% (95%CI: 72.8%-87.3%) with clarithromycin sequential therapy, 96.0% (95%CI: 90.9%-98.7%) with levofloxacin-250 sequential therapy, and 96.8% (95%CI: 92.0%-99.1%) with levofloxacin-500 sequential therapy	Levofloxacin-containing sequential therapy is more effective, equally safe and cost-saving compared to a clarithromycin-containing sequential therapy	[79]

ITT: Intention-to-treat; CI: Confidence interval; PP: Per protocol; *H. pylori*: *Helicobacter pylori*; PPI: Proton-pump inhibitor; t.d.s.: Ter die sum endum; b.i.d.: Bis in die; q.i.d.: Quater in die; q.d.s.: Quater die sum endum; b.d.: Twice daily.

The first rescue therapy including high-dose PPI dual therapy with amoxicillin or rabeprazole for 2 wk was highly tolerable and the PP and ITT success rate was 75.4% and 71.8% which was less than the second rescue therapy with amoxicillin and rabeprazole and levofloxacin[43].

In the study of Ince *et al*[44], dual therapy containing high-dose PPI (omeprazole) and amoxicillin was more cost-effective, successful and safe compared to standard triple therapy in patients with dyspepsia.

A prospective, open-label pilot study of *H. pylori* eradication revealed that 2-wk dual regimen of twice a day high-dose long acting lansoprazole plus amoxicillin treatment success was not acceptable[41].

Based on a large-scale multihospital trial study, high-dose dual therapy containing rabeprazole and amoxicillin is superior to standard regimens as sequential therapy or triple therapy for *H. pylori* infection, with similar safety profiles and tolerability[45].

If the theory, that consistently high intra gastric pH is required to reliably achieve more than 90% *H. pylori* eradication, the some mentioned studies results do not confirmed this theory. It seems many regiments were not sufficient to eradicate *H. pylori*.

Triple therapy

Triple *H. pylori* therapy comprising a PPI, amoxicillin and clarithromycin is used as the firstline therapy. Clarithromycin or metronidazole resistance has been related to a reduction of success rates, making it a significant reason leading to treatment failure of *H. pylori*[46]. The other factors such as rapid metabolism of PPIs by CYP2C19, poor patient compliance, high acidity of stomach and bacterial load seem to be the main causes of eradication failure[33,42]. One hundred and thirty-six patients enrolled in the study of 10-d triple therapy comprising esomeprazole plus amoxicillin and metronidazole. Cure rates of patients were 82.4% by ITT analysis and 88.2% by PP analysis[47].

Based on several available clinical trials, it seems that a quinolone-based triple therapy will be operative as the first-line therapy in *H. pylori* infection[11]. The use of levofloxacin as an alternative of clarithromycin in triple and sequential therapies has been investigated by Qian *et al*[48] 7-d levofloxacin based triple therapy (levofloxacin, amoxicillin, esomeprazole) generated unsatisfactorily therapeutic efficiency, only levofloxacin-containing sequential therapy reached adequate outcome.

The effectiveness of a triple bismuth-consisting regimen along with amoxicillin and nifuratel used for eradication of *H. pylori* in patients were evaluated. The results of this study revealed the therapy containing bismuth subcitrate, amoxicillin and nifuratel yielded a success rate of 86% in childhood[49].

Standard dose (amoxicillin 1 g, clarithromycin 500 mg and rabeprazole 20 mg, all two times per day for 10 d) *vs* half dose regimen in therapy of *H. pylori* infected subjects was equally efficient and better tolerated[50].

The results of triple therapy containing clarithromycin, amoxicillin and esomeprazole 40 mg or omeprazole 20 mg in different genotypes of CYP2C19 showed that esomeprazole containing regimen increased eradication rate in comparison with the triple therapy based on omeprazole in extensive metabolizers of CYP2C19. Regardless to genotyping of CYP2C19 the *H. pylori*, eradication rates remained similarly comparable among the omeprazole and the esomeprazole group[51].

One thousand four hundred and sixty-three *H. pylori* infected participated in a study to compare 10-d sequential, 14-d triple and 5-d concomitant therapies. The best eradication efficacy has been reported by standard 14-d triple therapy followed by sequential 10-d therapy[52].

Quadruple therapy

Quadruple therapy comprising bismuth subcitrate, PPI, metronidazole and tetracycline has been accepted better than standard triple therapy in several studies[53-55]. Ten-days quadruple therapy containing bismuthate dicitrate, esomeprazole, levofloxacin and tetracycline showed success rate of 95.8% after the failure of sequential therapy. This regimen could be used as a good choice in high clarithromycin resistance areas[56]. In a similar study 14-d therapy with esomeprazole, amoxicillin, levofloxacin, and bismuth achieved more than 90% eradiation rate after the failed sequential or concomitant therapies[10].

Four hundred and twenty-four patients (96.8% metronidazole resistance) did not respond to standard therapies treated by lansoprazole, bismuth potassium citrate plus (tetracycline and metronidazole or tetracycline and furazolidone or amoxicillin and tetracycline or amoxicillin and furazolidone) which all bismuth-containing quadruple therapies reached higher than 90% success rate[57].

The efficiency of quadruple *H. pylori* therapy has been confirmed as the first-line regimen in a randomized trial. During this study, 14-d quadruple therapy was compared with 7-d standard therapy. Fourteen-days quadruple therapy comprising bismuth, PPI, amoxicillin and clarithromycin exhibited acceptable success rate and could be prescribed as the first line therapy[58].

An open alabel, randomized, phase 3 trial compared 10-d quadruple therapy with 7-d standard therapy in 440 patients. The quadruple therapy produced higher success rates (80%) in comparison with standard triple therapy (55%). Quadruple therapy could be accepted as the first line of treatment because of increased incidence of clarithromycin-resistant. In addition, quadruple therapy showed higher eradication rate but comparable side effects with standard therapy[59].

One hundred and six Iranian duodenal ulcer patients participated in the study of furazolidone in comparison with metronidazole during a quadruple therapy for eradication of *H. pylori* infection. In furazolidone group eradication rate was 75% and 82% (in ITT and PP analysis) but in metronidazole group 55% and 56% respectively[60].

Sixty-four patients who failed previous clarithromycin, amoxicillin and omeprazole, (standard triple treatment) eradication treatment were treated for 10 d with tetracycline, bismuth subcitrate potassium and metronidazole four times per day and omeprazole two times per day. According to results, *H. pylori* eradication rates were between 93.2% to 95.0%[61].

