ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2020 December 27; 12(12): 1136-1371

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

PUBLICATION DATE
December 27, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
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World Journal of Hepatology

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World J Hepatol 2020 December 27; 12(12): 1158-1167

DOI: 10.4254/wjh.v12.i12.1158

ISSN 1948-5182 (online)

MINIREVIEWS

Spectrum of esophageal motility disorders in patients with liver cirrhosis

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Author contributions: Khalaf M, Castell D and Elias PS reviewed the literature and wrote the manuscript; and all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

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Abstract

Disorders of esophageal motility have been described in patients with cirrhosis in a small number of studies. In this review, we aim to provide an overview of the available evidence on esophageal motility disorders in cirrhosis and their clinical implications. This review delves into the following concepts: (1) Gastroesophageal reflux disease is common in liver cirrhosis due to many mechanisms; however, when symptomatic it is usually nocturnal and has an atypical presentation; (2) Endoscopic band ligation is better than sclerotherapy in terms of its effect on esophageal motility and seems to correct dysmotilities resulting from the mechanical effect of esophageal varices; (3) Chronic alcoholism has no major effects on esophageal motility activity other than lower esophageal sphincter hypertension among those with alcoholic autonomic neuropathy; (4) An association between primary biliary cholangitis and scleroderma can be present and esophageal hypomotility is not uncommon in this scenario; and (5) Cyclosporin-based immunosuppression in liver transplant patients can have a neurotoxic effect on the esophageal myenteric plexus leading to reversible achalasia-like manifestations.

Key Words: Esophagus; Motility; Cirrhosis; Dysmotility; Gastroesophageal reflux disease; Manometry

Core Tip: (1) The link between liver cirrhosis and esophageal motility; (2) The association of cirrhosis with gastroesophageal reflux disease; (3) Esophageal motility

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 1, 2020
Peer-review started: August 1, 2020
First decision: September 17, 2020
Revised: October 1, 2020
Accepted: November 6, 2020
Article in press: November 6, 2020
Published online: December 27, 2020

P-Reviewer: Dantas R, Wang D
S-Editor: Huang P
L-Editor: A
P-Editor: Xing YX

disorders in cirrhosis patients (with and without esophageal varices); (4) The impact of variceal treatment on esophageal motility and function; (5) The impact of some etiologies of cirrhosis on esophageal motility, particularly in cases of chronic alcoholism and primary biliary cholangitis; and (6) The effect of immunosuppressive therapy used in post liver transplantation patients on esophageal motility.

Citation: Khalaf M, Castell D, Elias PS. Spectrum of esophageal motility disorders in patients with liver cirrhosis. *World J Hepatol* 2020; 12(12): 1158-1167
URL: https://www.wjgnet.com/1948-5182/full/v12/i12/1158.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i12.1158

INTRODUCTION

Disorders of esophageal motility have been described in patients with cirrhosis in a small number of studies where conventional manometry was used to assess their esophageal function. Likely, due to the severity of their liver disease, symptomatic esophageal dysmotilities are rarely investigated in routine clinical practice for this population. However, the clinical implications, especially in the setting of dysphagia, can be potentially deleterious for a patient's quality of life and nutritional status, which may contribute to increased risk of complications and hepatic decompensation. In this review, we aim to provide an overview of the available evidence on esophageal motility disorders in cirrhosis and their clinical implications.

The review will cover the following topics: (1) The link between liver cirrhosis and esophageal motility; (2) The association of liver cirrhosis with gastroesophageal reflux disease (GERD); (3) Esophageal motility disorders in liver cirrhosis patients [with and without esophageal varices (EV)]; (4) The impact of variceal treatment on esophageal motility and function; (5) The impact of some etiologies of liver cirrhosis on esophageal motility, particularly in cases of chronic alcoholism and primary biliary cholangitis (PBC); and (6) The effect of immunosuppressive therapy used in post-liver transplantation patients on esophageal motility.

HOW LIVER CIRRHOSIS CAN AFFECT ESOPHAGEAL MOTILITY

The contraction of the esophageal smooth muscle is regulated by both central and peripheral control mechanisms in a complex mechanism. Vagal preganglionic motor nerves synapse with postganglionic motor neurons in the myenteric plexus (Auerbach's plexus). Both pre- and post-ganglionic motor neurons can be excitatory or inhibitory. The amplitude of contraction is determined by a balance between intrinsic excitatory cholinergic, and inhibitory nitric oxide (NO) producing neurons. It was found that of 60%-70% of myenteric neurons are connected to vagal excitatory efferent neurons. Thus, in situations where parasympathetic hypofunction is evident, the amplitude of peristaltic contractions would be hampered[1-3].

