Hepatic and Gastrointestinal Manifestations in Rheumatic and Connective Tissue Diseases

Shinji Shimoda, MD, PhD,1 Yong Chong, MD,1 Mitsuteru Akahoshi, MD,1 Hiroaki Niiro, MD,2 and Hiroshi Tsukamoto, MD1

1 Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
2 Clinical Education Center, Kyushu University, Fukuoka, Japan

Digestive diseases and digestive symptoms are among the most universal diseases in everyday clinical care. However, digestive diseases accompanying rheumatic and connective tissue diseases are often onset with a background of complicated pathologies. Therefore, it is necessary to distinguish these at an early stage and carry out treatment according to the pathology. It is necessary to give specialized support upon precise medical interviews and physical examinations along with making diagnoses by standard clinical and graphic examinations.

Introduction
Rheumatic and connective tissue diseases are disorders of the systemic connective tissue, with the cause or pathology believed to be some form of immune disorder. Except for the consultation of specialists for these diseases, patients with digestive symptoms often consult generalists as digestive diseases are among the most universal diseases. Digestive organ dysfunction due to abnormalities in the connective tissues, ulcers, bleeding, and perforations due to vascular lesions, etc. are some rheumatic and connective tissue diseases accompanied by digestive symptoms. Moreover, in addition to these causes, there are times in which other independent autoimmune diseases often complicating collagen vascular diseases during the course as well as side effects of treatments against other disorders may be the cause thereof. Therefore it must be recommended that generalists have a wide knowledge about hepatic and gastrointestinal diseases based on connective tissue diseases.

Hepatic Diseases That Often Generate as a Complication of Connective Tissue Disease
Primary biliary cirrhosis (PBC)
With PBC, anti-mitochondrial antibodies appear with small intrahepatic cholangitis and bile duct disappearance as pathological features specific to the disease. There are approximately 20,000 patients in Japan. When it becomes intractable to treatment, the patient can only be saved by liver transplantation; therefore, PBC with symptoms of cholestasis (jaundice, hyper ALPnemia/hyper g-GTPnemia) and itching has been
designated as an intractable disease in Japan. It often occurs in middle aged or older women, accompanying connective tissue diseases such as Sjogren’s syndrome, rheumatoid arthritis, etc.

UDCA is used in the treatment of PBC, with bezafibrate empirically used in addition to this. Some become intractable to treatment and advance to cirrhosis of the liver.

Autoimmune hepatitis

Hepatocellular injury is pathologically observed, with hyper immunoglobulinemia as well as anti-nuclear antibodies generated. There are approximately 10,000 patients in Japan. Drug-induced hepatic disorders or those caused by hepatitis virus, alcohol, etc. (mainly hyper ASTnemia/hyper ALTnemia) must be excluded during diagnosis. Sjogren’s syndrome, rheumatoid arthritis, Hashimoto’s disease, etc. are often observed as complications. Steroids are effective.

Hepatic Disorders Accompanying Connective Tissue Diseases

In the case of hepatomegaly, amyloidosis accompanying rheumatoid arthritis (RA) and cardiac insufficiency accompanying systemic lupus erythematosus (SLE) must be differentiated. Regarding both SLE and RA, the incidence of hepatic disorders increases during the active period of the disease. Generally, a variety of hepatic lesions accompany connective tissue diseases, with these often being hepatic disorders related to connective tissue disease if there are no specific findings upon liver biopsy. In such cases, the hepatic function improves along with control of the underlying disease.

With long term use of steroids, there are times in which hepatic disorders caused by fatty liver are observed regardless of the underlying disease being controlled. When hepatic disorders are observed (hyper ASTnemia/hyper ALTnemia as hepatocellular damage type, hyper ALPnemia/hyper g-GTPnemia as biliary tract damage type or combined), regardless of the rheumatic and connective tissue diseases having good course (for example no fever or no local inflammation), it is necessary to confirm that there is no intake of health food, Chinese medicine, or new drugs. It must

be borne in mind that drug-induced hepatic disorders are prone to occur when immunosuppressants are used in the treatment of rheumatic and connective tissue diseases along with therapeutic drugs for rheumatism. Ohira et al reported that liver dysfunction was observed in 39.2% of those with connective tissue diseases and that the incidence of hepatic disorders was high in those with adult-onset Still’s disease (81.3%), dermatomyositis (51.9%), and vasculitis syndrome (48.0%). With adult-onset Still’s disease, the degree of hepatic disorders was proportionate to the serum ferritin level, while it was proportionate to the ALP and CRP level in vasculitis syndrome. Further, drug-induced hepatic disorders (26.1%), fatty liver (7.6%), viral hepatitis (1.3%), etc. were also included as hepatic disorders in connective tissue diseases. Moreover, PBC was observed as a complication in 15.9% of those with rheumatic and connective tissue diseases, while autoimmune hepatitis was observed as a complication in 4.2%.

