Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases

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Preface

The first edition of *Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases* includes state-of-the-art knowledge of the field of digestive and hepatobiliary complications of the most common rheumatic disorders. Rheumatic diseases are disorders of systemic connective tissue and are thought to be caused by autoimmunity. They present with a diverse array of gastrointestinal and hepatobiliary manifestations, so it is important for rheumatologists to be aware of the diagnostic procedures and management of such complications.

The gastrointestinal disorders accompanying rheumatic diseases can be divided into two major categories: intestinal disorders and disorders of the liver, biliary tracts, and pancreas.

Gastrointestinal symptoms are common in patients with rheumatic diseases and can be classified as gastrointestinal damage from the rheumatic disease itself, adverse events caused by pharmacotherapies, and gastrointestinal tract infections following immunosuppressive treatments. No specific autoantibodies have been identified for the diagnosis of gastroenteropathy in rheumatic diseases, but imaging studies, particularly abdominal computed tomography and tissue pathology through biopsy, are helpful.

Abnormalities of liver function tests frequently occur in patients with rheumatic diseases, and many diagnostic possibilities exist. Rheumatic diseases can be accompanied by liver abnormalities secondary to the presence of a coexisting autoimmune liver disease (such as primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis), or portal hypertension and the toxicity of medical treatments (particularly methotrexate). The rheumatologist should also be aware of the impact of immunosuppressive agents on the reactivation of viral infections, particularly hepatitis B virus (HBV). Additionally, a number of extrahepatic manifestations of pancreatic disorders have been reported, including autoimmune pancreatitis. For example, immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory condition affecting the pancreas as a pathological form of autoimmune pancreatitis. It is also important to perform a systematic diagnostic workup for malignancy, including digestive and hepatobiliary organs in patients with

polymyositis/dermatomyositis (PM/DM), because there is a high incidence of cancer in PM/DM.

Gastro-hepatic manifestations in rheumatic diseases are not rare, so clinicians should be aware of their existence and the fact that they may occur concomitantly or serially. It is also necessary for both rheumatologists and gastroenterologists to cooperate with each other and proceed with precise management of these disorders.

We and our colleagues have reviewed the clinical findings and management of gastrointestinal and hepatobiliary manifestations accompanying rheumatic disorders. This book aims to be a practical guide for the identification, typical case presentation, diagnosis, and management of these digestive and hepatobiliary complications of rheumatic diseases that will be useful for both rheumatologists and gastroenterologists. We also highlight recent developments in relevant diagnostic procedures and therapeutic strategies. We hope that readers will enjoy these advances in their classification, diagnosis, and management and an understanding of the mechanisms responsible for immune-mediated digestive and hepatobiliary disorders. We thank our collaborators at the Department of Gastroenterology and Rheumatology, Fukushima Medical University, for their contributions in producing this valuable book.

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Contents

Chapter 1
Liver Involvement in Rheumatic Diseases

Atsushi Takahashi and Hiromasa Ohira

Abstract Liver dysfunction may be caused by various factors such as viruses, disease treatments, alcohol use, and metabolic or autoimmune diseases. The associations between rheumatic diseases and the liver are complex, because rheumatic diseases target multiple systemic organs, including the liver. In addition, both treatment with immunosuppressants and secondary viral infections can cause liver dysfunction. Although liver dysfunction in rheumatic diseases is usually mild, liver failure has been reported in some cases. Therefore, understanding the characteristics of liver failure that may occur with different rheumatic diseases is essential for the treatment of these diseases. Clinicians must consider and treat liver dysfunction in patients with a rheumatic disease with both disorders in mind.

Keywords Liver dysfunction · Rheumatic diseases · Image findings · Histological findings · Autoimmune hepatitis · Primary biliary cholangitis · Viral infection · Fatty liver · Macrophage activation syndrome

1.1 Introduction

Rheumatic diseases affect multiple organs, including the liver. Moreover, the treatment and clinical course of rheumatic diseases may lead to adverse effects or complications that also cause liver dysfunction. Therefore, liver dysfunction in patients with a rheumatic disease can be caused by multiple factors. In addition to various causes of liver dysfunction, understanding the differences in the association between each rheumatic disease and the liver is essential for treatment of patients with rheumatic disease. In this chapter, we differentiate liver dysfunction that occurs with rheumatic diseases from other causes of liver dysfunction.

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1.2 Prevalence of Liver Dysfunction in Patients with Rheumatic Diseases

Many studies have reported treating liver dysfunction in patients with a rheumatic disease using different definitions of liver dysfunction [1–31]. Therefore, determining the prevalence of liver dysfunction specific to a rheumatic disease is difficult. Table 1.1 summarizes the prevalence and major causes of liver dysfunction in patients with different rheumatic diseases. Rheumatic disease activity and drug treatments are major causes of liver dysfunction in rheumatic diseases. However, primary biliary cholangitis (PBC) is a major cause of liver dysfunction in patients with systemic sclerosis (SSc) or Sjögren's syndrome (SjS). Moreover, fatty liver can also cause liver dysfunction in patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

Table 1.1 Prevalence and major causes of liver dysfunction in patients with different rheumatic diseases

Rheumatic disease	Prevalence of liver dysfunction	Major causes of liver dysfunction	References
Systemic erythematosus (SLE)	43% (46/106)	Disease related (22/46), drug (8/46)	Kojima et al. [1]
	9.3% (47/504)	Disease related (47/47)	Zheng et al. [2]
	20.9% (43/206)	Fatty liver (19/43)	Runyon et al. [3]
	32.3% (84/260)	Drug (28/67), alcohol (8/67)	Miller et al. [4]
	35.6% (80/225)		Luangjaru and Kullavanijaya [5]
	20.8% (40/192)	Viral hepatitis (8/40), fatty liver (8/40)	Chowdhary et al. [6]
	18.6%(45/242)	Drug (18/45), disease related (14/45)	Piga et al. [7]
	32.6% (46/141)	Drug (11/46)	Her et al. [8]
	8.6% (134/1553)	Drug (35/134), fatty liver (31/134)	Huang et al. [9]
	59.7% (123/206)	Drug (38/123), disease related (35/123)	Takahashi et al. [10]
Rheumatoid arthritis (RA)	41% (24/59)	Drug (8/24), disease related (7/24)	Kojima et al. [1]
	35.9% (79/220)	Drug (32/79), fatty liver (5/79)	Takahashi et al. [11]
	45.0% (45/100)	Not reported	Fernandes et al. [12]
	45.9% (45/98)	Not reported	Spooner et al. [13]
	77.4% (48/62)		Lowe et al. [14]
	47.0% (86/183)		Akesson et al. [15]

Table 1.1 (continued)

Rheumatic disease	Prevalence of liver dysfunction	Major causes of liver dysfunction	References
Sjögren's syndromes (SjS)	52.1% (37/71)	Disease related (11/37), PBC (10/37)	Kojima et al. [1]
	45.5% (20/44)	PBC (14/20), AIH (2/20)	Takahashi et al. [11]
	7.0% (21/300)		Skopouli et al. [16]
	26.7% (12/45)		Lindgren et al. [17]
	44.2% (42/95)		Montaño-Loza et al. [18]
Systemic sclerosis (SSc)	37% (10/27)	Drug (3/10), disease related (2/10), fatty liver (2/10)	Kojima et al. [1]
	44.7% (21/47)	PBC (16/21)	Takahashi et al. [11]
	1.1% (8/727)		Chen [19]
Vasculitis syndrome	54.0% (7/13)	Disease related (5/7), drug (2/7)	Kojima et al. [1]
	48.0% (12/25)	Disease related (7/12)	Takahashi et al. [11]
	16–56%		Ebert et al. [20]
Adult-onset Still's disease (AOSD)	81.3% (13/16)	Disease related (13/13)	Takahashi et al. [11]
	75.8%(47/62)		Pouchot et al. [21]
	73.6% (53/72)		Fautrel et al. [22]
	62.1% (59/95)		Pay et al. [23]
	35.7% (30/84)		Cagatay et al. [24]
	62.3% (48/77)		Zhu et al. [25]
	62.5% (65/104)		Kong et al. [26]
	75.0% (57/76)		Colina et al. [27]
	70.5% (43/61)		Chen et al. [28]
	54.0% (27/50)		Gerfaud-Valentin et al. [29]
	89.3% (25/28)		Mehrpoor et al. [30]

1.3 Laboratory Findings

Liver dysfunction is generally classified into two patterns: predominantly hepatocellular (with elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels) or predominantly cholestatic (with elevated alkaline phosphatase [ALP] and gamma-glutamyl transferase [γ-GTP] levels). Liver dysfunction with rheumatic diseases has been generally defined as the elevation of liver and biliary enzyme levels. However, AST and ALT are also muscle-derived enzymes; thus, rather than liver dysfunction, elevations in these parameters may reflect disease activity in patients with polymyositis and dermatomyositis. Other muscle-derived enzymes such as creatine phosphokinase, aldolase, lactate dehydrogenase (LDH), and isozymes of LDH may be useful to diagnose liver dysfunction in these patients.

In addition, elevation of AST levels may simply reflect damage to systemic organs, except the liver, which is caused by macrophage activation syndrome (MAS) [32], a severe comorbidity with some rheumatic diseases. Therefore, elevations in AST levels without elevations in ALT levels require attention, whether or not they represent true liver dysfunction.

These elevations of liver and biliary enzyme levels are, on the whole, mild in patients with a rheumatic disease with liver dysfunction. However, liver dysfunction shows different tendencies by disease. ALT levels are higher in adult-onset Still's disease (AOSD) than in other collagen diseases [11]. This finding may explain the high frequency of MAS in AOSD. Conversely, ALP or γ-GTP levels are higher in vasculitis syndrome than in other collagen diseases [1, 11]. Aminotransferase and bilirubin levels are generally normal in patients with RA, though ALP levels are increased in 18–46% of these patients [11, 12, 33]. Moreover, γ-GTP levels are elevated in 23–77% of patients with RA and correlate with disease activity [12, 14, 33]. The degree of liver and biliary enzyme elevation is generally associated with disease activity and is generally the basis for liver dysfunction that occurs with a rheumatic disease.

1.4 Histologic Findings

Histologic liver findings have been reported to vary widely not only among different rheumatic diseases but among cases with the same rheumatic disease. Vascular changes such as arteritis, abnormal vessels in portal tracts, hemangioma, peliosis hepatis, and infarcts due to arthritis have been well described in rheumatic diseases with liver dysfunction [1, 34, 35]. Portal changes such as interface hepatitis, chronic active hepatitis, non-specific reactive hepatitis (Fig. 1.1), cholestasis, and

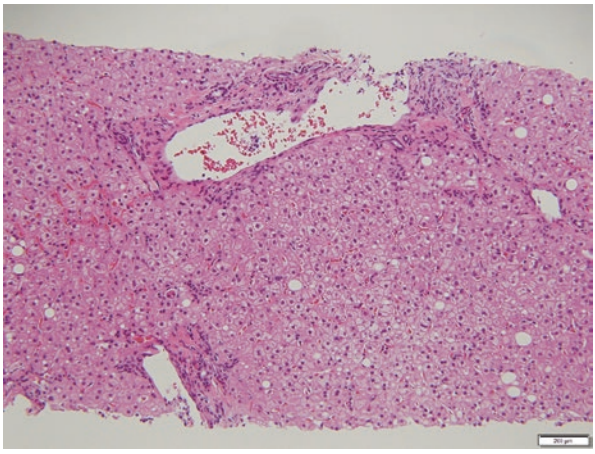

Fig. 1.1 Non-specific reactive hepatitis in a patient with SLE

cholangiolitis have also been reported [1, 34, 35]. Although lobular changes are not as frequent as portal changes, lobular inflammation, steatosis, and focal necrosis have been reported [1, 2, 36]. In addition to variations in rheumatic disease itself, viral infection, therapeutic drugs, hepatic congestion, and autoimmune disease mimic histologic liver findings. Therefore, interpretation of liver histology should consider the clinical course of the specific rheumatic disease.

1.5 Image Findings

Hepatomegaly is a relatively common finding in patients with a rheumatic disease. It is seen in about 40% of patients with SLE [3] and 76.5% of patients with AOSD with hemophagocytic lymphohistiocytosis [37]. Congestion of the liver is observed in patients with a rheumatic disease with heart failure.

Liver tumors are sometimes observed in patients with a rheumatic disease. Hepatocellular carcinoma (HCC) develops in patients with other risk factors, such as hepatitis B or C infection, alcohol intake, fatty liver disease, and use of immunosuppressants. On the other hand, HCC can develop in patients with a rheumatic disease without any other risk factors. We previously experienced a rare case of HCC with mixed connective tissue disease [38]. Liver hemangioma is seen in 0.4–20% of the general adult population [39], whereas it occurs in 54.2% of patients with SLE [40]. The high frequency of liver hemangioma can be explained by increases in circulating estrogen or angiogenetic factors, such as vascular endothelial growth factor and IL-18, which occur with rheumatic diseases [41–43]. Rheumatic diseases such as SLE, RA, and SjS have been associated with malignant lymphoma [44–46]. However, the liver is rarely the primary organ associated with malignant lymphoma, accounting for less than 1% of all extranodal lymphomas [47]. Immunosuppressive treatment for rheumatic disease tends to cause primary hepatic lymphoma [48, 49]. In particular, methotrexate (MTX) can cause lymphoid proliferation or lymphomas and is referred to as MTX-associated lymphoproliferative disorders (MTX-LPD) [45]. Some studies reported that patients with RA treated with MTX showed hepatic involvement [50–53]. Our case report is presented here [53].

Case. A 54-year-old woman was diagnosed with RA and treated with prednisolone, nonsteroidal anti-inflammatory drugs (NSAIDs), MTX, and biologic agents. Twelve years later, at the age of 66, she presented with retroperitoneal lymph node swelling and hepatosplenomegaly, but these symptoms disappeared after MTX withdrawal. Two years later, she was admitted to our hospital for anorexia and general fatigue with swelling in several lymph nodes and multiple liver tumors (Fig. 1.2). She was diagnosed with Hodgkin lymphoma based on the results of aspiration biopsy of a liver tumor. She died from liver failure and disseminated intravascular coagulation before chemotherapy could be initiated.

Enhanced computed tomography images are useful for diagnosis of liver tumors such as hepatocellular carcinoma and liver hemangioma. However, hypodense

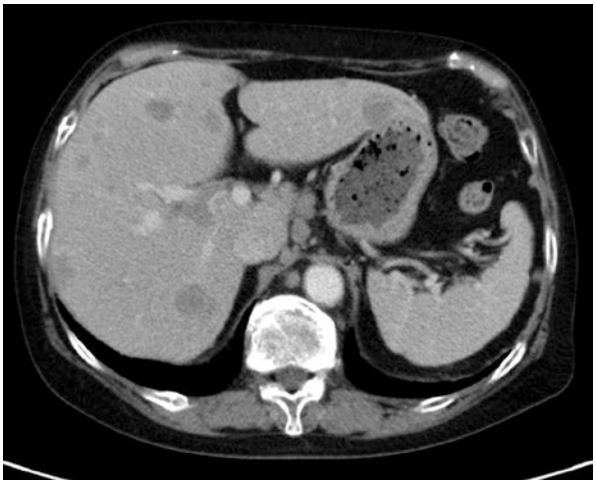

Fig. 1.2 Enhanced CT image in a RA patient with methotrexate-associated lymphoproliferative disorder

tumors are often difficult to diagnose accurately. Therefore, tumor biopsy is often performed to provide a definitive diagnosis. Hypodense lesions other than tumors can also appear in patients with rheumatic disease. Various causes such as abscess, piecemeal necrosis, necrotizing granuloma, infarction, and rupture show hypodense spots in the liver of patients with a rheumatic disease [20, 54]. With the exception of liver abscess, recognition of these lesions is especially important in determining the treatment strategy.

Vasculitis shows various image findings in the liver [20]. *Hepatic arteriograms* show caliber changes with corkscrew and distal microaneurysms. Vasculitis can also show *atrophy of a liver lobe*, liver infarction, and nodular regenerative hyperplasia involving the portal vein and hepatic arteries. *Intrahepatic sclerosing cholangitis* is also induced by vasculitis of small arteries that supply the small bile ducts.

1.6 Liver Dysfunction Associated with Rheumatic Diseases Alone

1.6.1 Systemic Lupus Erythematosus

The liver dysfunction caused by SLE itself has traditionally been referred to as "lupus hepatitis" [6, 55]. However, older reports may have used this term without ruling out other causes such as drug-induced liver injury, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and autoimmune liver diseases. The prevalence of liver dysfunction caused by SLE itself varies. Our

previous report based on lenient discrimination criteria reported a prevalence of 59.7% among 206 patients with SLE [10], whereas Zheng et al., using much stricter discrimination criteria, reported a prevalence of 9.3% among 504 patients with SLE [2].

The mechanism of liver damage in patients with SLE remains unknown. Apoptosis has been proposed as a potential cause based on histologic liver findings [56]. A recent longitudinal study showed a significant association between the prevalence of liver disease and the production of antiphospholipid antibodies [57]. This finding is consistent with results of a meta-analysis of patients with antiphospholipid syndrome (APS) [58]. The mechanistic target of rapamycin complex 1 (mTORC1)-dependent mitochondrial dysfunction contributed to the generation of antiphospholipid antibodies in lupus-prone mice [59]. On the other hand, hepatic-deposited immunoglobulin G (IgG) has been proposed as an important factor in the development of liver injury in SLE in experiments in mice [60]. However, hepatic deposition of IgG is also observed in liver histology of patients with autoimmune hepatitis [61]; thus, other mechanisms may be associated with liver dysfunction in patients with SLE.

Liver dysfunction in patients with SLE mostly presents as mild-to-moderate elevations of serum aminotransaminase levels, whereas ALP and γ-GTP elevations are less frequent [1, 2]. The diagnosis of liver dysfunction caused by SLE itself is achieved by ruling out other causes in addition to the activity of SLE itself [2]. The incidence of nervous system involvement is higher in patients with liver dysfunction caused by SLE itself [10]; thus, extrahepatic symptoms may help diagnose liver dysfunction caused by SLE itself.

Histologic findings of the liver in patients with SLE-induced liver dysfunction show a broad morphologic spectrum. Common histopathologic findings in SLE include fatty liver, portal inflammation, arthritis, congestion, nodular regenerative hyperplasia (NRH), abnormal vessels in portal tracts, and vascular changes such as hemangioma [34, 36].

Survival rates do not differ between patients with SLE with and without liver dysfunction [10]. Liver dysfunction caused by SLE itself is generally subclinical with a fluctuating course and responds well to moderate-to-high doses of prednisone without progression to end-stage liver disease [7]. Acute liver failure is rarely reported in patients with SLE. However, underlying MAS should be taken into account if acute liver failure does occur.

1.6.2 Rheumatoid Arthritis

The prevalence of liver dysfunction caused by RA itself is 2.5–29.2% [1, 11]. In general, the degree of liver dysfunction correlates with factors associated with RA activity, such as C-reactive protein levels and the erythrocyte sedimentation rate [33]. Elevation of biliary enzymes, but not aminotransferase, suggests liver involvement in patients with RA. Both levels of ALP and γ-GTP are usually

elevated, but one third of patients show elevation of ALP levels alone [62]. The ALP elevations in RA require attention, because increased ALP levels reflect not only liver damage but also bone lesions. Examination of ALP isozymes is therefore needed to evaluate the liver dysfunction caused by RA in patients showing ALP elevations alone. The histology of the liver with dysfunction caused by RA itself does not show any consistent structural abnormalities. A previous paper reported non-specific findings, such as non-specific reactive hepatitis, hepatic arthritis, and fatty liver [34]. Moreover, NRH is also associated with RA and has been seen in Felty's syndrome, a subtype of RA characterized by leucopenia and splenomegaly [63].

1.7 Autoimmune Liver Disease

1.7.1 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is an immune-mediated hepatic disease characterized by the presence of antinuclear antibody (ANA). Histopathologic liver findings such as interface hepatitis, hepatocyte rosette formation, and emperipolesis help diagnose AIH and are included in its diagnostic criteria. Some patients with AIH develop rheumatic disease (Table 1.2), and some patients with rheumatic disease develop AIH.

Table 1.2 Prevalence of rheumatic diseases in patients with autoimmune liver disease

Overlap	Prevalence	References
Autoimmune hepatitis (AIH)		
AIH + SLE	3.1% (51/1659)	Takahashi et al. [66]
	2.6% (27/1056)	Abe et al. [67]
	3.1% (5/162)	Oka [68]
	0.7% (2/278)	Teufel et al. [69]
AIH + RA	3.4% (56/1659)	Takahashi et al. [66]
	2.8% (30/1056)	Abe et al. [67]
	1.8% (5/278)	Teufel et al. [69]
AIH + SjS	5.7% (95/1659)	Takahashi et al. [66]
	7.2% (76/1056)	Abe et al. [67]
	1.4% (4/278)	Teufel et al. [69]
Primary biliary cirrhosis (PBC)		
PBC + SLE	0.4% (33/9233)	Hirohara [81]
	3.7% (12/322)	Wang et al. [83]
	1.3% (2/160)	Watt et al. [84]
	2.6% (27/1032)	Gershwin et al. [85]
	1.8% (3/170)	Marasini et al. [86]

Table 1.1 (continued)

Overlap	Prevalence	References
PBC + RA	3.5% (327/9233)	Hirohara [81]
	2.8% (9/322)	Wang et al. [83]
	16.9% (27/160)	Watt et al. [84]
	10.0%(103/1032)	Gershwin et al. [85]
	1.8% (3/170)	Marasini et al. [86]
PBC + SjS	11.2% (1031/9233)	Hirohara [81]
	37.6% (121/322)	Wang et al. [83]
	25.0% (40/160)	Watt et al. [84]
	9.9% (102/1032)	Gershwin et al. [85]
	3.5% (6/170)	Marasini et al. [86]
PBC + SSc (CREST)	2.9% (272/9233)	Hirohara [81]
	2.8% (9/322)	Wang et al. [83]
	7.5% (12/160)	Watt et al. [84]
	2.3% (24/1032)	Gershwin et al. [85]
	12.4% (21/170)	Marasini et al. [86]

SLE systemic erythematosus, *RA* rheumatoid arthritis, *SjS* Sjögren's syndromes, *SSc* systemic sclerosis; *CREST* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia

Liver damage, whether by AIH or SLE itself, is often difficult to treat in patients with overlap of AIH and SLE [64, 65]. The prevalence of SLE-AIH is 0.7–3.1% among patients with AIH [66–69]. Serum markers for SLE such as anti-double-stranded DNA (anti-dsDNA) and anti-ribosomal P protein are also found in patients with AIH [10]. Although specific markers such as anti-smooth muscle antibody (ASMA) and liver-kidney microsomal (LKM) antibody for AIH may help differentiate AIH from SLE serologically, their positive rate is relatively low in Japan. Histologic assessment of the liver is the gold standard for differentially diagnosing AIH and SLE-associated hepatitis [70].

The prevalence of RA among patients with AIH is similar to that of SLE. We diagnosed AIH in 1.3% of 79 patients with RA [11]. On the other hand, the prevalence of RA is 1.8–3.4% in patients with AIH [66, 67, 69]. A study of patients with RA on long-term, low-dose MTX therapy reported that 13 (52.5%) of 25 patients with elevated liver enzymes showed AIH-like lesions on liver biopsy specimens [71]. Interestingly, these AIH-like lesions improved by treatment with etanercept for 6 months [72]. On the other hand, use of biologic agents may lead to the development of autoimmune diseases, including AIH [73]. Among the biologic agents, antitumor necrosis factor (TNF)-α has frequently been shown to trigger AIH [74]. Discontinuation anti-TNFα and corticosteroid therapy are effective for AIH induced by anti-TNFα. Unfortunately, it is impossible to completely distinguish AIH from drug-induced liver injury in patients with rheumatic disease because characteristics may be similar in both diseases.

SjS is present in 1.4–7.2% of patients with AIH [66, 67, 69]. On the other hand, AIH is found in 1–4% of patients with SjS [17, 18, 75, 76]. Two thirds of cases of

AIH with SjS have been reported to be from Asia, and nearly 10% of them had positive antimitochondrial antibodies (AMA) [77]. SjS is the most frequent extrahepatic autoimmune disease in AIH-PBC overlap syndrome (6 [8.4%] of 71 patients) [78]. Histologic findings of patients with SjS patients and AIH include a predominance of CD3-positive T-cell infiltrates in both the salivary glands and liver [79].

1.7.2 Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is an autoimmune cholestatic disease of unknown etiology characterized by progressive destruction of intrahepatic bile ducts [80]. Overlapping conditions of PBC and rheumatic diseases are well recognized, indicating the involvement of autoimmune mechanisms in the pathogenesis of PBC. An epidemiologic study from Japan showed that 2559 (27.7%) of 9233 patients with PBC were affected by another autoimmune disease at the time of PBC diagnosis [81]. The autoimmune diseases co-occurring with PBC include SjS (11.2%), Hashimoto disease (6.3%), RA (3.5%), Raynaud's phenomenon (3.1%), and SSc (2.9%) [81].

PBC is a main cause (27–70%) of liver dysfunction in patients with SjS [1, 11]. In previous studies, 47–73% of patients with PBC had sicca symptoms [82]. Furthermore, 26–93% of patients with PBC showed histologic changes in the salivary gland that were compatible with SjS [82]. The prevalence of SjS is 4–38% in patients with PBC [81, 83–86]. On the other hand, the prevalence of PBC is 4–9% in patients with SjS [17, 18, 75, 87]. Antimitochondrial antibodies (AMA) are detected in 1.6–13% (using indirect immunofluorescence) or 22–27% (using indirect immunofluorescence) of patients with SjS [88]. Among AMA-positive patients with SjS, 60% have elevated ALP levels, and 82% have histologic findings of PBC [16]. Bile duct and salivary gland epithelia are common major findings in both SjS and PBC. In addition, SjS and PBC have a common histologic characteristic—a predominance of CD4-positive T-cell infiltrates—around the bile duct in PBC and around the salivary duct in SjS. Both biliary and salivary epithelial cells are associated with autoimmune mechanisms induced by cytokines, human leukocyte antigen (HLA) class II molecules, and adhesion molecules [88]. Although the prevalence of liver dysfunction caused by SjS itself has been reported to be 30% [1], some patients may be affected by PBC, including subclinical PBC.

PBC is also the main cause of liver dysfunction in patients with SSc [1, 11]. About 2–12% of patients with PBC have been reported to have scleroderma [81, 83–86]. In a large-scale, nationwide study in Japan, 272 (2.9%) of 9233 patients with PBC were reported to show an overlap with SSc [81]. CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome represents limited cutaneous SSc. PBC was detected in 16 (2%) of 817 patients with SSc, of whom 13 (81%) displayed CREST syndrome [89]. Anticentromere antibody (ACA), a hallmark antibody of SSc, has also been

detected in 9–30% of patients with PBC [90]. In a study of patients with PBC with ACA, 10 (63%) of 16 patients showed features of CREST syndrome [91]. The prevalence of ACA is higher in patients with PBC-SSc or PBC-CREST overlap than in patients with PBC alone [92]. In addition to a higher prevalence of ACA, characteristics of patients with PBC-CREST overlap compared with PBC alone are as follows: female gender, older age, milder clinical features of both PBC and CREST syndrome, more frequent occurrence of esophageal varices, better prognosis, lower serum levels of AST and IgM, lower median titers of AMA, and a higher prevalence of HLA-DR9 [93]. PBC-CREST overlap syndrome patients are generally incomplete types of CREST syndrome, such as CRST (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasia) and RST (Raynaud's phenomenon, sclerodactyly, and telangiectasia) [93]. Compared to patients with PBC alone, the rates of progressive jaundice and liver transplantation are significantly lower in patients with PBC-SSc [92].

SLE-PBC overlap is relatively rare. The prevalence of SLE in patients with PBC has been reported to be 0.4–3.7% [81, 83–86], whereas the prevalence of PBC in patients with SLE was shown to be 1.4–7.5% [6–8, 11]. In 15 SLE-PBC overlap cases, PBC developed before SLE (73.3%) [94]. Although the incidence of SLE in patients with PBC was significantly higher than that in the healthy controls [85], the frequency of AMA positivity in patients with SLE is similar to that of healthy controls [95]. This may be explained by the fact that AMA titers change negatively or decrease in one third of patients with SLE and AMA-positive PBC. SLE-PBC overlap patients had lower white blood cell counts and higher frequencies of renal involvement than patients with PBC alone [83]. SLE-PBC patients appeared to have much less extensive liver damage, suggesting that SLE may protect against progression of PBC [96]. There is no association between SLE activity and the incidence of PBC; moreover, SLE flare-ups are unusual in patients with SLE-PBC overlap [97, 98]. Although SLE-PBC overlap may involve a genetic abnormality (e.g., IRF5-TNPO3) [99], the detailed role of genetic factors remains to be established.

PBC is the most common autoimmune liver disease in patients with RA. PBC occurs in 1–10% of patients with RA [100], whereas RA occurs in 1.8–16.9% of patients with PBC (Table 1.2). Among 25 patients with PBC-RA overlap, 17 patients were diagnosed with RA before PBC [101]. About half of patients with PBC become rheumatoid factor-positive during the clinical course of PBC, whereas 10–18% of patients with RA are AMA-positive [102–104]. An AMA-positive status in patients with RA represents PBC overlap or future development of PBC [105]. Genome-wide association studies have indicated several common genes, such as HLA-DQB1, CTLA4, MMEL1, STAT4, IRF5, and CXCR5 in RA and PBC [106]. These common serum and genetic profiles support the possibility of PBC-RA overlap. Laboratory findings from patients with PBC-RA overlap have shown lower hemoglobin levels and higher ALP levels, IgG levels, erythrocyte sedimentation rate, and positive rheumatoid factor findings than in patients with PBC without RA [83].

1.8 Viral Infection

1.8.1 Hepatitis C Virus

Extrahepatic manifestations of hepatitis C virus (HCV) infection have been reported in rheumatic diseases such as SjS, inflammatory arthritis, and cryoglobulinemia vasculitis. A recent meta-analysis showed the prevalence of SjS in patients with HCV was 11.9% compared with 0.7% in non-HCV controls [107]. The risk ratio for SjS patients with HCV is 2.29 compared with non-HCV-infected individuals. A large cohort study of 783 patients with SjS reported patients who were HCV-IgG-positive were older, more frequently male, and more frequently presented with vasculitis, peripheral neuropathy, or neoplasia compared with patients without HCV [108]. HCV RNA is present in the salivary glands of patients with SjS with HCV infection [109]. Moreover, transgenic mice of the HCV envelope genes develop SjS-like exocrinopathy. These findings introduce the possibility of a direct impact of HCV on the development of SjS [110].

The prevalence of rheumatoid-like arthritis among patients with HCV is 1%, whereas the prevalence in non-HCV controls is 0.09% [107]. The risk for HCV-related inflammatory arthritis is two times higher than in non-HCV patients. Patients with RA with concomitant HCV have higher disease activity scores [111]. Patients who are HCV-positive were more likely to be treated with prednisone and anti-TNFα therapies and less likely to receive MTX compared with HCV-negative patients [111].

Cryoglobulinemia is defined as the presence of circulating immunoglobulins that precipitate at cold temperatures and dissolve with rewarming. This phenomenon was reported in patients with liver disease before the discovery of HCV [112]. Mixed cryoglobulinemia vasculitis is related to HCV infection in 70–80% of cases and is associated with a type II immunoglobulin M kappa mixed cryoglobulin [113]. Arthralgia is reported in 35–58% of patients with HCV with positive findings for mixed cryoglobulin [114, 115]. Although rheumatoid factor is found in 70–80% of patients with cryoglobulinemia vasculitis, anti-cyclic citrullinated peptide antibodies are usually negative, and there is no evidence of joint destruction [113].

Interferon is contraindicated in patients with HCV with rheumatic disease because it can induce a flare of rheumatic disease. Over the last few years, the development of direct-acting antivirals (DAAs) for HCV had enabled high cure rates and reduced the HCV-related disease progression to cirrhosis and hepatocellular carcinoma. One report showed a decrease of cryoglobulin levels in patients with HCV cryoglobulinemia vasculitis after DAAs [116]. Another study also reported improvement of symptoms in patients with HCV with cryoglobulinemia vasculitis after DAAs [113]. Future studies can elucidate the efficacy of DAAs on other rheumatic diseases such as SjS and inflammatory arthritis.

1.8.2 Other Viruses

Many viral infections other than HCV have been documented in SLE at presentation and during the course of the disease. The prevalence of *hepatitis B* is lower than that of hepatitis C in patients with SLE [3, 5, 7]. Among 1031 patients in Japan with SLE, the rate of hepatitis B surface antigen (HBsAg) is 0.3%, whereas that of hepatitis B core antibody (HBcAb) is 13.7% [117]. On the other hand, among patients in Japan, 50 (0.7%) of 7650 patients with RA are current HBV carriers, and 214 (25.6%) of 837 are positive for HBcAb, indicating that the prevalence of HBV infection in patients with RA was higher than that in patients with SLE [117]. Screening and careful monitoring of HBV is essential during immunosuppressive therapy in all rheumatic diseases to avoid HBV reactivation.

