Problem-based Approach to

GASTROENTEROLOGY AND HEPATOLOGY

Edited by John N. Plevris and Colin W. Howden

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Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Problem-based approach to gastroenterology and hepatology / edited by John N. Plevris, Colin W. Howden.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4051-8227-0 (pbk. : alk. paper)
ISBN-10: 1-4051-8227-X (pbk. : alk. paper)
1. Gastrointestinal system–Diseases xDiagnosis–Case studies. 2. Liver–Diseases–Diagnosis–Case studies. I. Plevris, John N. II. Howden, Colin W.
[DNLM: 1. Gastrointestinal Diseases–diagnosis–Case Reports. 2. Gastrointestinal Diseases–therapy–Case Reports. 3. Liver Diseases–diagnosis–Case Reports. 4. Liver Diseases–therapy–Case Reports. WI 140]
RC808.P76 2012
616.3'3–dc23

2011015322

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 9 on 11.5 pt Sabon by Toppan Best-set Premedia Limited
Printed and bound in Singapore by Markono Print Media Pte Ltd

1 2012

Problem-based Approach to Gastroenterology and Hepatology

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Preface

Problem-based approaches are commonly used in Medicine as effective learning tools; the problem drives knowledge, thus promoting critical thinking and making the whole educational process interesting and relevant. We hope that this book, based on the above principles, will be of value to physicians who are training in Gastroenterology and Hepatology and who may be preparing to take a specialty postgraduate examination. Given its size, this book is clearly not intended to be a major treatise on digestive disorders. Furthermore, we do not claim that reading it will guarantee success in a relevant postgraduate examination in Gastroenterology/Hepatology. Rather, we hope that it will stimulate further reading, will supplement other preparations for those examinations and provide valuable insight into how some of the experts – from both sides of the Atlantic – approach common, important clinical issues in these specialties. Each chapter contains a number of case scenarios that raise questions of diagnosis and management. Our expert authors then present valuable discussion and important learning points about each case.

We have been fortunate to be able to draw on the expertise of friends and colleagues from both sides of the Atlantic (and beyond). We therefore expect that this book will be of value to a broad, multinational readership. It has been said that the UK and the USA are "*two countries separated by a common language*". (The derivation of that is uncertain having been variously attributed to Winston Churchill, Oscar Wilde and George Bernard Shaw – any of whom could have prepared a more entertaining preface than this). We hope that this is not the perception of this book. Authors based in the USA have used American spelling and units of measurement; those based in the UK have used their own frames of reference. Hopefully, both are clear and readers will learn from both.

We would like to take this opportunity to thank all of our invited authors for their contributions to this book and their commitment to this project. We are also grateful to the editorial team at Wiley-Blackwell for all the support and effective co-ordination.

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January 2012

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PART ONE

Gastroenterology

1 Dysphagia

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Dysphagia refers to difficulty or inability in swallowing food or liquids. Most dysphagia patients are candidates for urgent upper digestive endoscopy, to exclude the presence of esophageal cancer. The annual incidence of upper gastrointestinal malignancy, particularly esophageal adenocarcinoma, is steadily increasing in the western world, being the 5th most common primary site in Scotland [1].

Traditionally, dysphagia has been classified as oropharyngeal or esophageal. Oropharyngeal dysphagia is due to impaired food bolus formation or propagation into hypopharynx. Causes include neuromuscular disorders, cerebrovascular events, mechanical obstruction in the oral cavity or hypophanynx, decreased salivation, Parkinson's and Alzheimer's disease or depression. Esophageal dysphagia can be due to mechanical obstruction, (benign or malignant stricture), dysmotility disorders or secondary to gastro-esophageal reflux. Significant dysphagia is often associated with aspiration pneumonia.

A detailed history is important to elicit a possible etiology. In younger patients dysmotility is more common. The presence of chest pain during swallowing strongly suggests esophageal spasm; dysphagia for both liquids and solids is common is achalasia. In young patients with food impaction eosinophilic esophagitis should always be considered. In the elderly, neurological causes should be considered if the dysphagia is high, while esophageal cancer usually presents with short duration progressive dysphagia for solids with regurgitation and weight loss. New onset hoarse voice and dysphagia, point towards malignant infiltration of the recurrent laryngeal nerve. High dysphagia associated with regurgitation of undigested food from previous days, is strongly suggestive of a pharyngeal pouch.