Gastrointestinal Disease Often Complicating Connective Tissue Diseases

Gastrointestinal lesions accompanying rheumatic and connective tissue diseases are broadly divided into the following: (1) gastrointestinal dysfunction accompanying the underlying disease; (2) side effects of the therapeutic drug; and (3) gastrointestinal infection caused by immunosuppression. There are various lesions ranging from the mouth to the large intestines, in which a variety of pathologies are indicated depending on the disorder (Table 1). In the following, we provide an outline of major gastrointestinal lesions observed in representative connective tissue diseases.

1) Systemic lupus erythematosus (SLE)

Gastrointestinal symptoms occur in 25–40% of SLE, in which gastrointestinal lesions directly caused by SLE are observed in 8–27.5% of patients.2

(1) Lupus enteritis

(1) Ischemic enteritis type

It occurs as an acute abdominal condition. Lesions are mainly observed in the small intestine. Narrowing of the lumen accompanied by swelling of the wall of the small intestine and thumb impression patterns are
### Table 1. Gastrointestinal lesions of rheumatic and connective tissue diseases

<table>
<thead>
<tr>
<th>Mouth/esophagus</th>
<th>Stomach/duodenum</th>
<th>Small intestine</th>
<th>Large intestine</th>
<th>Liver</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic lupus erythematosus</strong></td>
<td>Oral aphthous ulcers</td>
<td>Lupus enteritis (ischemic enteritis)</td>
<td>Lupus enteritis (multiple ulcers)</td>
<td>Autoimmune hepatitis</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td>Amyloidosis</td>
<td>Amyloidosis vaasculitis (ulcer, bleeding, perforation)</td>
<td>Amyloidosis vasculitis (ulcer, bleeding, perforation)</td>
<td>Autoimmune hepatitis</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td><strong>Systemic sclerosis</strong></td>
<td>Limited opening of the mouth, ankyloglossia</td>
<td>Impaired gastric emptying</td>
<td>Intestinal pseudo-obstruction, Malabsorption syndrome</td>
<td>Primary biliary cirrhosis</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td><strong>Polymyositis/dermatomyositis complex</strong></td>
<td>Dysphagia</td>
<td>Complications of gastric cancer</td>
<td>Cyst-like emphysematosa in the intestinal tract</td>
<td>Complications of colorectal cancer</td>
<td>Autoimmune hepatitis Pancreatitis</td>
</tr>
<tr>
<td><strong>Sjogren's syndrome</strong></td>
<td>Dry mouth, atrophy of tongue papillae Caries, taste disorder, dysphagia</td>
<td>Atrophic gastritis</td>
<td>MALT lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vasculitis syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td>Vasculitis (ulcer, bleeding, perforations)</td>
<td>Vasculitis (ulcer, bleeding, perforations) Pancreatitis</td>
</tr>
<tr>
<td><strong>Behçet's disease</strong></td>
<td>Oral aphthous ulcer, esophageal ulcer</td>
<td>Behçet's disease (ileocecal ulcer)</td>
<td>Behçet's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug-induced</strong></td>
<td>Esophageal ulcer (BP), Stomatitis (MTX)</td>
<td>NSAIDs ulcer</td>
<td>NSAIDs ulcer diaphragm disease (NSAIDs)</td>
<td>Hepatic dysfunction (MTX/AZP)</td>
<td></td>
</tr>
<tr>
<td><strong>Infectious diseases</strong></td>
<td>Gingival hypertrophy (CsA)</td>
<td>CMV enteritis</td>
<td>CMV enteritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GERD: Gastroesophageal reflux, BP: Bisphosphonate, MTX: Methotrexate, CsA: Cyclosporine, PPI: Proton pump inhibitor, AZP: Azathioprine, CMV: Cytomegalovirus (Quotation modified from Reference 1)
observed upon X-ray examination. It is observed as an edematous mucous membrane accompanying poor progress, with little change in the surface of the alimentary canal mucosa upon endoscopy. The affected range is a wide range of the small intestine. Ascites are frequently observed along with swelling of the entire small intestine upon CT and abdominal ultrasound. Regarding the pathology thereof, it is believed to occur as vasculitis accompanied by an immune complex in the subserous layer of the submucosa.\(^2\) Regarding treatment, steroids induce a complete response in which rapid improvement in the symptoms and image findings are observed, with relapse observed in many cases.