Liver cirrhosis is known to be associated with autonomic neuropathy (parasympathetic hypofunction and sympathetic hyperfunction), increased NO production, and gut hormonal changes that can impact esophageal motility and lead to esophageal hypomotility[4].

Miyajima *et al*[5] studied the autonomic nervous function in 27 patients with liver cirrhosis by using spectral analysis of heart rate variability. The results showed that decreased parasympathetic tone and increased sympathetic tone are commonly observed in patients with liver cirrhosis, particularly those in a hyperdynamic state. The cause of this autonomic dysfunction was presumed to be caused by increased NO production and increased activity of the renin-angiotensin system.

Also, Koshino *et al*[6] conducted a neuropathological study in autopsy specimens of the esophagus of 8 cirrhotic patients with large EV, in which esophageal motility disorders were demonstrated by esophageal manometry, esophagography, and endoscopy. The histological findings were compared to those of 7 control patients without esophageal or liver disease. The study demonstrated a significant reduction of the number of ganglion cells at the myenteric plexus in the esophagus of cirrhotic patients with large varices. Thus, the investigators suggested that such

neuropathological changes may have contributed to, at least in part, the development of impaired motility of the esophagus with large varices.

LIVER CIRRHOSIS AND GERD

Generally, the two mechanisms that mainly contribute to the pathogenesis of GERD are: (1) Increased rate of transient lower esophageal sphincter (LES) relaxations; and (2) Decreased LES resting pressure (LESP) leading to stress and spontaneous reflux. Many factors in liver cirrhosis contribute to increases in LES relaxation: (1) Increased NO concentration in patients with liver disease can lead to a decrease in the LESP and increased transient LES relaxations[7]; (2) Increased levels of some gastrointestinal (GI) hormones like vasoactive peptides and neurotensin are known to reduce the pressure of the LES[8,9]; (3) The presence of ascites creates an increase in intra-abdominal pressure[10,11]; and (4) Lastly, the presence of EV causes mechanical impairment of esophageal emptying, thus extending the contact time between the refluxate and the esophageal mucosa[12].

GERD can be viewed as a motility disorder involving the LES and the lower esophagus. Detection and treatment of GERD in the setting of liver cirrhosis are particularly important, as GERD can significantly affect the quality of life of those patients. Also, persistent GERD is considered to be the main cause of esophagitis and can lead to damage to the mucosal barrier possibly creating a nidus for bleeding. The presence of esophagitis in cirrhotic patients has the potential to result in more complications given the effects of cirrhosis on clotting factors and indirectly on platelets.

The prevalence of GERD in liver cirrhosis patients was reported to be ranging between 55%-64%[13,14]. Zhang *et al*[13] assessed 78 cirrhotic patients without EV using esophageal manometry, simultaneous ambulatory 24-h esophageal pH, and bilirubin monitoring and esophagogastric duodenal endoscopy (EGD). The study showed that the resting LES pressure in cirrhotic patients was diminished. This manometric finding was attributed to the high levels of NO in the systemic circulation of patients with cirrhosis, leading to hypotensive LES and increased GERD. Moreover, the same study reported a higher prevalence of reflux esophagitis (37%) compared to healthy controls. The study also demonstrated that mixed acid and bile reflux was the main pattern of reflux in cirrhotic patients with a stepwise increase of mixed reflux along with the severity of liver function damage. However, assessment of the symptom burden in those patients revealed that typical GERD symptoms were reported in just (32%) of patients with cirrhosis, with the symptoms being predominantly nocturnal.

Another study of 1280 patients with the chronic liver disease found that patients with the most severe cirrhosis had asymptomatic manifestations and/or atypical GERD symptoms[15]. In this study, typical GERD symptoms only accounted for around 10% of cirrhotic patients.

Therefore, adding questions about atypical GERD symptoms should be a part of the cirrhotic patient's history and possibly can be incorporated into variceal screening indications. If present, GERD work-up should be done with EGD, or at least empirical GERD treatment might be considered.