Despite the different presenting features associated with different causes of dysphagia, there is no reliable way to predict at presentation those patients likely to have a malignant cause. Recently, a scoring system based on 6 parameters (advanced age, male gender, weight loss of >3 kg, new onset dysphagia, localisation to the chest and absence of acid reflux at presentation) could strongly predict malignancy [2]. In this chapter, three selected cases will illustrate the different etiologies of this important alarm symptom.

Case 1: dysphagia for liquids and solids

Case presentation

A 52-year-old man reports a 9-month history of difficulty swallowing both liquids and solids with meals and localizes the problem to upper sternum. He gets frequent episodes of coughing and choking when lying flat at night after meals. More recently, he has noticed spontaneous regurgitation of clear, foamy liquid and undigested food into his mouth, especially when bending over after dinner. He has lost over 15 lb (6.8 kg) since his symptoms began. Heartburn, which had been a problem in the past, has notably improved

Problem-based Approach to Gastroenterology and Hepatology, First Edition. Edited by John N. Plevris, Colin W. Howden.
 Published 2012 by Blackwell Publishing Ltd.

since his dysphagia began. Additional complaints include episodes of squeezing pain lasting for several minutes to 1 hour without radiation that can occur at any time and are unrelated to physical activity or meals. Drinking cold water sometimes alleviates the pain.

Past medical history: hypertension

Medications: lisinopril

Social history: employed as a businessman. Moved to the USA from Bolivia 20 years ago. Smokes 20 cigarettes per day. Drinks 3–4 glasses of wine per week

Family history: no family history of cancer or swallowing disorders

Physical examination: unremarkable

In particular, oral cavity without mucosal abnormalities, intact dentition, with no neck masses, lymphadenopathy or goiter. No evidence of sclerodactyly or telangiectasia.

Upper endoscopy revealed a dilated esophagus with approximately 200 mL of retained, semisolid debris despite a 36-hour liquid diet (Figure 1.1a). The underlying mucosa appeared with scattered superficial erosions and mild, diffuse nodularity. Constriction of the esophagogastric junction was noted with minimal resistance to passage of the endoscope into the stomach (Figure 1.1b). Pylorus was patent and the duodenum was normal.

Esophageal manometry was performed using a high-resolution, solid-state catheter assembly with contour pressure topography (Figure 1.2) showed panesophageal pressurization or common cavity phenomenon in response to a water swallow. Failed deglutitive relaxation of the lower esophageal sphincter was evident. The presence of an esophagogastric pressure gradient is seen in the esophagus before the swallow suggestive of achalasia.

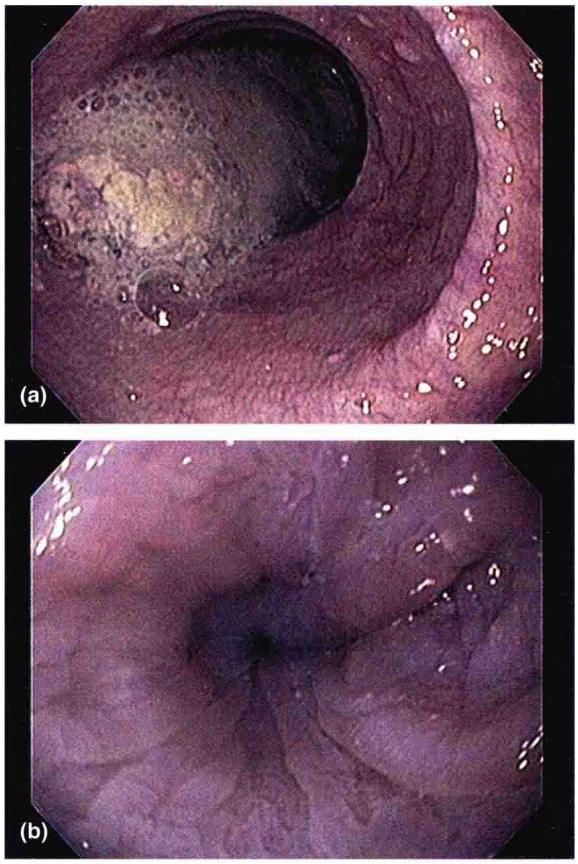

Figure 1.1 Endoscopic images of the esophagus: (a) a moderately dilated esophageal body with retained food and secretions in spite of a 12-hour fast; (b) a constriction at the level of the esophagogastric junction in the same patient.