One hundred and fifty patients in high resistance area were enrolled in a study to evaluate levofloxacin-containing quadruple therapy or high dose metronidazole plus bismuth subcitrate, esomeprazole, and tetracycline. Eradication rates were similar in both groups. Thus, metronidazole is a good choice because it is cheaper and more feasible[62].

Concomitant quadruple therapy is a non-bismuth quadruple based therapy comprising omeprazole, metronidazole, amoxicillin, and clarithromycin during 5 to 7 d[63,64]. The consequence of a meta-analysis of several randomized trials exhibited that concomitant quadruple therapy has been better than standard triple therapy[65] in addition, another meta-analysis of 2070 patients also confirmed this result[66].

Resistance to both metronidazole and clarithromycin considerably influence sequential therapy but did not affect the success rate of concomitant quadruple therapy. In addition, concomitant regimen has been confirmed to be safe and similarly active like sequential therapy in eradication of *H. pylori*[67]. In an area that 23.5% of subjects had clarithromycin resistant *H. pylori* strains, (33% resistant to metronidazole and 8.8% resistant to both drugs), the efficacy of 2 different optimized nonbismuth quadruple regimens was compared. According to the results, concomitant quadruple therapy with omeprazole, amoxicillin, clarithromycin and nitro imidazole two times a day for 14 d showed more than 90% cure rate of *H. pylori*[68].

Sequential therapy

An Italian innovation in the quadruple therapy leads to sequential therapy comprising dual therapy for 5 d with amoxicillin and PPI and 5 more days with tinidazole, clarithromycin and PPI[69]. This regimen was studied among 52 patients suffering from *H. pylori* infection and eradication rate around 98% was achieved with ITT analysis[70]. The other study which assessed the success rate of treatment by sequential therapy in compare with standard triple therapy showed that 10-d sequential therapy was better than standard triple therapy in children, that is confirmed by the researches done on adults[71].

A retrospective study compared eradication treatment in subjects that underwent triple treatment consisting of clarithromycin, PPI and amoxicillin or sequential treatment involving a clarithromycin, PPI and amoxicillin, and metronidazole in a high anti-microbial resistance setting. Eradication rate of *H. pylori* was comparable between the two treatment groups[72].

Two recently meta-analysis studies established above mentioned data, according to Jafri *et al*[73], review *H. pylori* treatment in 2747 patients. Success rates were 93.4% in sequential regimen where as 76.9% in common triple therapy.

The influence of different factors on success rate of *H. pylori* eradication assessed using two therapy regimens (sequential and triple therapy) for equal 10-d period of study. The data suggested that traditional factors such as smoking and *CagA* gene change efficacy of triple therapies but did not affect sequential therapy[74].

Ten-days sequential regime consisted of amoxicillin plus a PPI for 5 d, was continued by clarithromycin, metronidazole and a PPI for more 5 d demonstrated higher efficacy of triple therapy[75]. In another study 900 patients were examined for sequential therapy comprising amoxicillin and lansoprazole for 7 d continued by metronidazole, lansoprazole, and clarithromycin *vs* standard triple therapy. In the outcome, success rate was 90.7% in sequential therapy but 82.3% in triple therapy[76].

Cure rate of the sequential therapy was altered based on the type of used nitro imidazole, on the other hand, a therapy program with metronidazole provided results which were not as good as tinidazole[69]. Certainly, the results of Choi *et al*[77], study showed that *H. pylori* eradication rate was 77.9% of subjects treated by a metronidazole-based 10-d sequential regimen[77] compared to the results of the other study which indicated 97.4% of treatment by a tinidazole-based regimen. Eradication rate was 84.2% in the other metronidazole-based sequential therapy which was less than tinidazole-based therapy[75]. Most likely, such occurrence is because of longer half-life of tinidazole *vs* metronidazole[78].

In high clarithromycin resistance areas, clarithromycin substitution by levofloxacin has been investigated. Levofloxacin sequential therapy showed eradication rate more than 96% in comparison with 80.8% clarithromycin sequential therapy[79]. Levofloxacin-based sequential regimen is better than usual triple therapy as the first line in the sites with high incidence of resistance to clarithromycin[80].

Recently a retrospective study has been done among subjects that underwent triple treatment consisting of clarithromycin, amoxicillin and a PPI or sequential treatment involving amoxicillin, a PPI, clarithromycin, and metronidazole eradication treatment in a high anti-microbial resistance setting. The *H. pylori* eradication rate was not statistically different between the 2 treatment groups[72].

FUTURE PERSPECTIVES

Overuse of antibiotics and accumulation of point mutations in the *H. pylori* DNA is intended as the main cause of the increase in antibiotic resistance[81].

In the present, the recommendation of antibiotics for two weeks or high-dose PPI are commonly associated with the development of undesirable side effects and complaints during anti-*H. pylori* therapy[82].

A large number of *H. pylori* eradication reports from different geographic areas are indicating conflicting results and a treatment regimen may be extremely efficient in one geographic area and deliver unsatisfactory results in another[83]. In 2010, An *H. pylori* strain was isolated from a 31-year-old woman with gastric cancer that was resistant to all seven antibiotics that were tested: Clarithromycin, metronidazole, amoxicillin, tetracycline, furazolidone, erythromycin and ciprofloxacin[84]. Finding new molecules for treatment of *H. pylori* infection is a part of ongoing research programs[85-92].

Therefore, the development of a new and alternative treatment regimen for the eradication of *H. pylori* which also reduces the frequency of adverse effects would be an invaluable advancement.

PROBIOTICS

The probiotics, live microorganisms mostly within *Lactobacillus, Bifido bacterium* and *Saccharomyces* genus which, when administered in sufficient amounts, exert a health benefit on the host beyond inherent basic nutrition[93,94].

Current interest in probiotic effectiveness against *H. pylori* and its activity in reducing bacterial colonization and decreasing gastric inflammation have been stimulated because it provides a large-scale and low-cost alternate solution to prevent or decrease *H. pylori* colonization[94-97].

A number of mechanisms have been anticipated for probiotic efficacy against *H. pylori*. Probiotic bacteria can modulate *H. pylori* activity by either immunological (*e.g.*, increment of serum IgA and reduction in cytokine profiles such as IL-6) or non-immunological mechanisms (antagonism and competition with potential pathogens[97-100].

The studies those using probiotics alone, showed

only partial improvement in probiotics efficacy against *H. pylori,* while administration of probiotics with eradication regiments lead to increase in efficacy and/or reduction of side effects[98,101,102].

However, conflicting data have been obtained with probiotics treatment[101]. Addition of yogurt to PPI-based triple therapy improved the eradication rate but side effects were the same to that in the control group with standard triple therapy[103].