Immunosuppressive therapy increases the risk for bacterial and viral infections. *Cytomegalovirus* (CMV) infection is associated with the occurrence and development of SLE and also correlates with disease activity and mortality in SLE [118]. Liver dysfunction is the most common clinical manifestation in patients with SLE with active CMV infection [119]. Although biologic agents are recognized as having a low risk for CMV reactivation, the potential for CMV reactivation remains, as shown in a case report of a patient with RA [120]. Moreover, *hepatitis E virus* (HEV) infection should be suspected in patients with immunosuppressive therapy and elevated liver enzymes [121]. Discontinuation of immunosuppressive therapy and antiviral therapy usually lead to recovery in these patients; however, one death due to fulminant hepatitis has been reported [122]. Therefore, prevention or early diagnosis of HEV infection is essential for patients with rheumatic disease.

1.9 Drug-Induced Liver Injury

Drugs are a major cause of liver dysfunction in patients with rheumatic disease, and all drugs can cause drug-induced liver injury (DILI) in all individuals regardless of whether they are healthy or not. The causative drugs vary. About 80% of patients with SLE are treated with NSAIDs and analgesics for major symptoms such as arthralgia, serositis, and headache [123]. Patients with SLE usually present with a higher rate of NSAID-related complications than patients without SLE. Common complications include increased aminotransaminase levels, skin rashes, retention of body fluids, gastric ulcers, and aseptic meningitis [124]. Aspirin is the most common drug associated with DILI in patients with SLE; the liver toxicity of aspirin is considered dose-dependent. Aspirin can injure the mitochondria, leading to free fatty acid accumulation in the liver and hepatic steatosis [124]. Azathioprine (AZA) is an immunosuppressive drug used

to achieve or maintain remission in patients with SLE [125]. Liver injury caused by AZA generally presents as elevated serum transaminase levels [124]. It is not generally severe and responds to dose reduction. NRH can arise as a rare but severe complication of thiopurine-based therapies [124]. MTX is associated with significant reductions in the SLE disease activity index and the average dose of corticosteroid in patients with SLE [126]. In a study involving 18 patients with SLE who received MTX, 10 (55.5%) showed elevated AST levels [127].

DILI is also the main cause of liver dysfunction in patients with RA, with a prevalence of 33–41.5% [1, 11]. MTX is a disease-modifying antirheumatic drug (DMARD) that has been used to treat RA since the 1950s. A systematic review reported that the incidence of elevated liver enzymes in the first 3 years of MTX use was 13/100 patient-years, and the cumulative incidence was 31% [128]. The liver dysfunction caused by MTX in patients with RA is rather broad, ranging from mild elevation of transaminases to liver failure [129, 130]. NAFLD has also been associated with MTX therapy [131]. A recent study showed that the prevalence of MTX-associated NAFLD with transaminitis was 4.7% among 987 patients with RA receiving MTX therapy [129]. Moreover, the cumulative MTX dose was an independent predictor of MTX-associated NAFLD transaminitis, although the mechanism for this association remains unclear. Biologics are the first-line therapy for RA and are effective at reducing RA activity, achieving remission, and preventing joint destruction. Infliximab is a TNF-α antagonist that is used for the treatment of inflammatory diseases, including RA. A large study showed that 154 (3.1%) of 5000 patients with RA treated with infliximab had a hepatic disorder [132].

1.10 Fatty Liver

Fatty liver is one of the major causes of liver dysfunction in patients with SLE. On the other hand, fatty liver can develop in anyone with irregular eating habits, low physical activity, and excessive alcohol intake. The prevalence of fatty liver is 13–23.1% among patients with SLE with liver dysfunction [1, 5, 8]. Moreover, steatosis is one of the major liver histologic findings in patients with SLE with liver dysfunction [34]. Corticosteroids are standard and first-line therapy for SLE, but they can also cause secondary nonalcoholic steatohepatitis [133]. We previously confirmed that fatty liver usually develops during the course of SLE [10]. Fatty liver may include nonalcoholic hepatitis (NASH), which has the potential to progress to liver cirrhosis or hepatocellular carcinoma. Therefore, a diagnosis of NASH by liver histology is important in patients with fatty liver and elevation of aminotransferase levels or liver fibrosis markers. MTX is a risk for NASH [131]; thus, patients treated with MTX should be monitored for NASH. Recently, fibrosis-4 index has been validated as useful marker to diagnosis of NASH in patients with RA treated with MTX [134].

1.11 Acute Liver Failure

Liver dysfunction is mostly mild in rheumatic disease. However, some cases develop as acute liver failure regardless of rheumatic disease type. Hepatitis virus and DILI are well-known causes of acute liver failure in patients with rheumatic disease. On the other hand, rheumatic disease itself can cause acute liver failure. The presence of MAS explains the occurrence of acute liver failure in patients with rheumatic disease [135]. "MAS" is the term used for hemophagocytic lymphohistiocytosis (HLH) caused by an autoimmune disease [136]. The mechanism of MAS is a cytokine storm caused by the activation and uncontrolled proliferation of T lymphocytes and macrophages [135]. MAS was first reported in 1985 in a patient with juvenile rheumatoid arthritis (JRA) [137]. Diagnostic criteria for MAS that adjust for all rheumatic diseases have not been established. Therefore, MAS is diagnosed based on the criteria of systemic juvenile idiopathic arthritis (JIA) [138] or HLH [139]. Elevation of AST levels is one of eight diagnostic items in the criteria of JIA. This elevation reflects not only liver damage but systemic organ failure as well. MAS is most commonly reported in rheumatic disease and is a life-threatening complication in patients with JRA [136]. Therefore, early diagnosis and treatment are important. Hemophagocytic syndrome (HPS), which can include HLH and MAS, has often been reported in patients with rheumatic disease. Reactive HPS is a potentially fatal condition associated with neoplasms, viral infections, and autoimmune diseases, including SLE [140–142]. Reactive HPS in patients with SLE was first reported in 1991 [140]. The precise mechanisms underlying the development of reactive HPS in SLE are unclear, but a similar mechanism to MAS has been proposed [139–142]. Acute liver failure may be observed at the time of AOSD diagnosis, during tapering of immunosuppressive therapy, or long after diagnosis when other symptoms are well controlled by therapy. Patients with HPS with underlying AOSD have significantly higher levels of ALT than do patients with HPS and underlying SLE [143]. Elevation of IL-18, ferritin, and aminotransferase in levels patients with AOSD explain the association between AOSD and MAS. The systemic score, including hepatomegaly or abnormal liver function tests, in patients with AOSD at the time of diagnosis is significantly associated with mortality [144]. Moreover, among 116 patients with MAS (SLE in 52.3%, AOSD in 26.7%, and dermatomyositis in 6.9%), male sex (odds ratio [OR] 6.47), dermatomyositis (OR 5.57), and anemia (hemoglobin <8 mg/dL; OR 3.74) were associated with mortality. In addition to corticosteroids, intravenous cyclophosphamide or biologic agents are promising for MAS [143].

1.12 Conclusion

Liver involvement in rheumatic disease must be considered from both sides, that is, the causes of liver disease and the disease course of rheumatic disease. Understanding each type of rheumatic disease, including the clinical courses, is essential, as is a strong knowledge of liver disease itself. In particular, physicians should consider MAS in the treatment of liver dysfunction in patients with rheumatic disease.

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Chapter 2
Primary Biliary Cholangitis Is Associated with CREST Syndrome

Kazumichi Abe and Hiromasa Ohira

Abstract Primary biliary cholangitis (PBC) is a chronic and slowly progressive cholestatic liver disease of autoimmune etiology characterized by injury of the intrahepatic bile ducts that may eventually lead to liver failure. Patients with PBC occasionally suffer complications from other autoimmune diseases. When PBC is associated with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (CREST) symptoms, it has been proposed to be a distinct clinical entity. Moreover, PBC associated with CREST syndrome has been described in many case reports. However, complete CREST cases are rare, with high prevalence of Raynaud's phenomenon, sclerodactyly, and telangiectasias and lower prevalence of calcinosis and esophageal dysmotility. Because patients with anti-centromere antibody-positive PBC are at high risk of developing portal hypertension, particular attention should be paid to the management to gastroesophageal varices. This review provides a current overview of clinical characteristics and recent findings of PBC associated with CREST syndrome.

Keywords Primary biliary cholangitis · CREST syndrome · Anti-centromere antibody · Nail-fold capillaroscopy

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2.1 Introduction

Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease characterized by portal inflammation, immune-mediated destruction of the intrahepatic bile ducts, and the presence of highly specific anti-mitochondrial antibodies (AMA) in the serum [1]. The concept of "primary biliary cirrhosis" as a disease has been proposed for 50 years. Cases were previously diagnosed after progression to cirrhosis, but due to the development of diagnostic methods such as the measurement of AMA, many cases are diagnosed before progression to cirrhosis. In addition, ursodeoxycholic acid (UDCA) came into use, which has made it possible for patients to be diagnosed before progression to cirrhosis. Recently, the name of the disease has been changed to "primary biliary cholangitis" [2]. Patients with PBC occasionally suffer complications from the other autoimmune diseases [3–6] such as Sjögren's syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, or scleroderma caused by either systemic sclerosis (SSc) or CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) syndrome (Fig. 2.1). The association of PBC with CREST syndrome was first described by Murray-Lyon et al. in 1970 [7]. These authors reported two patients with PBC complicated

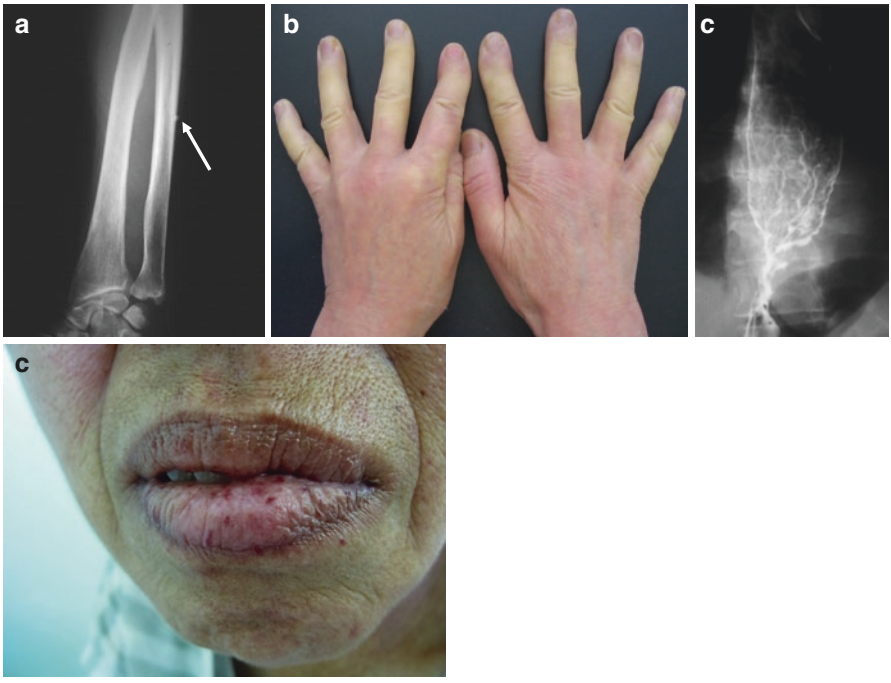

Fig. 2.1 The characteristics of CREST symptoms: (**a**) calcinosis, (**b**) Raynaud's phenomenon and sclerodactyly, (**c**) esophageal dysmotility, (**d**) telangiectasias

with scleroderma, of which one patient had CREST syndrome, and suggested that the association of the two diseases may be due to a common autoimmune mechanism. In 1971, Reynolds et al. reported six patients with PBC and CREST syndrome [8]. Although many cases have been reported since then, the etiology and outcome of this combined disorder remain largely unknown [9–16]. This review provides an overview of PBC associated with CREST syndrome along with recent findings this condition.

2.2 Epidemiology

Considering the prevalence of SSc among PBC patients in large-scale surveys, a survey in the USA showed the prevalence to be 8 out of 1032 (1%) patients [17], whereas a nationwide survey in Japan showed that 214 of 7926 (2.7%) patients with PBC also had SSc [18]. Furthermore, a large-scale survey revealed that PBC was detected in 16 (2%) of 817 patients with SSc, of whom 13 (81%) had CREST syndrome [19–21].

2.3 Etiology

Several studies have been conducted to determine the involvement of genetic, immunological, environmental, and other factors, although neither the etiology of PBC nor that of CREST syndrome has yet been elucidated. Recently, genome-wide association studies (GWAS) have identified TNFSF1 and POU2AF1 as novel disease-susceptibility genes related to the development of PBC in the Japanese population [22]. For immunological factors, the expression of Toll-like receptors (TLRs) has been observed in biliary epithelial cells. Reports suggest a mechanism in which the destruction of biliary epithelial cells by activated NK cells occurs via stimulation by TLR3 and TLR4 ligands and a shift to Th1 response, leading to chemokine production and the infiltration of inflammatory cells [23]. TLR9-mediated stimulation of B cells and subsequent increase in IgM production have also been reported [24].

TLRs have also been shown to play a major role in the pathogenesis of SSc by stimulating immune cells, fibroblasts, and vascular endothelial cells [25, 26]. A TLR4 ligand, which can be detected in the sera of SSc patients, has been shown to stimulate dendritic cells to produce IL-10, which is involved in the production of CCL18, a factor associated with fibrosis [27]. It also has been hypothesized that in SSc, type I interferon (IFN) enhances TLR3 expression in the affected skin and TLR3 stimulation leads to the production of IL-6, TNF-α, and IL-1β, resulting in accelerated fibrosis [28–30].

Limited findings have been reported regarding the etiology of combined PBC-SSc, including a higher expression level of T-cell receptor beta-chain variable region

3 on $CD8^+$ T cells and a higher prevalence of human leukocyte antigen (HLA)-DR9 expression in patients with combined PBC-SSc compared with patients having either disorder alone [15, 31]. Genetic factors that have been identified in both disorders include HLA-DRB1, DQA1, interferon-regulatory factor 5 (IRF5), and signal transducer and activator of transcription 4 (STAT4) [32]. In the Japanese population, no association has been found between IRF5 expression and PBC, whereas in SSc, IRF5 is more closely associated with systemic type than with the limited type (CREST syndrome) [33, 34].

Significant infiltration of mast cells, which are thought to play an important role in the transition from innate to acquired immunity, has been observed in the portal area in PBC and in the dermal layer of skin in SSc [35–38]. Both disorders are known as autoimmune fibrotic disease characterized by increased levels of profibrotic cytokines TGF-β and IL-6, which have recently been suggested to be involved in the production and function of Th17 cells and regulatory T (Treg) cells, which play a role in acquired immunity [39–43]. Although a reduced number of Treg cells is observed in both conditions, PBC is associated with a reduction in the $CD8^+$ Treg subset alone, whereas SSc is associated with reduction in both $CD8^+$ Treg and $CD4^+CD25^+$ Treg subsets [43]. B-cell abnormalities have also been reported in both disorders [44–47].

2.4 Clinical Features

Clinicolaboratory data from the major reports of patients with PBC associated with CREST symptoms (PBC-CREST) are given in Table 2.1 [9, 15]. Patient age at diagnosis ranged 48.1–60 years, and the majority of patients being female. These patients have a high prevalence of AMA and anti-centromere antibodies (ACA). Recent studies have also shown a higher prevalence of ACA in combined cases (80%) compared with cases of PBC alone [48]. In terms of disease type, 80% of PBC cases are asymptomatic, although complete CREST cases are rare, with a high prevalence of Raynaud's phenomenon, sclerodactyly, and telangiectasias and lower prevalence of calcinosis and esophageal dysmotility. Kasukawa summarized the relationship between ACA and PBC-CREST [49]. Anti-mitochondrial antibodies are found in approximately 90% of PBC patients. The positive rate of AMA is 90.5% for asymptomatic PBC and 92.3% for symptomatic PBC with no difference in the frequency of positivity. Even if asymptomatic PBC combines with CREST, the AMA-positive rate does not change as much as 95%. On the other hand, the positive rate of ACA shows a significant difference of 30% in SSc patients and 70% in CREST patients. Furthermore, when asymptomatic PBC occurs with CREST, the ACA-positive rate increases to 100%. Among CREST patients, the ACA-positive rate is 27% in complete CREST cases and 73% in incomplete CREST cases. Consequently, it is thought that ACA is strongly related to asymptomatic PBC associated with CREST.

The clinicolaboratory data of 31 patients with PBC-CREST, reported by Tojo, were compared with data of 68 patients with PBC alone. The following

Table 2.1 Comparison of clinicolaboratory findings between patients with PBC-CREST syndrome and patients with PBC alone

	PBC-CREST		
	Powell et al.	Tojo et al.	PBC alone
n	22	31	68
Age (years)	48.1	60*	53.7
Gender (male/female)	0/22	0/31*	12/50
Symptomatic/asymptomatic PBC	NA	5/26	17/51
AMA-positive, *n* (%)	19/22 (86)	27/31 (87)	58 (85)
ACA-positive, *n* (%)	12/22 (55)	29/31 (94)	NA
Scheuer's stage 1 or 2, *n* (%)	21/22 (95)	17/25 (68)	34/58 (59)
Esophageal varices, *n* (%)	NA	9 (29)	14 (21)
Esophageal varices in stages 1–3, *n* (%)	NA	6/21 (29)*	4/43 (9)
Calcinosis, *n* (%)	8 (36)	9 (29)	NA
Raynaud's phenomenon, *n* (%)	20 (91)	28 (90)	NA
Esophageal dysmotility, *n* (%)	10 (45)	9 (29)	NA
Sclerodactyly, *n* (%)	19 (86)	27 (87)	NA
Telangiectasia, *n* (%)	21 (95)	23 (74)	NA
Complete type of CREST, *n* (%)	2 (9)	4 (13)	NA
AST (U/L)	NA	39.8 ± 24.2*	63.6 ± 39.8
ALP (U/L)	NA	526 ± 258	512 ± 306
γGTP (U/L)	NA	152 ± 154	281 ± 331
TB (mg/dL)	NA	0.84 ± 0.60	2.15 ± 4.02
IgG (mg/dL)	NA	1953 ± 645	2203 ± 721
IgM (mg/dL)	NA	460 ± 175*	676 ± 368
10-year survival rate, %	NA	87.5*	45.5

PBC primary biliary cholangitis, *CREST* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, *AMA* anti-mitochondrial antibody, *ACA* anti-centromere antibody, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *TB* total bilirubin, *NA* not available; *: $P < 0.05$

significant differences were observed between these two groups of patients: a higher prevalence of older women, a higher association of esophageal varices in earlier stages of PBC, higher ACA titers, and lower AMA titers in the patients with PBC-CREST compared with the patients with PBC alone. Nakamura et al. reported that ACA-positive PBC patients are more likely to develop portal hypertension [50]. Another study showed that the prevalence of esophageal varices is significantly higher in patients with PBC-CREST than in those with PBC alone in a cohort that excluded cirrhotic patients [15]. Centromere protein (CENP)-B, a corresponding ACA antigen, is detected in almost all patients whose sera are positive for ACA and is therefore considered a major antigen of ACA [51]. Shoji et al. demonstrated an association between ACA positivity and Raynaud's phenomenon and found no significant difference in reactivity of pyruvate dehydrogenase (PDH) fractions (E2, E3, protein X, E1α, and E1β) in

the sera of PBC patients positive for ACA and of patients negative for ACA, including those with PBC-CREST [52]. Another study revealed that the significant inverse correlation was observed between aCENP-B and AMA titers in patients with PBC-CREST [15]. A significant inverse correlation was observed between aCENP-B and AMA titers in patients with PBC-CREST.

2.5 Nail-Fold Capillaroscopy

In Europe, noninvasive nail-fold capillaroscopy of the fingers is widely used to assess microcirculatory disturbances of skin capillaries as well as for the differential diagnosis and prognosis prediction in patients with rheumatic disease, particularly in those with scleroderma [53–56]. Fonollosa et al. reported a high frequency of nail capillary abnormalities in PBC patients [57]. With the prototype fingernail-fold capillaroscopy system and a DP71 digital camera, nail-fold capillaroscopy was performed on the left fourth finger of each patient under immersion oil, and captured images were saved (Fig. 2.2). The mean +2 standard deviation of the maximum capillary diameter was determined to be 24 μm. Using this value as a standard and

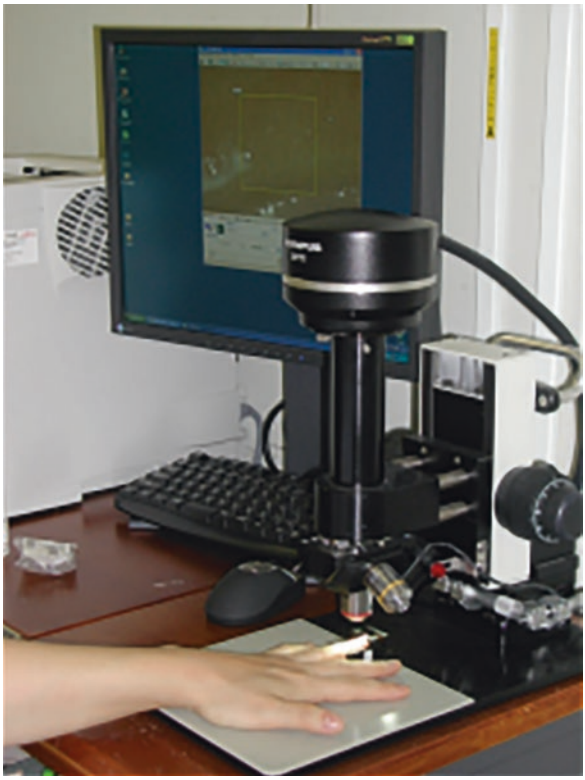

Fig. 2.2 Prototype fingernail-fold capillaroscopy system

based on a previous report [58], abnormal fingernail-fold-capillaroscopy findings were classified (Fig. 2.3). Monoe et al. reported that significantly more PBC patients with abnormal capillaroscopy findings were positive for ACA than those with normal capillaroscopy findings [59]. Many PBC patients also have Raynaud's phenomenon. The incidence of Raynaud's phenomenon is high in PBC patients positive for ACA, and such patients are susceptible to portal hypertension and CREST syndrome.

2.6 Prognosis

Tojo et al. reported that the survival rate 10 years after diagnosis of the disease was significantly higher in patients with PBC-CREST (87.5%) compared with patients having PBC alone (45.5%) [15]. Similarly, a better prognosis for survival was found in PBC patients who have ANA and ACA by Remmel et al. [60]. Other studies demonstrated that combined PBC-SSc includes a significantly better outcome in terms of 10-year survival, but not in terms of overall survival, and significantly lower rates of jaundice progression and liver transplantation in combined cases than

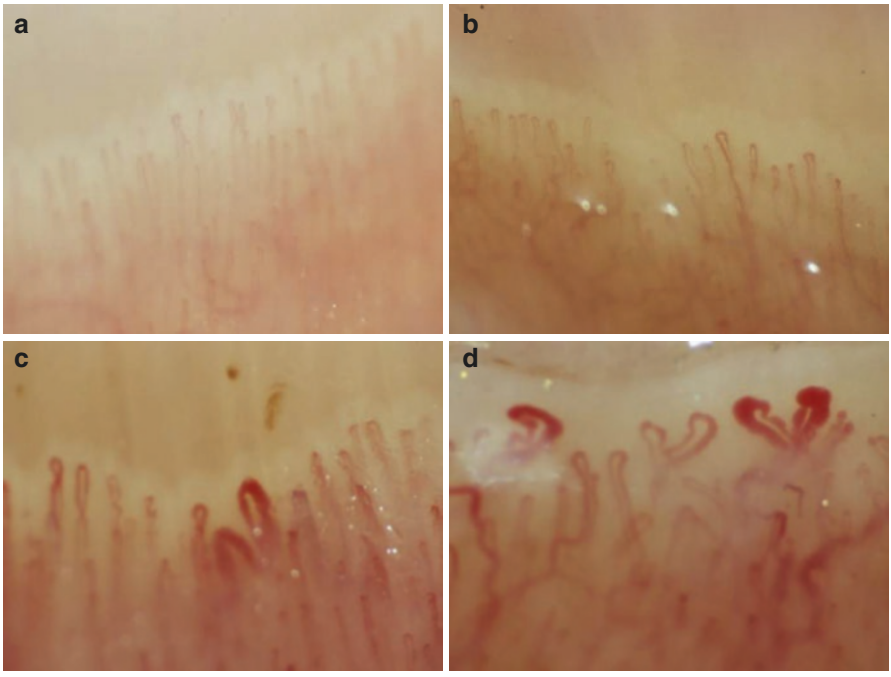

Fig. 2.3 Representative images of classification of fingernail-fold capillaroscopy findings: (**a**) normal, (**b**) mildly abnormal, (**c**) moderately abnormal, (**d**) severely abnormal

in cases of PBC alone [15, 61]. Given that ACA-positive PBC is associated with an increased risk of portal hypertension, the early control of gastroesophageal varices may lead to an improved outcome.

2.7 Conclusion

Patients with PBC-CREST manifested milder symptoms of both PBC and CREST but had a greater number of esophageal varices. Higher ACA titers, lower AMA titers, a higher prevalence of HLA-DR9, and better prognosis were found in patients with PBC-CREST. Because PBC is often complicated by rheumatic disease, hepatologists should consider the possibility of systemic disorder when examining PBC patients.

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Chapter 3
De Novo Hepatitis B Virus Infection

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Abstract Hepatitis B virus (HBV) reactivation is defined as HBV reproliferation under specific conditions, such as immunosuppression. A state of reactivation counteracts a state of immunosuppression. Thus, hepatitis that occurs due to an attack on HBV-infected hepatocytes by a recovered immune system is known as de novo hepatitis B infection. HBV reactivation is induced by various agents that are used for chemotherapy and immunosuppressive therapy, and the risk of reactivation determines the severity of both HBV infection and immunosuppression. Several reports have described HBV reactivation due to antirheumatic agents used to treat rheumatic and connective tissue disorders. However, HBV reactivation does not occur frequently, and immunosuppressive treatment is usually long term; thus, the risk of hepatitis onset due to an immune response is low. However, de novo hepatitis B infection tends to be severe, and if the patient becomes ill, the mortality risk is not only high, but treatment of the underlying disease is also complicated by hepatitis onset. Therefore, preventing onset itself is of primary importance. Currently, according to the "Guidelines for the Management of Hepatitis B Virus Reactivation Caused by Immunosuppression/Chemotherapy", it is imperative to perform monitoring and administer preventive treatment with nucleic acid analogues to all patients with rheumatic and connective tissue disorders who are likely to develop hepatitis B reactivation. In addition, future research should consider clarifying viral and host factors related to HBV reactivation and severity to define high-risk patients.

Keywords HBV reactivation · Immunosuppressive therapy · Rheumatoid arthritis · Nucleic acid analogue · Hepatitis B Treatment Guidelines

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3.1 Introduction

There are an estimated 400 million hepatitis B virus (HBV) carriers worldwide [1], and the infection rate in Japan is approximately 1%. Due to HBV infection in the puerperium and neonatal period, ≥90% of individuals are persistently infected, although most become stable, nonactive carriers. Nevertheless, chronic hepatitis occurs in approximately 10% of carriers due to persistent activation of the virus, which is known to subsequently cause hepatic cirrhosis and hepatocellular carcinoma [2–4]. Meanwhile, hepatitis infection during adulthood commonly entails a period of quiescence after a period of acute hepatitis mediated by an early immune response. Hepatitis B surface antigen (HBsAg) disappears, and anti-hepatitis B surface antibodies (anti-HBs) and anti-HB core antibodies (anti-HBc) appear, which are considered to reflect a clinical state of healing in patients with a history of HBV infection. However, HBV genes are also present in hepatocyte nuclei as covalently closed circular DNA (cccDNA) in patients with a history of HBV infection, and it has become clear that HBV DNA replication persists over the long term. Currently, once HBV infection has occurred, the cccDNA cannot be eliminated from the body completely, and viral proliferation may resume under specific conditions such as immunosuppression; thus, it becomes possible to detect serum HBV DNA. This is known as "HBV reactivation" [5]. A state of reactivation counteracts a state of immunosuppression that follows anticancer agent treatment or immunosuppressive therapy. As a result, hepatitis that occurs due to an attack on HBV-infected hepatocytes by a recovered immune system is known as de novo hepatitis B infection. The fact that hepatitis B recurs at a high rate after chemotherapy or immunosuppressive therapy for organ transplantation in HBV carriers has been known since 1980. However, HBV reactivation in HBsAg-negative patients was first reported by Dervite in 2001 after the use of chemotherapy regimens containing rituximab, and HBV reactivation has gained attention since then [6]. It has become clear that immunosuppressants, adrenocorticotrophic hormone, anticancer agents and antirheumatic agents are drugs that induce reactivation [7–9]. It is also common knowledge that the risk of HBV reactivation also needs to be considered during the unique management of bone marrow and living-donor liver transplants, as well as in conventional chemotherapy to treat haematological malignancies and solid tumours and immunosuppressive therapy to treat autoimmune disorders. De novo hepatitis B infection tends to be severe, and if the patient becomes ill, the mortality risk is not only high [5, 6, 10], but treatment of the underlying disease is also complicated by hepatitis onset; therefore, preventing onset itself is of primary importance. HBV reactivation can occur in HBsAg-positive inactive carriers/chronic hepatitis patients or in HBsAg-negative, HBc or HBs antibody-positive patients with a history of HBV infection. The risk of HBV reactivation determines the severity of both HBV infection and immunosuppression.

3.2 Definition of HBV Reactivation

HBV reactivation is usually defined as HBV infection that occurs in HBsAg-positive inactive carriers/chronic hepatitis patients or in HBsAg-negative, anti-HBc or anti-HBs antibody-positive patients with a history of HBV infection.

Characteristics of patients who test positive for the HBsAg

1. HBV DNA elevated by ≥tenfold.
2. Patients test negative for the HB envelope antigen (HBeAg) and later test positive for this antigen.

Characteristics of patients who test negative for the HBsAg and test positive for anti-HBc or anti-HBs antibodies

1. Patients seroconvert to testing positive for the HBsAg.
2. Patients below the HBV DNA detection limit convert to testing positive for HBV DNA.

3.3 HBV Reactivation Risk and Frequency

The risk of HBV reactivation determines the severity of both HBV infection and immunosuppression. The risk of HBV reactivation is highest in patients with chronic active hepatitis, inactive hepatitis and a history of infection. Risk factors for reactivation in patients who test positive for the HBsAg include testing positive for HBeAg and high HBV DNA values. If patients with a history of infection test positive for anti-HBs antibodies, this may be useful for suppressing reactivation, although patients who only test positive for anti-HBs antibodies are also known to readily develop reactivation. However, if the anti-HBs antibody titre is ≥100 mIU/mL, the risk of HBV reactivation is low [11].

The risk of HBV reactivation with hepatitis onset and the propensity for severity differ based on the agents used for immunosuppression and chemotherapy. However, the frequency of reactivation has not been sufficiently clarified. Among patients who received chemotherapy in Japan, 1–3% were HBsAg positive, while approximately 20–30% were anti-HBs or anti-HBc antibody positive, and these patients are at risk of HBV reactivation [12–14]. Reactivation is reported to occur at a frequency of approximately 20–50% in HBsAg-positive patients with any type of tumour or who are receiving anticancer drug treatment (Table 3.1) [13, 15–20]. Risk factors include male sex, younger age, HBeAg positivity, high HBV DNA titres, breast cancer, concomitant use of steroids, use of anthracyclines as anticancer drugs, use of rituximab and lymphoma [21, 22].

The frequency of HBV reactivation in patients with a history of HBV infection is reported to be 0.3–9.3% after systemic chemotherapy and 2.7–23.8% after chemotherapy including rituximab (Table 3.2) [8, 11, 13, 23–30].

Table 3.1 Reports of HBV reactivation after chemotherapy (HBsAg (+) patients)

Types of cancer	Regimen	Reactivation rate (%)	Reporter
Breast cancer	5FU + CPA, CAF, AC	14–31	Yeo, Kim, Sohn
Hepatocellular carcinoma	PIAF, Everolimus, Epi + CDDP	34–59	Yeo, Dai, Jang
Gastrointestinal cancer	Various	7	Yeo
Head and neck cancer	Various	29	Yeo
Lung cancer	Various	23	Yeo
Lymphoma	PACE, various	48–73	Cheng, Lok

CPA cyclophosphamide, *CAF* cyclophosphamide + doxorubicin + 5-FU, *AC* Doxorubicin + cyclophosphamide, *PIAF* Cisplatin + interferon + doxorubicin + 5-FU, *Epi* Epirubicin, *CDDP* Cisplatin, *PACE* Prednisolone + epirubicin + cyclophosphamide + etoposide

Table 3.2 Reports of HBV reactivation after chemotherapy (HBsAg (−) and HBcAb (+) and/or HBsAb (+) patients)

Types of cancer	Regimen	Reactivation rate (%)	Reporter
Lymphoma	Rituximab-CHOP	4–23.8	Koo, Yeo
	Rituximab-based therapy	2.7–12.2	Pei, Targhetta, Hui, Metzler, Kusumoto, Hsu
	Various	0.8–3.9	Targhetta, Lok, Markovic
Hepatocellular carcinoma	Everolimus, MMC + CPT11-TACE	2.9–9.3	Zhu, Peng
Solid cancer	Various	0.3–7.4	Kim, Furuse, Hagihara

CHOP Cyclophosphamide + doxorubicin + vincristine + prednisolone, *MMC* Mitomycin C, *TACE* transcatheter arterial chemoembolization

3.4 Rheumatic and Connective Tissue Disorders and HBV Reactivation

Treatment for rheumatoid arthritis (RA) has changed dramatically since the dissemination of biologics, and the treat-to-target (T2T) concept has entered everyday vocabulary. This concept describes the therapeutic target of remission or low-activity disease due to early diagnosis and treatment. While this is expected to improve the RA prognosis, it may increase adverse events, and HBV reactivation is one such event that requires attention [31].