Questions

- What are the diagnostic considerations in this patient?
- What are the clinical symptoms of achalasia?
- What diagnostic tests are useful in achalasia?
- What is the pathophysiology of achalasia?
- What are the benefits and risks of different treatment options that should be discussed with this patient?
- What are the complications of achalasia?

Differential diagnosis

Esophageal dysmotility should be considered in any patient presenting with dysphagia for both liquids and solids. A few caveats to this rule exist:

- First, patients with oropharyngeal dysphagia may present with liquid and solid dysphagia and, in fact, may have greater difficulty with liquids than solids. However, the fact that this patient localizes his dysphagia to the sternal area excludes an oropharyngeal etiology.
- Second, patients with esophageal food impaction typically have difficulty swallowing liquids and even their own saliva. However, the history was not consistent with repeated food impactions in this case.

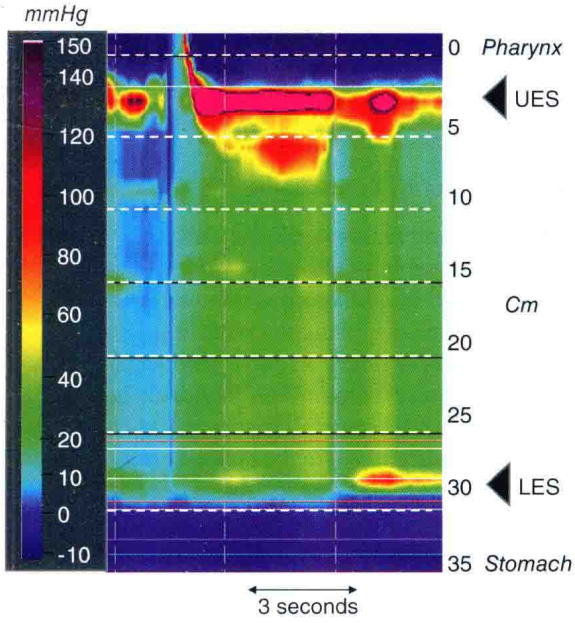

Figure 1.2 High-resolution esophageal manometry pressure contour plot depicting a water swallow. Panesophageal pressurization above intragastric pressure is seen and failed lower esophageal sphincter relaxation is evident.

• Third, the dysphagia that accompanies an advanced esophageal malignancy produces progressive obstruction. Although a consideration here, such patients present with a more rapid transition from solid to semisolid to liquid dysphagia over time.

The three major esophageal motor disorders are achalasia, scleroderma, and diffuse esophageal spasm (DES). Patients with scleroderma have typically mild dysphagia and in most cases is accompanied with cutaneous manifestations. Although both DES and achalasia are possible diagnoses in this patient, dysphagia in DES is generally less severe and more intermittent than in achalasia.

Clinical presentation of achalasia

Achalasia is an uncommon but important disease. The clinical manifestations as well as treatment center on the integrity of the lower esophageal sphincter (LES). Dysphagia and regurgitation are the most commonly reported symptoms. Nocturnal regurgitation can lead to night cough and aspiration. With progressive disease weight loss can occur. Chest pain is well recognized in achalasia and has been reported in 17–63% of patients but its mechanism is unclear although proposed etiologies include secondary or tertiary esophageal contractions, esophageal distension by retained food, gastro-esophageal reflux, esophageal irritation by retained medications, food, and bacterial or fungal overgrowth. Paroxysmal pain may be neuropathic in origin. Inflammation within the esophageal myenteric plexus could also be a contributory factor. More than one mechanism is likely operative in an individual patient.

A prospective study found no association between the occurrence of chest pain and either manometric or radiographic abnormalities [3]. Patients with chest pain were younger and had a shorter duration of symptoms compared with patients with no pain, but treatment of achalasia had little impact on the chest pain, in spite of adequate relief of dysphagia. Counter to this, a recent surgical series reported adequate relief of chest pain after a Heller myotomy [4]. Importantly, chest pain is not a universal feature in achalasia. In fact, many patients appear unaware of either esophageal distension or the prolonged the prolonged esophageal retention of food. Recent studies using esophageal barostat stimulation have demonstrated that some patients with achalasia have diminished mechanical and chemosensitivity of the esophagus [5]. Such differences may explain the heterogeneity of visceral sensitivity in the achalasia population.