The effect of probiotic supplementation on *H. pylori* eradication and side effects which was conducted on May 2014 showed that specific strains of probiotics supplementation can improve rates of eradication specially when antibiotic therapies are relatively inefficient. This meta-analysis observed no significant decrease of side effects so that, noticeable heterogeneity was observed for the overall occurrence of adverse events[104].

In another study addition of bovine lactoferrin leads to increase in the eradication rate of *H. pylori*, and probiotics reduced the side effects of antibiotic therapy in the standard triple treatment[105]. Dajani *et al*[106], designed a study to evaluate the effect of adding the probiotic *Bifidus infantis* to triple therapy or pretreatment by probiotic before triple therapy. They showed pretreatment with 2 wk of *B. infantis* before standard triple therapy increased the eradication rate to 90.5% in compare with triple therapy plus probiotic (83%) and triple therapy alone (68.9%)[106].

The effectiveness of probiotics in a standard triple *H. pylori* therapy which analyzed in a systematic review and meta-analysis study suggests that supplementation of a standard triple therapy regimen with probiotics improved the *H. pylori* eradication rates specially in Asian patients and the prevalence of total side effects[15].

The other meta-analysis, by Lv *et al*[107], in 2015 compared the probiotics as adjuvant agents of anti-*H. pylori* standard triple therapy regimens with placebo or no treatment. It was concluded that supplementing triple *H. pylori* therapy regimens with probiotic can enhance eradication rates and reduce the adverse events occurred during eradication treatment. Administration of probiotic before or subsequent to eradication treatment for a duration of > 2 wk probably improve the eradication efficacy[107]. Probiotic pretreatment plus quadruple therapy can decrease *H. pylori* loads despite antimicrobial resistance, thus increasing the treatment efficacy of quadruple therapy in the *H. pylori* eradication[108].

A randomized, prospective, double-blind, placebo controlled study corresponding to 100 *H. pylori*-positive naive patients demonstrated *Lactobacillus reuteri* combination alone is capable of exerting an inhibitory activity against *H. pylori*, and when administered with eradication therapy, it increases eradication rates by about 9% and cause a significant reduction in antibiotic related adverse events[109].

The use of probiotics, as adjuvant therapy, appears promising for the current *H. pylori* eradication treatment, in order to reduce the frequency of antibiotic induced side-effects, though it still requires optimization[110,111].

HERBAL COMPOUNDS

In recent years, a number of studies have suggested that phytomedicine has a complementary function in *H. pylori* treatment, and *H. pylori* infection can be prevented through the use of inexpensive, safe and non-toxic anti-*H. pylori* formulations from medicinal plants. Many plant extracts, partially purified reactions and natural compounds with the anti-*H. pylori* activity has been reported[3,112-114]. Some bioactive compounds from medicinal plants with anti-*H.pylpri* activity include carvacrol[115], polyphenolic catechins[116], tannins[113], cinnamaldehyde, eugenol[117], quercetin[118], licoricidin, licoisoflavone B[119], Berberine, sanguinarine, chelerythrine, protopine, β-hydrastine[120], mastic[121,122], plumbagin[123] protocatechuic acid[124].

Concerning the reducing power of plant extracts on antibiotic resistance, the anti-mutagenic properties of some plant extracts on the incidence of mutations conferring resistance to clarithromycin in *H. pylori* was evaluated. The results of this study showed the considerable efficacy of *Mirtus communis*, *Teucrium polium* extracts in prohibiting antibiotic resistance. This may be more beneficial if the medicinal plants in combination with present antibiotic regimens are used to develop more effective eradication regimens[125]. However, mode of action, potential cytotoxicity and benefits of herbal medicine are complex, incomplete and confusing[126]. Further evaluation of pharmacokinetics for those products in animals and the design of precise clinical trials of promising herbal products should be addressed in future investigations.

PHOTODYNAMIC THERAPY

Photodynamic inactivation of microorganisms is on the basis of the combination of a dye known as a sensitizer or photo sensitiser and harmless visible light of an appropriate wavelength to generate the triplet excited state ($^3O_2$) of the dye molecules which, in turn, may react with molecular oxygen which lead to production of different cytotoxic reactive oxygen species such as superoxide radical-anion ($O_2^{\bullet -}$) and singlet molecular oxygen ($^1O_2$)[127,128].

Recently, some *in vitro*[129-131] and *in vivo*[132,133] studies to develop anti-*H. pylori* photodynamic therapy for the eradication of *H. pylori* were successful[128].

In an *in vitro* study, a photosensitizer such as Chlorin e6 (Ce6) as a natural product reduced from chlorophyll, was used to achieve an optimal irradiation conditions like initial Ce6-concentration, incubation time, light intensity and exposure time for an effective inactivation of *H. pylori*. Photodynamic inactivation of *H. pylori* using Ce6 shows that the exposure time of irradiation, followed by the light intensity and the concentration of Ce6 were the major cause of strains inactivation[130].

Hamblin *et al*[131] demonstrated multiple strains of *H. pylori* are killed *in vitro* by photodynamic action upon illumination.

H. pylori is sensitive to inactivation by blue light which may represent a novel therapy approach especially in patients with failed standard antibiotic therapy. Blue light phototherapy produces a rapid decline of bacterial numbers in endoscopically delivered blue light in the gastric antrum of the 10 patients who were positive for the *H. pylori*[133].

Based on a controlled, prospective pilot trial study, intra-gastric violet light phototherapy is safe and feasible and may demonstrate a new approach for *H. pylori* eradication, particularly in patients who have failed therapy with standard antibiotic regiments[132].

Choi *et al*[129] applied endoscopic white light and methylene blue dye to show impressive antibacterial effect against *H. pylori*. The primary mechanism of the bactericidal effect has been shown to be oxidative DNA damage of *H. pylori*[129].

In vitro photodynamic therapy against *H. pylori* using endoscopic light (NBI and conventional white light), with low or high concentration of protoporphyrin Ⅸ as a photosensitizer revealed the bactericidal activities are very efficient and the main mechanism of this photodynamic therapy involves damage to the cell membrane[134].

According to the results, it is necessary to perform *in vivo* photodynamic therapy using animal model of disease and indicate the limitations and effectiveness of this novel technique. Also the cost, side effects and ease of administration should be also taken into account and develop new photosensitizer materials to improve the antibacterial activity or using light of a wavelength specific to the photosensitizer instead of light of a broad wavelength spectrum[127,129].