EV AND MOTILITY

Liver cirrhosis without varices

Two notable studies in the literature examined the effects of liver cirrhosis (without the effect of varices) on the motility of the esophagus. A Chinese research group assessed seventy-eight cirrhotic patients with no EV confirmed by upper endoscopy *vs* thirty healthy control volunteers[13]. The study showed that cirrhotics without EV had significantly abnormal LESP, peristaltic amplitude, peristaltic duration and velocity, in comparison to those in the control group. LESP was significantly lower in patients with severe liver function damage, and had a negative correlation with Child-Pugh score ($P < 0.01$, $r = -0.625$). These results confirmed that liver cirrhosis itself is another important factor impacting esophageal motility.

Another study by Passaretti *et al*[16], assessed esophageal motility in 45 patients with cirrhosis and EV, 15 patients with cirrhosis without EV, and 20 healthy controls. The study demonstrated diminished peristaltic wave amplitude in the lower esophagus.

In summary, the majority of cirrhotic patients without varices presented with

esophageal dysmotility (particularly hypomotility), and it was concluded that cirrhosis itself was an important causative factor.

Liver cirrhosis and varices

Abnormalities in esophageal motility may be further aggravated by the presence of EV. A study that included 45 patients with EV and 45 healthy controls showed decreased peristaltic wave amplitude and increased frequency of tertiary contractions in the former group, but these abnormalities were not associated with symptoms[17].

Another study showed that the presence of varices was associated with an increase in LES length and reduced lower esophageal contraction pressure and failure of sphincter relaxation during swallowing[18].

Passaretti *et al*[16] compared cirrhotics with varices *vs* those without varices *vs* controls. Cirrhotics with varices showed a decreased amplitude of peristaltic waves in the lower half of the esophagus ($P < 0.01$). Resting LES pressure and duration of sphincter relaxation were similar in patients and controls. The study proved that the presence of EV is associated with more pronounced esophageal motility disorders and that maybe the mechanical effect of the presence of varices. However, the clinical significance of this observation is unclear as these disorders are rarely associated with retrosternal pain or dysphagia. Thus, it seemed that EV itself, independent of the cirrhosis, delayed esophageal clearance and increased the contact time between acid and mucosa.

Furthermore, another study assessed esophageal transit used radionuclide material; reported longer transit time in patients with large varices than in those with small varices (8.3 ± 1.7 s *vs* 7.2 ± 0.7 s, $P < 0.05$)[19]. Another study using scintigraphy found that esophageal transit was prolonged in 47.3% of patients with EV and 29.2% of patients without varices ($P < 0.05$). Also, the frequency of esophageal transit alteration was related to the severity of liver disease using the Child-Turcotte-Pugh (CTP) score, ($P < 0.01$)[20].

Flores *et al*[21] included 74 patients suffering from liver cirrhosis and EV, without previous endoscopic treatment. All of them performed esophageal manometry while 55 patients had 24-h pH monitoring. Esophageal motility disorders have been found in 44 patients (60%). The most prevalent was the ineffective esophageal motility (IEM), observed in 28%. This showed that the majority of cirrhotic patients with treatment-naive EV have esophageal motility disorder, mainly IEM. The clinical relevance of these manometric findings needs more research in the scope to determine the real significance of these abnormalities.

ESOPHAGEAL MOTILITY CHANGES AFTER VARICEAL TREATMENT

Band ligation

Endoscopic variceal ligation (EVL) has largely replaced sclerotherapy based on comparative effectiveness in the management of acute variceal bleeding and eradicating EV with considerably fewer complications. Also, EVL does not seem to have a significant effect on esophageal motility[22]. Chen *et al*[17] examined forty-five patients who had liver cirrhosis and EV before and after EVL. Another 45 matched patients without hepatic, esophageal, or systemic disease served as the control group. The study demonstrated that the LESP and contractile amplitude in the lower esophagus was significantly lower in patients before EVL ($P < 0.05$) but returned to the level of control subjects after EVL ($P > 0.05$). The percentage of tertiary waves was significantly higher in patients before and after EVL than in the control group ($P < 0.05$). However, no significant swallowing disturbance was noted in patients after EVL. The study further confirmed that the presence of varices affects esophageal motility. Interestingly, EVL normalized esophageal motility and did not induce any motility abnormality.