(2) Multiple ulcers
Chief complaint is usually abdominal pain. Ulcerative lesions similar to intestinal Behçet’s disease are sometimes observed in the lower digestive tract. Vasculitis and thrombus formations are often pathologically observed which are believed to be ischemic injuries and vascular insufficiencies localized in the digestive tract.\(^2\) The standard treatment thereof is moderate to large doses of steroid administration; however, it is important to carefully follow-up the course and determine the indication of surgical treatment due to a high risk of perforation and penetration.

(2) Protein-losing gastroenteropathy
Prominent swelling and serious hypoalbuminemia are generated due to protein loss from the small intestine. Although the incidence is low, there are many reports on Asian patients. It often accompanies hypogammaglobulinemia and hypocomplementemia. Regarding the pathology, vasculitis of the intestinal tract and hyperlucency of the capillary vessels caused by activation of complement, deposition of immune complex, and lymphangiectasis may be considered.\(^3\) Although most patients react to high dose steroid treatment, immunosuppressants are used in combination in some cases.

(3) Intestinal pseudo-obstruction (IPO)
This is a rare intestinal tract complication of SLE that exhibits intestinal obstruction symptoms such as abdominal bloating, abdominal pain, vomiting, etc. despite the fact that there is no mechanical occlusion due to peristaltic movement disorder of the intestinal tract. It is surmised that this is caused by dyskinesia of the internal smooth muscle and abnormalities in the intestinal tract nerves and internal autonomic nervous system.\(^3\) Although high dose steroids are the standard treatment, there are cases in which antibiotics such as various immunosuppressants, erythromycin, etc. are effective.

2) Rheumatoid arthritis (RA)
Gastrointestinal lesions accompanying RA are more often generated as secondary diseases in relation to disorders such as therapeutic drug-related gastrointestinal dysfunction, secondary amyloidosis, etc. than those that are directly caused by the disease.

(1) Vasculitis
Fever, abdominal pain and anemia due to bleeding are generated. In the case of malignant rheumatoid arthritis (MRA), there are times when gastrointestinal lesions of RA are caused by vasculitis. Lesions often occur in the small intestine (jejunum > ileum), and it has been reported as common in the cecum and sigmoid colon regarding the large intestine.\(^2\) The shape of the ulcer is well-defined, occurring as single or multiple oval ulcers, with bleeding, erosion, etc. generated. RA intestinal lesions caused by vasculitis suddenly generate and progress fast, leading to serious pathologies such as massive bleeding, infraction, perforations, etc. Interleukin-6 inhibitor is expected to be efficacious.

(2) Amyloidosis
Amyloidosis must be ruled out in case of paralytic ileus caused by intestinal tract dyskinesia along with malabsorption syndrome is evident. The incidence of amyloidosis subsequently developing following RA in Japan is 7–10% upon gastrointestinal biopsy, approximately 20% upon renal biopsy, and 20–30% in RA autopsy cases. Digestive symptoms are most prone to occur in the early stages of secondary amyloidosis. When amyloid deposition on the lamina propria and smooth muscles of the intestinal tract becomes serious, blood vessels and nerves are affected. Moreover, ulcers and infraction due to ischemia caused by embrittlement of the vascular wall may occur, leading to ischemic enteritis (bloody stool/perforations).\(^4\) Amyloidosis successively occurring following RA generally has a poor prognosis; however, a possibility has been suggested that prognosis may be improved by early
diagnosis and carrying out therapeutic intervention with the aim of remission induction of RA.