VACCINE

All known gastric *H. pylori* species are urease positive that catalyze the hydrolysis of urea. UreB is the relatively conserve urease activity unit and It has very strong antigenicity and is the critical for the bacterial survival and colonization under acidic condition of the stomach. UreI, a *H. pylori* urea channel protein, is a key factor for bacterial colonization in acidic mammalian stomach[135]. In a research, a multi-epitope vaccine was designed by coupling two antigenic fragments (UreB and UreI) of *H. pylori* and cholera toxin B subunit (CTB), resulting considerable protection effects against *H. pylori* challenge in BALB/c mice[136].

Both intramuscular injection and oral administration of multi-epitope antigen, UreI and UreB, with CTB had immune protective effect against *H. pylori* challenge, and oral administration had the higher infection protection rate against *H. pylori*[135].

Several other *H. pylori* proteins have already been reported as effective vaccine antigens such as cytotoxin-associated gene A, vacuolating cytotoxin A (Vac A)[137] heat-shock proteins[138], neutrophil-activating protein[139], surface-localized protein HpaA[140] and so on. It is probable a combination of some mentioned antigens with each other or with a suitable adjuvant may induce a protective effect through vaccination[140,141].

Recently, a reverse vaccinology approach was employed to predict the potential vaccine candidates against *H. pylori* and search novel antigens using computational methods or bioinformatics. In this study, 5 antigenic epitopes including adhesion protein babA, sabA, omp16, iron (Ⅲ) dicitrate transport protein fecA and vacuolating cytotoxin vacA have been prioritized as potential vaccine candidates against *H. pylori* infections[142].

Therapeutic antibodies present valuable tools in targeting a wide range of enteric diseases and pathogens during the years[143]. A recent study by den Hoed *et al*[144] has shown monotherapy with bovine antibody-based oral immunotherapy is well tolerated, but does not significantly reduce intragastric *H. pylori* density in humans[144].

The generation and application of virus-like particles and nanobeads with a surface adsorbed antigen that can elicit strong T and B cell immune responses would be as a useful tool for the development of vaccines[145]. The development of safe and effective vaccine against *H. pylori* infection becomes particularly important.

CONCLUSION

The use of antibiotics as first-line therapies may be appropriate if they are selected based on country-wide studies of the local and regional antimicrobial resistance patterns. Development of alternative antibiotics for the eradication of *H. pylori* would be an invaluable advancement, although it takes number of years before to evaluate these potentially interesting molecules in humans.

Adjuvant therapy with probiotics is recommended due to immunomodulation, stimulation of mucin production and inhibition of colonization and survival of *H. pylori*. On the other hand, potential options such as medicinal plants, Photodynamic therapy and vaccine are still in the experimental phase.

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Papillary carcinoma of breast: Minireview

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Abstract

The term "intracystic papillary ductal carcinoma *in situ*" constitutes only 0.5% to 1% of all breast cancers. It is usually seen in postmenopausal age group. Herein, we are presenting a minireview about this unusual breast malignancy usually difficult to diagnose on clinical grounds and highlighting modalities of diagnosis and management.

Key words: Papillary carcinoma breast; Intracystic; Solid; Diagnosis and management

Core tip: The oncosurgeon and surgical pathologist should keep in mind this rare type of *in situ* carcinoma as a differential diagnosis in palpable breast lumps as it often mimics a benign lesion clinically. However, careful histopathological evaluation superadded by immunohistochemistry is an effective tool to arrive at the correct pathological diagnosis to avoid untoward complications related to under diagnosis and/over diagnosis.

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INTRODUCTION

Papillary carcinoma (PC) of the breast constitutes 0.5% to 1% of all breast cancers[1-10]. PC can be either localized or diffuse[3,8,10-13]. In comparison with intracystic PC, solid PC is featured by mucin production exhibiting neuroendocrine features, and is usually multinodular[13,14]. Papillary ductal carcinoma *in situ* (DCIS) is characteristically surrounded by a myoepithelial cells[3,11]. Clinical presentation is either as subareolar mass and/or nipple discharge[11]. The newer entity encapsulated PC has been described[15-17] and solid papillary carcinoma[13,14] are well encapsulated and well circumscribed circumscribed with absence of myoepithelial cells.

EPIDEMIOLOGY

Age
Mainly seen in postmenopausal age.

Sex predilection
Intracystic papillary carcinoma (IPC) is extremely rare in males[18-20]. The clinical presentation in males is similar to that in females except for a higher median age in males (60 *vs* 53 years)[19].

Incidence
Majority of the cases had localized involvement (89.6%). Approximately 7.8% had regional disease, with local spread, and (0.4%) presented with distant metastases[20,21].

PATHOPHYSIOLOGY

The contributing predisposing factors are risk factors are genetic predisposition, age, family history, dietary factors, alcoholism, weight gain and endocrine factors.

Age
It had been observed that breast cancer the incidence gradually increases with age. By the age 90 one fifth of women are affected[22-25].

Gender
Males are affected less commonly as compared to females (incidence less than 1%)[22,26].

Genetic factors
Family history is an important contributing risk factor[22]. Women with one or more first degree relatives with breast cancer have more risk[23].

Diet and alcohol
The diet low in phyto-oestrogens and alcohol intake are predisposing factors for the disease[22]. Ingestion of dietary fibres is protective[25].

Obesity lifestyle and physical activity
Due to excess estrogen synthesis from adipose tissue, obesity is an important contributory factor[23,25].

Endocrine factors (endogenous)
Incidence of breast cancer is more in infertile females as the level of estrogen is lower in pregnancy and in women that had many children[22,23].

Exogenous factors
Hormone replacement therapy and oral contraceptives is associated with breast cancer[23,25].

Molecular genetics of breast cancer
Five to ten percent of breast malignancies arise due to germ-line mutations in genes such as *BRCA1*, *BRCA2*, *p53* and *PTEN*[22,23,25,26].

Role of HER-2/neu antigen
HER-2/neu antigen is a growth factor protein, *i.e.*, over-expressed in breast cancers and is bad prognostic indicator[27-29].

Steroid hormones and their receptors
The adipose tissues forms estrogen from circulating cholesterol predisposing to breast cancer[30].

Malignancies that depend on steroid hormones include breast, prostate, testicular, ovarian and endometrial cancer[24,31-33].

CLINICAL PRESENTATION

PC is commonly seen in postmenopausal age group. This form of breast cancer generally presents with painless breast lump hemorrhagic nipple discharge. Only few cases were reported below the age of 40 years[34,35].

DIAGNOSTIC EVALUATION

Mammography
On a mammography usually revealed as a round, oval calcific opacity. The margin of the mass is usually well circumscribed, but may be indistinct at places indicating inflammation or invasion. The differential diagnosis includes colloid or medullary carcinoma, invasive ductal carcinoma, hematoma benign cyst or adenofibroma[35].