Another study showed similar results where manometric abnormalities detected before banding were corrected after the procedure[23]. However, a different study demonstrated an inverse correlation between the frequency of EVL sessions and esophageal peristaltic amplitudes[24].

Regarding the relationship between EVL and GERD, de la Peña *et al*[25] assessed the presence of GERD in twenty-six cirrhotic patients using pH monitoring before and after EVL**.** Five patients had excess gastroesophageal reflux before the band ligation. A further six patients developed excess gastroesophageal reflux after endoscopic treatment. The only factor implicated in the development of excess gastroesophageal reflux was the use of sclerosant at the end of treatment to ensure complete eradication.

The study concluded that EVL does not significantly provoke excess GERD if sclerosant is not used in the endoscopic technique.

Sclerotherapy

Endoscopic injection sclerotherapy (EIS), has a documented effect on esophageal structure and motility. EIS mainly impacts the function of the lower esophagus resulting in decreased amplitude and/or velocity and increased duration of the peristaltic contractions, which may be replaced by non-propagating contractions[22]. It may also prolong acid clearance, but this is usually transient and resolves within a week. Therefore, a short course of antacid therapy is justified following EIS. A small study, assessed esophageal motility pre and post EIS, showed decreased LES pressure in the latter, but without a significant increase in GERD episodes[26]. The hypothesized mechanism of this motility abnormality is that the sclerosing agent may induce vagal nerve injury. EIS has been also associated with structural abnormalities, mainly sclerosant-induced esophageal ulcerations and fibrotic strictures[27], and less commonly with esophageal perforation[28]. Strictures can be associated with dysphagia and may require endoscopic dilatation.

Bretagne *et al*[29] assessed the effects of EIS on esophageal symptoms and function. The study included 24 cirrhotic patients 60 d after variceal eradication had been achieved (group I); nine cirrhotics with varices (group II) and 16 normal volunteers (group III) as a control group. After sclerotherapy, nine patients developed an esophageal stricture and most of them had dysphagia. The percentage of patients with abnormal peristaltic waves (non-propulsive contractions) was significantly more in the sclerotherapy group. Also, the percentage of time below pH 4 did not differ between the EIS group and the normal control group on 3 h postprandial esophageal pH monitoring.

A similar conclusion was obtained by Sauerbruch *et al*[30], in which the study group found that sclerotherapy of EV may lead to a reduced peristaltic esophageal motility with an impaired transport function. This could contribute to the development of dysphagia or esophagitis.

Masclee *et al*[31] tried to test the hypothesis that these complications result from vagal nerve injury due to EIS. This was done by measuring pancreatic polypeptide secretion in response to insulin-induced hypoglycemia (insulin 0.1 U/kg i.v.), a well-known stimulus for vagal nerve function. Six patients with cirrhosis and variceal bleeding were included before and 3 d after the first sclerotherapy (group A). Also, six other patients with cirrhosis after 6 mo of successful repeated EIS (group B) and 12 control subjects (group C) were tested. No significant reduction in the integrated pancreatic polypeptide secretion between or within groups. However, only a transient and reversible reduction in pancreatic polypeptide secretion were observed directly after sclerotherapy.

GERD after EIS was investigated as a possible contributing factor in the development of strictures following EIS[32]. Twelve randomly selected patients underwent repeated EIS for the management of bleeding EV. Half of the patients developed strictures; however, there were no significant differences between stricture and non-stricture patients during 24 h of esophageal pH monitoring. It was concluded that GERD is not likely to play a major role in EIS stricture formation.

Esophageal band ligation vs sclerotherapy

A randomized controlled study comparing esophageal function in patients receiving EIS *vs* EVL following an episode of variceal bleeding. The esophageal function was assessed utilizing esophageal manometry and 24-h pH study at presentation and a month later[33]. EIS was associated with decreased peristaltic wave amplitude, increased simultaneous contractions, and increased exposure to pH < 4. No esophageal dysfunction was observed in the EVL group. As mentioned earlier, EVL led to the partial improvement of esophageal dysmotility in 45 patients with cirrhosis at 4-6 wk following variceal obliteration[17].

A comparison between these two endoscopic techniques was conducted by another study by Goff *et al*[34]. Twenty-eight patients (seven with no prior treatment, eight undergoing sclerotherapy, and 12 undergoing variceal ligation) were evaluated with a symptom questionnaire and esophageal manometry. The study showed that variceal ligation therapy causes less esophageal dysfunction and has fewer local complications, as eight of the nine sclerotherapy patients had a stricture after treatment that required dilatation, whereas none of the ligation patients had strictures.