Diagnostic evaluation

Upper endoscopy is the first line investigation in suspected achalasia. Findings include esophageal dilation with retained saliva or food and annular constriction of the gastroesophageal junction. Intubation of the stomach is achieved with minor resistance due to raised LES pressure. Significant difficulty passing an endoscope through the gastroesophageal junction should raise the index of suspicion for pseudoachalasia due to neoplastic infiltration of the distal esophagus or gastric cardia. In spite of these recognized endoscopic features, upper endoscopy was reported as normal in 44% of a series of newly diagnosed achalasia patients [6]. A barium esophagogram (swallow) can be highly suggestive of achalasia, particularly when there is the combination of esophageal

dilation with retained food and barium, and a smooth, tapered constriction of the gastroesophageal junction. However, the diagnosis of achalasia was suggested in only 64% of barium examinations in the previous study [6].

Esophageal manometry has the highest diagnostic sensitivity for achalasia and should be performed when the etiology of dysphagia is not evident by endoscopy alone. Findings include distal esophageal aperistalsis and incomplete or absent LES relaxation. Additional supportive features include a hypertensive LES and low-amplitude esophageal body contractions. by endoscopic or radiographic examination.

Although manometry is regarded as the "gold standard" for the diagnosis of achalasia, heterogeneity exists in the manometric presentation. The most commonly recognized variant is known as "vigorous achalasia," variably defined by the presence of normal to high amplitude esophageal body contractions in the presence of a non-relaxing LES. Such contractions are generally simultaneous and can be difficult to distinguish from common cavity phenomena. Although vigorous achalasia may represent an early stage of achalasia, studies have failed to demonstrate differences in terms of clinical presentation, although botulinum toxin has been reported to be more effective in patients with vigorous achalasia. Additional manometric variants of achalasia include rare individuals with intact peristalsis through most of the esophageal body and with preservation of either deglutitive or transient LES relaxation [7]. The significance in defining these variants lies in the recognition that these sometimes confusing manometric findings are still consistent with achalasia when combined with clinical data supportive of the diagnosis.

High-resolution esophageal manometry (HRM) combined with contour plot topographic analyses can significantly improve the accuracy of esophageal manometry. HRM allows for automated analysis of more detailed quantitative data. An example of the utility of this methodology is the interpretation of impaired LES deglutitive relaxation in the setting of exaggerated respiratory contractions of the crural diaphragm. Intrabolus pressure elevations are more readily apparent and quantified using HRM. A recent retrospective study subclassified 99 achalasia patients into those with classic achalasia with minimal esophageal pressurization, achalasia with esophageal compression (panesophageal pressurization in excess of 30 mmHg), and achalasia with spasm [8]. Panesophageal pressurization was a positive predictor whereas esophageal spasm was a negative predictor of treatment response.

Secondary forms of achalasia

The most concerning secondary etiology is cancer, which can present as achalasia by one of three mechanisms. The first and most common occurs through direct mechanical obstruction of the gastroesophageal junction. This is referred to as pseudoachalasia, and has been most commonly described with distal esophageal and proximal gastric adenocarcinomas. Cancer can also infiltrate the submucosa and muscularis of the LES and disrupt the myenteric neurons, resulting in achalasia without an endoscopically visible mucosal abnormality. Finally, achalasia can be a manifestation of paraneoplastic syndrome with circulating autoantibodies that are directed at the myenteric neurons. This syndrome is a rare but important complication of small cell lung cancer.

Chagas' disease, a parasitic infection caused by *Trypanosoma cruzi*, is endemic to areas of Central and South America. The esophagus is most commonly involved, and manifests itself as secondary achalasia in 7–10% of chronically infected individuals. Chagas' disease should be a consideration in the evaluation of achalasia patients in the USA, given that the gastrointestinal sequelae can manifest years or decades after the acute infection. Our patient had positive serological testing for antibodies to *T. cruzi*, consistent with chronic infection. The management of his achalasia does not change but evaluation for other cardiac and visceral manifestations of the parasite are indicated.