3) Systemic sclerosis (SSc)
In SSc, expansion of the digestive tract and declined peristaltic movement occurs. Gastrointestinal lesions have the highest incidence among all visceral pathologies of SSc (70–90%). Contraction of the smooth muscles, substitution by fiber, and neurological disorders are caused in specific muscle layers. It has been reported that gastrointestinal lesions account for 6–12% of causes of death (5). While lesions may occur in various sites of the digestive tract, esophagus lesions are the most common. Lesions of the mouth include sclerema in the vicinity of the mouth, limited opening of the mouth and shortening of the lingual frenum. In the bottom 2/3 of the esophagus, declined sphincter function, declined peristaltic movement, and swelling are caused, leading to reflux esophagitis. When erosion and ulcer formation is repeated due to reflux gastric acid, stricture is caused by fibrous scarring. Proton pump inhibitors and gastrointestinal function adjusting drugs are used in treatments against reflux esophagitis. Delays in gastric emptying are caused in the stomach; moreover, gastric antral vascular ectasia and bleeding are generated as complications. Declined peristaltic movement and expansion of the lumen are observed in the small intestine, causing the formation of pseudo-diverticulum and intestinal pseudo-obstruction when advanced. Moreover, increased pneumatosis cystoides intestinalis is caused. In the treatment of small intestinal lesions, gastrointestinal function-adjusting drugs and lactobacillus preparations are used for improving peristaltic movement, with antibiotics used to prevent excessive proliferation of enteric bacteria; however, it is intractable to treatment in many cases. When malnutrition persists due to difficulty in oral feeding and malabsorption, home parenteral nutrition is required. In large intestinal lesions, constipation due to declined peristaltic movement and pseudo-diverticulum is observed. Expansion of the capillary vessels inside the large intestine causes gastrointestinal bleeding.

4) Behçet’s disease
Recurrent aphthous ulceration inside the mouth is the predominant symptom of the present disorder and is observed in approximately 90% of cases. The incidence of gastrointestinal lesions in sites other than the mouth is 20–30%. The ulcer site histologically exhibits chronic active non-specific inflammation with various mixed inflammatory cells. Esophageal ulcer is observed from the early stages of onset of Behçet’s disease, often occurring in the central part. Symptoms include retrosternal pain, odynophagia and difficulty swallowing. Intestinal lesions often generate in the ileocecal region, mostly generating several years following onset. Clinical symptoms include abdominal pain, diarrhea and bloody stool, and it is characterized by multiple deep undermining ulcers. Ulcers frequently cause perforations and penetration. Although steroids and mesalazine are used against Behçet’s disease, many cases are intractable to treatment. TNF inhibitors are effective against intestinal lesions that are intractable to treatment.

5) Drug-induced gastrointestinal lesions
Gastrointestinal disorders caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are the gastrointestinal lesions most frequently observed in medical examinations of rheumatism and connective tissue diseases. According to the report by the Japan Rheumatism Foundation in 1991, among 1004 RA patients taking NSAIDs for three months or longer, gastric ulcers were observed in 15.5%, while duodenal ulcers were observed in 1.9%. Almost half of all cases are asymptomatic. Risk factors for NSAIDs ulcer include old age, within 30 days following commencement of administration, high dose administration, and past history of ulcer. In recent years, COX-2-selective inhibitors have been generated as NSAIDs and since these inhibitors do not inhibit COX-1 related to gastric mucosal barrier reaction, gastrointestinal disorders are on the decline. Peptic ulcers due to steroids were recognized as major side effects along with infectious diseases, diabetes, etc.; however, upon meta-analysis, it has been reported that the there is no significance in the incidence of peptic ulcers generated due to the use of steroids. Meanwhile, it has been reported that the use of steroids leads to a risk of perforation of the digestive tract.
6) Infectious gastrointestinal lesions
Immunosuppression frequently occurs in patients suffering from rheumatism and connective tissue diseases due to the use of steroids and immunosuppressants, with the complication of infectious gastrointestinal lesions common. Oral candidiasis and esophageal candidiasis are observed at a high frequency. Esophageal candidiasis occurs from the center to the bottom, exhibiting symptoms of odynophagia, retrosternal pain, nausea, etc. Treatment is carried out by intake or drip infusion of antifungal drugs. Cytomegalovirus (CMV) is generally a subclinical infection, but may activate and cause enteritis under immunosuppression. It may become fatal if diagnosis is delayed, and when gastrointestinal lesions occur during immunosuppressive therapy, there is a need to distinguish CMV infectious diseases. Symptoms include abdominal pain and bloody stool. While punched out ulcers with poor tongue fur generation are typical upon endoscopy, there are many non-typical cases. Definite diagnoses are made when proof of the presence of intranuclear inclusion bodies in the epithelium and vascular endothelial cell is provided at the lesion site. Although CMV antigen-positive in peripheral blood is a major reference finding, there are times when it is negative. Antivirus drugs such as ganciclovir, etc. are used for treatment.

Conclusion
Various digestive symptoms and digestive diseases complicate connective tissue diseases, providing a very diverse clinical picture. Complications may become fatal; therefore, early finding of complications and sufficient understanding of the pathologies thereof is necessary. In order to do so, it is very important that specialists with expert knowledge on connective tissue diseases and digestive diseases have a good understanding regarding both disorders. Therefore, it is necessary for both specialists to cooperate with each other and proceed with treatment against complications.

References