Radionuclide esophageal transit tests were used to compare esophageal emptying following EIS *vs* EVL[19]. The results showed significant impairment of esophageal transit time with EIS but the impact was reversible. However, EVL exerts no

significant impact on esophageal emptying.

Surgical treatment of varices

Ten to 15% of patients with variceal bleeding do not respond to non-operative methods and require surgical intervention. Surgical options include shunt and non-shunt procedures. Devascularization (non-shunting) operations can serve in bridging the interim waiting period until the definitive treatment (live transplantation) is available to be done. In the United States, the options of non-surgical modalities, as well as liver transplantation, are more easily available. However, in other parts of the world where the facilities are not as well developed, devascularization procedures still have a significant role to play in the emergency management of esophagogastric variceal bleeding[35].

We found only one study discussing the effects of surgical variceal treatment on esophageal function. Draczkowski *et al*[36] assessed the esophageal motility in patients undergoing extensive devascularisation and esophageal transection. The study examined eight patients before and after the operation. It demonstrated no significant differences between pre and postoperative manometric findings, suggesting that the surgery does not affect a significant effect on esophageal motility. Future studies are needed to validate these findings.

IMPACT OF ALCOHOL ON ESOPHAGEAL MOTILITY

Alcohol consumption can affect the upper GI tract by multiple mechanisms relying either on direct contact of ethanol and/or its metabolite acetaldehyde with the mucosa as well as by the fermentation products of alcoholic beverages. These mechanisms can lead to: (1) Inflammation of the esophageal and gastric mucosa; (2) Impairment of motility and affection of GI sphincter pressures; and (3) Alteration of gastric acid secretion. All these effects are considered reversible and dose-dependent[37-40].

Increased prevalence of GERD or reflux esophagitis has been reported in alcoholics[41]. Inflammation of the esophageal mucosa induced by ethanol is caused by direct damage of the mucosal barrier which predisposes tissue to acid injury. In animal models, exposure of esophageal epithelium to HCl alone induced little or no morphological or functional changes. However, the simultaneous exposure to both ethanol and HCl resulted in significant morphologic and functional impairment[42].

Both acute and chronic alcohol consumption affects esophageal motility. Acute ethanol administration *in vivo*, in man as well as in cats, caused a transient decrease in the LESP, amplitude of contraction of the lower esophagus, and mucosal clearance due to a primary and secondary peristalsis reduction[43]. In a cat model, cervical vagotomy or nerve block did not prevent the effects of acute ethanol administration suggesting a direct inhibitory effect of alcohol on esophageal muscle cells[44,45]. In an *in vitro* model, carbachol-dependent shortening of the cells was significantly diminished when esophageal smooth muscle cells were pre-exposed to ethanol, thus confirming that ethanol directly inhibits the contractile activity of the esophageal muscle cells[44].

Conversely, the chronic effect of alcohol on esophageal motility resulted in an increased tone of the LES and reduced esophageal clearance[43]. Yazir *et al*[46] reported that chronic alcohol consumption in an alcohol-fed rat model, caused impairment of LES relaxation and contractile responses of both LES and muscularis mucosa layer of the esophagus.

Ferdinandis *et al*[47] examined twenty-three chronic alcoholic subjects and 12 control subjects. Eight alcoholic subjects had heartburn and regurgitation but none had dysphagia. Ten (43%) alcoholic subjects had autonomic neuropathy and four (17%) had increased GERD. LES hypertension was observed in alcoholic subjects with autonomic neuropathy. Esophageal body motility parameters (*i.e.*, frequency, duration, amplitude, and percentage of peristaltic waves) were not significantly different between alcoholic subjects and controls.

These results of esophageal manometry on chronic alcoholic subjects, seem to show that long-term ethanol intake has no major effects on the esophageal motility activity other than LES hypertension among those with alcoholic autonomic neuropathy.

COEXISTENT PBC WITH CREST SYNDROME (REYNOLDS SYNDROME)

Esophageal motility abnormalities are well known in progressive systemic sclerosis

(scleroderma/CREST syndrome), Sjögren's syndrome, and some rheumatic diseases with sicca syndrome[48-50]. However, there is not enough data about esophageal dysmotility in patients with PBC.