Sonography
On ultrasonography, it appears as cystic masses, with or without presence of septa[36,37]. Although some radiologic features, such as posterior acoustic enhancement and associated micro calcifications, are more frequently associated with malignancy, the radiologic appearance cannot accurately predict the behavior of papillary lesions, and histological evaluation is necessary[38].

Magnetic resonance imaging
Magnetic resonance imaging using contrast enhancement can give details of morphology, *i.e.*, enhancement of cyst wall, septations and mural nodules[39].

Cytology
Cytological diagnosis may be missing as we can aspirate the fluid only. Fine needle aspiration cytology (FNAC) reveals atypical cells in the smear[1] (Figure 1). Sonography-guided vacuum-assisted core biopsy is much better option over aspiration cytology[40]. The gun biopsy mainly hits the solid centre of tumor and the invasive component can only be recognized at the periphery of the tumor; so, excisional biopsy of B3 papillary lesions is an effective approach to demonstrate invasion[38]. Recently ductoscopy can be used as a valuable tool in diagnosing such lesions[41].

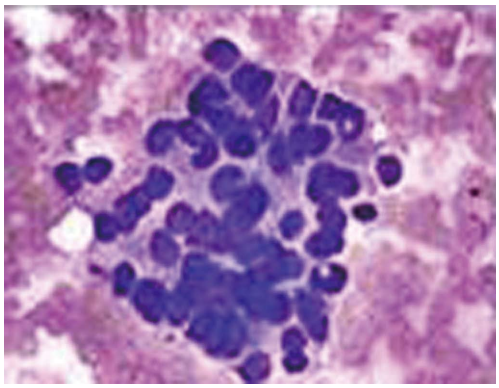

Figure 1 Fine needle aspiration cytology confirmed the presence of atypical cells.

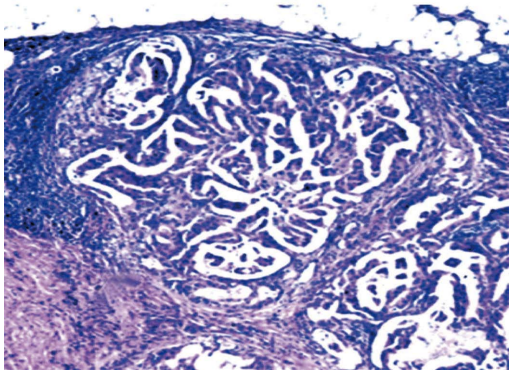

Figure 2 Low power view 10 × showing intraductal malignant cells arranged in papillary fronds exhibiting features of malignancy (*in situ* papillary carcinoma of breast).

Histology

Prognostically IPC is a borderline lesion[42-44]. Microscopically *in situ* intracystic papillary tumor shows papillary, adenoid and cribriform structures lined by columnar cells exhibiting features of marked cytological atypia, *i.e.,* nuclear hyperchromasia, pleomorphism, abnormal mitosis and increased N:C ratio (nucleocytoplasmic ratio) with fibro vascular cores[1] (Figure 2). High nuclear grade and the presence of necrosis are bad prognostic indicators[43,45].

A minority of the cases are associated with invasive component. The invasive areas rather exhibit histological features of an invasive ductal carcinoma not otherwise specified instead of usual papillary pattern[43].

Usually it is difficult to differentiate between *in situ* and invasive lesions on FNAC and core biopsy, as invasion is often recognized at the periphery of the lesion. Hence, surgical excision is done for correct histological diagnosis and proper management[44,45].

DIFFERENTIAL DIAGNOSIS

Invasive features into the stroma, higher nuclear grade and necrosis differentiates the IPC from the intracystic (encapsulated) papillary breast which is usually of low or intermediate nuclear grade with no evidence of necrosis, strongly estrogen receptor (ER) positive, negative for C-erb2(Her2neu)[46].

Differential diagnoses also include lesions like atypical ductal epithelial hyperplasia, lobular hyperplasia and DCIS[47,48].

Immunohistochemistry

Papillary carcinomas of the breast tend to be ER, progesterone receptor positive and Her2Neu negative[47,49,50]. Immunohistochemistry markers for myoepithelial cell layer (MCL) have an important role in invasion assessment with smooth muscle actin, p63, CD10, S-100, calponin, maspin commonly employed among which smooth muscle myosin heavy chain and p63 are more MCL specific[50,51].

TREATMENT

Treatment options are wide local excision, with or without adjuvant radiotherapy (RT), or mastectomy[9]. Tamoxifen is important drug as this cancer seems to be almost certainly hormonal positive and HER-2 negative[4,52].

RT

Adjuvant RT play role for invasive disease and or DCIS[4].

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CASE REPORT

Peristomal variceal bleeding treated by coil embolization using a percutaneous transhepatic approach

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Abstract

Peristomal variceal bleeding due to portal hypertension is an entity that has rarely been reported with 3%-4% risk of death. A 68-year-old woman who had undergone a palliative colostomy (colorectal carcinoma) presented with a massive hemorrhage from the colostomy conduit. Considering her oncological status with medial and right hepatic veins thrombosis due to liver metastasis invasion, an emergency transhepatic coil embolization was successfully performed. Standard treatment modality for these cases has not been established. Percutaneous transhepatic coil embolization of varices is a safe and effective choice in patients who present with life threatening bleeding and exhibit contraindications to transjugular intrahepatic portosystemic shunt.

Key words: Ectopic variceal bleeding; Stomal bleeding; Percutaneous transhepatic embolization; Colostomy; Cirrhosis; Hemostasis

Core tip: Peristomal variceal bleeding in patients with portal hypertension is a rare entity with increased risk of death. In situations when life-saving procedures are required in such patients, standard treatment modality has not been established. We illustrate a successfully performed emergency transhepatic coil embolization of bleeding varices in an oncological patient with contraindications to transjugular intrahepatic portosystemic shunt. Additionally, we discuss other

different treatment options described in the literature and its technical challenges.

Maciel MJS, Pereira OI, Motta Leal Filho JM, Ziemiecki Junior E, Cosme SL, Souza MA, Carnevale FC. Peristomal variceal bleeding treated by coil embolization using a percutaneous transhepatic approach. *World J Clin Cases* 2016; 4(1): 25-29 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i1/25.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i1.25

INTRODUCTION

Patients with portal hypertension commonly develop varices that typically arise in the gastro-esophageal region. On the other hand, ectopic varices - a rare condition - may occur along the entire gastrointestinal tract. Sites other than the gastroesophageal junction account for only 5% of all variceal bleeding[1]. Peristomal variceal initial bleeding mortality rate is as high as 40% due to the challenges related to the diagnosis, management and treatment of this condition. Variceal bleeding from a stoma is a well-known entity that has rarely been reported[2]. A bleeding episode has an estimated risk of death of 3% to 4%[3].