According to a 2010 report by the Study Group of Intractable Liver Diseases for Research on a Specific Disease, Health Science Research Grant, Ministry of Health, Labour and Welfare of Japan titled “Nationwide Survey of Hepatitis B Virus Reactivation in Patients Receiving Immunosuppressive and/or Anticancer Drugs to Establish the Therapeutic Strategy to Prevent Severe Liver Injury”, among 84 patients with rheumatic disorders enrolled in the survey, serum HBV DNA was

Table 3.3 Reports of HBV reactivation in rheumatoid arthritis following immunosuppressive therapy (HBsAg (−) and HBcAb (+) and/or HBsAb (+) patients)

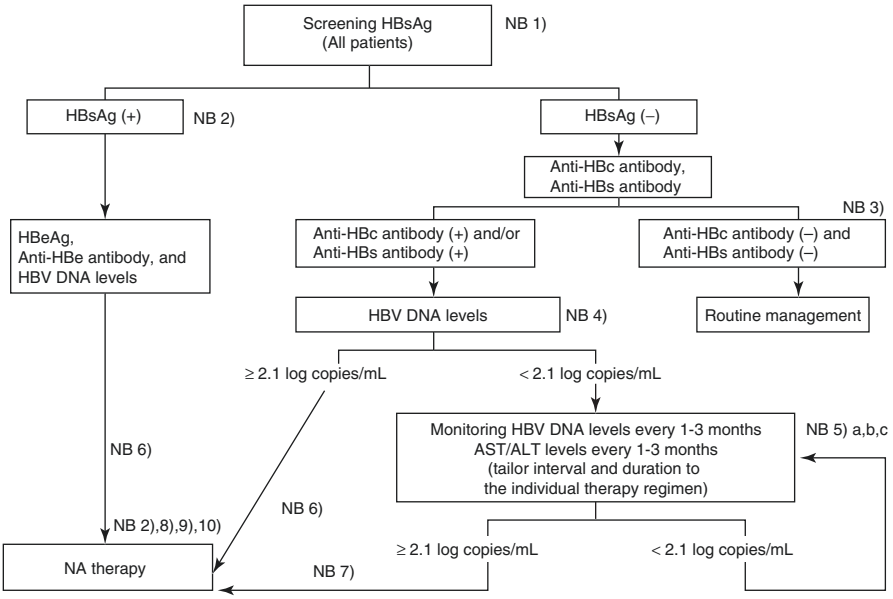
Usage rate (%)			
Biologics	MTX	Reactivation rate (%)	Reporter
100	48	0	Charpin
100	76	0	Caporali
39	48	5.2	Urata
93	ND	2.2	Tamori
100	100	1.4	Lan
0	ND	1.1	Tan
100	74	5.3	Nakamura

detected in 3 patients before treatment despite them being HBsAg negative. Among 77 patients with a history of infection, including these 3 patients, HBV reactivation was observed in 6 patients. In addition, 509 HBsAg-negative RA patients were surveyed in 2011, and 157 (30.8%) tested positive for both anti-HBc antibodies and anti-HBs antibodies and were reportedly patients with a history of HBV infection [32]. Furthermore, according to the same study, when the 157 patients with a history of infection were followed up for 18 months, 13 (8.3%) became seropositive for HBV DNA, and HBV reactivation was observed. The 13 patients who became HBV DNA seropositive were compared to the 144 patients who remained negative, and the use of methotrexate (MTX), high-dose adrenocorticosteroids and tacrolimus hydrate was significantly increased in the positive conversion group ($p < 0.01$). Moreover, numerous reports have described HBV reactivation due to antirheumatic agents, and a list is shown in Table 3.3 [32–38]. Numerous reports have also shown that patients with a history of HBV infection have a low frequency of reactivation. Additionally, even if reactivation occurs, immunosuppressive therapy for rheumatic and connective tissue disorders is usually long term; therefore, the risk of hepatitis onset due to an immune response is low [32, 39–41]. However, if the risk is acute, the prognosis is extremely poor [42]. Thus, until it is possible to select high-risk patients in the future, it is imperative to perform monitoring and administer preventive treatment in accordance with the hepatitis B management guidelines shown in the following section in all patients with rheumatic and connective tissue disorders.

3.5 HBV Reactivation Guidelines

HBV reactivation is problematic, and guidelines on its management have been published in every country in the world. Consistent with the “Guidelines for the Management of Hepatitis B Virus Reactivation Caused by Immunosuppression/

Chemotherapy", the American Association for the Study of Liver Diseases Practice Guidelines were published in 2007, the National Institutes of Health (NIH) Consensus Development Conference Management of Hepatitis B was published in 2008, the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines were published in 2009, and the US Food and Drug Administration guidelines were published in 2015. The Ministry of Health, Labour and Welfare (MHLW) Acute Hepatitis Subcommittee of the "Investigative Studies of Intractable Hepatobiliary Disorders" group and the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis published guidelines in Japan in 2009. Revisions made in 2018 have resulted in the "Hepatitis B Treatment Guidelines" (third edition) (Fig. 3.1). The guidelines are similar, and all recommend preventive administration of antiviral agents in HBsAg-positive patients when chemotherapy or immunosuppressive therapy is administered. According to the aforementioned "Hepatitis B Treatment Guidelines", in HBsAg-negative patients with a history of infection, the objective of HBV DNA monitoring is to return the HBV DNA levels to 20 IU/mL (1.3 logIU/mL), based on the criteria for nucleic acid analogues. However, caution is required in this regard.



Excerpt from "Drafting Committee for Hepatitis Management Guidelines the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis B Virus Infection. Hepatol Res. 2014;44 Suppl S1:40-41"

Fig. 3.1 Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

Caution is required when administering powerful chemotherapeutic agents for hematological malignancies, as during or following completion of treatment some HBsAg positive or negative patients will develop hepatitis B due to reactivation of HBV, and some of these will go on to suffer fulminant hepatitis. Consideration should also be given to the possibility of HBV reactivation in association with standard chemotherapy for hematological malignancies or solid cancers, and immunosuppressive therapy for autoimmune diseases, such as rheumatic and collagen diseases. The incidences of HBV reactivation, hepatitis and fulminant hepatitis associated with standard chemotherapy and immunosuppressive therapy are not known, and there is a lack of evidence on which to base guidelines. Furthermore, prevention of fulminant hepatitis is not guaranteed with NA therapy.

- (NB 1) HBV carriers and patients with resolved hepatitis B should be screened prior to immunosuppressive therapy or chemotherapy. First HBsAg testing should be performed to determine whether they are an HBV carrier. HBsAg negative patients should be tested for anti-HBc antibody and anti-HBs antibody, to confirm past infection. Highly sensitive testing methods should be used for measurements of HBsAg, anti-HBc antibody and anti-HBs antibody.
- (NB 2) A hepatologist should be consulted concerning HBsAg positive patients. A hepatologist should preferably be consulted for all patients administered NAs.
- (NB 3) In some patients undergoing retreatment who did not undergo testing for anti-HBc or HBs antibody at the time of their initial chemotherapy, and in patients who have already commenced immunosuppressive therapy, antibody titers may be low, in which case measurement of HBV DNA levels is preferable.
- (NB 4) Patients with resolved HBV infection should be screened using real-time PCR measurement of HBV DNA levels.
- (NB 5)

  (a) Caution is required when treating patients with resolved HBV infection with rituximab+corticosteroid or fludarabine chemotherapy, or when they undergo hematopoietic stem cell transplantation, as these patients are at high risk of HBV reactivation. HBV DNA levels should be monitored on a monthly basis during treatment, and for at least 12 months afterward. Long-term monitoring is required for hematopoietic stem cell transplant recipients.

  (b) Although the incidence is low, there is a risk of HBV reactivation with standard chemotherapy regimens. HBV DNA levels should be measured every 1–3 months, with the interval and duration tailored to the individual therapy regimen. It is best to err on the side of caution with patients undergoing treatment for hematological malignancies.

  (c) There is also a risk of HBV reactivation associated with immunosuppressive therapy using corticosteroids, immunosuppressant agents, or molecular targeted therapy with immunosuppressant or immunomodulator activity. HBV DNA levels should be monitored on a monthly basis in patients on immunosuppressive therapy for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen.

- (NB 6) Administration should be commenced as soon as possible, before commencement of immunosuppressive therapy or chemotherapy.
- (NB 7) Administration should be commenced as soon as the HBV DNA levels exceed 2.1 log copies/mL, during or after immunosuppressive therapy or chemotherapy. If this occurs during treatment, it is preferable to consult with a hepatologist, and not immediately cease the immunosuppressant or antineoplastic agent with immunosuppressive activity.
- (NB 8) Entecavir is the recommended NA.
- (NB 9) Cessation of NA therapy can be considered if the following criteria are met. In patients who were HBsAg positive at the time of screening, when the criteria for cessation of NA therapy in cases with chronic hepatitis B are met. In patients who were anti-HBc antibody and/or anti-HBs antibody positive at the time of screening:

    1. NA therapy has been continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy.
    2. ALT (GPT) levels have been normalized during this period (excluding causes of elevated ALT levels other than HBV).
    3. negative conversion of HBV DNA has occurred during this period.

- (NB 10) Patients should be carefully monitored, including measurement of HBV DNA levels, for at least 12 months following completion of NA therapy. Monitoring methods depend on package inserts of each NA. NA therapy should be immediately resumed if HBV-DNA levels exceed 2.1 log copies/mL during monitoring period

Meanwhile, the "Recommendations on Immunosuppressive Therapy for Hepatitis B-Infected Patients with Rheumatoid Disease" were published by the Japanese Society of Rheumatology and should be noted. In addition, a fourth edition of the "Guidelines for the Management of Hepatitis B Virus Reactivation Caused by Immunosuppression/Chemotherapy" was published in 2014 after revisions based on outcomes from various studies. In these guidelines, immunosuppressive therapy is listed as including adrenocorticosteroids (moderate or higher doses), antirheumatic drugs (such as methotrexate, tacrolimus, leflunomide and mizoribine) with immunosuppressant effects, all antirheumatic biologics and immunosuppressive agents (such as azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil). Patients with rheumatic disorders due to HBV infection as a result of the administration of these drugs are managed in accordance with the "Guidelines for the Management of Hepatitis B Virus Reactivation Caused by Immunosuppression/Chemotherapy". Of particular note is the frequency of HBV DNA measurements, which is stated to be every 1–3 months, although the majority of patients receiving immunosuppressive therapy for rheumatic disorders develop HBV reactivation 6 months or more after starting treatment or switching therapy. The risk of reactivation subsequently decreases; therefore, HBV DNA should be monitored every month for at least 6 months if new immunosuppressive agents are started or existing ones are switched. If this is not a concern, measurement of HBV DNA values every 3 months

is recommended, although based on the treatment details, this measurement may also be substituted with highly sensitive HBsAg measurements (sensitivity: 0.005 IU/mL). Furthermore, if highly sensitive HBsAg monitoring shows positive values <1 IU/mL (weakly positive), nucleic acid analogues should be started after serial HBV DNA values of 20 IU/mL are confirmed.

3.6 Treatment for HBV Reactivation

Evidence for the preventive administration of antiviral agents in HBsAg-positive patients was obtained from a meta-analysis that showed the usefulness of preventive lamivudine administration [12, 43–45]. A randomised, comparative study that compared the preventive administration of lamivudine and entecavir as antivirals showed that the genetic barrier to lamivudine is low. Another report described the usefulness of entecavir because resistant mutations readily arise when viral proliferation ability is high or if the administration period is prolonged, and entecavir is recommended for HBsAg-positive patients. The latest "Hepatitis B Treatment Guidelines" (third edition) recommend entecavir and tenofovir disoproxil, which are not associated with treatment resistance. Meanwhile, there is a mean time lag of 18.5 weeks from HBV DNA detection until alanine transaminase (ALT) elevation in patients with a history of HBV infection. Accordingly, based on the reactivation risk, HBV DNA is measured periodically, and starting nucleic acid analogue treatment soon after the DNA is detected is important for preventing hepatic dysfunction.

3.7 Reference Guide for Ending Nucleic Acid Analogue Administration

A high rate of hepatitis recurrence is observed after nucleic acid analogue treatment is withdrawn [46]. It is therefore important to select patients who can undergo successful withdrawal by determining which patients readily develop recurrence, investigate nucleic acid analogue treatment withdrawal for any reason and withdraw nucleic acid analogue treatment. When we investigated patients who experienced recurrence of hepatitis after the withdrawal of nucleic acid analogue treatment, the HBV core-related antigen (HBcrAg) titre was significantly lower in the nonrecurrence group than in the recurrence group (3.2 vs. 4.9, $p = 0.009$) [47]. This finding suggests that HBcrAg is an indicator of nucleic acid analogue treatment. In addition, the effects of nucleic acid analogue reverse transcription on HBsAg and HBcrAg are similarly low, and the group with low HBsAg titres (<1000 IU/mL) during nucleic acid analogue treatment withdrawal had significantly lower rates of repeat treatment after withdrawal (18% vs. 63%, $p = 0.049$) [48]. Considering these results, the "Study on the Usefulness of Interferon Therapy Aimed at Creation of Treatment Withdrawal Criteria and Withdrawal of Treatment when Nucleic Acid

Analogues are Used to Treat Hepatitis B" MHLW research group created the following policy for withdrawing nucleic acid analogues [49, 50].

Patients who test positive for HBsAg

The following necessary conditions must be fulfilled in accordance with the Criteria for Ending Nucleic Acid Analogue Administration to Treat Chronic Hepatitis B.

- Necessary patient characteristics:
  - Hepatitis recurrence is frequently observed after withdrawal of nucleic acid analogue treatment, and the danger of severity sometimes needs to be understood by both the attending doctor and the patient.
  - Follow-up observation is possible after withdrawal, and despite recurrence, appropriate management is possible.
  - Patients have mild hepatic fibrosis and good hepatic reserve, and severity tends to be low when hepatitis recurs.
- Necessary conditions during nucleic acid analogue treatment:
  - Clinical course ≥2 years after nucleic acid analogue treatment.
  - Below the detection limit of serum HBV DNA (real-time PCR method) during withdrawal.
  - During haemostasis, the patient tests negative for HBeAg.

Patients who fulfil the necessary conditions for withdrawal are scored using their HBsAg and HBcrAg titres at the time of withdrawal. They are then divided into three groups based on their total score, which indicates the risk of recurrence, and the success rates are then predicted (Table 3.4). Successful withdrawal is defined as "an ultimate inactive carrier state, i.e., when values decrease to ALT ≤ 30 U/L and HBV < 2000 IU/mL (3.3 logIU/mL)".

Patients who test negative for the HBsAg and test positive for anti-HBc or anti-HBs antibodies

1. Administration is continued for at least 12 months after immunosuppression or chemotherapy has ended.
2. ALT normalises during the period of persistence (causes of ALT abnormalities other than HBV are excluded).
3. During the period of continuation, the patient seroconverts to testing persistently negative for HBV DNA.
4. It is preferable for the HBsAg and HBcrAg to both convert to testing consistently negative.

However, as mentioned above, sufficient evidence has not been established, and therefore, we consulted the Board of Certified Hepatologists of the Japan Society of Hepatology. They recommended diligent follow-up observation including HBV DNA monitoring for at least 12 months after nucleic acid analogue administration has ended. Nucleic acid analogues are restarted immediately if the HBV DNA values are ≥20 IU/mL (1.3 logIU/mL) during follow-up observation.

Table 3.4 Risk of relapse following cessation of NA therapy

HBsAg load at cessation (IU/mL)	Score	HBcrAg load at cessation (U/mL)	Score
< 1.9 log (80)	0	<3.0 log	0
≥ 1.9 log (80), < 2.9 log (800)	1	≥ 3.0 log, < 4.0 log	1
≥ 2.9 log (800)	2	≥4.0 log	2

Relapse risk	Total score	Predicted success rate	Evaluation
Low-risk group	0	80–90%	Group for which cessation may be considered However, even in the low risk group, recurrence of hepatitis can occur, so vigilance is required
Moderate-risk group	1–2	Approximately 50%	Group for which cessation may be considered depending on circumstances This group requires further evaluation concerning cessation criteria and methods
High-risk group	3–4	10–20%	Continued treatment is recommended for this group However, for patients aged <35, the cessation success rate is relatively high at 30–40%

Excerpt from "Drafting Committee for Hepatitis Management Guidelines the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis B Virus Infection. Hepatol Res. 2014;44(Suppl S1):27"

3.8 Management of Hepatic Dysfunction Onset During or After Immunosuppressive Therapy for Rheumatic Disorders

If hepatic dysfunction occurs during or after immunosuppressive therapy in patients with rheumatic disorders, a differential diagnosis of the following disorders, in addition to hepatitis due to HBV reactivation, is required.

1. Drug-induced hepatic disorder
2. Hepatic disorder associated with an underlying disease
3. Alcoholic and nonalcoholic fatty liver disease
4. Autoimmune hepatitis and autoimmune liver disorders, such as primary biliary cirrhosis
5. Biliary tract disorders and pancreatic disorders
6. Acute hepatitis due to infection with the hepatitis (A, B, C, E) virus
7. Acute hepatitis due to other viruses (such as Epstein-Barr virus, cytomegalovirus, herpes virus, adenovirus, coxsackie virus, measles virus, rubella virus, human immunodeficiency virus or parvovirus)
8. Abnormal thyroid function
9. Other hepatic disorders (including malignant hepatic metastases)

A hepatologist should be contacted for differential diagnosis and treatment, and detailed investigation using blood tests and imaging examinations is required. In addition, rapid withdrawal of immunosuppression may increase hepatitis severity

and acuteness, and continuation or withdrawal of immunosuppression must be diligently investigated by a hepatologist. Currently, we believe that it is possible to continue immunosuppression with nucleic acid analogues.

3.9 Conclusion

The guidelines for the prevention of HBV reactivation state that early detection of HBV reactivation due to immunosuppression or chemotherapy is useful, and it may be possible to prevent onset of severe hepatitis with appropriate treatment interventions. Meanwhile, the risk of HBV reactivation causing severe hepatitis due to the effects of immunosuppressive agents is low in medical conditions where long-term immunosuppressive therapy is used, such as rheumatic and connective tissue disorders; therefore, a prudent policy for medical economics is the suppression of acute hepatitis onset. In addition, future research should seek to clarify viral and host factors related to HBV reactivation.

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Chapter 4
Dermatomyositis and Gastrointestinal Cancer

Rei Suzuki, Takuto Hikichi, and Hiromasa Ohira

Abstract Inflammatory myopathies, including dermatomyositis (DM) and polymyositis (PM), are idiopathic disorders characterized by symmetrical proximal skeletal muscle weakness and often accompanied by inflammatory cell infiltration into the muscle tissue. Several lines of evidence suggest an association between myopathies and malignancies. The incidence of malignancy in PM patients is consistently reduced compared with that of DM. The incidence of malignancy in DM patients is varied in studies, but it is estimated that the incidence of malignancy in myopathies is increased five- to sevenfold compared with the general population.

Regarding the type of cancer, individuals with DM exhibit an increased risk of gastroenterological cancers, such as colon, pancreatic, oesophageal, and stomach cancer. The risk of malignancy remains for many years after a DM diagnosis, but the risk for malignancy was increased among patients DM within the first year of diagnosis compared with subsequent years. Although several clinical and laboratory findings suggest the presence of malignancy, autoantibodies against TIF-1γ or NXP-2 serve as promising markers for DM with malignancy.

Keywords Inflammatory myopathy · Dermatomyositis · Malignancy · Gastroenterology · Standardized incidence ratio

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4.1 Introduction

Inflammatory myopathies, including DM (dermatomyositis) and PM (polymyositis), are idiopathic disorders characterized by symmetrical proximal skeletal muscle weakness and often accompanied by inflammatory cell infiltration into muscle tissue [1–6]. Other systemic involvements, including skin involvement, interstitial pulmonary disease, dysphagia, and polyarthritis, are frequently observed. Furthermore, several lines of evidence suggest associations between myopathies and malignancies.

The first report of myopathy accompanied with gastric cancer was published in 1916 [7]. Since then, a number of studies have reported associations between myopathies and malignancies. The incidence of malignancy in PM patients is consistently reduced compared with that in DM patients. In DM patients, the frequency of cancer was 9.4%, and the standardized incidence ratio (SIR) was 5.11. On the other hand, the frequency of cancer was 4.4% with SIR of 2.15 in the PM group [8]. Additionally, it has been hypothesized that the increase in the risk of malignancy in PM patients might be attributed to frequent surveillance compared with the general population [9]. The association between PM and malignancy remains controversial, but that of DM is evident.

In this chapter, we provide a literature review and case presentation for gastroenterological cancers associated with DM.

4.2 Incidence of Malignancy in DM

In 1976, Barns et al. reviewed 258 out of 1250 DM cases associated with malignancy reported since 1916 [10]. From this review, they estimated that the incidence of malignancy in myopathies appeared to increase by five- to sevenfold compared with the general population.

Numerous papers have sought to clarify the incidence of malignancy in myopathies. Hill et al. conducted a pooled analysis of published national data from Sweden, Denmark, and Finland [11]. They identified 618 patients with dermatomyositis from national registries and calculated standardized incidence ratios (SIR) for individual cancer sites for DM using national cancer rates based on country, sex, age, and date. Among DM patients, 115 developed cancer after DM diagnosis. This disease was strongly associated with malignant disease (SIR 3.0, 95% CI 2.5–3.6). Another larger population-based study was published in Taiwan [12]. This study sought to estimate the incidence, occurrence of cancer, and mortality of DM in Taiwan. They utilized national registries to calculate estimates of the incidence, cancer association, and mortality of DM between 2003 and 2007. A total of 803 DM cases were identified, and 107 (13.8%) patients had cancers. The diagnosis of most cancers was made after the diagnoses of DM ($n = 71$; 64.0%). Overall, the SIR for cancer was 5.36 (4.12–6.87) among patients with DM; however, during the first

year, the SIR for cancer was 24.55 (95% CI 18.62–31.79). The most common types of cancer were nasopharyngeal cancer for men and breast cancer for women. Patients with DM had a standardized mortality ratio of 7.68 (6.41–9.01).

Olazagasti et al. conducted a meta-analysis using seven population studies and three hospital-based studies published between 1992 and 2013 [8, 13–22]. DM cohorts ranged from 49 to 1012 patients and had mean follow-up times of 3.7–10.4 years. The pooled SIR for the incidence of overall cancer in DM patients was 4.79 (3.71–5.87).

The results from these studies clearly suggested that DM patients are at a significantly increased risk for developing cancer compared with the general population.

4.3 Pathogenesis

DM associated with malignancy is considered a paraneoplastic syndrome given that several observations demonstrated that DM improved with malignancy treatment and worsen with malignancy recurrence [23–26]. Several lines of evidence suggest a pathogenetic relationship between DM and cancer.

One possible mechanism of the association between DM and malignancy is autoantigen overexpression in tumour and normal tissues. Casciola-Rosen et al. reported that myositis autoantigens (HRS/Jo-1, Mi-2, and DNA-PKcs) were expressed at very low levels in control muscle but highly expressed in myositis muscle. Myositis autoantigen expression was also markedly increased in several cancers associated with autoimmune myositis but not in related normal tissues, demonstrating that tumour cells and undifferentiated myoblasts were antigenically similar. Based on these results, the authors proposed that an autoimmune response directed against cancer cross-reacted with regenerating muscle cells in cancer-associated myositis, enabling a feedforward loop of tissue damage and antigen selection [27].

4.4 Type of Gastroenterological Malignancy

A large population-based study reported by Hill et al. revealed that the following cancers exhibited the highest risks of occurrence after dermatomyositis diagnosis: ovarian (SIR 10.5; 6.1–10.8), lung (SIR 5.9; 3.7–9.2), pancreatic (SIR 3.8; 1.6–9.0), stomach (SIR 3.5; 1.7–7.3), and colorectal cancers (SIR 2.5; 1.4–4.4) and lymphomas (SIR 3.6 for non-Hodgkin lymphoma and 5.9 for Hodgkin lymphoma). However, the relative risk of numerous other malignant diseases was also increased [11].

Chen et al. reported the results of a large population-based study from Taiwan in 2010 [8]. They found that the highest risks after diagnosis of DM were observed for

nasopharynx (SIE 139.9; 137.8–148.1), lung/mediastinum cancers (SIR 20.6; 19.7–21.4), bone/joint cancers (SIR 14.9; 11.6–17.4), and lymphomas/leukaemias (SIR 24.7; 22.6–27.6). In DM patients, an increased risk was observed for oesophageal cancer (SIR 3.1; 2.5–3.7), pancreatic cancer (SIR 3.0; 2.5–3.7), and colon cancer (SIR 4.12; 3.8–4.5) but not stomach cancer (SIR 1.0; 0.8–1.3).

Another population study published from Taiwan by Kuo et al. included 803 DM patients [12]. In total, 111 cancers were diagnosed in these patients. Unlike the other study, SIR was not calculated in this study. However, these patients exhibited increased risks for nasopharyngeal cancer (26.1%), breast cancer (15.3%), and lung cancer (11.7%). Regarding GI cancers, colon cancer was observed in six patients (5.4%), and hepato-biliary cancer was noted in five patients (4.5%).

Olazagasti et al. summarized results of published studies and estimated SIR for each cancer. Increased risks were observed for the following cancers: lymphatic and haematopoietic system (SIR 22.72), lung (SIR 19.74), ovary (SIR 5.39), colon (SIR 4.13), bladder (SIR 4.05), breast (SIR 3.52), cervix (SIR 3.28), pancreas (SIR 3.07), and oesophagus (SIR 3.06) [13]. However, an increased risk for stomach and prostate cancer was not observed. On the other hand, another review that summarized cases of myositis with malignancy in Asian countries reported that nasopharyngeal and lung cancers were the most common malignancies in this region followed by breast, colon, and gastric cancer [8, 21, 28–40].

This result implied that different cancer mechanisms in different populations influence the association between specific types of malignancy and myositis. We summarized previous studies from which we could obtain sufficient information regarding the number of DM patients and type of cancer in DM patients (Table 4.1).

4.5 Timing of Cancer

Malignancy can be diagnosed prior to, concurrent with, or after the diagnosis of DM [41]. Most studies suggest that the risk of malignancy is highest during the year prior to and the year after DM diagnosis.

Hill et al. reported that the risk of cancer was highest within the first year of myositis diagnosis and was substantially reduced thereafter. In those patients with polymyositis, the risk was reduced to expected rates 5 years after diagnosis; however, the risk in DM did not return to expected population values for most cancers. The risks of ovarian, pancreatic, and lung cancer remained high up to 5 years after the diagnosis of dermatomyositis, and the increased risk of pancreatic and colorectal cancer extended past the 5-year follow-up. The risk of non-Hodgkin's lymphoma was increased in the first year but not thereafter [11].

Chow et al. reported that the increased cancer incidence was reduced as years since the initial diagnosis of PM/DM increased. Within the first year of diagnosis, the overall cancer risk was elevated by approximately sixfold (SIR 5.9; CI 3.8–8.7), and the most pronounced risks were noted for lung cancer (SIR 9.1; 2.9–21.2) and

Table 4.1 Literature review of GI cancer in DM patients

Authors	Country	DM	DM with malignancy	Oesophageal	Stomach	HPB	Colorectal	Total number of GI cancer (%)
Buchbinder (2001) [16]	Australia	85	36	0	2	0	5	7 (19.4)
Stockton (2001) [22]	Scotland	286	77	1	3	0	8	12 (15.6)
Hill (2001) [11]	Europe	618	115	1	7	5 pancreas	12	25 (21.7)
Amerio (2002) [49]	Italy	59	14	0	3	0	1	4 (28.6)
Sparsa (2002) [72]	France	33	13	1	2	0	2	5 (38.5)
Mebazaa (2003) [69]	Tunisia	130	20	0	1	1 liver	0	2 (10.0)
Burnouf (2003) [44]	France	26	8	0	0	0	0	0 (0.0)
Lee (2006) [32]	Korea	16	5	0	1	0	0	1 (20.0)
Tani (2007) [38]	Japan	14	3	0	0	0	0	0 (0.0)
Andras (2008) [73]	Hungary	103	30	0	3	0	1	4 (13.3)
Antiochos (2009) [15]	USA	61	24	0	0	3 pancreas	3	6 (25.0)
Chen (2010) [8]	Taiwan	1012	95	1	1	1	5	8 (8.4)
Azuma (2011) [29]	Japan	70	17	0	7	2 pancreas	2	11 (64.7)
Teh (2012) [39]	Malaysia	9	5	0	0	0	1	1 (20.0)
Ortigosa (2014) [74]	Brazil	109	7	0	1	0	1	2 (28.6)
Neri (2014) [67]	Italy	73	18	0	1	0	2	3 (16.7)
Hida (2016) [75]	Japan	143	36 TIF-1γ (+)	3	8	0	0	11 (30.6)
Fang (2016) [76]	China	NA	26	0	1	0	1	2 (7.7)
Liu (2018) [68]	China	239	43	1	5	1 liver	5	12 (27.9)
Sellami (2018) [77]	Iran	NA	14	0	0	0	1	1 (7.1)
Leatham (2018)	USA	400	54	0	0	5	0	5 (9.3)

GI gastrointestinal, *DM* dermatomyositis, *HPB* hepato-pancreato-biliary, *TIF-1*γ transcription intermediary factor 1 γ

among women for ovarian cancer (SIR 38.2; 10.8–102.4). In the second year of follow-up, a significant but smaller increased risk was observed for overall cancer (SIR 2.5; 1.1–4.8) and lung cancer (SIR 6.3; 1.3–18.3). In subsequent intervals of follow-up, a 50% increase in cancer risk was observed; however, the result was not significant overall or for any particular cancer site [18].

In a meta-analysis reported by Yang et al., the risk of malignancy remains for many years after a DM diagnosis. However, the overall RR for malignancy was 19.4 (14.1–24.7) among patients DM within the first year of diagnosis, which was significantly increased compared with the rate after the first year (overall RR 1.98; 1.6–2.4 for DM) [42].

4.6 Risk Factor

A number of clinical and laboratory findings indicate an increased risk of malignancy in DM patients [41].

4.6.1 Demographics

Older age and male sex are a risk factor for malignancy in DM.

Hill et al. reported an increased risk of malignant disease in people aged 15–44 years at time of DM diagnosis (SIR 2.2; 1.1–4.2) and in those aged 45 and older (3.1; 2.6–3.7). Stockton et al. also reported that the increased risks were significant in the 45–74 age group with SIRs of 4.8 (0.6–17.4), 3.6 (2.0–5.9), and 2.1 (0.4–6.1) in the age groups 15–44, 45–74, and 75+, respectively. No cancers were noted in the 35 children (aged <15) diagnosed with DM. Therefore, age older than 45 years old is the most commonly known risk factor for malignancy in DM.

Although male sex is considered to be associated with an increased risk of malignancy in DM patients, a final conclusion has not been reached to date. A recent meta-analysis of 31 studies reported by Wang et al. suggested that male sex was risk factor for malignancy (odd ratio 1.9; 1.5–2.5) [43]. On the other hand, a recent meta-analysis reported by Olazagasti et al. reported a similar incidence of malignancy in males and females. The pooled SIR for the overall risk of cancer in male DM patients was 5.4 (5.2–5.5), whereas the pooled SIR for the overall risk of cancer in female DM patients was 5.1 (4.9–5.2) [13].

4.6.2 Skin Manifestation

Skin necrosis and cutaneous vasculitis have been reported as risk factors of malignancy.

Burnouf et al. prospectively assessed 26 adults presenting with dermatomyositis and found that cutaneous necrosis was more frequently observed in DM patients with malignancy compared with those without malignancy (5 vs. 2 patients, $P = 0.01$) [44]. Furthermore, a meta-analysis reported by Wang et al. also suggested a strong relation between cutaneous necrosis and malignancy in DM patients (OR 5.5; 3.5–8.7) [43].

Skin vasculitis may represent another risk factor for malignancy in DM patients. The association between skin vasculitis and malignancy in DM patients was first suggested by Feldman [45]. In this case, series, skin vasculitis was observed in 28.6% of DM patients with malignancy compared with only 4 (5.8%) patients without vasculitis. Another case series with 23 DM patients also reported that 4 of the 5 patients with an associated malignancy histologically demonstrated skin vasculitis (80%) compared with only 3 out of 18 cases (17%) without malignancy ($P < 0.05$). However, skin vasculitis is often observed in patients with malignancy regardless of the presence of DM; this manifestation can be considered a maker of malignancy [46].

4.6.3 Muscle Histology

Uchino et al. evaluated the muscle biopsy findings of 215 patients with either PM or DM. The pathology of muscle biopsy sections was classified into three types: endomysial infiltration type, perivascular infiltration type, and rare-infiltrative type. The incidence of rare-infiltrative type muscle pathology in DM patients with malignancy was significantly increased compared with those without such tumours ($P = 0.03$).

4.6.4 Laboratory Marker

Given that DM is not always accompanied with elevated inflammation markers, elevation of these markers can be a clue of the presence of malignancy in DM patients [21, 47, 48]. Amerio et al. performed a case-control study on the patients admitted in our institutions for dermatomyositis. In this study, they found that no significant difference in the clinical (skin manifestations and muscular weakness) or laboratory parameters (LDH, CK, aldolase) between the dermatomyositis patients with or without malignancy, with the exception of the erythrocyte sedimentation rate, especially ESR more than 35 mm/h was very strongly associated with the presence or the development of a malignancy [49].