PBC is a chronic progressive autoimmune disease affecting intrahepatic bile ducts[51]. A distinctive feature of PBC is its association with autoimmune disorders. Sjögren's syndrome and autoimmune thyroiditis appear to be the most common extrahepatic[52].

PBC is reported to be associated with CREST syndrome in 1%-6% of cases[51]. Márquez Galán *et al*[53] described this entity in a mini-series of 6 patients with other characteristics and thus, it is sometimes called PACK syndrome (PBC, anti-centromere antibody, CREST syndrome, and keratoconjunctivitis sicca) or Reynolds syndrome. Tojo *et al*[54] reported that, compared with PBC alone, patients with coexistent PBC and CREST syndrome had a higher association of EV in earlier stages of PBC, higher titers of anticentromere antibody, lower titers of antimitochondrial antibody, and a higher prevalence of HLA-DR9.

Esophageal involvement in PBC was investigated using esophageal manometry in 18 patients with PBC *vs* control group of 18 matched subjects[55]. All patients were screened for clinical manifestations of scleroderma and the presence of Sjögren's syndrome. Four patients had scleroderma. Three patients with scleroderma had aperistalsis and diminished lower sphincter pressure. These results indicate that esophageal motility dysfunction is often present in patients with PBC who have scleroderma.

Another study detected esophageal dysmotility in 17 of 37 patients (45.9%) with PBC[52]. The study showed that the most common esophageal motility abnormality in this group of patients was IEM (10 non-specific esophageal motility disorder and 5 patients with esophageal hypomotility).

In summary, it should be remembered that PBC can be associated with an extrahepatic autoimmune disorder such as limited cutaneous SSs (CREST syndrome). Screening for these autoimmune disorders can prevent further morbidity and keep patients viable candidates for a liver transplant.

IMPACT OF IMMUNOSUPPRESSIVES ON ESOPHAIN POST LIVER TRANSPLANTATION PATIENTS

Cyclosporine A (CsA) is an immunosuppressive agent commonly used in liver transplant patients. It is a calcineurin inhibitor drug that exerts its immunosuppressive effect by preventing interleukin-2 (IL-2) production in T cells[56].

Koch *et al*[57] reported a case of a 59-year-old man who underwent liver transplantation for cryptogenic liver cirrhosis. Initial immunosuppressive therapy consisted of CsA-based immunosuppression.

Approximately 3 mo after discharge, the patient started to suffer from dysphagia usually involving solids, associated with intermittent retrosternal pain and globus sensation. A few weeks later, the case presented with vomiting/regurgitation, weight loss, and severe dysphagia for solids and liquids. Esophageal manometry revealed the pattern of achalasia with poor relaxation of the LES and simultaneous, repetitive contractions in the esophageal body. CsA was then discontinued resulting in a significant improvement of the esophageal symptoms. The dysphagia was completely resolved during the follow-up, and the patient returned asymptomatic. Esophageal manometry was repeated three months later, which showed recovery of the LES and esophageal body functions to the normal range.

CsA (calcineurin inhibitor) exerted a neurotoxic effect on the intrinsic nerves of the myenteric plexus, most likely affecting NO-producing neurons. Calcineurin is widely distributed throughout the nervous system and, experimentally, calcineurin inhibition leads to blockage of NO synthase activity, which may contribute to the reported reversible esophageal motility disorder. In conclusion, esophageal manometry should be considered early in the diagnostic workup in transplant patients on CsA-based immunosuppression and presenting with dysphagia.

CONCLUSION

(1) GERD is common in cirrhosis and usually presents with atypical symptoms; (2) EV can impact motility and band ligation is better than sclerotherapy regarding correcting

dysmotilities; (3) Chronic alcoholism has no major effects on the esophageal motility activity other than LES hypertension, on the other hand, acute ethanol consumption seems to lower LES pressure; (4) Reynolds syndrome involves an association between PBC and scleroderma. Esophageal hypomotility is expected in this setting; (5) Cyclosporin-based immunosuppression in liver transplant patients can have a neurotoxic effect on the esophageal myenteric plexus leading to reversible achalasia-like manifestations; and (6) Future studies are needed to determine the association of the liver disease with esophageal dysmotility particularly IEM. As an initial step, studying the prevalence of non-obstructive dysphagia and non-cardiac chest pain in this population will allow us to determine the utility of motility testing in this population.

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