The standard of practice for the handling of stomal variceal hemorrhage has not yet been established. Treatment options range from conservative therapies (medication and/or sclerotherapy), to surgical procedures - such as stomal reconstruction or portosystemic shunting[3]. Minimally invasive therapies such as transjugular intrahepatic portosystemic shunt (TIPS) creation have been immensely useful for portal pressure decompression and have been demonstrated to be an effective treatment for individual with stomal bleeding. Albeit, some patients are not suitable candidates for TIPS procedure because they have subjacent hepatic encephalopathy or poor liver function[4].

Transhepatic coil embolization of bleeding stomal varices could be an option for treatment in cases in which TIPS is contraindicated; however, it demands a transhepatic approach with the related risk of hepatic damage or bleeding[5,6]. Another minimally invasive treatment option is embolization of the offending varix *via* transjugular transhepatic approaches[2].

The purpose of this paper is to describe a rare case of variceal hemorrhage from a colostomy that was successfully treated with coil embolization using a percutaneous transhepatic approach. This study was approved by the Clinical Hospital of the University of Sao Paolo Medical School institutional review board.

CASE REPORT

A 68-year-old woman who had undergone palliative loop colostomy due to locally advanced colorectal carcinoma two years prior presented to our service with chronic bleeding from the colostomy conduit. The primary disease was stage T4 Nx M1 with ovary, uterus and ureter invasion, as well as liver and lung metastases; the patient has been treated with four cycles of palliative chemotherapy with leucovorin, 5-fluorouracil (5FU) and oxaliplatin. The patient also had right portal vein compression, medial and right hepatic vein thrombosis caused by the liver metastasis invasion, and no previous history of liver dysfunction (child-pugh A5).

At the end of the fourth cycle of chemotherapy, she developed recurrent episodes of stomal bleeding that required transfusion and hospitalization. The bleeding was first thought to originate from the colon and was treated with tranexemic acid (500 mg, three times daily for 7 d), fresh frozen plasma and red blood cell transfusion. The clinical exam demonstrated stomal mucosal erithema and edema. Because the hemorrhaging persisted, an enhanced multislice computed tomography (CT) scan was performed, along with 3D reconstructions; it showed ectopic varices at the colostomy site that were fed by the inferior mesenteric vein (Figure 1), which was suggestive of portal hypertension.

Massive hemorrhage occurred during the hospitalization, and the patient developed hemorrhagic shock. Considering her oncological status (T4 M1 clinical stage Ⅳ) in palliative chemotherapy and hepatic metastasis, an emergency transhepatic embolization was planned as a less invasive procedure than TIPS.

Technique

Percutaneous transhepatic access was obtained through a left portal vein branch ultrasound guided puncture with a 22-gauge Chiba needle and catheterization using the NPAS kit (Cook, Bloominton, IN, United States). Portal and mesenteric venography were performed using a Cobra Ⅱ 5 French catheter that showed varices appearing from the hepatofugal flow onto the colostomy conduit by inferior mesenteric tributaries (Figure 2). The portal-pressure gradient (between the portal vein and the right atrium measured by central venous catheter placement) was 16 mmHg. Ectopic varices were accessed by catheterization using a Cobra Ⅱ 5 French catheter and a 0.035' hydrophilic guidewire (Merit Medical, Jordan, UT, United States), and coil embolization was then performed. A total of 11 platinum coils, 14 to 20 cm long (Nester, Cook, Bloominton, IN, United States and Interlock, Boston Scientific, Natick, MA, United States), were used. After embolization, venography demonstrated complete obliteration of the variceal branches (Figure 3). The portal-pressure gradient measured after embolization was 24 mmHg. Gelfoam was used to occlude the hepatic parenchyma catheter path after sheath removal.

The patient developed no complications from the procedure, no hemorrhages developed during the first month post embolization. Improvement of stomal mucosal erythema and edema were observed and no

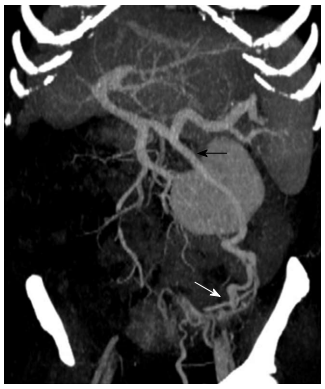

Figure 1 Computed tomography-scan three-dimensional reconstruction in maximum intensity projection showed the ectopic varices (white arrow) at the colostomy conduit fed by the inferior mesenteric vein (black arrow).

colostomy disfunction was noted. Over the most recent six-month follow-up period, the patient was maintained on palliative treatment with chemotherapy and radiotherapy despite minor stomal and rectal bleeding that was managed conservatively with compression and tranexemic acid.

DISCUSSION

Hemorrhaging of ectopic varices is a rarely reported subject in the literature and is mostly related to digestive tract or umbilical bleeding. Hemorrhage arising from peristomal varices has been related in case reports, and most occur from an ileostomy conduit[2,4-7]. This sort of bleeding is commonly chronic and recurrent rather than massive. Doppler ultrasound, CT and magnetic resonance angiography may identify varices in the region of the stoma and facilitate the diagnosis of cirrhosis, portal hypertension and the assessment of portal patency[8]. This patient had a precise diagnosis of peristomal variceal bleeding with portal hypertension based on enhanced multislice CT and venography.

The combination of extensive liver metastasis and chemotherapy was assumed to be the etiology of this patient's portal hypertension. Several authors have reported portal hypertension due to perisinusoidal fibrosis, severe sinusoidal obstruction, and fibrotic venular occlusion in patients receiving oxaliplatin. The use of oxaliplatin and 5FU has been related to obliterative portal venopathy as a consequence of nodular regenerative hyperplasia that causes portal congestion and sinusoidal dilation[9].

Recent reviews have not yet defined the standard of care in these cases of ectopic variceal bleeding. Recommended care includes conservative medical therapy, endoscopic therapy, interventional radiology therapy, surgical shunt placement and even liver transplantation. Band ligation and sclerotherapy are feasible options in the management of these cases, but the high risk of necrosis, perforation, massive hemorrhage, and sustained portal hypertension result in disappointing outcomes[8]. When the bleeding is life threatening or unresponsive to conservative treatments, surgical shunts have been performed. Surgical decompression of the portal vein is effective for controlling and preventing variceal bleeding, but may cause liver failure or hepatic encephalopathy, with mortality ranging from 1% to 50%[5,7].