4.6.5 Others

TIF-1γ: An autoantibody recognizing a protein with molecular weight of 155 kDa with or without a 140-kDa target was first reported in two separate studies [50, 51]. The target was subsequently proven to be transcription intermediary factor 1 γ

(TIF-1γ). Transcription intermediary factor 1 γ (TIF-1γ) is also known as anti-p155 or anti-p155/140. The percentage of patients with this autoantibody harbouring a malignancy ranges from 42 to 100% depending on the study [52–56]. A meta-analysis including six studies including a total of 312 adult patients with DM revealed that the pooled sensitivity of TIF-1γ for diagnosing cancer-associated DM was 78% (45–94%), and the specificity was 89% (82–93%). The diagnostic OR was 27.2 (6.6–112.8), and LRs for positive and negative test results were 6.79 (4.1–11.2) and 0.25 (0.1–0.7), respectively [54].

NXP-2: Oddis et al. first described an anti-MJ autoantibody in a US cohort of juvenile DM (JDM), and Targoff et al. subsequently identified that the antigen of anti-MJ autoantibody was nuclear matrix protein NXP2 [57, 58]. Ichimura et al. investigated the frequencies and clinical associations of anti-NXP2 Ab in adult patients with DM. Clinical data and serum samples were collected from 445 patients with DM. Seven patients (1.6%) with adult DM were positive for anti-NXP2 Ab. With the exception of two patients with JDM, none of the disease controls were positive for this autoantibody. Among eight adult patients with IIM, two patients with NXP-2-positive DM (29%) had malignancies within 3 years of diagnosis. All of the carcinomas were diagnosed at an advanced stage [58].

4.7 Screening

Considering the high prevalence of malignancy in inflammatory myositis, cancer screening is typically recommended in these patients. In this section, we attempt a literature review of 'general' cancer screening in patients with inflammatory myositis given the lack of studies that exclusively focus on gastroenterology or DM.

Tumour markers have been utilized for cancer screening. Amoura et al. assessed the diagnostic usefulness of serum tumour markers, including carcinoembryonic antigen (CEA), CA15-3, CA19-9, and CA125, for the detection of solid cancer in 102 patients with DM and PM [59]. All patients underwent a complete physical examination, chest X-ray, gastrointestinal tract endoscopy, and whole-body computed tomography scan (CT), and all women underwent a gynaecologic examination and mammogram. During the follow-up, solid cancer was detected in ten patients (9.8%). Elevated CA125 was associated with an increased risk of developing solid cancer [$P = 0.0001$; odds ratio (OR), 29.7; 95% confidence interval (95% CI), 8.2–106.6]. A combination of elevated CA125 and CA19-9 at screening was also associated with an increased risk of solid cancer [$P = 0.0007$; OR, 86.3; 95% CI, 4.06–1832]. Although DM was not the focus in this analysis, CA125 and CA19-9 assessment could be useful for screening of tumours in patients with inflammatory myositis. However, a recent study by Lim et al. failed to demonstrate the clinical utility of tumour markers, including CEA, AFP, CA15-3, CA19-9, and CA125, in cancer screening for patients with inflammatory myositis [60]. Moreover, considering the low diagnostic yield of tumour markers for GI cancer screening in the general population, tumour marker measurements alone cannot be a reliable modality in cancer screening [61–65].

To identify more reliable screening modalities, Selva-O'Callaghan et al. conducted a prospective study to compare the diagnostic yield of whole-body FDG-PET/CT and conventional cancer screening, which included whole-body CT, mammography, gynaecologic examination, ultrasonography, and tumour marker analysis [66]. They included 55 consecutive patients with a recent diagnosis of myositis. Positive and negative predictive values of FDG-PET/CT for the diagnosis of cancer were 85.7% and 93.8%, respectively. Conventional screening results were cancer positive in 9 patients (2 false positive) and negative in the remaining 46 patients (2 false negative). Positive and negative predictive values were 77.8% and 95.7%, respectively. The overall predictive value of broad conventional screening was the same as that of FDG-PET/CT (92.7 vs. 92.7). The authors concluded that FDG-PET/CT was equivalent to conventional screening methods for detecting cancer in this population, and multiple steps of conventional screening methods were not required with this modality. This result is promising but requires further validation in a large number of patients.

Regardless of these studies, there is no established consensus about cancer screening [59–61]. Age- and gender-appropriate screenings considering different cancer mechanisms in different populations should be considered.

4.8 Prognosis and Treatment

Given that no study reported prognosis or treatment strategies for DM patients with a specific malignancy, we would like to discuss the general principles of the prognosis and treatment for DM patients with malignancy.

In general, prognoses of DM patients with malignancy were poorer compared with those without malignancy. Neri et al. conducted a retrospective study in which 162 patients were included, and 27 (17%) had malignancy [67]. The survival rate at 2 years from diagnosis was 57.0% in patients with malignancy and 90.0% in patients without malignancy. The survival rate of patients without malignancy at 5 years was significantly increased (82%) compared with patients with malignancy (44%). More recently, Liu et al. reported that the survival rate was significantly reduced in patients with malignancy compared with patients without malignancy ($P = 0.001$) [68]. The 1- and 5-overall survival rates were 88.7% and 85.4%, respectively. The cumulative survival rates in the malignancy group were 81.4% at 1 year and 58.14% at 5 years. These results were consistent with other previous studies [40, 69].

Regarding treatment for DM associated with malignancy, specific treatments for malignancy and DM should be considered at appropriate time points. Given that DM associated with malignancy tends to be refractory to conventional immunesuppressive treatment, preceding treatment for DM may increase risk of infection or delayed wound healing in patients who require surgery for malignancy. Additionally, as observations of previous studies suggest, removal of cancer may contribute to remission of DM [25, 70, 71]. Based on these facts, specific treatment for malignancy prior to DM should be considered if applicable.

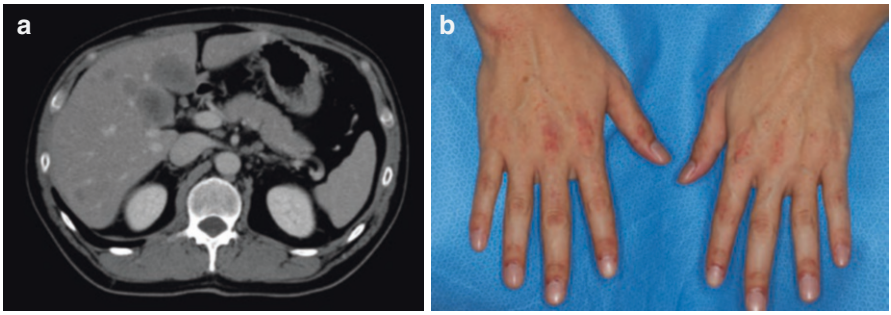

Fig. 4.1 Dermatomyositis and colon cancer. (**a**) Multiple liver metastases were detected on CT. (**b**) Skin findings were characterized by erythematous papules that occurred on the dorsal side of both hands (Gottron's sign)

4.9 Case Presentation

4.9.1 DM and Colon Cancer

A 38-year-old male was referred from an outside hospital for systemic muscle pain and erythematous papules that occurred on the dorsal side of both hands. Rectal cancer with liver metastasis was diagnosed 1 month prior to the visit (Fig. 4.1a). The patient complained of systemic muscle pain. Physical evaluation revealed mild weakness in lower extremities. Skin findings were characterized by erythematous papules that occurred on the dorsal side of both hands (Gottron's sign) and papules on the palms of both hands (inverse Gottron's sign) (Fig. 4.1b). Laboratory findings revealed remarkably elevated muscle enzyme (CPK 5697 U/L, aldolase 46.1 U/L, myoglobin 1295 ng/mL) and high inflammation (CRP, ESR). Serum anti-TIF1γ antibody was positive in this case. Given that clinical and laboratory findings were diagnostic for dermatomyositis, a skin biopsy was not performed. An imaging study revealed no interstitial pneumonia, but multiple lymph node liver metastases were observed (Fig. 4.1c). This patient was treated with systemic chemotherapy (FOLFOX) with bevacizumab for rectal cancer concurrent with high-dose corticosteroid for DM. He died 7 months after the first visit due to rectal cancer progression.

4.9.2 DM and Oesophageal Cancer

A 71-year-old male was referred from an outside hospital for systemic skin rash and muscle weakness (Fig. 4.2a). His symptoms developed 2 months prior to the first visit to our hospital. Additionally, he also complained of dysphagia, which occurred simultaneously with skin rash. Upper endoscopic assessment at the referring hospital revealed a tumour in the lower oesophagus (Fig. 4.2b). Upon arrival, his body

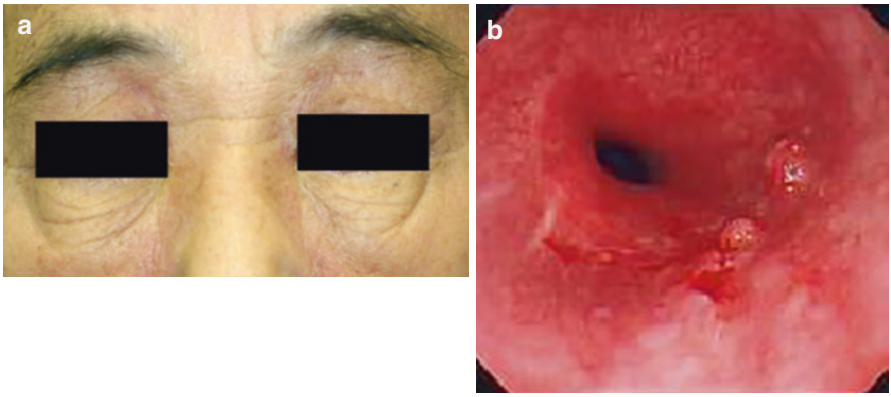

Fig. 4.2 Dermatomyositis and oesophageal cancer. (**a**) Typical skin finding (heliotrope eyelids) was observed. (**b**) Upper endoscope revealed oesophageal cancer

temperature was 38.0 °C, and oxygen saturation was 92% in room air. Laboratory data revealed mildly increased muscle enzyme (CPK 533 U/L), but the patient was negative for autoantibodies, including anti-Jo-1 and anti-TIF1γ. Computed tomography revealed bilateral interstitial pneumonia. Even after administration of high-dose corticosteroid and supportive care, his general condition progressively deteriorated within a week due to severe interstitial pneumonia. The patient died 2 weeks after admission.

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Chapter 5
Portal Hypertension in Rheumatic Diseases

Tadayuki Takagi and Hiromasa Ohira

Abstract Some rheumatic diseases are complicated by portal hypertension which can cause gastrointestinal varices and ascites requiring adequate treatment. The mechanism leading to portal hypertension often involves idiopathic portal hypertension, pulmonary hypertension, and liver cirrhosis. In systemic lupus erythematosus, mixed connective tissue disease, and systemic sclerosis, in particular, portal hypertension is often reported.

Esophagogastric varices can frequently occur in association with portal hypertension, with high bleeding ratios; special attention is necessary. In addition, in the long-term follow-up process, hepatic atrophy and ascites can be encountered, making treatment of the primary disease quite difficult. Attention should be paid not only to the treatment of the primary disease but also to the possible development of portal hypertension.

Keywords Portal hypertension · Rheumatic disease · Varices · Idiopathic portal hypertension (IPH) · Pulmonary hypertension (pulmonary artery hypertension)

5.1 Introduction

Some rheumatic diseases are accompanied by portal hypertension underlain by idiopathic portal hypertension (IPH) or pulmonary hypertension (pulmonary artery hypertension), resulting in gastrointestinal varices and ascites, which may require treatment. In this paper, we describe the relationship between rheumatic diseases and portal hypertension and discuss their characteristic features.

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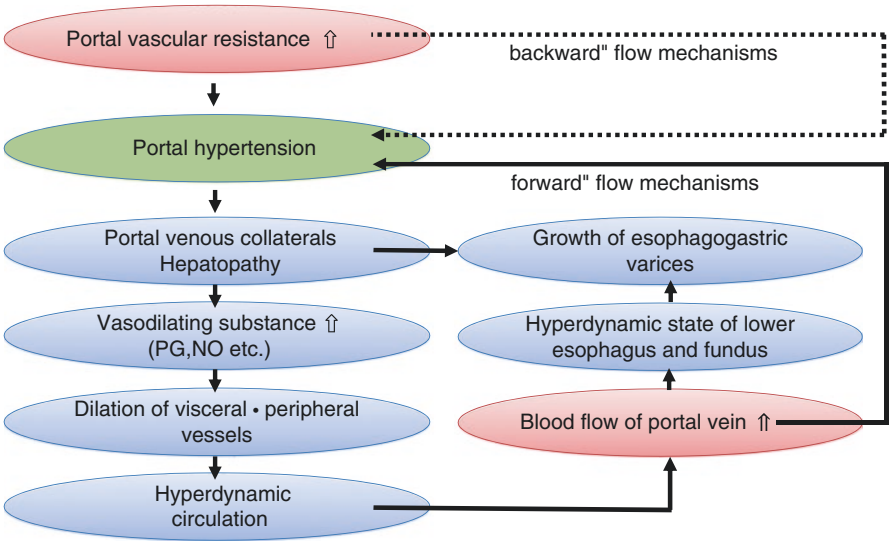


Fig. 5.1 Mechanisms of portal hypertension

5.2 Portal Hypertension

This is a condition in which the portal vein stasis increases portal pressure as a result of increased endovascular resistance in the pathway from the intrahepatic portal vein to sinusoid and hepatic vein, or increased blood inflow from intraperitoneal organs, other than the kidney. The mechanism of onset of portal hypertension involves vasodilating substances such as prostaglandin and nitric oxidases (NOs: inducible nitric oxide synthase [iNOS], endothermic nitric oxide synthase [eNOS]) [1] (Fig. 5.1). Normal portal venous pressure is 100–150 mmH_2O, whereas portal hypertension can involve an increased portal pressure of 200 mmH_2O or higher. There are three types of portal hypertension categorized according to the site of disturbance of blood flow: prehepatic, intrahepatic, and posthepatic. Relevant factors include extrahepatic portal vein obstruction and portal vein defects as prehepatic factors; presinusoidal idiopathic portal hypertension and schistosomiasis japonica and postsinusoidal liver cirrhosis as intrahepatic factors; and Budd-Chiari syndrome and right heart failure as posthepatic factors. Clinical symptoms include gastrointestinal varices (especially in the esophagus and stomach), splenomegaly, and ascites.

5.2.1 Rheumatic Diseases and Portal Hypertension

Although there are only a few reports on rheumatic diseases complicated by portal hypertension, they have been found in various diseases, including systemic lupus erythematosus (SLE) [2–8], mixed connective tissue disease (MCTD) [9–16],

systemic sclerosis (SSC) [17–29], limited cutaneous systemic sclerosis (CREST syndrome) [30, 31], Sjogren's syndrome (SjS) [32], Takayasu arteritis [33], rheumatoid arthritis (RA) [34], dermatomyositis (DM) [35], and Behçet's disease (BD) [36].

In the aforementioned diseases, portal hypertension is caused mainly by the following three factors: IPH, pulmonary hypertension (pulmonary artery hypertension), and liver cirrhosis can occur as complications in the disease. IPH is the most common cause of portal hypertension in all rheumatic diseases. Pulmonary hypertension is one complication of MCTD. As a form of liver cirrhosis due to factors other than infections and alcohol, primary biliary cholangitis (PBC) can complicate CREST syndrome. Proposed causal factors are described in detail below.

5.2.2 Conditions Characterized by Portal Hypertension in Rheumatic Diseases

5.2.2.1 Idiopathic Portal Hypertension (IPH)

IPH is a disease characterized by portal hypertension due to obstruction and stenosis of the peripheral portal vein branch. This disease does not lead to liver cirrhosis and is only rarely accompanied by hepatoma. Although much remains unknown about the mechanism of onset, some hypotheses have been proposed: the intrahepatic peripheral portal vein thrombosis theory, splenic origin theory, and autoimmune abnormality theory [37]. IPH is more prevalent in females than in males, and onset is more often in the 40s–50s age groups than in other age groups. Pathologically, it is characterized by sclerosis in the small portal areas, and it is often accompanied by elastic fiber deposition. The basic pathologic feature of this disease is collapse and obstruction of the peripheral portal vein branch associated with sclerosis in small portal areas; inflammatory cell infiltration can occur, but it is mild. IPH and SSC are histologically similar with increased expression of transforming growth factor-β (TGF-β) and increased collagen fibers in the peripheral portal vein and the skin. In SSC skin, endothelial to mesenchymal transition (EndMT) is observed. It has been hypothesized that endothelial cells acquire a myofibroblastic feature by the action of TGF-β, resulting in fibrosis in the distal portal veins and increased portal pressure [29] (Fig. 5.2). Hepatic parenchyma is reported to include hepatic cord atrophy and sinusoid dilation, with hyperplasic nodules; sometimes no surrounding fibrosis is observed [38]. Hyperplasic nodules are found in 35% (14/35 patients) of IPH necropsies. In recent years, benign hepatocytic nodules, such as IPH, nodular regenerative hyperplasia (NRH), and focal nodular hyperplasia (FNH), have been collectively termed "anomalous portal tract syndrome" (APTS), a group of related diseases underlain by a common causal factor of portal area formation abnormalities [39]. Although FNH rarely complicates portal hypertension, IPH in autoimmune disease has been reported to often complicate NRH. It is relatively common in adults, with rare occurrences in

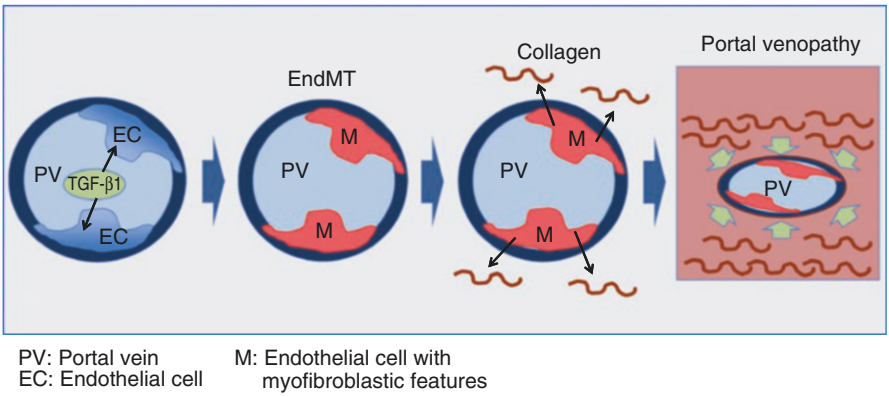


Fig. 5.2 Presentation of portal venopathy and TGF-β1. Transforming growth factor-β (TGF-β1) acts as an inducer of endothelial to mesenchymal transition (EndMT) of endothelial cells (EC) of the peripheral portal vein (PV). ECs acquire myofibroblastic features via the activation of Smad and produce extracellular matrix molecules inducing collagen. Collagen deposits in peripheral portal tracts compress the PVs, resulting in portal venous stenosis and perisinusoidal hypertension

children, the prevalence is higher in females than in males, and it occurs usually as a complication in systemic disease [40]. In Japan, 6–12% of cases of IPH have been reported to occur as a complication in autoimmune disease [41]; in many of the aforementioned rheumatic diseases accompanied by portal hypertension (e.g., SLE, MCTD, SSC), IPH is accompanied by NRH, and this seems a characteristic feature of the disease. Proposed causal factors for NRH include blood flow abnormalities, including portal hypertension, influences of steroids and other drugs, and involvement of autoimmune disease; however, no definite conclusion has been reached.

5.2.2.2 Pulmonary Hypertension

Pulmonary hypertension, a condition defined by a pulmonary arterial pressure of 25 mmHg or higher, is caused by an imbalance in pulmonary vascular dilation and constriction. Increased endothelin levels and decreased NO/PGI2 levels are observed, in addition to vasoconstriction and abnormal proliferation of vascular endothelial cells. Pulmonary vessels show immunoglobulin and complement depositions [42]. The incidence of pulmonary hypertension in rheumatic diseases is relatively high at 19.1% (18/94 patients) in MCTD and 27.7% (193/697 patients) in SSC [43]. However, the pathologic association between rheumatic diseases and portal hypertension or pulmonary hypertension still remains to be elucidated. Pulmonary hypertension in portal hypertension is known as portopulmonary hypertension (POPH). POPH is ranked as the fourth highest cause of pulmonary hypertension, at an incidence of 10.4% (70/674 patients), after idiopathic pulmonary

hypertension 39.2% (674/264 patients), pulmonary hypertension in rheumatic disease at 15.3% (103/674 patients), and pulmonary hypertension due to congenital heart disease at 11.3% (76/674 patients) [44]. In POPH, unlike IPH, the pulmonary vascular resistance is initially normal because of high cardiac outputs due to onset of a shunt and systemic vasodilation. However, increased stress and remodeling in pulmonary vessels and direct inflow of vasoactive factors, which should be inactivated in the liver, into pulmonary vessels can lead to increased pulmonary vascular resistance.

5.2.2.3 Primary Biliary Cholangitis (PBC)-CREST Syndrome

CREST syndrome is a disease characterized by four conditions: calcinosis, Raynaud's phenomenon, sclerodactyly, and multiple telangiectasia of the skin, oral mucosa, and other parts of the body. It differs from SCC by better prognosis and telangiectasia in the normal skin and mucosal membrane and is thus classified as a subtype of SCC. CREST syndrome has been reported to be complicated by PBC [45–48] and can be a cause of portal hypertension. PBC reportedly produces higher portal pressure than common liver cirrhosis (infections, alcohol) and is likely to lead to varices [49].

CREST-complicated PBC is more likely to be complicated by esophageal varices than noncomplicated PBC (28.6% vs. 9.3%); however, good findings of liver function parameters such as AST are found, and the 10-year survival rate is higher (87.5% vs. 45.5%); the prognosis is good [31].

5.2.3 Complications in Portal Hypertension and Their Treatment

Complications in portal hypertension include esophagogastric varices developing as a pressure buffering collateral circulation, splenomegaly, and splenomegaly-associated cytopenia and ascites. Esophagogastric varices, in particular, can cause bleeding and aggravate systemic conditions, often requiring treatment.

5.2.3.1 Esophagogastric Varices

Generally, endoscopic treatments (endoscopic injection sclerotherapy [EIS], endoscopic variceal ligation [EVL]) are performed, with balloon-occluded retrograde transvenous obliteration (B-RTO) sometimes chosen to treat gastric varices. In cases where medical treatment is difficult, a Hassab operation and splenectomy are performed for surgical treatment [37]. Drug therapies include angiotensin II receptor antagonists and nitrites to reduce intrahepatic vascular resistance and propranolol to reduce portal blood flow.

Regarding IPH-underlain portal hypertension, esophageal varices were observed in 73.8% (31/42) of SLE patients [6], and esophageal varix ruptures were observed in 53.3% (8/15) [4]. Esophageal varices were observed at a very high incidence of 95% (19/20) in SCC [28] and 83.3% (5/6) in MCTD [14] (Table 5.1).

Given pulmonary hypertension as the underlying disease, can esophageal varices be deemed a result of increased shunt blood flow and other changes due to increased portal pressure? On the other hand, although the pathologic mechanism remains to be elucidated considering any right cardiac load due to pulmonary hypertension as the cause of portal hypertension, the two conditions often occur concurrently; attention should be paid to esophagogastric varices as well as to IPH.

5.2.3.2 Splenomegaly and Hypersplenism

Japan's guideline requires that splenectomy and splenic embolization are considered in symptomatic patients and patients with a platelet count of $\leq 5 \times 10^4/mm^3$, WBC count of $\leq 3000/mm^3$, and RBC count of $\leq 300 \times 10^4/mm^3$ [37]. Splenectomy is sometimes followed by thrombosis, necessitating special attention.

5.2.3.3 Ascites Fluid

Although no studies have reported detailed data on the proportion of cases of rheumatic diseases complicated by portal hypertension or ascites, many descriptive case reports have reported ascites. In addition, some patients in the case presentation described below experienced ascites and symptom aggravation over a long-term follow-up. In addition to treatment for the primary disease, protein replenishment, diuretics (spironolactone, tolvaptan), and other therapies are used.

5.3 Case Presentation

5.3.1 Case 1: A Patient with SLE Complicated by IPH and Aplasia Pure Red Cell

This patient was diagnosed with myasthenia gravis at the age of 33 years in 1986 and underwent thymectomy in 1993. In 1996, the patient experienced marked anemia, with aplasia pure red cell diagnosed by bone marrow biopsy, and was treated with cyclosporin A. In 2002, the patient was admitted to hospital with polyarthralgia and renal impairment. Although Raynaud's phenomenon was found, facial erythema was not observed. Swelling was noted in the right heel.

Table 5.1 Literature survey of rheumatic disease and portal hypertension

Cases	Disease	Age Med (range)	Gender (M/F)	Esophageal varices %	Rupture of esophageal varices %	Therapy (EIS/EVL/Ope/Steroid/UK)	Outcome (alive/dead/UK)	Reference
42	SLE	40 (14–64)	4/33 (5:UK)	73.8 (31/42)	41.9 (13/31)	5/2/11/4/20	13/9/20	Yamamoto et al.
15	SLE	37 (14–54)	2/12 (1:UK)	UK	53.3 (8/15)	1/6/2/6	7/5/3	Inagaki et al.
20	SCC	53.5 (33–65)	0/20	95 (19/20)	UK	0/3/7/2/8	10/6/4	Takagi et al.
6	MCTD	45.5 (30–68)	0/6	83.3 (5/6)	UK	UK	4/2/0	Rai et al.

EIS endoscopic injection sclerotherapy, *EVL* esophageal variceal ligation, *Ope* Splenectomy, devascularization, esophageal transection, portosystemic anastomosis, etc., *UK* unknown

Blood testing revealed an increased erythrocyte sedimentation rate of 120 mm/h, decreased levels of WBC 1900/mm^3, Hb 9.9 g/dL, Plt 13.1 × 10^4/mm^3, C3 59 mg/dL, C4 10 mg/dL, and antinuclear antibody 20,480-folds (homogeneous and speckled patterns). Antibody testing was positive with an anti-DNA antibody of 19.8 IU/mL and Sm antibody of 56.7 IU/mL. Based on findings of arthralgia, proteinuria, leukopenia, and increased levels of anti-DNA antibody and antinuclear antibody, SLE was diagnosed. Renal biopsy led to the diagnosis of the WHO class IIIc. Ultrasonography and CT detected portal vein dilation and splenomegaly. Nodular regenerative hyperplasia (NRH) was absent. Liver biopsy did not reveal portal area fibrosis, nor was there any liver cirrhosis finding. Based on the above findings, the condition was diagnosed as IPH. Esophageal varices were observed and treated by EIS, and PSL was administered at a starting dose of 40 mg. From that time, the patient was followed up. In 2007, an esophageal varix recurred (Fig. 5.3a) and was again treated by EIS in 2008 (Fig. 5.3b). At that time, CT showed portal vein dilation and splenomegaly but not HRH; no major change was found (Fig. 5.3c). In 2009, portal vein thrombosis occurred; thrombolytic therapy with warfarin was started. The portal vein thrombosis followed come-and-go cycles; in 2014, ascites developed. Albumin and diuretic treatments were administered. In 2016, CT revealed advanced atrophy of the liver and intensified ascites (Fig. 5.3d). Although tolvaptan was added to the regimen in 2017, ascites has been accumulating.

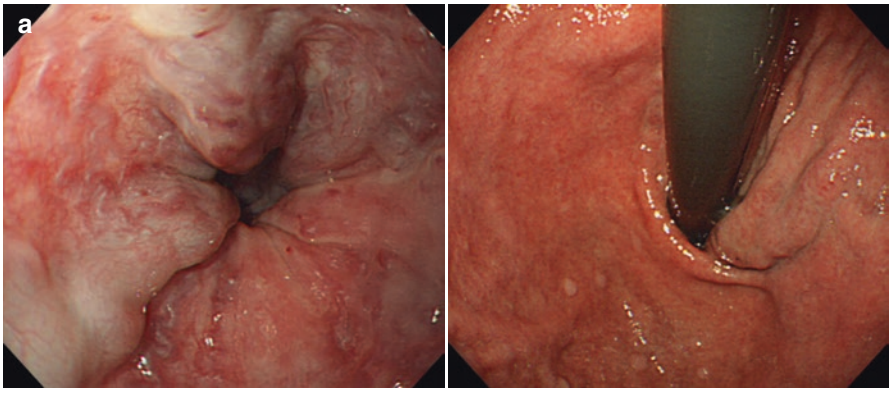


Fig. 5.3 (**a**) Esophagogastroduodenoscopy (EGD) showed recurrence esophageal varices (LmF2CbRC2) and gastric varices (Lg-c F1 RC0). (**b**) EIS was performed using EO (ethanolamine oleate). EVIS (endoscopic varicealography during injection sclerotherapy) revealed palisade vessels and cardiac venous plexus. (**c**) Abdominal-enhanced computed tomography showed portal vain dilation and splenomegaly but not nodular regenerative hyperplasia (NRH) and ascites. (**d**) After 8 years, abdominal-enhanced computed tomography revealed advanced atrophy of the liver and intensified ascites

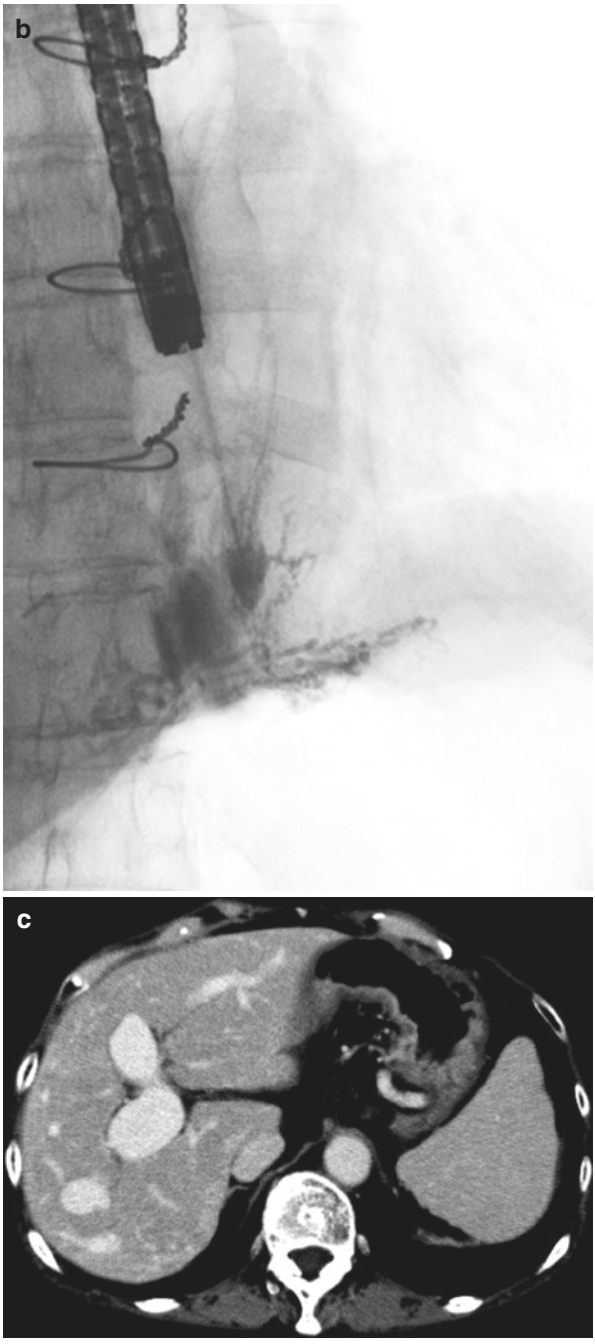


Fig. 5.3 (continued)

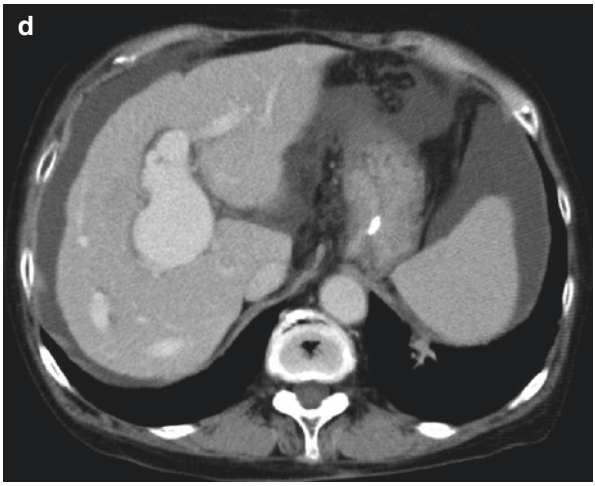


Fig. 5.3 (continued)

5.3.2 Case 2: A Patient with SLE Complicated by Pulmonary Hypertension

This patient experienced edema in the crus and renal impairment at 18 years of age in 2008. In 2010, the patient presented with limb pain, a fever of 37–38.1 °C, facial edema, thirst, dermal erythema, and Raynaud's phenomenon.