Pathogenesis

While the etiology of primary achalasia remains unknown, several hypotheses have been proposed. Several studies have implicated viral agents. A study using DNA hybridization techniques found evidence of varicella-zoster virus in three of nine myotomy specimens from patients with achalasia [9]. The herpes virus family was specifically targeted in this study, given their neurotropic nature. The predilection of the herpesviruses for squamous epithelium as opposed to columnar epithelium makes this an attractive hypothesis and could explain why achalasia

involves only the esophagus, while sparing the remainder of the gastrointestinal tract. More recent studies however, failed to detect the presence of measles, herpes, or human papillomaviruses in myotomy specimens of 13 patients with achalasia. This negative study does not exclude the possibility of either an alternate viral species or past viral infection with clearance of the inciting pathogen from the host tissue. Supporting the viral hypothesis is a recent study demonstrating immunoreactivity of lymphocytes from the LES of patients with achalasia in response to herpes simplex virus HSV-1 antigens. In this study, analysis of oligoclonal expansion of T cells provided evidence for immune activation thus resulting in autoimmune destruction of enteric neurons [10].

An autoimmune etiology of achalasia is supported by the presence of circulating autoantibodies against the myenteric plexus. These have been shown in a few studies to be more prevalent in achalasia patients than in controls. However, a recent study detected significantly higher immunostaining of the esophageal myenteric plexus neurons using serum from both achalasia and gastroesophageal reflux disease (GERD) patients than controls, suggesting that such antibodies represent an epiphenomenon rather than a causative factor [11]. The presence of a lymphocytic infiltrate consisting of CD3+ and CD8+ T cells in the myenteric plexus not found in controls, also supports an autoimmune etiology [11,12].

Treatment

Treatment options for idiopathic achalasia include medical therapy, endoscopic botulinum toxin injection, endoscopic pneumatic dilation, and surgical myotomy [13–15]. All forms of therapy seek to reduce the LES pressure to allow for improved esophageal clearance by gravity because the esophageal peristalsis is impaired.

Medical therapy with calcium channel antagonists or nitrates has demonstrated limited efficacy. Medical therapy is generally restricted to patients awaiting more definitive therapy or patients who are not candidates for more invasive therapies and who have not responded to treatment with botulinum toxin.

Botulinum toxin is both easy and safe to administer [16]. To date, there have been over 15 prospective studies involving over 450 patients from around the world that have examined its efficacy. Response rates at 1 month after administration average 78% (range 63–90%). By 6 months, the clinical response drops to 58% (range 25–78%), and to 49% (range 15–64%) at 12 months. Moreover, improvement in objective measures of esophageal function are significantly lower after botulinum toxin than other more definitive therapies for achalasia [17]. Given the limitations to the efficacy and durability of response, botulinum toxin is generally reserved for patients who are not candidates for pneumatic dilation or Heller myotomy.

Dilation of the esophagus is the oldest form of therapy for achalasia. Currently, the Rigiflex pneumatic dilator (Boston Scientific Corp, Boston, MA) is the most widely used dilating system. A non-compliant polythylene balloon that comes in three sizes designed to inflate to fixed diameters of 3, 3.5, or 4 cm is used. The overall success rates defined by good to excellent relief of symptoms averages 85% (range 70–92%) with a mean follow-up period of 20 months. Age, balloon diameter, post-dilation LES pressure, clearance of barium on an esophagogram, and prior dilation have been identified as predictors of success. Similar to the botulinum toxin experience, several studies have reported that older patients respond better. Eckardt found a 2-year remission rate of 29% in patients under 40 compared with 67% for those over 40 [18]. Long-term follow-up studies of the effectiveness of pneumatic dilation have reported a substantially lower response rate of 30–40% – approximately half that reported in the short-term studies. Thus, repeated dilations are to be expected when using pneumatic dilation as primary therapy. The main complication of pneumatic dilation is esophageal perforation. Published series have reported perforation rates of 0–8% with a mean rate of 2.6%.

Laparoscopic Heller myotomy has greatly advanced the surgical approach to achalasia. It allows for shorter hospital stays and less recovery time than open cardiomyotomy. Furthermore, the laparoscopic approach has substantially challenged the use of dilation as primary therapy since perforation from pneumatic dilation generally necessitates repair via open thoracotomy. Success rates reported in large series approximate 90%, with mean follow-up approaching 2 years. Perioperative complications of perforation, hemorrhage, or pneumothorax are uncommon and readily managed intraoperatively. Reflux is a not