Direct percutaneous ultrasound-guided endoluminal embolization with cyanoacrylate glue or coils has been described as a potential alternative treatment[10,11]. Although this approach has been described as a safe and effective technique for controlling stomal bleeding, it is particularly useful when a single dominant feeding varix is identified[12]. Other limitations are that additional varices or venous collateral may still develop as well as the increased risk of embolization material migration to the main portal vein and mucosal damage at the stomal site.

TIPS alone or in combination with varix embolization is effective for stop bleeding of ectopic variceal in patients suffering with portal hypertension because it treats the underlying pathological process by reducing portal hypertension[8,13]. Even though TIPS appears to be a safe and effective treatment modality, 25% and 30% of patients develop rebleeding with a patent TIPS and are at risk of developing encephalopathy, respectively[3,10].

Transhepatic variceal coil embolization is a feasible and safe option reported in the literature[10,12]. Our patient was in poor clinical condition in the emergency setting of an acute life threatening peristomal variceal bleed; therefore, an approach based on coil embolization of the varices using a percutaneous transhepatic approach was selected, with TIPS being reserved for recurrent bleeding. After the bleeding was successfully treated, it seemed appropriate for this patient to be treated with TIPS, whereas there was an increase in the portal-pressure gradient after coil embolization. Nevertheless, the present common understanding of TIPS creation for hemostasis is that it raises the incidence of hepatic encephalopathy and spoils liver function[7]. It was decided that the TIPS procedure was contraindicated in this case after a multidisciplinary discussion, considering that this was an oncological patient who was receiving palliative treatment for worsening clinical status due to disease progression with vertebral metastasis and medullar compression. Other conditions that would make the procedure technically challenging was the hepatic tumor burden with medial and right hepatic vein thrombosis.

The transhepatic approach was the best option for this case considering the patient had no ascites and there were no contraindications to this access despite the liver metastases. This route allowed access to numerous vessels in the same setting. The procedure was successfully performed with occlusion of the peristomal varices, and no complications such as mesenteric or stomal ischemia occurred. Kishimoto *et al*[6] reported a similar case of stomal varices treated with percutaneous transhepatic coil embolization with

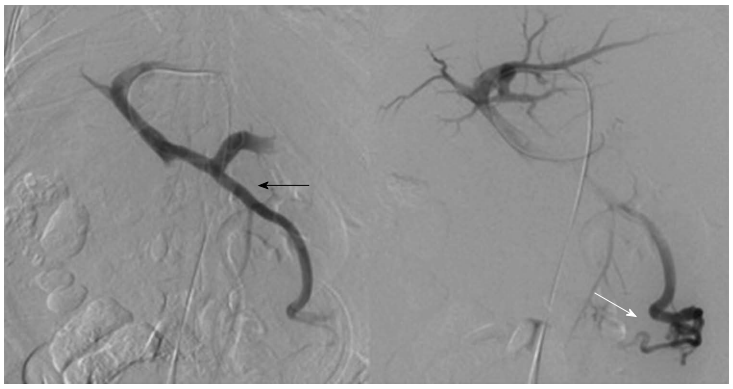

Figure 2 Digital subtraction venography showed hepatofugal flow toward the stoma by inferior mesenteric vein (black arrow) feeding the stomal varices (white arrow).

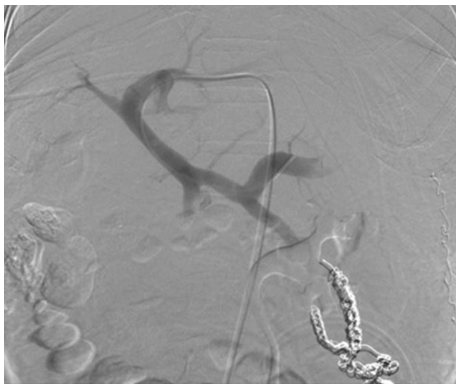

Figure 3 Digital subtraction venography after embolization demonstrated complete obliteration of variceal branches.

the use of a total of 28 coils including fibered platinum microcoils, platinum coils and stainless steel coils to stop the bleeding. In our case, a total of 11 fibered platinum coils with lengths varying from 14 to 20 cm were used. The long lengths of the coils contributed to the use of a smaller number of coils in the present case.

Recurrent bleeding may occur in patients who have undergone transhepatic embolization as a result of variceal recanalization or the development of new ones because it did not decrease the portal pressure. Sclerotherapy with absolute ethanol followed by coil occlusion has been reported to prevent recurrent bleeding, but the procedure was not shown to prevent it[5]. Toumeh *et al*[5] described a patient who developed recurrent bleeding from recanalized ileostomy varices one year after the first coil embolization treatment, which was controlled by transhepatic embolization. The embolic agents used were alcohol, Gelfoam and Gianturco coils[5]. Although the method of coil embolization has a high incidence of recurrent hemorrhage, it is effective for the treatment of life threatening acute variceal bleeding. Our patient stabilized with a major reduction in bleeding and no need of blood transfusion, and the oncologic palliative treatment was continued.

Complications of transhepatic embolization are related to liver trauma with bleeding, bile leakage and portal vein thrombosis[5-7]. Transhepatic tract bleeding after percutaneous portal vein access has been reported to be up to 30% of cases when access site closure was not performed. When surgeons routinely embolize or close transhepatic tracts in percutaneous portal puncture, this bleeding risk decreases to 0%-6.5%[14]. Gelfoam or small coil use to occlude the parenchymal track is effective at preventing bleeding from the puncture site. Although rare, liver trauma can be avoided by ultrasound guided transhepatic puncture. The progress of the embolization should be closely monitored to prevent reflux of the embolic agent into the portal vein. Similar to transhepatic portal puncture, the reported rate of fatal complications due to TIPS procedure access is between 0.6% and 4.3%, including intraperitoneal hemorrhage as a result of extrahepatic rupture of the portal vein, laceration of the hepatic artery, and transcapsular puncture with the transjugular needle[15].

In conclusion, percutaneous transhepatic embolization could be considered for patients with stomal variceal bleeding, in whom TIPS is contraindicated.

COMMENTS

Case characteristics

A 68-year-old woman who had undergone palliative loop colostomy due to locally advanced colorectal carcinoma presented to our service with recurrent episodes of stomal bleeding that required transfusion and hospitalization.

Clinical diagnosis

At the end of the fourth cycle of chemotherapy, she developed recurrent episodes of stomal bleeding that required transfusion and hospitalization.

Differential diagnosis

Coagulation disturb; colorectal neoplasm; gastro-esophageal varices.