With decreased counts of WBC 1600/mm^3, Hb 10.4 g/dL, plt 12.3 × 10^4/mm^3, urinary occult blood (+), and a positive test for antinuclear antibody, the condition was diagnosed as SLE in China. In 2010, the proteinuria and urinary occult blood intensified, and PSL was administered at a starting dose of 30 mg. In August 2016, the patient got married and came to Japan. In September, the patient experienced hematemesis and was admitted to an emergency room. A gastric varix was found, and EIS with Histoacryl was performed. Abdominal CT detected portal vein and splenic vein dilations and megalosplenia, but no intrahepatic nodules or ascites were found. A varix was found in the gastric wall, and pulmonary artery dilation was also observed (Fig. 5.4a). Echocardiography revealed tricuspid regurgitation, with an increased maximum TRPG of 64 mmHg, resulting in the diagnosis of pulmonary hypertension. Secondary to SLE and pulmonary hypertension, portal hypertension was diagnosed, and the patient was transferred to our department. Esophagogastroduodenoscopy revealed a shape of esophagogastric varix, but EIS was not performed (Fig. 5.4b). The patient was treated by steroid pulse therapy. In 2017, endoxan pulse therapy was performed. In 2018, however, abdominal distention and disturbance of consciousness occurred, with CT revealing marked hepatic atrophy and ascites fluid retention (Fig. 5.4c). The patient received an increased dose of diuretic, achieved ascites fluid control, and returned to home country but died soon after at the age of 28 years there.

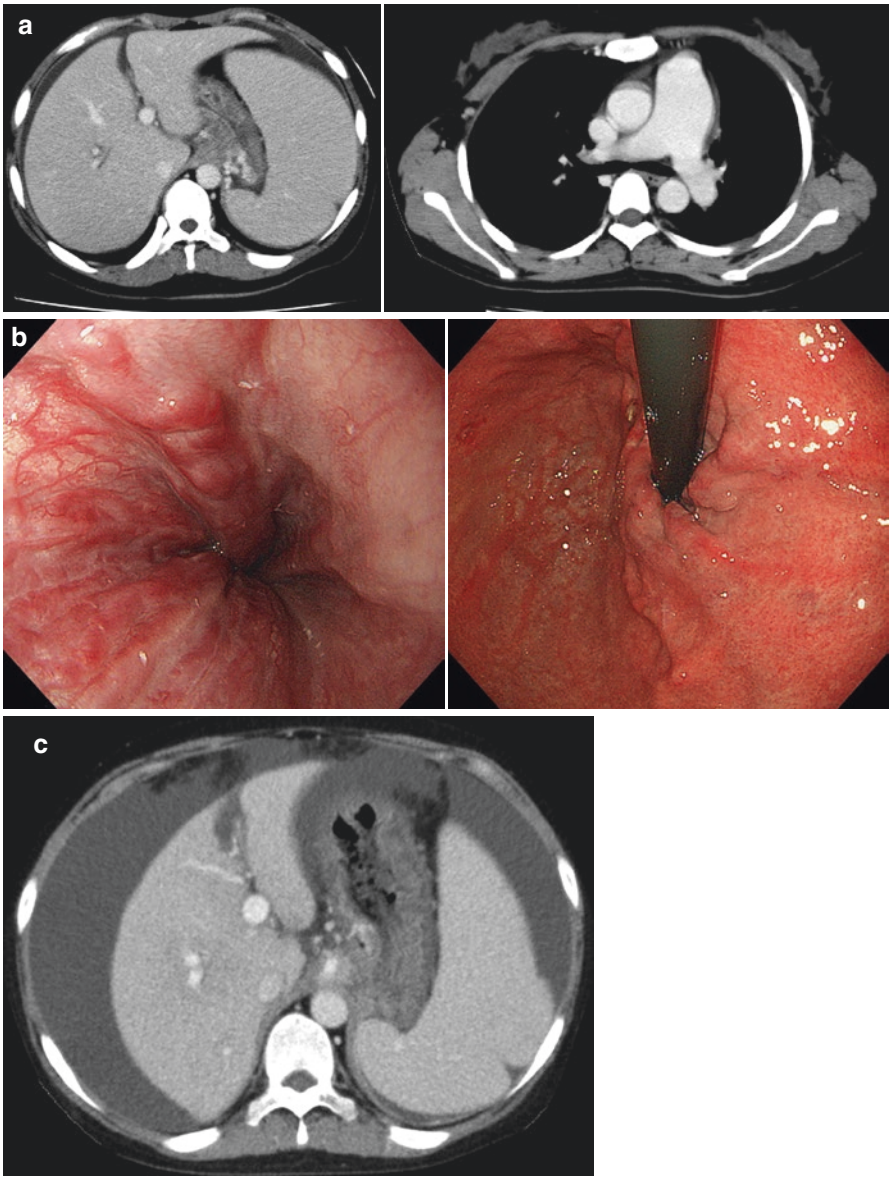


Fig. 5.4 (**a**) Abdominal CT detected portal vein and splenic vein dilations and megalosplenia, but no NHR or ascites were found. A varix was found in the gastric wall, and pulmonary artery dilation was also observed. (**b**) EGD showed esophageal varices (LmF1CbRC1) and gastric varices (Lg-c F1 RC0). (**c**) After 2 years, abdominal-enhanced computed tomography revealed advanced atrophy of the liver and intensified ascites

5.3.3 *Case 3: A Patient with Sjogren's Syndrome Complicated by Pulmonary Hypertension*

This patient began to complain of general malaise around 16 years of age in 2014. In 2015, the patient became unable to attend school and visited a nearby psychiatric clinic, where hematological examination detected hepatopathy and cytopenia. Chest radiography detected cardiomegaly and pulmonary congestion (Fig. 5.5a), and abdominal echography suggested ascites fluid and splenomegaly. Echocardiography suggested a tricuspid regurgitation pressure gradient of −66.0 mmHg and pulmonary hypertension. Esophagogastroduodenoscopy detected a solitary gastric varix (F2-3, RC sign negative) in the gastric fundus (Fig. 5.5b). Thoracoabdominal contrast-enhanced CT suggested ascites, splenomegaly, and portal collateral circulation hyperplasia. 3D-CT revealed a gastric varix hemodynamic profile in which blood is supplied from short gastric vein (SGV) and post gastric vein (PGV) and discharged via a renal venous shunt and inferior phrenic venous shunt (Fig. 5.5c). The patient was referred and admitted to our hospital for extensive examination and treatment. Blood pressure was 154/87 mmHg, and tachycardia was noted at a heart

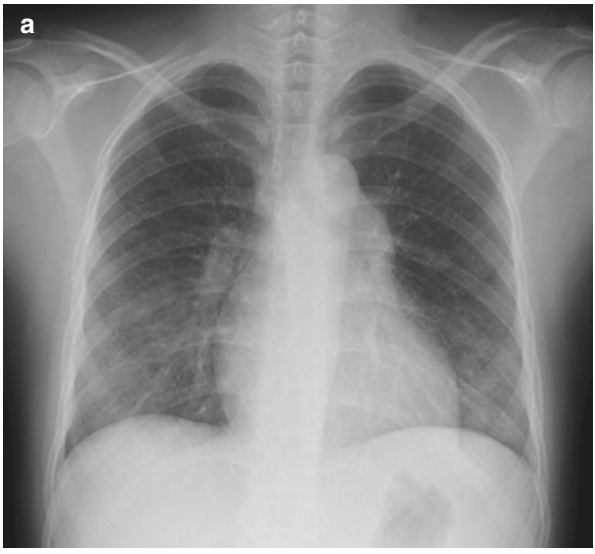
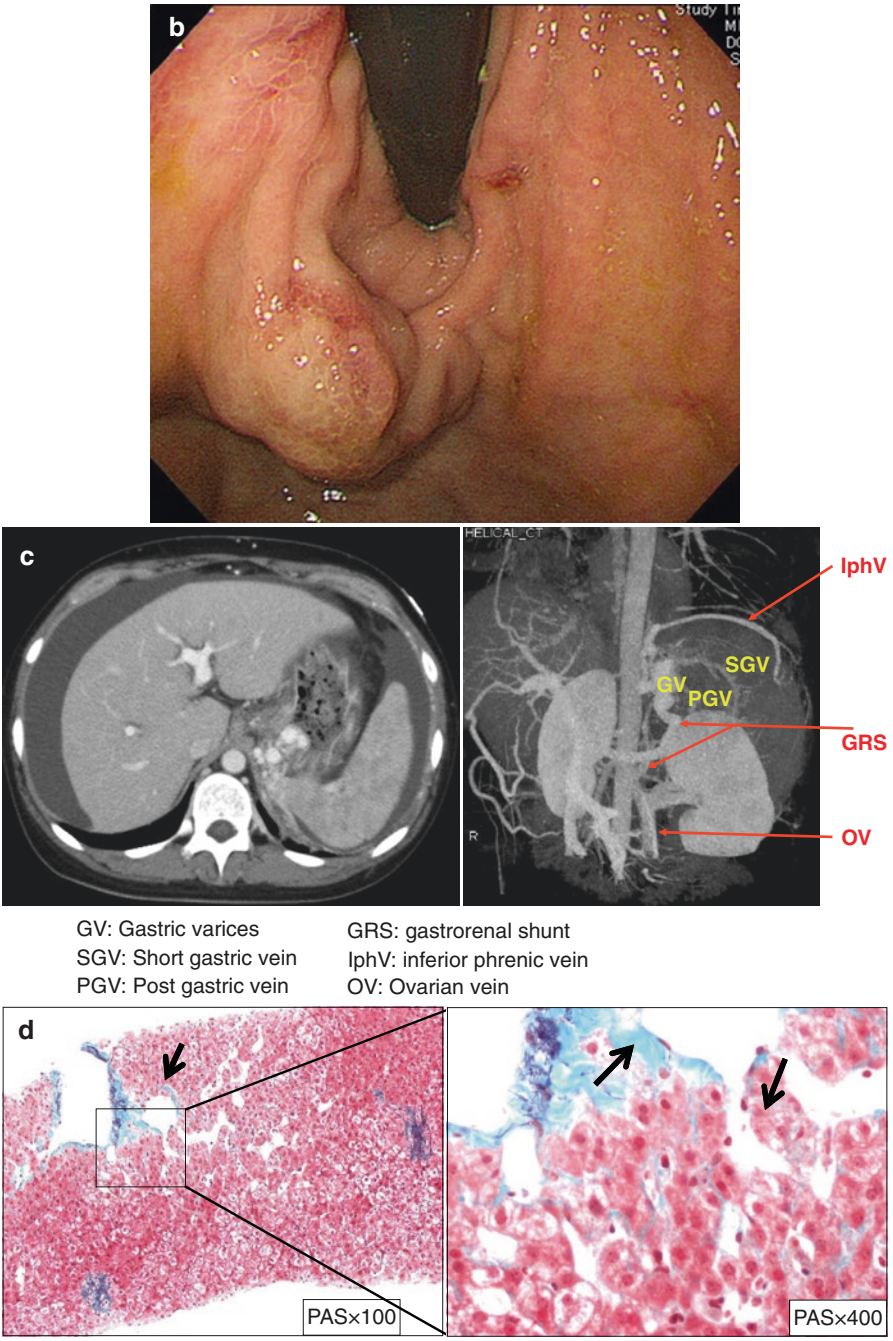


Fig. 5.5 (**a**) Chest radiography revealed cardiomegaly and pulmonary congestion. (**b**) EGD showed gastric varices (Lg-c F3 RC0). (**c**) Abdominal-enhanced computed tomography revealed splenomegaly with massive ascites and gastric varices in the gastric wall. 3D-CT revealed a gastric varix hemodynamic profile in which blood is supplied from short gastric vein (SGV) and post gastric vein (PGV) and discharged via a renal venous shunt and inferior phrenic venous shunt. (**d**) Photomicrograph of the liver biopsy specimen was revealed neither fibrosis nor bridging but a dilated sinusoid continuous to the central vein dilation in the form of cysts. (**e**) A gastric varix was treated by EIS using Histoacryl. EVIS revealed short gastric vein, post gastric vein, and a part of inferior phrenic venous shunt



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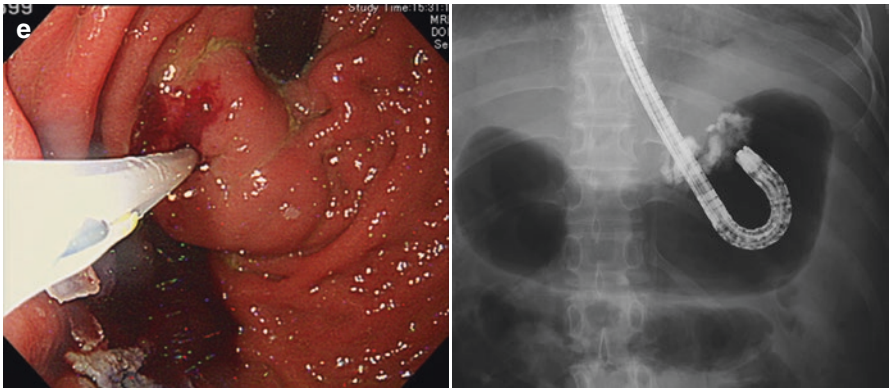

Fig. 5.5 (continued)

rate of 120 beats/min, with edema found in the lower extremities. WBC 2100/mm^3, Hb 7.6 g/dL, plt 4.3 × 10^4/mm^3, Alb 2.6 g/dL, AST 61 U/L, AST 30 U/L, C3 40 mg/dL, C4 9 mg/dL, ANA 160-folds, anti-DNA antibody 7.8 IU/mL, anti-Sm antibody 1.3 IU/mL, anti-SS-A antibody 185 IU/mL, and anti-SS-B antibody 1.3 IU/mL. The patient tested positive in Schirmer's test and had a Saxon test value of 2.31 g; SjS and pulmonary hypertension were diagnosed. Liver biopsy did not detect portal area fibrosis or cross-linking. A dilated sinusoid continuous to the central vein dilation in the form of cysts was observed, suggesting influence on the inferior vena cava and hepatic vein sides (Fig. 5.5d). Steroid pulse therapy was initiated, and endoscopic injection sclerotherapy (EIS) with Histoacryl was performed for the gastric varix (Fig. 5.5e). The patient received tolvaptan and spironolactone to control ascites fluid and was discharged from hospital.

5.3.4 Case 4: A Patient with MCTD Complicated by IPH and Pulmonary Hypertension

At 29 years of age in 1998, the patient was diagnosed with MCTD because of the presence of Raynaud's phenomenon, SLE-like symptoms (pyrexia, pleurisy, pericarditis), SCC-like symptoms (finger ulceration), increased ANA, and a positive test for U1-RNP antibody. At the age of 40 years, the patient was diagnosed with hepatosplenomegaly, with esophagogastric varix detected by esophagogastroduodenoscopy. Extensive examination of the liver led to the diagnosis of IPH, and EIS was performed (Fig. 5.6a). At 45 years of age, the patient underwent a Hassab operation for IPH and had postoperative portal vein thrombosis (Fig. 5.6b). Thrombolytic therapy was performed, and since then, the patient has been followed up periodically. At 59 years of age, echocardiography revealed an increased TRPG of 60 mHg, and intensified pulmonary arterial dilation was detected by CT, and thus a diagnosis of pulmonary hypertension was made (Fig. 5.6c).

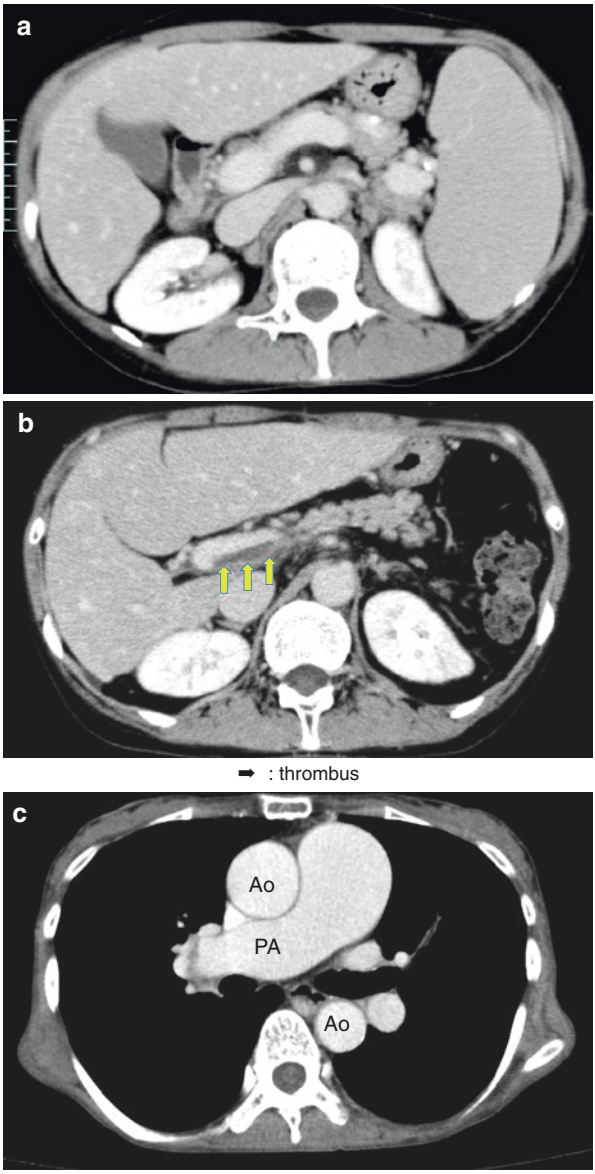

Fig. 5.6 (**a**) Abdominal-enhanced computed tomography showed portal vain dilation and splenomegaly but not NRH and ascites. (**b**) After Hassab operation, CT revealed thrombus in the portal veins (arrow). (**c**) After 14 years, abdominal-enhanced computed tomography revealed dilated pulmonary artery in thoracic cavity

5.4 Conclusion

Rheumatic diseases, portal hypertension, and the accompanying symptoms have been described briefly, including discussion of some case reports. In rheumatic diseases accompanied by portal hypertension, attention should be paid to the onset of gastrointestinal varices and gastrointestinal bleeding in the early stages and to hepatic atrophy, increased ascites fluid volume, onset of pulmonary hypertension, and other changes in the medium- to long-term perspectives.

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Chapter 6
Gastrointestinal Manifestations of Systemic Lupus Erythematosus

Hiroko Kobayashi

Abstract Gastrointestinal (GI) symptoms are common in patients with systemic lupus erythematosus (SLE). SLE-related GI symptoms are distributed from the mouth to the anus. Lupus enteritis is one of the most common GI manifestations and defined as either vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings. Vasculitis also causes lupus colitis. Protein-losing enteropathy is one of the GI manifestations that shows hypoalbuminemia or increased fecal excretion of intravenous radiolabeled albumin. Radiological examination including computed tomography scan, histological analysis, and evaluation of infectious diseases are important to differentiate SLE-related GI symptoms from non-SLE conditions. Most cases of SLE-related GI symptoms respond well to a treatment with high doses of corticosteroids; however, some cases are recurrent and need surgical intervention because of life-threatening complications.

Keywords Systemic lupus erythematosus · Gastrointestinal manifestation · Lupus enteritis · Lupus colitis · Protein-losing enteropathy

6.1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease and a heterogeneous disease that can affect any organ system in a number of different ways with highly variable prognoses. SLE is characterized by production of a broad array of autoantibodies and a female predominance with a peak incidence occurring during the reproductive years; however, its pathogenic mechanism remains unclear.

Clinical features in individual SLE patients are quite variable. The most common presenting manifestations are constitutional symptoms such as fever, fatigue, and weight loss (90–95% frequency); mucocutaneous manifestations such as malar rash, alopecia, mucosal ulcers, and discoid lesions (80–90% frequency); and

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articular manifestations such as arthritis and/or arthralgia (80–90% frequency) [1]. The other clinical features of SLE are serositis such as pleuritis, pericarditis, and peritonitis (50–70% frequency); glomerulonephritis (40–60% frequency); neuropsychiatric involvement such as cognitive impairment, depression, psychosis, seizures, stroke, demyelinating syndromes, and peripheral neuropathy (40–60% frequency); and autoimmune cytopenia (20–30% frequency). These features are incorporated into the classification criteria such as the 1997 update of the 1982 revised American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus [2] and the derivation and validation of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [3]. Gastrointestinal (GI) manifestations have been considered to be less common than the other features listed. Even though GI symptoms are not considered in diagnosing SLE, a number of reports have reported that GI symptoms are common in SLE patients. For example, Dubois and Tuffanelli reported 53.2% of the 520 SLE patients had nausea and vomiting, 49.0% complained of anorexia, 19.2% had abdominal pain, 6.3% had hemorrhage, and 5.9% diarrhea [4]. Consequently, after a diagnosis of SLE, GI manifestations are considered to measure disease activity in the Systemic Lupus Activity Measure Index [5], European Consensus Lupus Activity Measurement [6], SLICC/American College of Rheumatology Damage Index [7], and British Isles Lupus Assessment Group (BILAG) index [8]. However, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [9], one of the most common indexes, does not account for GI symptoms its scoring.

For physicians, it is challenging to evaluate GI symptoms in SLE patients, because the symptoms manifest in diverse ways, and differential diagnoses vary. When evaluating SLE patients with GI symptoms, it is critical to rule out non-SLE conditions such as infections and pregnancy. Various medications used in the treatment of SLE can also induce GI pathology. Furthermore, physicians must be aware that clinical signs of an acute abdomen such as rebound tenderness can be masked when patients are treated with corticosteroids or other immunosuppressive agents. Thus, delays in diagnosis may be severe consequences for the affected patient.

SLE-related GI symptoms are distributed from the mouth to the anus [10]. Oral ulceration is one of the most common GI symptoms, and the presence of oral ulceration is one of the criterion in the diagnosis of SLE. Esophageal ulcerations and dysphagia are rarely found. Gastric and duodenal ulcers sometimes develop in SLE patients; however, the data are insufficient to determine whether SLE is causative in the development of peptic ulcer disease. Some of the most dangerous GI manifestations occur in the small and large intestines. In the BILAG 2004 index, “lupus enteritis or colitis” is defined as either vasculitis or inflammation of the small or large bowel with supportive image and/or biopsy findings [8]. Other SLE-related GI manifestations are protein-losing enteropathy (PLE) and chronic intestinal pseudo-obstruction. Additionally, infarction and ischemia have been seen in the lupus intestine in patients with the antiphospholipid syndrome.

In this chapter, we describe representative cases of lupus enteritis (cases 1 and 2), lupus colitis (case 3), and PLE (case 4). All patients were admitted to our department.

6.2 Case Presentations

6.2.1 Case 1: Lupus Enteritis with Small Bowel Wall Thickening

A 23-year-old woman had a diagnosis of SLE on the basis of photosensitivity, oral ulcers, arthralgia, proteinuria, lymphocytopenia, positive antinuclear antibodies, high titers of anti-DNA antibodies, and a high titer of anti-Sm antibodies. Renal biopsy revealed class III (A) focal lupus nephritis. Initial treatment with prednisolone in combination with intravenous pulse cyclophosphamide followed by tacrolimus or cyclosporine maintenance did not alleviate the nephritis. At the age of 32, she complained of abdominal pain, vomiting, and diarrhea; symptoms had been present for 48 hours. A plain abdominal radiograph showed air-fluid levels with little quantity of air (Fig. 6.1a). A contrast-enhanced computed tomography (CT) scan showed marked thickening of the small bowel wall and enhancement of the mucosa and serosa, resulting the presence of the "target" and "comb" signs (Fig. 6.1b). The patient also had a small amount of ascites. Methylprednisolone pulse therapy followed by a high dose of prednisolone largely resolved her symptoms over a period of 7 days. Treatment with oral prednisolone in combination with tacrolimus and mizoribine resulted in the patient being symptom free with no proteinuria.

Abdominal pain is reported to occur in 8–40% of SLE patients, and it can result from a variety of causes [11]. For example, Kwok et al. conducted a retrospective study to determine the causes of abdominal pain in a total of 706 patients with SLE [12]. In their study, 87 patients complained of acute abdominal pain, and lupus enteritis was diagnosed in 41 (47.1%) of these patients. The other diagnoses were acute pancreatitis (12 patients), acute gastroenteritis (10), infectious diarrhea (5), peptic ulcer (4), acute appendicitis (3), acute cholecystitis (2), pelvic inflammatory disease (2), hemorrhagic gastritis (2), acute cholangitis (2), reflux esophagitis (1), missed abortion (1), tubal obstruction (1), and ovarian cyst rupture (1). In 63 episodes of lupus enteritis, including 13 relapsed cases, 60 cases showed bowel wall thickening by abdominal CT. The jejunum and ileum were the sites most commonly affected, being involved in 48 (80%) and 44 (73.3%) cases, respectively. Of 60 cases, 49 had bowel involvement in multiple vascular territories, and none had mesenteric vascular thrombosis. Buck et al. found that only patients complaining of abdominal pain with high SLEDAI scores had a diagnosis of lupus enteritis [13]. Lee et al. showed that lupus enteritis was the most common cause of acute abdominal pain in SLE patients [14]. They also showed that SLEDAI at the time of diagnosis and at the time of acute abdominal pain did not differ between a group of patients with lupus enteritis and a group of patients with the non-SLE-related abdominal pain and that levels of complement, erythrocyte sedimentation rate, C-reactive protein, and anti-double strand (ds) DNA antibodies at the time of acute abdominal pain did not differ between the groups.

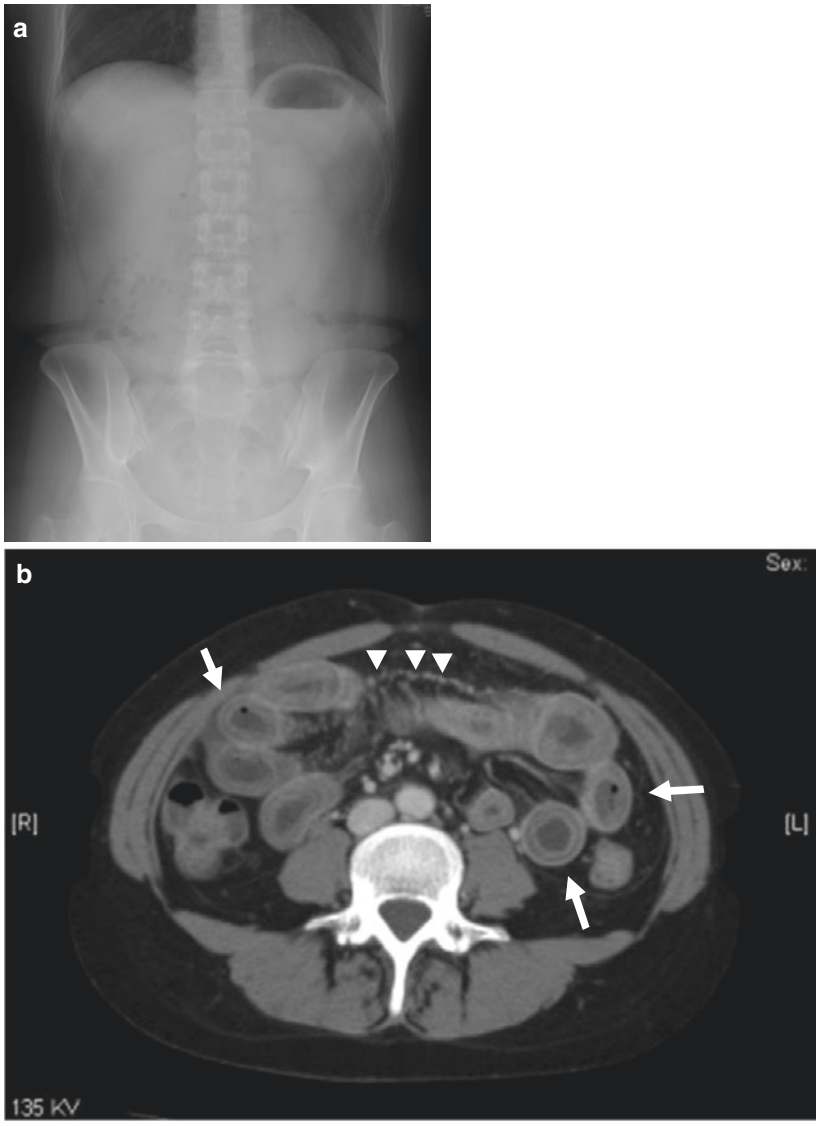

Fig. 6.1 Radiologic findings from case 1. (**a**) A plain abdominal radiograph shows air-fluid levels with little quantity of air. (**b**) A contrast-enhanced CT scan image. The arrows indicate the "target sign" which consists of distension of the small bowel with marked thickening of the wall and enhancement of the mucosa and serosa. The triangles indicate the "comb sign" which consists of dilatation of intestinal segments and engorgement of mesenteric vessels

In the BILAG 2004 index, lupus enteritis is defined as either vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings [8]. Its clinical and pathological spectrum varies widely from simple enteritis to ulceration, hemorrhage, infarction, and perforation. The underlying lesion in most of these conditions is vasculitis of smaller arteries or veins resulting from deposition of circulating immune complexes [10]. Patients with lupus enteritis present with acute abdominal pain, nausea, vomiting, and diarrhea. Gastrointestinal bleeding and perforation with fever may be present in severe cases. Imaging plays a key role in diagnosing lupus enteritis because it is difficult to obtain appropriate biopsy samples that demonstrate vasculitis histologically. Bowel ischemia due to vasculitis makes the bowel wall edematous and thickened, which can result in an obstruction such as incomplete ileus. In this case, abdominal plain X-ray shows fluid level as shown in the Fig. 6.1a. A contrast-enhanced CT scan may assist in the diagnosis of bowel ischemia by showing bowel wall thickening (target sign), dilatation of intestinal segments, engorgement of mesenteric vessels (comb sign), and increased attenuation of mesenteric fat [15]. The target sign is defined as a thickened bowel wall with peripheral rim enhancement or an enhancing inner and outer rim with hypoattenuation in the center. The comb sign is defined as an increased number of visible vessels with a comb-like pattern. Other common CT findings are ascites and retroperitoneal lymphadenopathy. Physicians must be aware that these signs are also seen in pancreatitis, mechanical bowel obstruction, peritonitis, or inflammatory bowel disease that induces bowel ischemia. Case 1 showed the typical target and the comb signs as shown in the Fig. 6.2b, which helped us make early diagnosis and initial treatment after excluding non-SLE conditions.

Because of the rarity of lupus enteritis, there is no case-control studies of its management. Most cases of lupus enteritis respond well to the treatment with high-dose intravenous corticosteroid therapy, followed by oral prednisolone with subsequent tapering, as in case 1. If patients are refractory to the initial therapy, high-dose cyclophosphamide is administered intravenously. Beneficial effects of rituximab and azathioprine have also been described [16]. Case 1 had a favorable outcome following steroid therapy; however, some cases are recurrent and need surgical intervention because of life-threatening complications. In the case 2, we present one of the most severe conditions – lupus enteritis with uncontrollable hemorrhage.

6.2.2 Case 2: Lupus Enteritis with Hemorrhagic Ulcer

A 19-year-old woman had a diagnosis of SLE on the basis of the presence of malar rash, arthritis, proteinuria, leukopenia, positive antinuclear antibodies, and a high titer of anti-DNA antibodies. Initial treatment with prednisolone including the pulse therapy alleviated the malar rash and arthritis and normalized the laboratory values. However, she had vomiting, diarrhea, and melena 5 months after the initial treatment. A barium meal X-ray study showed shortening and effacement of the mucosal

folds at the small intestine. Colonoscopy, including terminal ileum examination, showed edematous mucosa of the colon and diffuse ulceration with bleeding in the ileum. Those findings suggested ischemic enteritis mainly in the ileum. Her symptoms were refractory to the treatment with a high dose of intravenous corticosteroids, anticoagulants, and pulse cyclophosphamide. Surgical intervention was then planned to remove the ischemic ileum that was causing severe hemorrhage and fluid loss. On exploration, the small intestine was found to be markedly shortened and edematous; however, the line of transection could not be visually identified. Colonoscopy did not reach far enough, so an esophagogastroduodenoscopy was performed and clearly revealed the border between the ulcer and normal area, which was located 100 cm from the Treitz ligament. One hundred twenty centimeters of the ileum was resected, and ileostomy was performed. Although the patient's postoperative course was complicated by short bowel syndrome, she was discharged with fluid replacement via a central venous catheter.

The resected intestine showed diffuse ulceration. Pathological examination revealed ulcer and marked inflammatory cell infiltration into the submucosa (Fig. 6.2a). Arterioles in the submucosal layer were obstructed with fibrinoid degeneration (Fig. 6.2b), which indicated ischemic enteritis. These findings were compatible with lupus enteritis.

Generally, the frequency of ischemic enteritis is very low compared with that of ischemic colitis because a large number of arteries supply the small intestine. However, compared with ischemic colitis, ischemic enteritis is a life-threatening pathophysiology that can result in bowel infarction, necrosis, hemorrhagic ulcer, and perforation. Major causes of ischemic enteritis are strangulation of the small intestine, occlusion of the mesenteric arteries and veins, and nonocclusive mesenteric ischemia. Vasculitis is rare but is one of the causes of ischemic enteritis. Early diagnosis is critical to ensure that surgical treatment can be performed before developing sepsis, and the multiple organ failure syndrome develops in patients with any type of ischemic enteritis.

Vasculitis in the small intestine mostly occurs secondary to systemic vasculitis such as IgA vasculitis, anti-neutrophil cytoplasm antibody-associated vasculitis, polyarteritis nodosa, Behçet's disease, and SLE. Small-vessel or leukocytoclastic vasculitis is characterized by mucosal ischemia, whereas vasculitis involving medium-sized or larger vessels may result in peritonitis, perforation, or both. Other serious complications are obstruction, PLE, and intussusception.