Laboratory diagnosis

Laboratory exams are compatible with massive hemorrhage (hemorrhagic shock).

Imaging diagnosis

Computed tomography showed ectopic varices at the colostomy site that were fed by the inferior mesenteric vein.

Treatment
Coil embolization using a percutaneous transhepatic approach was performed to stop the variceal bleeding.

Related reports
Patients with portal hypertension commonly develop varices that typically arise in the gastro-esophageal region. Ectopic varices are rare and may occur along the entire gastrointestinal tract. Sites other than the gastroesophageal junction account for only 5% of all variceal bleeding. Variceal bleeding from a stoma is a well-known entity that has rarely been reported. The risk of death from an episode of bleeding is estimated to be 3% to 4%.

Experiences and lessons
Ectopic varices are rare (5% of all variceal bleeding) and may occur along the entire gastrointestinal tract. The risk of death from an episode of bleeding is estimated to be 3% to 4%, so the bleeding should be treated. Percutaneous transhepatic embolization should be considered for patients with stomal variceal bleeding, in whom transjugular intrahepatic portosystemic shunt is contraindicated.

Peer-review
This article describes about a successful case of percutaneous transhepatic coil embolization for peristomal variceal bleeding. This case report is meaningful and informative.

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Is endoscopic resection a correct treatment for atypical gastrointestinal lipomas?

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Abstract

We would like offering our experience about a very rare and underestimated type of gastrointestinal lipoma, which is the lipoma with precancerous or frankly malignant features of the mucosal epithelium, the so-called atypical lipoma. So far, only few cases have been described in the world literature. Recently, we grappled with what we think the first case of atypical colonic lipoma presenting with adenocarcinomatous transformation of the overlying epithelium, as discussed in more detail below. We propose a new definition and classification for this kind of lesions and discuss about their diagnosis, treatment and prognosis.

Key words: Malignant epithelial transformation; Typical colonic lipoma; Atypical colonic lipoma; Oncologically malignant potential; Preoperative endoscopy

Core tip: We report a case of atypical lipoma of the colon with malignant transformation of the mucosal epithelium. No standardized treatment exists. Endoscopic resection with close follow-up is probably the most appropriate management to pursue for this kind of lesions.

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TO THE EDITOR

We read with great interest the article written by Yeom *et al*[1] on an unusual case of lipoma of the right colon covered by hyperplastic epithelium. As for us, we would like to offer our experience about another very rare type of gastrointestinal lipoma, which is the lipoma covered with precancerous or frankly malignant

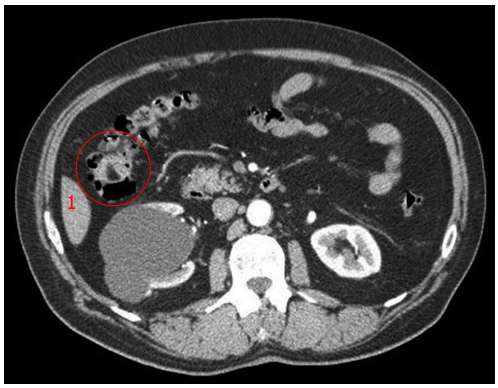

Figure 1 Computerized tomography scan of the abdomen showing a tumor in the right colic flexure (within the red circle).

features of the overlying epithelium, the so-called atypical lipoma. Recently, in fact, we grappled with what we think the first case of colonic lipoma with malignant transformation of the mucosal epithelium, as discussed in more detail below.

A 64-year-old man was referred to us for surgical evaluation of an ulcerated mass of the right colic flexure measuring 3.5 cm in diameter (Figure 1); preoperative biopsies showed both tubule-villous adenoma with focal severe dysplasia and abundant granulation tissue. We performed a right hemicolectomy; histology yielded the unsuspected diagnosis of well-differentiated colonic lipoma with an ulcerated overlying mucosa and 22 reactive lymph nodes. Follow-up is now 8 mo with no evidence of recurrence.

Colonic lipoma is a benign tumor well-known from the literature[2,3]. However, its oncological significance is not so simple as generally argued. The term "atypical" was introduced by Snover[4] in 1984 and has always been referred to those lipomas showing cytological alterations in fat cells (hyperchromasia, pleomorphism and mitosis) suggestive of sarcomatous changes. However, what appears to us still underestimated is the fact that atypical lipomas have a double malignant potential represented not only by liposarcoma (as assessed by Snover), but also adenocarcinoma. The former represents the direct malignant counterpart deriving from the same mesenchymal cell line whereas the latter affects a different layer, the epithelium of the overlying mucosa. In this viewpoint, the term "atypical" should be extended to include those lesions with hyperplastic, precancerous or frankly malignant features of the covering epithelium. Hence, we propose a classification of atypical lipomas: Atypical type-A lipoma could indicate the original lipomatous alterations described by Snover, type-B those lesions with mucosal changes and type-C the lipomas presenting alterations in both components. According to this three-tier classification system, atypical type-A lesions are somewhat uncommon, type-B lipomas have been reported 6 times and type-C lesions only 2 times[1,3-6]. In atypical lipomas, mucosal hyperplasia and hyperplastic polyps are secondary to ischemia and inflammation; furthermore, polyps may develop adenocarcinomas. In such cases, endoscopic ultrasound can help achieve the diagnosis of atypical lipoma saving the patient from the risk and complications of major surgery[3,5]. Actually, preoperative diagnosis of colonic lipoma (typical or not) is rarely obtained by endoscopic biopsy: Since lipomas are located in the inner layers of colonic wall (90% of cases in submucosa, 10% in subserosa, less than 1% in muscularis propria), most times biopsies result non-contributory as they cannot get the adipose tissue lying beneath the lamina propria[1]. Furthermore, they should not be performed for oozing lesions. On the other hand, they can discover the epithelial benign and malignant changes occurring in the overlying mucosa[1,3,5]. Biopsy can also take part in the so-called "self-amputation" of colonic lipomas: When the overlying mucosa of a large lipoma becomes damaged due to biopsy, enucleation can occur through the ulcerated region and the lesion can be expelled naturally from the rectum. This unusual presentation was first described in 1940 and only 20 cases have been reported so far[7]. Recently, resorting to the same principle, Soares and colleagues successfully treated a large colonic lipoma through an endoscopic unroofing technique[8]. As for treatment, there is general consensus that small (< 2 cm) asymptomatic colonic lipomas do not need any intervention as they show no significant risk of malignant degeneration[2-4]. However, in the light of our experience, we think such lesions do possess a malignant potential and prophylactic endoscopic removal is probably the most correct management to pursue.

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