In SLE, vasculitis develops as a consequence of complex interactions between vascular endothelium, inflammatory cells, cytokines, autoantibodies, and immune complexes [17]. The prevalence of vasculitis in large studies of SLE patients ranges from 11 to 36% with cutaneous, central and peripheral nervous system, pulmonary, heart, and genitourinary system manifestations [2, 18, 19]. Vasculitis also affects the vessels within the mesentery, pancreas, peritoneum, liver, and gall bladder, and it used to be associated with a high mortality rate. Mesenteric vasculitis is estimated to occur in approximately 1–6% of SLE patients and affects the vessels supplying the stomach, small intestine, and large intestine [2, 11–13, 19–21]. Vasculitis involving the intestinal tract is typically a small-vessel vasculitis affecting the arterioles

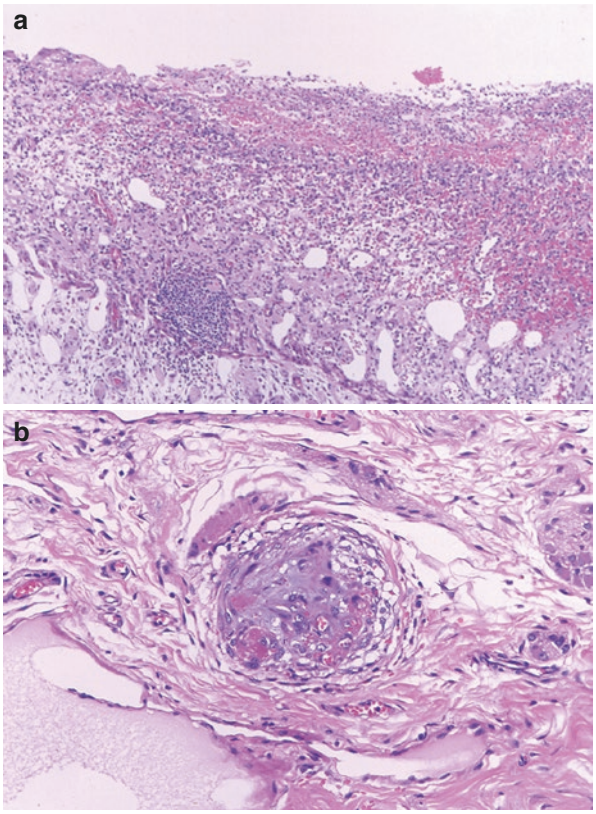

Fig. 6.2 Microscopic findings of resected ileum from case 2. (**a**) Massive mucosal ulceration with hemorrhage and cell infiltration in the submucosa indicates a result of ischemic enteritis (hematoxylin and eosin staining, ×100). (**b**) Arteriole obstructed with fibrinoid degeneration in the submucosal layer shows necrotizing vasculitis (hematoxylin and eosin staining, ×200)

and venules. In case 2, histological examination clearly showed arteriolitis resulting in ulceration and hemorrhage.

Currently, most patients with lupus enteritis received high doses of corticosteroids and have favorable outcomes, as shown in case 1; severe cases like the case 2 are rare. Yuan et al. conducted a retrospective study to define the occurrence of severe complications in SLE patients [22]. In their study, mesenteric vasculitis was diagnosed in 97 SLE patients, with an overall prevalence of 2.5%. Among the 97 patients with mesenteric vasculitis, 13 died because of serious complications, and 2 presented with intestinal perforation during the induction therapy stage. A logistic regression multivariate analysis indicated that leukopenia, hypoalbuminemia, and elevated serum amylase were associated with severe adverse events, and cyclophosphamide therapy led to better outcomes during the remission-induction stage. Janssens et al. reported that 17 patients out of 150 patients with lupus enteritis underwent laparotomy and that 4 patients died [23]. Reported causes of death

included diffuse necrosis of intestinal tract (1 case), associated neurologic complications (1 case), and sepsis (1 case). Early laparoscopy or laparotomy is recommended if necrosis or perforation is suspected in patients with lupus enteritis; however, case 2 indicates that laparoscopy is not always useful in disclosing lesions or determining the extent of resection [24].

Cases 1 and 2 presented with typical clinical features of lupus enteritis. Lupus colitis is also caused by vasculitis, but it is rarely seen compared with lupus enteritis. Next, we present a case of lupus colitis.

6.2.3 Case 3: Lupus Colitis

A 22-year-old woman had a diagnosis of SLE on the basis of malar rash, arthritis, and positive antinuclear antibodies, and she received a low dose of oral prednisolone. At the age of 24, she presented with complaints of abdominal pain and diarrhea for 3 weeks at her age of 24. A barium enema X-ray study showed several niches with cuff link-like lesions in the sigmoid colon (Fig. 6.3a). Colonoscopy showed several ulcers with an irregular punched-out shape surrounded by edematous mucosa in the sigmoid colon (Fig. 6.3b). Treatment with a high dose of oral prednisolone resolved the patient's symptoms within a few days. Barium enema X-ray study and colonoscopy showed healed mucosa 5 weeks after the high-dose prednisolone treatment.

In 1964, Dubois and Tufanelli reported that the incidence of large intestine ulcers in SLE was 0.4% (2/520) [4]. Lee et al. reported 3 cases with rectal involvement out of 175 SLE patients [14]. Physicians must differentiate lupus colitis from nonsteroidal anti-inflammatory drug-induced colitis, infectious colitis such as cytomegalovirus (CMV) colitis or intestinal tuberculosis, ischemic colitis, ulcerative colitis (UC), Crohn's disease (CD), Behçet's disease, and lymphoma when inflammatory lesions or ulcers are noted in the large intestine in SLE patients. Unlike the small intestine, the large intestine is well examined by colonoscopy, and it is crucial to obtain biopsy specimens by colonoscopy for histopathological analysis.

Abdominal symptoms of lupus colitis are similar to that of the other inflammatory bowel diseases: lower abdominal pain, diarrhea, and bloody stools. Tsuchiya et al. reported 34 cases of SLE with colonic ulcers [25]. They described a range of radiographic findings ranged from "loss of haustral marking with fine serrations along the wall" to the typical "color button" type of penetrating ulcers. They also described colonoscopic findings that included multiple discrete round or oval ulcers with pale mucosa, "punched-out" ulcers, and larger, deeper, and variable-shaped ulcerations with edematous mucosa, all are similar to the intestinal lesions of Behçet's disease. Histopathological examination of lupus colitis reveals vasculitis similar to that observed in lupus enteritis: fibrinoid necrosis and fibrous thickening of the vascular walls, as well as infiltrations of inflammatory cells mainly in the small arteries [10].

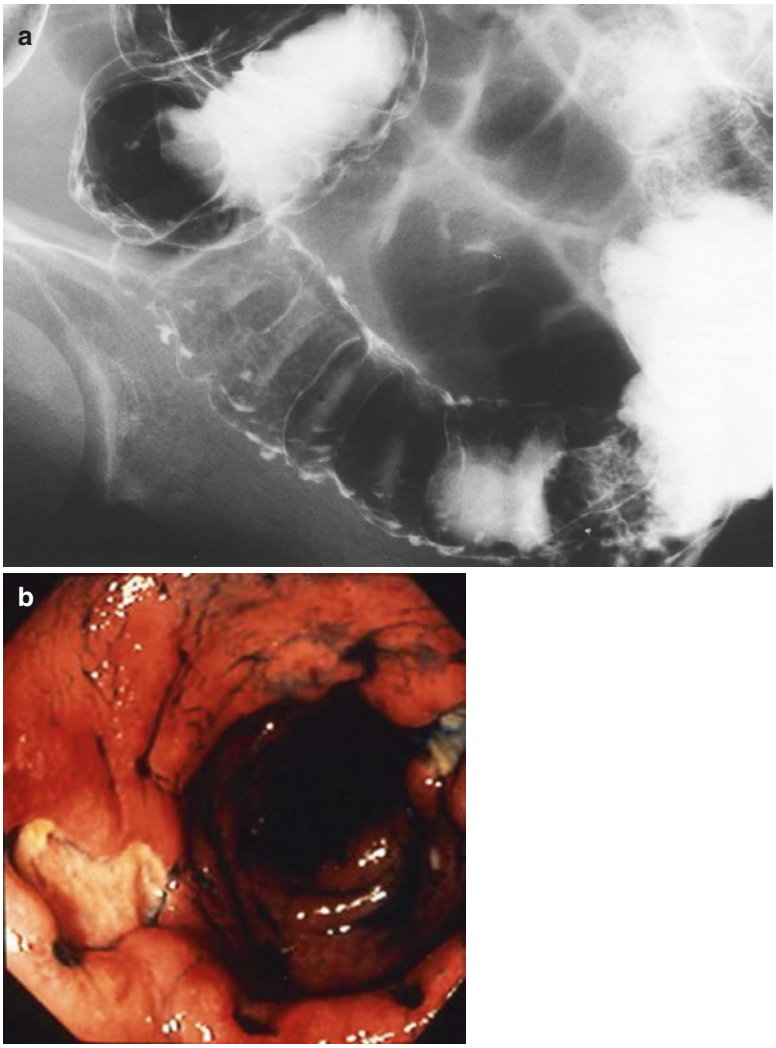

Fig. 6.3 Barium enema X-ray study and colonoscopy images from case 4. (**a**) Barium enema X-ray study visualizes multiple cuff link-like ulcerative lesions with reduced mucosal folds in the sigmoid colon. (**b**) Colonoscopy shows multiple irregular-shaped punched-out ulcerative lesions surrounded by edematous mucosa

Case 3 showed typical radiographic and colonoscopic findings of lupus colitis, and the clinical history was compatible with that of SLE. The shapes of the colonic ulcers were similar to those associated with Behçet's disease, but none of the clinical findings suggested a diagnosis of Behçet's disease. There are no reports of SLE cases accompanied by Behçet's disease. Although uncommon, several reports describe SLE cases accompanied by UC or CD. Nitzan et al. reported six SLE cases accompanied by UC and four SLE cases accompanied by CD [26]. Intestinal biopsy

was performed in all patients who underwent a colonoscopy or a sigmoidoscopy. Histological findings suggestive of UC include mucosal ulceration, chronic inflammatory reaction in the lamina propria, depletion of goblet cells with destruction of the glands, and neutrophilic crypt microabscesses. Histological findings suggestive of CD include chronic inflammation in all layers of the colon, aphthous ulcers, multinucleate giant cell granulomas, and acute and chronic inflammatory changes. Nitzan et al. also reviewed cases of UC/CD and drug-induced SLE. The diagnoses of UC/CD were made first, and SLE developed after treatment with sulfasalazine, 5-aminosalicylic acid, or infliximab. It is well-known that antinuclear antibodies and anti-dsDNA antibodies are expected to develop in some patients treated with tumor necrosis factor-α blockers. However, these antibodies are not generally associated with clinical symptoms and signs of autoimmunity. Diagnosis is suggested by clinical history, not by serological findings.

CMV colitis is another important differential diagnosis when colitis or colonic ulcer is observed in SLE patients. CMV colitis is the second most common manifestation of end-organ disease, following CMV retinitis [27]. Most of the time, CMV colitis is caused by reactivation of a latent infection in immunosuppressed patients, but it can also occur in an immunocompetent host in the setting of a primary infection. Patients with CMV colitis present low-grade fever, weight loss, anorexia, malaise, diarrhea, bloody stool, and abdominal pain. In Japan, many physicians use the pp65 antigen assay and histologic examination to diagnose CMV infection in clinical practice. The most commonly identified endoscopic abnormalities are well-demarcated ulcerations, ulcero-infiltrative changes, and formation of pseudomembranes. Extensive mucosal hemorrhage and perforation related to CMV infection can be life-threatening complications. Therefore, antiviral treatment should be considered for CMV-related colitis in immunocompromised hosts such as SLE patients.

Miyahara et al. reviewed 25 SLE patients with multiple ulcerative lesions in the large intestine [28]. Most of the complications occurred during the active stage of SLE in relatively young patients. The most serious complications such as perforation and fistula were observed in 9 of the 25 patients, including 4 who died. The treatment strategy is very similar that of lupus enteritis, but there are many steroid-resistant cases. Risk factors for aggravations of the ulcers are thought be delayed healing of the ulcerative lesions and weakening of the mucosal tissues, in addition to ischemic tissue damage caused by locally reduced blood flow.

Interestingly, Maruyama et al. described a large intestine-dominant type in lupus enteritis that developed in Japanese patients [29]. They diagnosed lupus enteritis if the following criteria were satisfied: (1) abdominal symptoms (abdominal pain and/or diarrhea and/or nausea and/or vomiting), (2) diffuse long-segment bowel wall thickening detected by CT or ultrasonography, and (3) a requirement for glucocorticoid therapy. Lupus enteritis was diagnosed in 17 of 481 SLE patients. Using CT scans, the cases were classified into two distinct types based on the affected region of the gastrointestinal tract: a small intestine-dominant type and a large intestine-dominant type. All of the patients with large intestine-dominant type had rectal wall thickening. Maximum bowel thickness was greater in the large intestine-dominant type. The response to glucocorticoid treatment was generally good in both groups.

Information on mucosal lesions was not available because none of the patients underwent colonoscopy in the Maruyama et al. study, but their findings may suggest that contrast-enhanced CT plays important roles in early diagnosis – before the presentation of bloody stool, which suggests mucosal damage – and a favorable outcome, by allowing prompt initiation of treatment.

Of note, no SLE patient has been given a diagnosis of lupus colitis since 1999 in our facility. The reason is unclear; however, we presume that widespread availability of CT, careful monitoring of infection including CMV infection, and aggressive immunosuppressive therapy, including cyclophosphamides, have resulted in generally favorable outcomes.

Case 1, 2, and 3 present pathological findings primarily based on vasculitis. Next, we present another type of enteropathy that developed in a patient with SLE.

6.2.4 Case 4: Protein-Losing Enteropathy

A 71-year-old woman complained of edema and showed severe hypoalbuminemia without diarrhea, proteinuria, liver cirrhosis, or malignant diseases. She had been suffering from dry eyes and mouth for a year. Sjögren's syndrome was diagnosed on the basis of a high titer of anti-SSA antibodies and histologic findings of extensive focal lymphocytic infiltration in the minor salivary glands. A diagnosis of SLE was also made on the basis of leukopenia, positive antinuclear antibodies, a high titer of anti-DNA antibodies, and hypocomplementemia. Scintigraphy using technetium-99 m-labeled (^{99m}Tc)-human serum albumin scintigraphy clearly showed a leak of the radiotracer into the stomach and its distribution to the small intestine and the colon (Fig. 6.4a, b). An α1-antitrypsin stool clearance study revealed profound protein loss into the gut. Those findings supported the diagnosis of PLE, which

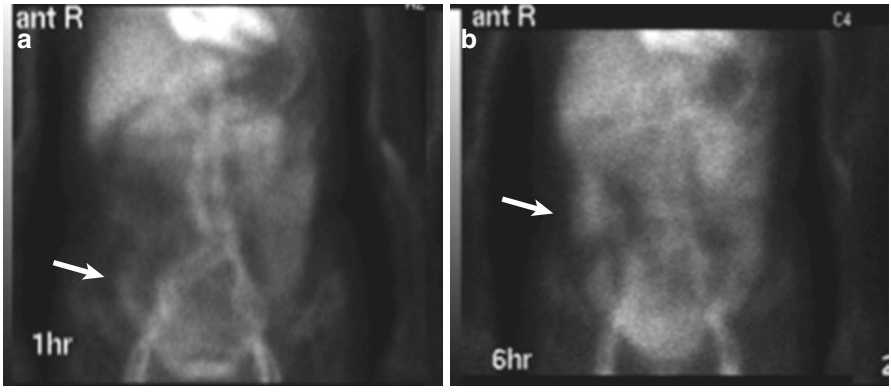

Fig. 6.4 ^{99m}Tc-human serum albumin scintigraphy images from case 3. (**a**) The arrow indicates that the tracer distributed to the small intestine 1 h after the injection. (**b**) The arrow indicates that the tracer distributed to the ascending colon 6 h after the injection

caused the patient's edema and hypoalbuminemia. Treatment with oral corticosteroids and tacrolimus elevated the levels of serum albumin and then alleviated the edema.

PLE has been described as a gastrointestinal disorder that is associated with excessive loss of plasma protein into the gut [30]. PLE develops with or without mucosal erosions and is associated with many disorders, including neoplasms, infectious enteritis, allergic gastroenteropathy, intestinal lymphangiectasia, Ménétrier's disease, celiac sprue, Whipple's disease, ulcerative colitis, congestive heart failure, and nephrosis. PLE is also associated with autoimmune diseases such as SLE, Sjögren's syndrome, and systemic sclerosis. BILAG 2004 includes PLE as one of the items as follows: diarrhea with hypoalbuminemia or increased fecal excretion of intravenous radiolabeled albumin after exclusion of gut vasculitis [8]. A diagnosis of PLE is suspected in patients with hypoproteinemia and no other obvious source of protein loss. The diagnosis is confirmed by ^{99m}Tc-labeled human serum albumin scintigraphy and 24-h stool α1-antitrypsin clearance [30, 31]. Several mechanisms have been proposed for the passage of plasma proteins across the gastrointestinal mucosa, both normally and in certain disease states. First, plasma proteins may pass into the gastrointestinal tract through an inflamed or ulcerated mucosa and account for the protein loss. Second, plasma protein loss may occur as a result of disordered mucosal cell structure. Third, in the presence of increased lymphatic pressure, there may be increased passage of plasma proteins into the lumen via the intercellular spaces of the mucosal epithelium. Fourth, dilated lymph vessels in the mucosa may rupture through the surface epithelium, discharging their contents into the intestinal lumen.

Chen et al. reported 44 patients with SLE-related PLE [32]. Interestingly, their study revealed that the patients with SLE-related PLE had greater frequencies of anti-SSA and anti-SSB seropositivity than SLE patients without PLE. Anti-SSA seropositivity, hypoalbuminemia, and hypercholesterolemia are independent risk factors for SLE-related PLE. In the Chen et al. study, most patients were prescribed a high dosage of glucocorticoid combined with cyclophosphamide for SLE-related PLE, and the most responded to the therapy. They did not reveal the number of patients in whom Sjögren's syndrome was diagnosed.

Case 4 showed typical clinical features of PLE with anti-SSA seropositivity and clinical features of Sjögren's syndrome; however, histopathological analysis using specimens obtained from the gastric and duodenal mucosa showed no specific findings. Some case reports clearly revealed edema of the lamina propria and lymphangiectasia with infiltration of inflammatory cells, which suggests one of the mechanisms of PLE developed in SLE [33, 34].

6.3 Summary

Gastrointestinal manifestation in SLE is used to be considered rare, but recent clinical studies have shown that it is a common feature of SLE. This chapter reviewed gastrointestinal manifestations in SLE as highlighted four distinct cases.

Imaging with CT is helpful in differentiating the severity of the bowel lesions and making decisions for surgical intervention; however, histological analysis and evaluation of infectious diseases remain important to ensure a better prognosis.

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Chapter 7
Rheumatoid Arthritis and Gastrointestinal Tract Lesions (NSAID Ulcers, Amyloidosis)

Tatsuo Fujiwara, Kyoko Katakura, and Hiromasa Ohira

Abstract This chapter discusses the relationship of rheumatoid arthritis (RA) to nonsteroidal anti-inflammatory drug (NSAID)-associated ulcers and intestinal amyloidosis, both of which are gastrointestinal tract lesions. NSAID ulcers associated with RA are not as common as they once were. There are three reasons for this. First, the role of NSAIDs in rheumatoid arthritis treatment has changed. Second, NSAIDs less damaging to the intestines have become available. Third, there is now much greater awareness of NSAID ulcers. Changes in the role of NSAIDs are attributable to less and shorter-term use of NSAIDs, which were previously used widely and for a long time to treat inflammation, thanks to the appearance of antirheumatic drugs and biological products. NSAIDs less damaging to the intestines that are now available include NSAIDs that selectively inhibit cyclooxygenase (COX) 2. These were developed after it was found that COX-1, to which conventional NSAIDs bind to reduce inflammation and pain, helps protect the stomach lining. Finally, with greater awareness of the gastrointestinal damage NSAIDs cause has come greater focus on preventing ulcers. Health insurance now covers prophylactic proton pump inhibitors, which are widely used to treat gastric ulcers, for high-risk patients. The result has been a significant drop in ulcers.

Almost all amyloidosis associated with RA is AA amyloidosis, which is known as secondary or reactive amyloidosis. As these names suggest, amyloidosis occurs secondarily during the course of RA and other chronic inflammatory diseases. Progress in RA treatment has made long-term control of inflammation possible in more patients and, consequently, less amyloidosis occurring in association with the

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disease. Even so, patients treated for RA should undergo regular screening for AA amyloidosis and be checked for clinical symptoms so that AA amyloidosis can be detected early.

This chapter describes in detail RA-associated NSAID ulcers and amyloidosis, which, although now less common, remain as risks to RA patients.

Keywords Rheumatoid arthritis · Nonsteroidal anti-inflammatory drug (NSAID) · Amyloidosis · Gastrointestinal tract damage · AA amyloidosis

7.1 NSAID Ulcers

7.1.1 Indications and Usage of NSAIDs in Rheumatoid Arthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs) were previously first-line therapy for rheumatoid arthritis (RA). Progress in RA treatment, however, has made available various antirheumatic drugs and biological products that have shifted the goal of treatment from alleviating pain and inflammation to reducing joint destruction. With this shift, NSAIDs, which do not reduce joint destruction, have gone from a first-line to a supportive role in which they are used to improve quality of life by alleviating pain [1, 2]. Despite this demotion, however, NSAIDs remain critical in pain management and are still in widespread use. NSAIDs are used in patients who have already suffered bone damage and deformation and primarily require pain control and as stopgap pain control for patients yet to be definitively diagnosed or waiting for an antirheumatic drug or biological product to become available to them or begin working. NSAIDs should be used at the lowest necessary dose and for the shortest necessary duration rather than until the patient responds to treatment to reduce joint destruction because, as was mentioned earlier, substantial adverse drug reactions can occur. NSAID use should be curtailed, discontinued, or switched to as-needed use just as soon as the patient's antirheumatic drug or biological product has reduced or eliminated the pain.

7.1.2 Mechanism of Action of NSAIDs

NSAIDs bind to cyclooxygenase (COX), inhibiting its action to reduce inflammation and pain [3]. After the discovery of this mechanism, COX was found to occur as two isozymes: COX-1 and COX-2 [4, 5]. According to these papers, COX-1 is present in almost all tissues, and in the eicosanoids, its actions produce help maintain homeostasis. Prostaglandin (PG) E2 produced via COX-1 expressed in the healthy gastric mucosa protects the mucosa [6]. COX-1 therefore inhibits PG biosynthesis in the gastric mucosa, reducing its protective effect. The expression of COX-2, however, is normally limited to tissues and cells in the brain and kidneys,

as well as megakaryocytes, osteoblasts, and vascular epithelium. COX-2 is expressed in other tissues and cells only in response to inflammatory stimulation or tissue damage, playing a role in regulating immune and inflammatory responses. Different NSAIDs selectively inhibit different COX isozymes and, therefore, have different efficacy and safety profiles. Most conventional NSAIDs inhibit both COX-1 and COX-2. The NSAID celecoxib was developed to selectively inhibit COX-2 to reduce gastrointestinal tract damage. Sakamoto and colleagues [7] endoscopically compared the incidence of gastroduodenal ulcers in healthy volunteers treated for 2 weeks with celecoxib (a COX-2 selective inhibitor), loxoprofen (prodrug in the propionic acid class of nonselective NSAIDs), or placebo. Finding ulcer incidence to be 1.4% for celecoxib, 27.6% for loxoprofen, and 2.7% for placebo, they concluded that celecoxib caused significantly fewer ulcers than loxoprofen. Although NSAIDs that selectively inhibit COX-2 cause fewer gastrointestinal tract events, they may cause cardiovascular damage [8]. Since NSAIDs with high COX-2 selectivity do not inhibit the COX-1 of platelets, it was reasoned that they could promote thrombus formation by inhibiting the production of PGI2, which has vasodilating activity, by inhibiting COX-2 without suppressing platelet aggregation [9]. Myocardial infarction and other cardiovascular events, however, have since been reported in association with NSAIDs without COX-2 selectivity [10, 11], prompting the USA to mandate warning statements about cardiovascular adverse reactions for all NSAIDs. These adverse reactions are of particular concern in RA since the disease disproportionately affects the elderly.

7.1.3 Epidemiology and Pathology of NSAID Ulcers

Many people are aware that NSAIDs cause gastric and duodenal ulcers and other disorders of the upper gastrointestinal tract, but these drugs also commonly cause mucous membrane disorders and other complications in the lower gastrointestinal tract.

The different pathologies involved in the upper and lower gastrointestinal tract are discussed separately here.

7.1.3.1 Upper Gastrointestinal Tract Damage

The upper gastrointestinal tract damage that NSAIDs cause appears to be rooted in the abovementioned decreased gastric mucosal protection resulting from inhibition of PG synthesis. The following discussion follows the guidance in the second edition of the evidence-based clinical practice guidelines for peptic ulcer disease by the Japanese Society of Gastroenterology [12].

The guidelines state that NSAID users are clearly at higher risk of peptic ulcers and upper gastrointestinal hemorrhage (evidence level A). A systematic review showed that NSAID users have a general risk of upper gastrointestinal hemorrhage and perforation 4.5-fold higher than nonusers [13].

A meta-analysis of studies on preventing NSAID-induced gastric and duodenal ulcers found that patients treated for 1 week to 6 months with an NSAID had a 14.2% (3.4–48.6%) incidence of endoscopic gastric ulcers and a 5.4% (0–26.7%) incidence of endoscopic duodenal ulcers [14]. In a multicenter, case-control study conducted in Japan, the odds ratio of upper gastrointestinal hemorrhage was 7.6 for NSAIDs and 7.7 for aspirin [15].

Other studies investigated the timing of the onset of NSAID-induced gastrointestinal hemorrhage [16, 17]. The odds ratio of onset was 7.6 (6.0 to 9.5) within a month of the start of NSAID use, 7.3 (4.0 to 13.2) for 1 to ≤3 months, 2.6 (1.6 to 4.1) for 3 months to ≤1 year, and 2.5 (1.8 to 3.4) for 1 year and beyond. Thus, NSAID ulcers are a concern even with the common practice in RA treatment of using NSAIDs as a stopgap until the patient responds to antirheumatic or biological drug treatment. Caregivers must therefore stay vigilant for ulcers. Caregivers must also tell long-term NSAID users of the ongoing risk of gastrointestinal tract damage and instruct them to keep the dose as low as possible.

About half of all NSAID ulcer cases are asymptomatic, lacking abdominal pain and other symptoms [18]. Asymptomatic NSAID ulcers must be identified before they develop into gastrointestinal hemorrhage and other serious adverse reactions. Specific ways to identify NSAID ulcers include asking the patient about malaise, fatigue, and other symptoms of anemia through an interview and checking for black or bloody stool and other signs of bleeding. Close observation of facial color and the palpebral conjunctiva for signs of anemia and monitoring for weight loss and other physical findings are also warranted. Routine blood tests and endoscopy will also help find NSAID ulcers in the early stages. The routine care of RA patients typically centers on treating arthralgia and other rheumatic complications but must, when the patient uses an NSAID, also include interviews, physical examinations, and routine bloodwork and endoscopy to address the risks of NSAID use.

Different studies have considered the relevance of NSAID type and dose to ulcer occurrence. As stated previously, COX-2-specific NSAIDs cause ulcers less frequently. Different NSAIDs carry different risks. The COX-2-specific drug celecoxib increases the risk by 1.42-fold. This figure is 2.23-fold for ibuprofen, 3.61-fold for diclofenac, 8.0-fold for piroxicam, and 14.54-fold for ketorolac. Differences in the half-lives of selective and even nonselective NSAIDs are thought to contribute to these differences; drugs with a longer half-life carry a higher risk [13]. A meta-analysis showed that the risk of ulcers is elevated even at low doses of ibuprofen, naproxen, and indomethacin and that these drugs carry a higher risk of hemorrhage and perforation at high doses [13]. Since many RA patients use a high-dose NSAID or multiple NSAIDs, patients should be encouraged to use only one NSAID or reduce the dose to lower their risk of NSAID ulcers.

Kamada and colleagues compared the sites of ulcers in 50 patients with ulcers attributable to NSAID use to those in 100 sex- and age-matched patients with

non-NSAID ulcers. A total of 56% of the NSAID ulcers were in the antral zone, and 34% occurred in the body, compared with 6% and 62%, respectively, for non-NSAID ulcers. NSAID ulcers thus occurred significantly more often in the antral zone [19]. In this study, Kamada and colleagues also investigated the morphology and number of NSAID ulcers. There were no appreciable morphological differences, since about 80% of both NSAID and non-NSAID ulcers were round or oval. The NSAID ulcers in 68% of the patients, however, involved multiple lesions, which were significantly higher than the figure of 20% for non-NSAID ulcers. Endoscopy showed that not all NSAID ulcers are shallow. Examined ulcers included deep ulcers of geographic, ovoid, and other shapes [20] (Fig. 7.1). Although some consistent trends are seen in the number of lesions present at different sites, NSAID ulcers show true diversity in endoscopy, which is alone often insufficient to make a diagnosis. Diagnoses should factor in other information, such as whether the patient is on an NSAID and when use began.

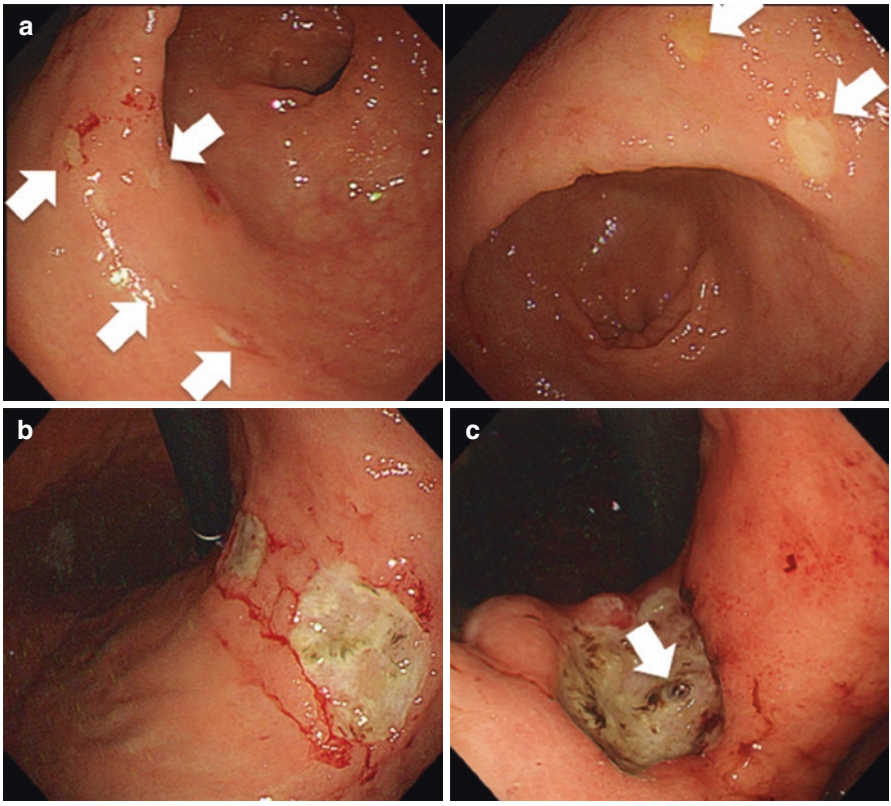

Fig. 7.1 Images of gastric NSAID ulcers on upper gastrointestinal endoscopy. (**a**) Multiple small ulcers of varying shapes. (**b**) Multiple oval ulcers. (**c**) Deep ulcer with exposed blood vessels

7.1.3.2 Lower Gastrointestinal Tract Damage

NSAIDs suppress prostaglandin synthesis by inhibiting COX. Of the two COX variants, COX-1 and COX-2, COX-1 contributes to mucosal protection, while COX-2 protects the mucosa of the lower gastrointestinal tract [21]. Since mice reared in a sterile environment or given antibiotics do not develop NSAID enterocolitis, gut bacteria are likely a key aggressive factor in mucosal damage in the lower gastrointestinal tract [22]. Inflammation in NSAID enterocolitis occurs when inflammatory cytokines are induced by the activation of toll-like receptor signaling by Gram-negative cocci or damaged intestinal epithelium or the inflammasome activation by extracellular ATP signals acting as alert signals [23]. NSAIDs themselves are another aggressive factor, since they undergo bile acid conjugation and are returned to the ileum in the enterohepatic circulation. The mitochondrial damage and apoptosis in small intestinal epithelial cells and damage from binding to epithelial cells caused by NSAIDs increase mucous membrane permeability. Higher permeability allows gut bacteria and digestive fluids to invade the mucosa, causing inflammation and damage [24]. Thus, not only NSAIDs themselves but also gut bacteria and digestive fluids, including bile and pancreatic fluid, are aggressive factors in the small intestine. NSAID damage of the colon's mucosa is generally classified as ulcerative- or colitis-related. The mechanism of ulcerative mucosal damage is considered similar to that of mucosal damage of the small intestine. Ulcerative lesions are therefore thought to predominate in ulcers and the right colon, where local NSAID concentrations are higher [25]. The mechanism behind colitis-related damage is unknown, but allergies and local circulatory disorders have been implicated [26, 27].

The endoscopic findings of NSAID ulcers are discussed next. In a paper on endoscopic findings associated with damage to the small intestinal mucosa, Torisu and colleagues [28] noted that spotty redness and oval aphthous erosions are seen most frequently (Fig. 7.2). Erosion is sometimes extensive and shows geographic patterning. Villus loss is also frequently seen, and extensive villus loss is a characteristic finding in NSAID users [29]. Severe mucosal damage can lead to ulcer formation, but such ulcers are generally relatively discrete and shallow. Ulcers take many shapes, including oval, indefinite, annular, and longitudinal, but they lack the longitudinal tendencies and other regularity seen in Crohn's disease and have normal intervening mucosa. Long-term NSAID users have annular ulcers with associated submucosal fibrosis and thickening of the muscularis mucosa, as well as characteristic membranous stenosis on imaging [30, 31]. Endoscopic examination of mucosal damage to the colon often shows ulcers in the right intestine that most often appear near the ileocecum. Often, more than one lesion is present, and lesions of the proximal colon near the ileocecum tend to be more severe. Ulcer shapes include oval, geographic, indefinite, and longitudinal, but ulcers are often relatively shallow and discrete (Fig. 7.3). Colitis-related findings include hemorrhagic colitis and aphthous colitis. No specific site is affected more than others, with lesions appearing throughout the colon [26, 27].

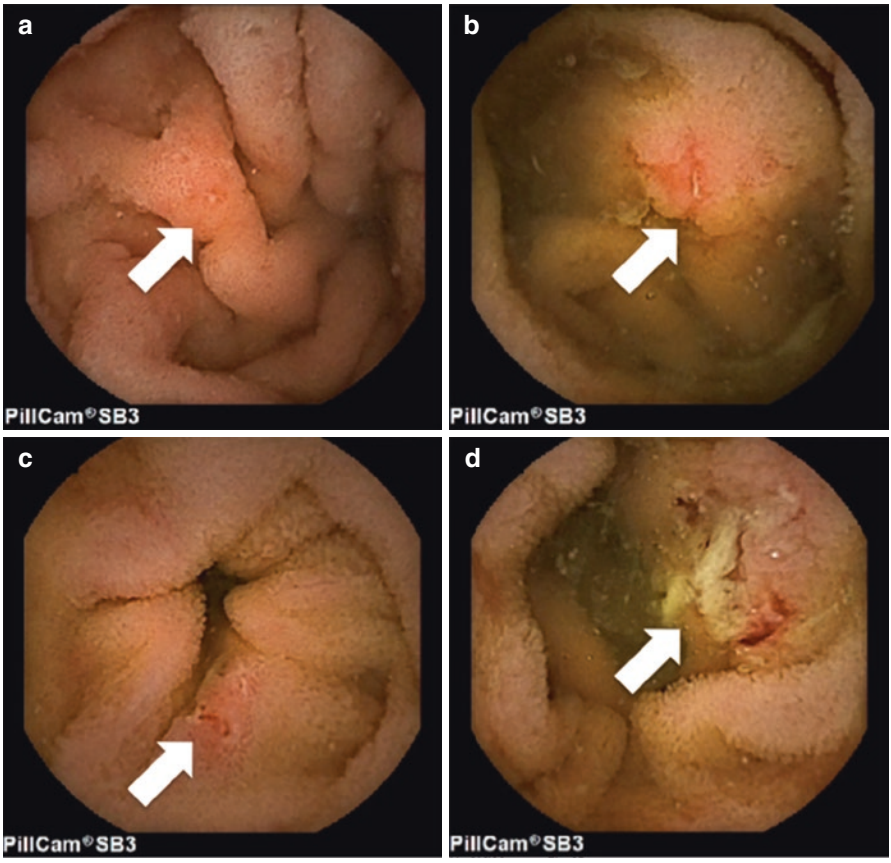

Fig. 7.2 Images of small intestinal NSAID enterocolitis on capsule endoscopy. (**a–c**) Spotty redness and aphthous erosion. (**d**) Small ulcer with mucus

Various papers proposing diagnostic criteria for NSAID-induced colon mucosal damage have been published since the paper of Goldstein and colleagues [32]. The criteria are based on (1) history of NSAID use, (2) exclusion of the contribution of other diseases, and (3) whether improvement comes following NSAID discontinuation. The criteria of Kurahara and colleagues [26] require (1) investigation of colon lesions (ulcers, enterocolitis); (2) determination of history of NSAID use; (3) exclusion of other diseases (e.g., inflammatory bowel disease, amyloidosis, infectious enteritis, ischemic enterocolitis) on the basis of disease history and endoscopic findings, histopathological findings from biopsy, and bacteriological findings from culture; and (4) investigation of whether lesions resolve with NSAID discontinuation alone, and specific procedures for the exclusion criteria are also presented. Given the extreme difficulty in the clinic of excluding all possible diseases, however, caregivers who suspect NSAID-induced colon damage must actively proceed with testing and treatment, even when the diagnostic criteria are not completely satisfied.

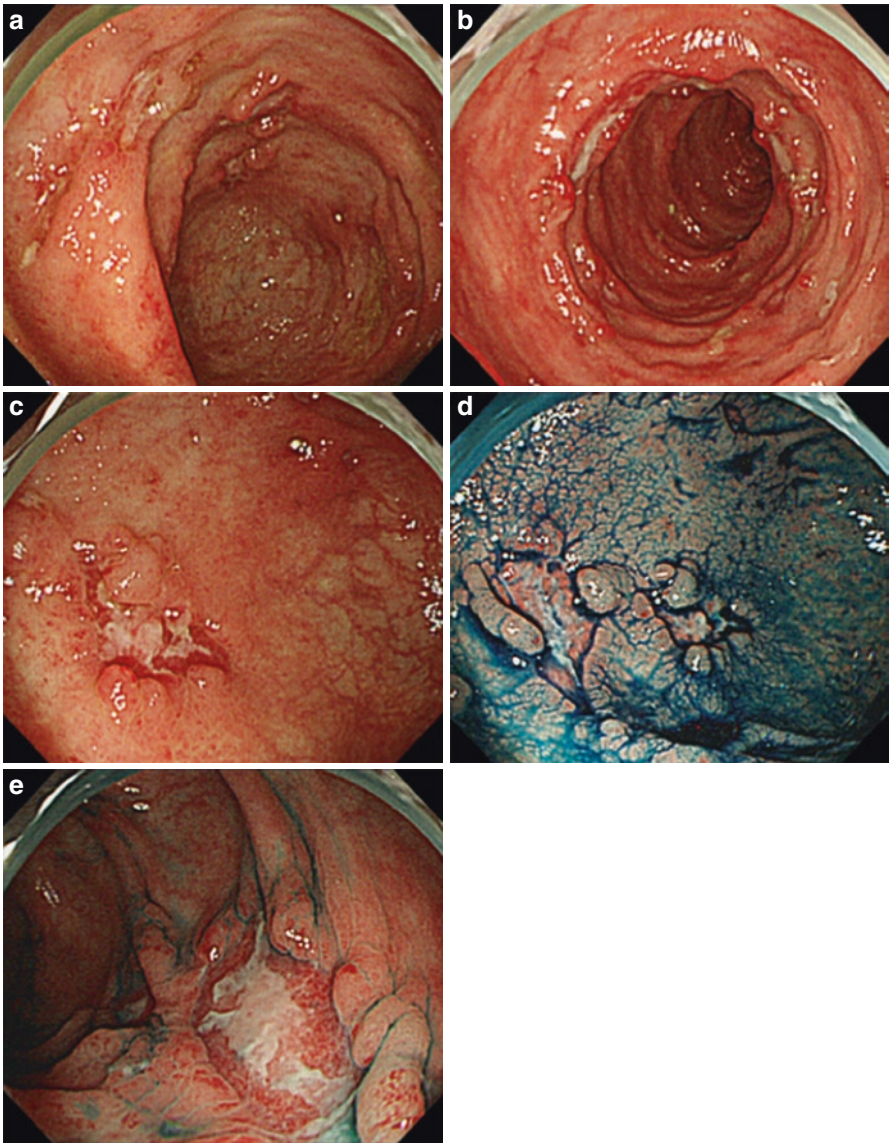

Fig. 7.3 Images of large intestinal NSAID enterocolitis on colonoscopy. (**a** and **b**) Multiple small red ulcers. (**c** and **d**) Irregularly shaped ulcer. (**e**) Oval discrete ulcer with relatively well-defined boundaries

7.1.4 Treating and Preventing NSAID Ulcers

Again, for the topic of treating and preventing NSAID ulcers, the different pathologies involved in the upper and lower gastrointestinal tract are discussed separately here.

7.1.4.1 Upper Gastrointestinal Tract

The following discussion on treating and preventing NSAID ulcers follows the guidance in the second edition of the evidence-based clinical practice guidelines for peptic ulcer disease [12].

For treating NSAID ulcers, the guidelines recommend discontinuing the offending NSAID if possible and then giving treatment with an antiulcer drug (recommendation strength 1, evidence level A). Gastric ulcers and duodenal ulcers associated with NSAID use often resolve with NSAID discontinuation alone [33, 34]. NSAIDs should therefore be discontinued whenever possible. Many patients with RA, however, will be unable to stop using NSAIDs because of their arthralgia. The guidelines recommend treatment with a proton pump inhibitor (PPI) or PG for patients unable to discontinue NSAIDs (recommendation strength 1, evidence level A). Gastroduodenal ulcers in patients on NSAIDs resolve more frequently in response to PPI treatment than to treatment with an H2 receptor antagonist (H2RA), PG, or drugs that enhance mucosal defense factors [35–39].

Preventing NSAID ulcers is discussed next. The guidelines recommend prophylactic measures for NSAID ulcers even in patients with no history of ulcers (recommendation strength 2, evidence level A). A meta-analysis of preventing gastrointestinal toxicity in patients taking an NSAID for at least 3 weeks found PG drugs effective in preventing bleeding and other complications of ulcers, PPIs and PG drugs effective in preventing symptomatic gastric and duodenal ulcers, and PPIs, PG drugs, and high-dose H2RAs effective in preventing endoscopic gastric and duodenal ulcers [40]. PG drugs and PPIs were found to have a prophylactic effect on gastric and duodenal ulcers in patients with no history of ulcers (i.e., primary prevention), while H2RAs were found to more effectively prevent duodenal ulcers than gastric ulcers [41–44]. Although the need for primary prevention is clear, caregivers in Japan must realize that the prophylactic use of the above drugs is not covered under the country's national health insurance program. The guidelines of the American College of Gastroenterology list risk factors for NSAID ulcers, classifying gastrointestinal risk into the categories of low risk (no risk factors), moderate risk (1–2 risk factors), and high risk (multiple (>2) risk factors or history of a recent complicated peptic ulcer) [45]. The guidelines proceed by proposing treatment procedures separately for patients at low risk and high risk of cardiovascular complications (the latter defined as those requiring low-dose aspirin). The guidelines list *Helicobacter pylori* infection (discussed later in this chapter) as an independent risk factor. In Japan, a factor posing a high risk of NSAID ulcers is a history of ulcers with accompanying gastrointestinal bleeding, while moderate risk factors include advanced age, a history of ulcers, concomitant steroid use, the use of a high-dose NSAID or 2 or more NSAIDs, concomitant use of a drug with antiplatelet effects, being positive for *H. pylori*, having a serious systemic disease, and the concomitant use of a bisphosphonate. The risk of gastrointestinal hemorrhage increases as the number of these factors present grows. Many patients with RA are elderly and take NSAIDs at a high dose, putting them at moderate to high risk of gastrointestinal hemorrhage and warranting close monitoring.

PPIs and PG drugs are also effective in preventing relapses in patients with a history of ulcers or bleeding gastric ulcers who are on an NSAID (secondary prevention). The guidelines recommend PPI co-administration as a first-line treatment (recommendation strength 1, evidence level A). Japan's national health insurance program covers PPIs and PG drugs for this population. A Japanese study found 15 mg of lansoprazole (a defense factor enhancer) to be more beneficial than placebo in patients with a history of ulcers who were observed for 24 weeks [46]. Another study of the incidence of ulcers following treatment with 20 mg of esomeprazole or placebo in patients at high risk of ulcer recurrence who remained on NSAID treatment showed that esomeprazole prevented ulcer recurrence significantly better than placebo [47]. The Japanese health insurance program also covers prophylactic treatment with potassium-competitive acid blockers, which suppress acid secretion for longer and more potently than PPIs.

7.1.4.2 Lower Gastrointestinal Tract

As with NSAID-induced upper gastrointestinal ulcers, NSAID-induced lower gastrointestinal ulcers should be first treated by discontinuing the offending NSAID. Ulcers typically scar over within 8 weeks of discontinuation, while enterocolitis normally shows endoscopic improvement within 2 weeks [48]. When membranous stenosis is associated with a lesion, however, the stenosis itself will not resolve with discontinuation. Endoscopic balloon dilation or surgical resection will be necessary if the stenosis is severe or obstructs passage.

No sufficiently clinically effective pharmacotherapy has been established for these conditions, which should be treated with NSAID discontinuation. PPIs, which are recommended for upper gastrointestinal ulcers, may actually exacerbate intestinal damage because they alter gut microbiota. In an animal study of PPI co-administration in NSAID enterocolitis, Wallace and colleagues [49] noted exacerbated small intestinal injury in association with PPI use. PPI co-administration altered the gut bacteria of rats, substantially reducing actinobacteria and bifidobacteria. It has been proposed that alterations of gut microbiota can affect the synthesis of cytotoxic secondary bile acids [22, 50], exacerbating small intestinal injury. Health insurance began covering capsule endoscopy (CE) in October 2007. Many studies have since been published on the small intestine, which was previously the "dark continent" of the gut. Washio and colleagues examined CE findings before and after the COX-2 selective inhibitor celecoxib was administered for 2 weeks with or without a PPI. The incidence of small intestinal lesions was 17% for celecoxib monotherapy but 44% for celecoxib plus PPI [51]. In the jejunum, where gut microbiota alterations are pronounced, celecoxib monotherapy produced no lesions, while the incidence for celecoxib plus PPI was 26%. The gastric mucosal protectant rebamipide and PG drugs are reported to be clinically beneficial. Ten healthy subjects were given rebamipide, an NSAID, and a PPI for 1 week and then, after a 4-week washout, placebo, an NSAID, and a PPI for 1 week,

with CE performed [52]. The incidence of small intestinal injury was lower, at 20%, in the rebamipide group than in the placebo group, at 80%. Studies on the efficacy of PG drugs have also been conducted. Fujimori and colleagues [53] compared CE findings 2 weeks before and after treatment in a control group (NSAID+PPI) and a PG group (NSAID+PPI + PG). The incidence of small intestinal injury was significantly lower, at 13% (0.7 injuries), in the PG group compared with 53% (2.9 injuries) in the control group. PPI plus PG, however, failed to produce a clinically significant benefit in NSAID-induced lower gastrointestinal ulcers, leaving NSAID discontinuation as the only established intervention.

7.1.5 H. pylori *Involvement*

Both *H. pylori* and NSAIDs are independent risk factors for upper gastrointestinal ulcers. *H. pylori* infection rates vary by year of birth because infections are related to drinking water and other aspects of childhood hygiene. Infection rates approached 50% in the 1950s, before decreasing to 30% in the 1960s, 20% in the 1970s, and 10% in the 1980s [54]. *H. pylori* infection is a widely known risk factor for gastric ulcers and gastric cancer. After health insurance began covering eradication therapy for peptic ulcers in 2000 and *H. pylori* infectious gastritis in 2013, many patients began undergoing eradication therapy. Not all those infected, however, have undergone eradication therapy, and *H. pylori* infection rates likely remain high in RA patients, who tend to be older people. Many people, moreover, learn that they have *H. pylori* infection only after developing an ulcer. Those with an *H. pylori* infection have poor gastric mucosal defense and are at a threefold greater risk of NSAID-induced peptic ulcers than uninfected people [55]. Patients positive for *H. pylori* should therefore undergo eradication therapy, but just when *H. pylori* is eradicated is critical. The evidence-based clinical practice guidelines for peptic ulcer disease 2015 propose not performing *H. pylori* eradication in patients with ulcers associated with NSAID use because the cure rate is low (recommendation strength 2, evidence level A). One study found that the cure rate for ulcers in patients on an NSAID is unaffected by *H. pylori* involvement [36], and many studies have concluded that *H. pylori* eradication does not affect the treatment of NSAID ulcers [56]. Patients with an NSAID ulcer who are *H. pylori*-positive thus need not undergo eradication immediately. The caregiver should consider administering eradication therapy after the NSAID ulcer has healed. Eradication therapy is effective in patients who have not yet begun to take an NSAID, but it has not been found to prevent ulcers in patients already on an NSAID [55]. The guidelines further recommend *H. pylori* eradication for preventing ulcers in patients scheduled to begin NSAID treatment (recommendation strength 1, evidence level A), but they recommend against eradication for ulcer prevention in patients already on an NSAID (recommendation strength 1, evidence level A). *H. pylori* eradication, however, helps prevent gastric cancer and should therefore be done before atrophy

progresses. Most RA patients could be convinced to stop taking NSAIDs used as a stopgap until RA therapy takes effect, but patients taking an NSAID for the long-term control of pain would be less likely to stop the use. Deciding just when to undertake eradication therapy is therefore difficult. Patients considering using an NSAID should therefore first undergo upper endoscopy to check for *H. pylori* infection, malignancies, gastric ulcers, and gastric scarring to allow the caregiver to decide whether to perform eradication therapy on the basis of the particular patient's risk.

7.1.6 NSAID Usage for Elderly RA Patients

A September 2017 report by the Statistics Bureau of the Japanese Ministry of Internal Affairs and Communications stated that the total population of Japan was 126,710,000 and declined by 210,000 people since the previous year. Elderly people (i.e., those at least 65 years of age) increased by 570,000 people since the previous year to 35,140,000, amounting to a record 27.7% of the total population. RA, osteoarthritis, and rheumatic diseases will further increase in this aging society, in which 1 in every 4 people of each sex is elderly. Those affected, moreover, will increasingly turn to NSAIDs. Of concern in elderly patients using NSAIDs are interactions between age-related changes in pharmacokinetics and drugs taken to treat underlying diseases. These age-related changes in pharmacokinetics can lead to gastrointestinal disorders, renal impairment, and cardiovascular complications. NSAID-induced upper gastrointestinal disorders increase in incidence and severity with age, occurring twice as commonly in elderly adults as in non-elderly adults. An endoscopic investigation of peptic ulcers in 58 elderly patients on NSAIDs [57] found that 11% of PPI users had an ulcer, compared with 40% of the H2RA users, 50% of the users of a gastric mucosal protectant, and 75% of the patients not receiving antiulcer treatment. Caregivers must monitor especially carefully for NSAID-induced upper gastrointestinal ulcers in elderly adults, prescribing a COX-2-specific NSAID and a PPI as prophylaxis. Elderly people often have renal impairment, since age-related reductions in the glomerular filtration rate lower kidney function. Dehydration further lowers the base kidney function, which could intensify adverse reactions to NSAIDs. In a study of 1799 elderly patients with acute renal failure [58], 18.1% took an NSAID. The study investigated NSAID use in different age groups, finding that a large proportion of patients at least 85 years of age used NSAIDs. A comparison of NSAID doses showed dose dependency in renal impairment. This shows the importance of monitoring for renal impairment at higher NSAID doses as patients age. COX-2-specific NSAIDs could cause cardiovascular damage [8], and increased incidences of myocardial infarction and other cardiovascular events have been associated with even COX-2-nonspecific NSAIDs [10, 11]. As many elderly people suffer a decline in cardiac function as they age, caregivers must closely monitor for cardiovascular complications in their RA patients on NSAIDs.

7.2 Amyloidosis

7.2.1 Definition of Amyloidosis

Amyloidosis, which involves the conversion of soluble proteins with beta-pleated sheet architecture to a specific protein type with fibrillar architecture called amyloid fibrils, is a group of diseases that cause organ damage through the extracellular deposition of these fibrils in the body's organs [59]. More than 30 known amyloid precursors become amyloid in this disease process. Amyloidosis can be classified into systemic amyloidosis with amyloid deposition in the organs throughout the body and localized amyloidosis in which only one organ is affected. The disease is further classified according to the type of amyloid protein deposited [60]. Common types of systemic amyloidosis are AL amyloidosis, AA amyloidosis, and familial amyloid polyneuropathy. Typical types of localized amyloidosis include Alzheimer's disease, prion diseases, and amyloidosis with endocrine involvement. Since this manuscript covers RA and gastrointestinal disorders, a brief description of typical systemic amyloidoses is given followed by a discussion of AA amyloidosis.

AL amyloidosis involves an immunoglobulin light chain called the lambda chain (Aλ) or kappa chain (Aκ). Aλ amyloidosis is about twice as common as Aκ amyloidosis. Localized amyloidoses limited to the eyelids, pharynx, lungs, or skin are often AL amyloidoses. AA amyloidosis occurs when the deposition of amyloid from an acute phase reaction protein called serum amyloid A (SAA) leads to chronic inflammatory disorders [61]. SAA is an apolipoprotein, and its hydrophobic sequence embedded in lipid has been associated with amyloid production. AA amyloidosis was previously reported to be frequently associated with Crohn's disease, inflammatory bowel disease, and tuberculosis, but reports of AA amyloidosis associated with these diseases are fewer now that disease-controlling treatments that stop long-term inflammation are available. As will be discussed later, AA amyloidosis is also often associated with RA, but less than previously so, because biological drugs for RA soon bring inflammation under control. In familial amyloid polyneuropathy, amyloid precursors arise from mutations in *TTR*, *gelsolin*, and *apoAI*, leading to amyloid deposition primarily in the nervous system, as well as the heart, kidneys, digestive tract, and eyes. A mutation called *ATTR* Val30Met is prevalent worldwide, but many mutations, some of which are unique, exist.

7.2.2 Diagnosis

Diagnosing amyloidosis requires identifying amyloid deposition in a tissue biopsy. The diagnostic process invariably begins with finding clinical symptoms indicative of amyloidosis. Amyloid deposition in different organs in systemic amyloidosis produces a variety of symptoms suggestive of amyloidosis. Amyloid deposition in the gastrointestinal tract can cause poor digestive tract performance (decreased

peristaltic movement), malabsorption, and protein loss, leading to nausea, vomiting, diarrhea, hypoproteinemia, and occasionally gastrointestinal hemorrhage. When the liver is involved, this organ enlarges and has an irregular surface, and serum alkaline phosphatase levels often rise. Symptoms associated with cardiac amyloidosis include congestive heart failure from ventricular enlargement. Bradyarrhythmia from conduction disorders can lead to Adams-Stokes syndrome. These disorders are more prevalent in primary AL amyloidosis and TTR-related amyloidosis. Renal damage seen in renal amyloidosis leads to characteristic urinary protein and often causes nephrotic syndrome. Renal impairment is present beginning in the early stages and progresses to renal failure. Edema and hypoalbuminemia are often present in patients who develop nephrotic syndrome. Peripheral nerve damage includes sensory disorders, anesthesia, and muscular weakness. Autonomic nervous damage manifests as orthostatic hypotension, impotence, gastrointestinal motility disorders such as diarrhea and constipation, and bladder dysfunction. Other complications of amyloidosis include thickening of the skin and soft tissue, subcutaneous and oral bleeding from deposition under the skin and in the oral mucosa, and reduced adrenal and thyroid function from lesions in these glands.

Laboratory tests relevant to amyloidosis are discussed here. When clinical symptoms suggest amyloidosis, testing should begin with relatively noninvasive tests. The first round of testing includes blood chemistry tests and urinalysis. Since AA amyloidosis develops from chronic inflammatory conditions, patients will have elevated inflammatory markers such as C-reactive protein and erythrocyte sedimentation, as well as elevated serum amyloid A. Elevated serum creatinine and urinary protein on urinalysis are typical of renal amyloidosis. Primary AL amyloidosis and other immunoglobulin-related amyloidoses often feature M-protein in the serum and urine. The second round of testing includes electrocardiography, echocardiography, myocardial scintigraphy, and contrast-enhanced MRI when cardiac amyloidosis is suspected. Electrocardiograms often show low potential in the limb leads, a QS pattern in leads V1 to V3, bundle branch block, and atrioventricular block. Echocardiography may show thickening of the myocardial wall and a granular sparkling appearance. Technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy may show abnormal accumulation. On contrast-enhanced MRI, delayed-phase endocardial findings are a key indicator of amyloid deposition.

If these tests implicate amyloidosis, organs with amyloid deposition must be identified and biopsied to arrive at a histopathological diagnosis. Biopsy requires that the tissue from affected organs be properly collected. Biopsy sites recommended for diagnosing amyloidosis include abdominal wall fat, the skin, tissue from the stomach and duodenum in the upper gastrointestinal tract, and tissue from the rectum in the lower gastrointestinal tract. When myocardial damage is the chief feature, endomyocardial biopsy is of high diagnostic relevance [62]. Congo red dye stains amyloid red-orange, giving it green birefringence when observed under polarized light microscopy. Once amyloid has been found, immunohistochemistry with antibodies specific to different amyloid precursors should be performed to complete the diagnosis.

7.2.3 Treatment

The treatment of amyloidosis consists of curative treatment, which seeks to modify the actual amyloid deposition process, and symptomatic treatment targeted at the organ damage and consequent symptoms caused by amyloid deposition. Amyloid deposition is a process spanning from the production of amyloid precursors and amyloid protein production from the processing of precursors to the misfolding, clumping, and deposition of amyloid protein. Treatments targeting each of these steps have been developed. Treatments that potently suppress amyloid precursor production have been most effective clinically. They include high-dose chemotherapy with autologous peripheral blood stem cell transplantation for AL amyloidosis, biological drug treatment for AA amyloidosis, and liver transplant for hereditary ATTR amyloidosis (familial amyloid polyneuropathy). Some amyloidosis variants have no established curative treatments. For these, a symptomatic treatment suited to the variant, performance status of the patient, and degree of organ damage should be selected. Treatment policies for different variants are not presented here. Treatments for AA amyloidosis are discussed below.

7.2.4 Amyloidosis as a Complication of RA

AA amyloidosis, one type of systemic amyloidosis, arises during the course of chronic inflammatory diseases. AA amyloidosis is therefore also known as secondary or reactive amyloidosis. Tuberculosis and similar chronic infections once accounted for much AA amyloidosis in Japan, but now RA and other rheumatic diseases underlie 90% of AA amyloidosis cases in the country. These other rheumatic diseases include seronegative spondyloarthritis, juvenile idiopathic arthritis, and adult-onset Still's disease. AA amyloidosis may also complicate Crohn's disease, inflammatory bowel disease, the autoinflammatory disease Familial Mediterranean fever, and the rare disease Castleman disease.

7.2.4.1 Mechanism and Factors of Onset

AA proteins form from serum amyloid A (SAA) precursor. SAA, a 104-amino acid protein belonging to the same gene family as C-reactive protein, increases in the blood during acute inflammation [63]. The C terminus of SAA is normally cleaved by an enzyme produced by macrophages such that SAA dissociating from HDL is absorbed into macrophages and processed by cathepsin and other proteases in lysosomes. In amyloidosis, however, SAA is not properly metabolized, and insoluble AA protein deposits onto tissues as fibers. Deposited amyloid is thought to stabilize on binding to proteoglycans and serum amyloid P protein [64].

SAA occurs as the three major subtypes SAA1, SAA2, and SAA3. Since levels of SAA1 and SAA2 surge during acute inflammation, these isoforms are also called acute-phase SAA. The SAA subtypes that are precursors of AA protein are SAA1 and SAA2, and in humans, AA protein from SAA1 is predominantly involved in amyloid deposition. The long-term SAA elevation in the blood typically seen in RA and other rheumatic diseases is a major factor behind amyloidosis. Survival is closely correlated with circulating SAA levels [65]. SAA1 is present as the three haplotypes SSA1.1, SAA1.3, and SAA1.5, and SAA2 is present as the two haplotypes SAA2.1 and SAA2.2. For SAA2, the haplotype involved has no bearing on disease susceptibility. This is not, however, the case for SAA1. The *SAA1* gene contains four exons. Single-nucleotide polymorphisms (SNPs) appearing in the protein portion are mostly present in exon 3, and different SNPs have different associated levels of disease susceptibility. In Japanese, SSA1.1 protects against AA amyloidosis onset, while SAA1.3 promotes onset [66]. SAA1.3 is not only a risk factor, but it is also predictive of poor remaining life expectancy [67].

7.2.4.2 Organ Manifestations

Gastrointestinal tract symptoms often appear first. Amyloidosis should be suspected when a patient with RA or other chronic inflammatory disease develops unexplained diarrhea, loss of appetite, or digestive disorders. Deposition of amyloid protein in the intestines can cause digestive disorders, malabsorption, protein loss, and a variety of other gastrointestinal tract conditions. Like the gastrointestinal tract, the kidneys are commonly affected. The kidneys, however, rarely show noticeable symptoms like the gastrointestinal tract symptoms. Renal involvement is suspected when blood and urine tests show renal impairment or proteinuria. Although AL amyloidosis often causes abnormal blood pressure and electrocardiographic findings, deposition in the heart is minimal in AA amyloidosis, which rarely causes cardiovascular complications. Those affected, however, may develop cardiac failure or arrhythmias as the disease progresses. Deposition in the thyroid and parathyroid glands may bring hypothyroidism and hypoparathyroidism that in turn cause symptoms.

7.2.4.3 Diagnosis

As stated previously, a definitive diagnosis requires a tissue biopsy from the affected organ or organs. Convenience, safety, and diagnostic precision must be factored into decisions about which organ to biopsy. The upper gastrointestinal tract is most suitable. In endoscopy, one must look for telltale rough mucosa with multiple yellow-white granular protrusions. Disease progression will bring multiple nodular

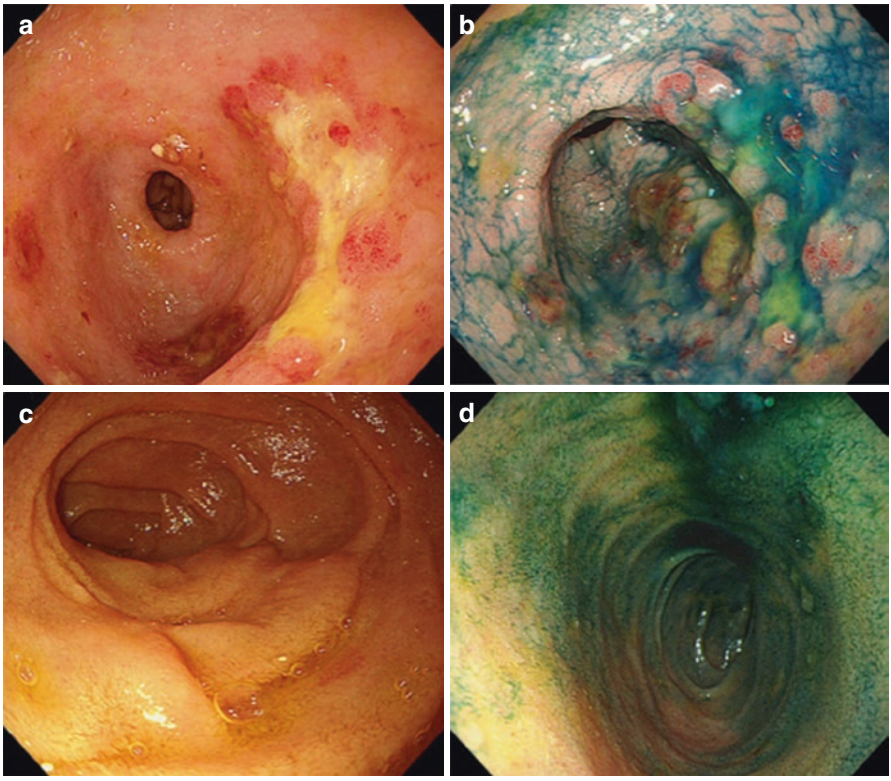

Fig. 7.4 Images of intestinal AA amyloidosis in upper gastrointestinal endoscopy. (**a**) Antrum (imaged normally): An irregularly shaped ulcer with redness is seen on the posterior wall of the antrum. (**b**) Antrum (sprayed with indigo carmine). (**c**) Descending part of the duodenum (imaged normally): Yellowish rough mucosa is seen. (**d**) Descending part of the duodenum (sprayed with indigo carmine). Deposition associated with AA amyloidosis is found in biopsy tissue collected from the stomach and duodenum

protrusions and fragile mucosa featuring erosion, ulceration, and a tendency to bleed (Fig. 7.4). Studying 124 patients with amyloidosis secondary to RA, Okuda and colleagues found gastroduodenal biopsies to have high diagnostic value, achieving the highest proportion of positive results from biopsies of the descending duodenum, followed by the duodenal bulb and antrum [68]. In the early stage, amyloid deposition predominates in the blood vessel walls, so tissues must be biopsied to collect submucosal tissue. Deposition, moreover, is not uniform throughout the intestine, so samples should be collected from multiple locations when possible. Amyloid deposition is also readily detected on renal biopsy specimen examination, although the procedure is more invasive than upper gastrointestinal tract biopsy. Since deposition in the kidneys without duodenal deposition is rarely seen, an upper gastrointestinal biopsy should be sufficient.

7.2.4.4 Treatment of AA Amyloidosis Secondary to RA

The goal of treating AA amyloidosis is inhibiting the AA precursor protein SAA. RA disease activity should be controlled because of its relevance to SAA production. Inducing and maintaining RA remission with early, aggressive treatment reduces the risk of secondary AA amyloidosis. In RA patients with AA amyloidosis, intensifying RA treatment can reduce SAA levels. A close correlation between SAA concentrations and AA amyloidosis outcome has been reported [65]. In patients with AA amyloidosis that has advanced enough to cause organ damage, priority should be given to treating the symptoms, since beginning treatment for AA amyloidosis may not be feasible. Marked SAA elevations may accompany infections caused by strong immunosuppression, further exacerbating AA amyloidosis, so that patients must be carefully monitored for infections.

Outcomes associated with different RA treatments are discussed next. In a study of the benefits of the immunomodulator cyclophosphamide or methotrexate in 62 patients with AA amyloidosis secondary to RA, the inflammation marker C-reactive protein and renal function indicator serum creatinine were used to assess the patients. The findings suggested that cyclophosphamide treatment may be beneficial in managing these patients [67]. Anti-TNF-α antibody therapy strongly inhibits inflammatory markers such as SAA and C-reactive protein, as well as disease activity, and is considered beneficial in treating AA amyloidosis [69–72]. Gottenberg and colleagues [69] evaluated the therapeutic effect of anti-TNF-α antibody therapy on renal damage in 15 patients with AA amyloidosis secondary to inflammatory arthritides. Three patients achieved reduced proteinuria and elevated eGFR, and five showed no progression in renal damage, while renal function worsened or damage progressed in seven patients. More than half of these patients with renal damage therefore responded to this treatment. Nakamura and colleagues [71] investigated the therapeutic effect of the anti-TNF-α antibody etanercept in amyloidosis secondary to RA. Etanercept significantly lowered C-reactive protein by week 20 by significantly increased serum albumin by week 96, and calculated Ccr improved, although not significantly so. In a multicenter, prospective cohort study, Fernandez-Nebro and colleagues [72] evaluated therapeutic outcomes achieved with anti-TNF-α antibody therapy for 36 RA patients with AA amyloidosis. Overall, 54.4% of the patients achieved a renal response, while 17% had renal progression. Although treatment significantly changed proteinuria, posttreatment serum creatinine was not significantly different from baseline. Inflammatory markers decreased significantly, but not to normal levels. Severe proteinuria was a risk factor involved in treatment response, continuation, and survival. Although the overall incidence of adverse reactions did not differ significantly from the control, sepsis and severe infections were three times as common in treated patients. Eight patients in the amyloid group and one patient in the control group died. A possible higher risk of infections was listed as a safety concern. Biopsy tissue was collected during upper gastrointestinal

endoscopy from RA patients with AA amyloidosis who were on anti-TNF-α antibody treatment, which significantly reduced the area of amyloid deposits [70]. Although anti-TNF-α antibody therapy is effective in patients with a rheumatic disease complicated by AA amyloidosis, patients with advanced organ damage generally have poor overall health and reduced immune function, and they are therefore at increased risk of infections. Since anti-TNF-α antibody therapy may have to be stopped if the patient develops an infection, caregivers should initiate therapy early while organ damage is still minor, carefully monitoring for infections and other complications.

Next, the therapeutic effects of the immunomodulator cyclophosphamide are compared with those of the anti-TNF-α antibody etanercept [73]. Etanercept produced a significantly better response in terms of C-reactive protein, albumin, and creatinine. In this study, the SAA1.3 allele, which is a genetic risk factor for AA amyloidosis and remaining life expectancy in Japanese RA patients, was unrelated to therapeutic efficacy.

Treatment with the anti-IL-6 receptor antibody tocilizumab is discussed next. Tocilizumab is considered the most effective treatment for AA amyloidosis by virtue of its SAA-reducing action. SAA production requires STAT3 activation by IL-6 stimulation, but IL-6 inhibition is needed to return SAA production to normal levels. Tocilizumab therapy normalizes SAA levels in most patients who maintain a therapeutic concentration of tocilizumab in the blood [74, 75]. Okuda and colleagues [76] did a head-to-head comparison of the clinical effects of tocilizumab ($n = 22$) and anti-TNF-α antibody ($n = 32$) in AA amyloidosis. The 5-year continuation rate was 90.4% in the patients on tocilizumab but just 34.3% in the patients on anti-TNF-α antibody. Median SAA levels normalized (i.e., ≤8 μg) from 219.2 to 4.95 μg/mL in the patients on tocilizumab and also decreased significantly, but did not normalize, going from 143.6 to 38.1 μg/mL, in the patients on anti-TNF-α antibody ($P < 0.0194$). Overall, 72.7% of the patients on tocilizumab had an improved glomerular filtration rate, while only 34.3% of the patients on anti-TNF-α antibody showed improvement. IL-6 blockade thus more effectively treated AA amyloidosis in RA patients than TNF-α blockade.

Steroid drugs may be used for treatment when multi-organ disorders or complications prevent the use of the abovementioned drugs. However, since long-term steroid use can cause adverse reactions, amyloidosis should be identified in the early stages when aggressive treatment with an immunomodulator, anti-TNF-α antibody, or anti-IL-6 receptor antibody is still possible. Eprodisate is thought to interfere with the glycosaminoglycan binding sites of amyloid fibers, destabilizing and reversing amyloid deposits. A multicenter, randomized, double-blind, placebo-controlled study of the drug in primarily Western countries found that treatment produced a 42% reduction in the risk of worsening renal disease. Progression to end-stage renal failure and mortality, however, was not significantly reduced [77]. The T-cell inhibitor FK506 reversed AA amyloid deposition in an animal model and patients with RA with amyloidosis [78].

7.2.5 Prevention of AA Amyloidosis in RA Patients

AA amyloidosis secondary to RA must be identified early and controlled closely. Anti-TNF-α antibody therapy and other highly effective RA treatments are available, providing long-term control of inflammation to many patients. This has reduced the number of RA patients who develop AA amyloidosis. These treatments, however, may not benefit patients who cannot receive full treatment because of an infection or allergy, patients with the SAA1.3 allele, and patients who already have advanced organ damage at the time of diagnosis. In summary, AA amyloidosis is best treated by first controlling the underlying disease to reduce the likelihood of onset.

7.3 Summary

Among the many gastrointestinal complications of RA, this chapter has focused on NSAID ulcers and intestinal amyloidosis. Identifying these complications early requires regular screening and close monitoring for clinical symptoms during the routine care of RA patients.

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Chapter 8
Gastrointestinal Involvement of Systemic Sclerosis

Hiroshi Watanabe

Abstract Systemic sclerosis (SSc) is a rare autoimmune disease characterized by microvascular abnormalities that result in fibrosis of the skin and other organs. Gastrointestinal (GI) manifestations are frequently observed in patients with SSc and occur in both diffuse cutaneous SSc and limited cutaneous SSc. The entire GI tract displays the pathological findings of SSc, including vasculopathy, smooth muscle atrophy, and excessive collagen deposition in the submucosa. As SSc progresses, the GI manifestations not only impair the quality of life by causing symptoms such as pain, nausea, vomiting, constipation, and fecal incontinence but are also related to poor prognosis. At present, the management of GI manifestations in patients with SSc is empirical and symptomatic. The goals of the treatment are the prevention of malnutrition and improvement of the quality of life.

Keywords Systemic sclerosis · Gastrointestinal involvement

8.1 Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy and excessive fibrosis, which leads to dysfunction of the skin as well as internal organs such as the lung, heart, kidneys, and gastrointestinal (GI) tract.

GI manifestations are observed in both patients with limited cutaneous SSc and diffuse cutaneous SSc [1]. GI manifestations affect almost 90% of patients with SSc, although nearly half of the patients with SSc with GI manifestations are asymptomatic [2, 3]. The most common site for GI manifestations in patients with SSc is the esophagus (affected in almost 90% of patients with SSc), followed by the small intestine and anorectum [2–7].

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GI manifestations of SSc not only decrease the quality of life by causing symptoms including pain, nausea, vomiting, constipation, and fecal incontinence but are also associated with poor prognosis and reduced survival. In general, the 5-year survival rates are 80% in diffuse cutaneous SSc and 90% in limited cutaneous SSc. However, GI manifestation of SSc is strongly correlated with decreased survival, which is reportedly 10% at 5.2 years [8] and 15% at 9 years [7, 9]. In particular, the mortality rate of patients with SSc who develop malabsorption is reportedly increased by 50% at 8.5 years compared with those without malabsorption [10, 11]. This chapter contains a discussion of the clinical features of and treatment approaches for each GI manifestation of SSc.

8.2 Pathogenesis of Systemic Sclerosis and Gastrointestinal Manifestations

Although the cause of SSc is still unknown, it is hypothesized to comprise a combination of vasculopathy and immune system disorders with the presence of background genetic factors. Excessive fibrosis in SSc is accompanied by vasculopathy and immunological disorders that lead to the production of autoantibodies and abnormalities of innate immunity.

The pathological findings of SSc are similar along the entire GI tract. Biopsy and autopsy findings show that the histological features of SSc in the GI tract include diffuse vasculopathy, smooth muscle atrophy, and excessive deposition of collagen in the submucosa [5, 10]. Although the pathogenesis of GI manifestation in SSc remains unclarified, the effect of SSc on the GI tract is thought to occur in three stages [10]. In the first stage, neural dysfunction occurs in the GI lesion due to ischemia caused by vasculopathy or compression of nerve fibers by collagen deposits. The second stage involves the development of smooth muscle atrophy in the GI tract, with symptoms most commonly appearing in this stage. In the final third stage, muscle fibrosis occurs in the GI tract; the muscle now cannot respond to any stimuli, and functional recovery is impossible.

Autoantibodies may contribute to the pathogenesis of GI manifestations in SSc. Nishimagi et al. reported that patients with severe GI manifestations were less likely to be positive for either anti-topoisomerase I antibodies or anti-centromere antibodies, while anti-U1RNP and anti-U3RNP antibodies were more frequently present in those with severe GI disease [12]. In addition, recent studies suggest that autoantibodies to muscarinic-3 receptor (M3R) participate in the pathogenesis of GI manifestations in patients with SSc. Titers of anti-M3R antibodies are reportedly positively correlated with the severity of GI manifestation in patients with SSc, and additional studies suggest that anti-M3R antibodies cause GI dysfunction by binding to M3R and thus preventing the myenteric nerves from releasing acetylcholine [13–16].

8.3 Clinical Features of Gastrointestinal Manifestations

8.3.1 Esophagus

Over 90% of patients with SSc have esophageal manifestations, and these patients frequently experience symptoms such as dysphagia, heartburn, regurgitation, and chronic cough. These symptoms are mostly due to structural and functional disorders such as esophageal motility disturbance, lower esophageal sphincter (LES) abnormalities, and gastroesophageal reflux disease (GERD) [2, 3, 17–20]. As the esophageal disorder progresses, dilatation occurs along the whole esophagus (Fig. 8.1).

Esophageal motility disturbance often leads to decreased LES pressure and reduced peristalsis in the lower esophagus, which allows gastric acid to reflux into the esophagus, resulting in a GERD. Initially, this GERD comprises simple peptic esophagitis (Fig. 8.2); however, if left untreated, it could progress to erosive esophagitis, bleeding, and ulcer formation (Fig. 8.3). GERD may also lead to Barrett's esophagus. Barrett's esophagus occurs in 6.8–12.7% of patients with SSc and carries a high risk of adenocarcinoma [4–6, 19]. Furthermore, recent studies revealed a positive correlation between gastroesophageal reflux and the progress of interstitial lung disease in patients with SSc [5, 20–24].

8.3.2 Stomach

Gastric complications occur in 10–75% of patients with SSc [25]; these complications include gastroparesis and gastric antral vascular ectasia (GAVE). Half of all patients with SSc reportedly develop gastroparesis [7], which leads to prolonged gastric emptying, progressing to gastroesophageal reflux. Prolonged gastric

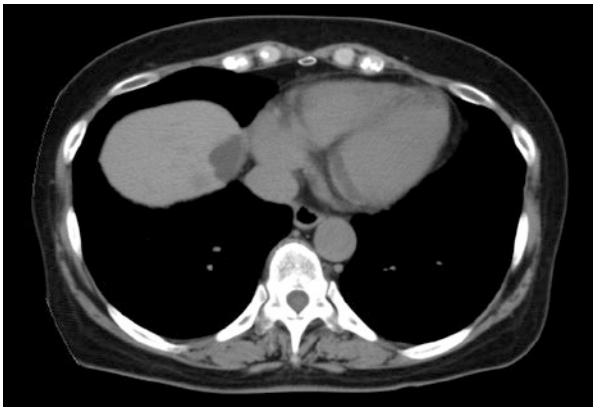

Fig. 8.1 Abdominal computed tomography image showing a hepatic cyst and dilation of the distal lower third of the esophagus

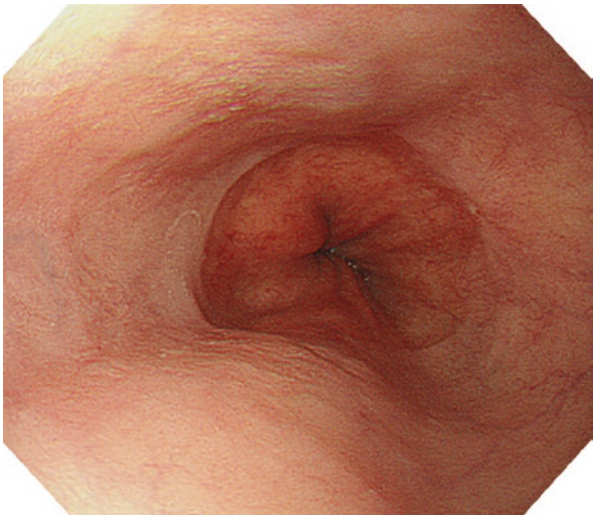

Fig. 8.2 Esophagogastroduodenoscopy in systemic sclerosis. Gastroesophageal reflux disease, Los Angeles Classification grade A

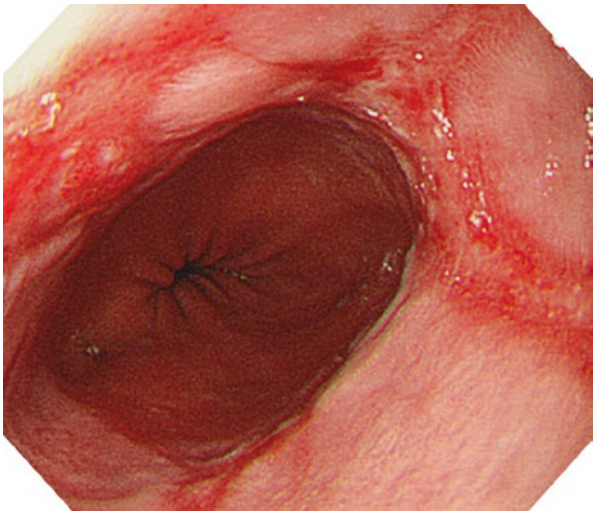

Fig. 8.3 Esophagogastroduodenoscopy in systemic sclerosis. Gastroesophageal reflux disease, Los Angeles Classification grade C

emptying, especially of solids, is very common in patients with esophageal motility disorder and in those with diffuse cutaneous SSc [4, 25–27].

GAVE reportedly occurs in 5.7–22.3% of patients with SSc [28]. Other than SSc, GAVE is often associated with liver cirrhosis and chronic renal failure [29]. Esophagogastroscopy findings show columns of red tortuous ectatic vessels along

the longitudinal folds of the antrum radiating to the pylorus, resulting in an appearance that resembles watermelon stripes. GAVE can cause gastrointestinal bleeding and can thus cause anemia in patients with SSc [28].

8.3.3 Small Intestine

Although small intestine is involved in 60–80% of patients with SSc [30, 31], over 65% of these patients are asymptomatic [7, 32, 33], as the symptoms often remain subclinical until muscle atrophy of the GI tract occurs. The main clinical features of small intestinal involvement in SSc are small intestinal bacterial overgrowth (SIBO), intestinal pseudo-obstruction, and pneumatosis cystoides intestinalis (PCI) [34].

Intestinal dysmotility is observed in 40–88% of patients with SSc and elicits symptoms such as nausea, vomiting, bloating, distension, and abdominal pain [35]. Mobility disturbance of the small intestine induces stasis of the intestinal contents, resulting in SIBO. SIBO is defined as the presence of 1×10^5 colony-forming units/mL in the jejunal aspirate culture, and this occurs in 43–56% of patients with SSc [36, 37]. The diagnosis of SIBO also includes the glucose hydrogen breath test [38] or lactulose breath test [39]. SIBO is reportedly more common in limited cutaneous SSc than in diffuse cutaneous SSc [6]. SIBO sometimes causes malabsorption in patients with SSc, leading to low levels of albumin, vitamin B12, and ferritin and malnutrition.

Pseudo-obstruction is a syndrome characterized by impaired coordinated propelling of the GI tract contents, leading to acute or chronic intestinal obstruction in the absence of any mechanical cause. Pseudo-obstruction presents as nausea, vomiting, bloating, abdominal pain, and diarrhea and is frequently associated with SIBO. Valenzuela et al. reported that patients with SSc with pseudo-obstruction had a high in-hospital mortality rates and were 30% more likely to die than other patients with SSc and those with idiopathic pseudo-obstruction [37].

Patients with SSc rarely develop PCI, which is characterized by the presence of air-filled cysts in the submucosa or subserosal layer in the GI tracts [7, 40, 41]. PCI mainly occurs in the small intestine but can also develop in the large intestine and stomach. Although the etiology of PCI remains unclear, it is attributed to excess gas production by bacterial overgrowth and increased luminal pressure caused by intestinal obstruction. Elevated luminal pressure may allow excess gas to migrate into the intestinal wall through damaged mucosa. The rupture of an intraluminal cyst can induce pneumoperitoneum [35, 41–43].

8.3.3.1 Case 1

A 67-year-old male with a 3-year history of SSc treated with corticosteroids presented with 2 weeks of abdominal distension, pain, and, more recently, nausea and vomiting. Physical examination revealed sclerodactyly in the hands. Abdominal

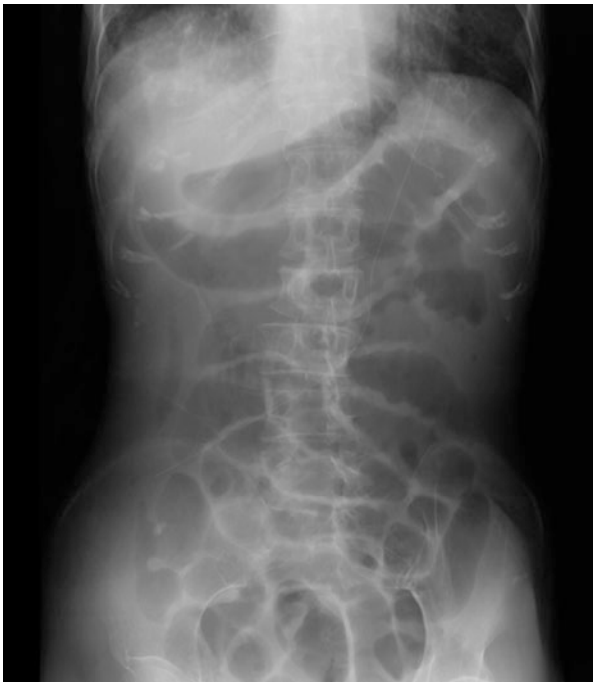

Fig. 8.4 Abdominal radiograph showing the dilated small intestine

examination showed a distended, tympanic, and non-tender abdomen. Laboratory tests showed that the patient had a normal white blood cell count and was positive for antinuclear antibody (1:2560, nucleolar type) and anti-topoisomerase I antibody but negative for anti-centromere antibody. Plain abdominal radiography showed dilatation of the small and large intestine (Fig. 8.4). Abdominal computed tomography revealed marked dilatation of the small and large intestine, without organic obstruction. The patient was diagnosed with intestinal pseudo-obstruction, and the clinical signs were resolved via conservative treatment comprising intravenous hydration, prokinetic agents, and laxatives.

8.3.3.2 Case 2

A 52-year-old female with a 2-year history of SSc treated with corticosteroids presented with 2 days of nausea, vomiting, abdominal pain, and constipation. Exacerbation of lung fibrosis had occurred 14 weeks previously and had been treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone. Physical examination revealed thickening of the skin of the extremities and face and a digital ulcer on the right third finger. Fine crackles were audible over

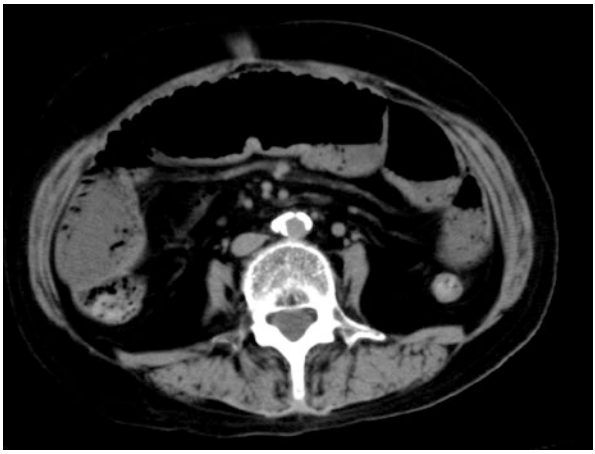

Fig. 8.5 Abdominal computed tomography image showing free air in the abdominal cavity and small cysts within the wall of the bowel

the bilateral lung bases. Abdominal examination showed a soft, slightly distended, tympanic, and non-tender abdomen, without signs of peritonitis; no tumorous mass was palpable. Laboratory tests showed an elevated white blood cell count (17,000/mm), elevated C-reactive protein level (17.7 mg/dL), positive antinuclear antibody titer (1:2560, speckled type), and positive anti-topoisomerase I antibody titer. The patient was negative for anti-centromere antibody. Plain abdominal radiography showed dilatation of the small intestine and colon. Abdominal computed tomography revealed free air in the abdomen and a dilated small intestine and colon with gas inside the bowel wall (Fig. 8.5). There was no organic obstruction. The patient was diagnosed with PCI and underwent conservative management comprising administration of metoclopramide and octreotide. The patient had clinical resolution of her symptoms and was discharged 12 weeks after admission to hospital.

8.3.4 Colon

Colon complications occur in 20–50% of patients with SSc [5, 35]. The main clinical symptoms of colonic manifestations in patients with SSc are constipation, diarrhea, and fecal incontinence. Severe constipation results from dysmotility of the colon, followed by delayed colon transit. Patients with SSc with colonic manifestations frequently also have SIBO. Therefore, the constipation is generally not prolonged because of the diarrhea caused by SIBO [6].

Fecal incontinence is characterized by a reduction in the resting pressure and dysfunction of the internal anal sphincter [43], and this complication seriously decreases quality of life. Up to 40% of patients with SSc reportedly have fecal

incontinence [44]. Recent studies suggest that fecal incontinence in SSc is mainly related to neurologic abnormalities [45, 46].

Patients with SSc sometimes develop diverticulosis in the colon, although most diverticulosis is asymptomatic. Atrophy of the muscles in the colonic wall reportedly results in dilation and the loss of haustra, leading to wide-mouthed diverticulosis [7, 47].

Patients with SSc commonly develop colonic telangiectasia, which occasionally causes bleeding that leads to anemia.

8.4 Treatment

At present, the management of GI manifestations in patients with SSc is empirical and symptomatic. The goal of treatment is the prevention of malnutrition and improvement of the quality of life.

8.4.1 Esophagus

Esophageal dysmotility is managed by excluding daily diet and lifestyle factors that worsen the symptoms. These diet and lifestyle changes include alcohol abstinence, cessation of smoking, avoiding large meals, sitting upright for 3 h after eating, avoiding bedtime snacks, and elevating the head of the bed [48]. GERD is usually treated via the administration of proton-pump inhibitors (PPI) and H2 blockers. The most effective PPI agents in the treatment of GERD in patients with SSc are omeprazole and lansoprazole [20, 49, 50]. Esophageal reflux can also be reduced via the administration of prokinetic agents, such as metoclopramide; several studies report that metoclopramide increases the LES tone in patients with SSc [51–53]. Furthermore, in patients with SSc with GERD that is partially responsive to PPI administration, add-on therapy with domperidone effectively improves the symptoms and quality of life [20]. However, these treatments become ineffective when the esophageal lesion progresses and muscle atrophy occurs.

8.4.2 Stomach

8.4.2.1 Gastroparesis

The first-line agent used in the treatment of gastroparesis is metoclopramide, as recommended by the American College of Gastroenterology [54]. Metoclopramide is a dopamine receptor 2 (D2R) antagonist. It prevents nausea

via its D2R antagonistic activity in the central nervous system and accelerates gastric emptying by inhibiting dopamine-induced gastric muscle relaxation [20, 55–57]. However, as metoclopramide crosses the blood-brain barrier, its D2R antagonistic effects can sometimes cause extrapyramidal symptoms including akathisia and dyskinesia [54].

Domperidone is also recommended in the treatment of gastroparesis. Domperidone is a peripheral D2R antagonist. As it does not cross the blood-brain barrier, it has a low risk of causing extrapyramidal symptoms. Domperidone reportedly improves the quality of life in up to 90% of patients with SSC with gastroparesis [58].

Patients with refractory gastroparesis are treated with erythromycin, which has a stimulatory effect on motilin receptors; Janssens et al. reported improvement of gastric-emptying time in patients with SSc who were administered erythromycin [59].

Five-hydroxytryptamine 4 receptor agonists, including prucalopride and mosapride, are also reported to aid in the management of reduced antroduodenal motility [60]. Furthermore, rikkunshito, a Chinese herbal medicine, reportedly improves symptoms such as nausea and heartburn by accelerating gastric motility [61].

8.4.2.2 Gastric Antral Vascular Ectasia

In cases of GI bleeding due to GAVE, endoscopic therapies such as argon plasma coagulation, laser photocoagulation, or endoscopic band ligation are recommended [29, 62, 63]. If endoscopic therapy fails, radiofrequency ablation therapy is considered [64].

8.4.3 Small Intestine

8.4.3.1 Small Intestinal Bacterial Overgrowth

SIBO is generally treated with 2–4 weeks of empirical therapy with broad-spectrum antibiotics, including amoxicillin, ampicillin, norfloxacin, levofloxacin, and gentamycin [7]. The antibiotic regimen should be rotated monthly to limit or circumvent bacterial resistance [6]. In cases with persistent diarrhea, the administration of metronidazole is also recommended. Compared with metronidazole, rifaximin is reportedly more effective with fewer adverse effects [20, 65] and is commonly used for SIBO in Western countries; however, rifaximin is not approved for use in Japan at present.

Probiotics are safe and helpful in relieving symptoms caused by SIBO [66].

8.4.3.2 Intestinal Pseudo-obstruction

Intestinal pseudo-obstruction is initially treated via conservative management such as bowel rest, intravenous fluid administration, and electrolyte correction. In cases where conservative management is not effective, prokinetics such as metoclopramide and domperidone are helpful. Metoclopramide reportedly increases the motility of the small intestine in patients with SSc [20, 67]. If patients fail to respond to other prokinetics, octreotide may be considered. Octreotide is a somatostatin analog, and it reportedly alleviates symptoms and is well-tolerated by patients with SSc [68]. Furthermore, the combination of octreotide and erythromycin reportedly improves symptoms and induces weight gain in patients with SSc [69]. When those therapies are not effective, total parenteral nutrition is recommended to prevent malnutrition [1]. Total parenteral nutrition is expected to improve the quality of life. Except for cases with bowel perforation and ischemia, surgical therapy is not recommended.

8.4.3.3 Pneumatosis Cystoides Intestinalis

In general, the prognosis of PCI is good. Cases with pneumoperitoneum are treated via conservative treatment including bowel rest, antibiotics, and oxygen administration [33].

8.4.4 Colon

There is currently only symptomatic therapy available for colonic complications of SSc. Unless there is only mild constipation, a high-fiber diet is not recommended, as this may worsen constipation. Colonic movement is reportedly stimulated by laxatives such as polyethylene glycol, bisacodyl, lactulose, and senna. In cases of diarrhea due to bacteria, administration of antibiotics is considered.

The symptoms of fecal incontinence can reportedly be alleviated through sacral nerve stimulation therapy [70] and posterior tibial nerve stimulation therapy [20].

8.5 Conclusion

GI manifestation is a serious complication of SSc. In the early stage, the symptoms of GI manifestations are generally mild and tend to be disregarded by doctors. Progression of the GI manifestations decreases the quality of life, carries a high risk of malnutrition, and reduces survival. Unfortunately, the main treatments of GI

manifestations are currently empirical and symptomatic, as there are no disease-modifying drugs available. However, it is important to diagnose the presence of GI manifestations of SSc in the early stage to enable adequate management and prevention of malnutrition.

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Chapter 9
Gastrointestinal Involvement of Systemic Vasculitis

Shuzo Sato and Kiyoshi Migita

Abstract Systemic vasculitides can affect any organ and any part of the gastrointestinal tract, including the hepatobiliary system. Depending on the size of the inflamed blood vessels, gastrointestinal symptoms may range from mild abdominal pain and elevated transaminase levels to potentially life-threatening intestinal perforations and peritonitis. Because gastrointestinal manifestations are not specific, a diagnosis of systemic vasculitis based on gastrointestinal symptoms alone is challenging. However, diagnostic delay can cause unfavorable outcomes. This article reviews the epidemiology, gastrointestinal manifestations, and treatment of systemic vasculitides including Takayasu arteritis, polyarteritis nodosa, antineutrophil cytoplasm antibody-associated vasculitis, and single-organ vasculitis limited to the gastrointestinal tract.

Keywords Takayasu arteritis · Giant cell arteritis · Polyarteritis nodosa · Kawasaki disease · ANCA-associated vasculitis · IgA vasculitis · Cryoglobulinemic vasculitis · Gastrointestinal manifestation

9.1 Introduction

Systemic vasculitides are a heterogeneous group of diseases characterized by inflammation of the blood vessel walls. Vasculitis categorization is based on the predominant type of vessel involved and includes large-vessel vasculitis, medium-vessel vasculitis, and small-vessel vasculitis (2012 International Chapel Hill Consensus Conference [CHCC]) [1]. Of note, all three major categories can affect any size artery. Despite numerous studies, most vasculitides still have unknown etiologies. As the name states, large-vessel vasculitides, Takayasu arteritis (TA) and giant cell arteritis (GCA), mainly affect large arteries, including the aorta and its

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major branches. Medium-vessel vasculitides, including polyarteritis nodosa (PN) and Kawasaki disease (KD), predominantly affect medium arteries, including main visceral arteries and their branches. Small-vessel vasculitides affect predominantly small arteries such as arterioles, capillaries, and venules, but medium arteries and veins may be affected. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are considered small-vessel vasculitides. Immune complex vasculitis, anti-glomerular basement membrane (GBM) disease, cryoglobulinemic vasculitis, IgA vasculitis (formerly Henoch-Schönlein purpura), and anti-C1q vasculitis are also small-vessel vasculitides [1]. For gastrointestinal (GI) manifestations of vasculitis, large-vessel vasculitis causes widespread intestinal or other organ infarctions, while small-vessel vasculitides mainly affect intramural arteries and cause focal ischemia and ulcerations [2–4].

GI manifestations of systemic vasculitis range from mild abdominal pain to severe, life-threating peritonitis and perforations of the GI tract. The frequency and type of symptoms vary among vasculitides. Indeed, the Five Factor Score (FFS), which is widely used to evaluate the severity of systemic vasculitides, includes the presence of severe GI manifestations as a major predictor of mortality in PN, MPA, and EGPA, along with severe involvement of the central nervous system, heart, or kidneys [5]. Despite recent advances in the treatment of systemic vasculitis, the occurrence of GI manifestations remains a serious concern. In this review, we focus on the GI manifestations of systemic vasculitides and describe their management and use several case presentations and images to illustrate the concepts.

9.2 Large-Vessel Vasculitides

9.2.1 Takayasu Arteritis

TA mainly affects the aorta and/or its major branches, such as the subclavian and common carotid arteries [1]. Stenotic lesions are found in a majority of TA patients (90%), with aneurysms found in up to 25% [1, 2]. The histological features of TA and GCA are indistinguishable and show granulomatous lesions with infiltrating lymphocytes and giant cells [1, 6]. TA predominantly occurs in females who are 20–30 years old and is most common in Japan, Southeast Asia, India, and Mexico [7]. The prevalence of TA in Japan was >40 cases per million in 2012 [8]; in contrast, the prevalence in North America was 1–3 cases per million [9].

9.2.1.1 GI Manifestations of TA

GI manifestations of TA are relatively rare. A previous study of 126 TA patients found that 16% had abdominal pain, 4% had mesenteric ischemia, and 14% had abdominal bruits [10]. In imaging studies, up to 25% of patients showed stenotic or

occlusive lesions in the celiac and/or superior mesenteric arteries. A case of aorto-esophageal fistula due to TA has also been reported [11]. Several cases of TA with concurrent inflammatory bowel disease (IBD) have been reported, which suggests a possible association with TA and IBD [12]. For instance, Kilic et al. reported that 3 of 52 (5.8%) TA patients had coexistent IBD [13]. The genetic overlap between TA and ulcerative colitis has also been reported [14], with HLAB*5201 as an associated genetic determinant. IBD diagnosis usually precedes TA diagnosis (69% of cases, as reported by Sy et al.) [12]. We have previously reported a case of TA complicated by ulcerative colitis [15]. Recently, we also had a case of TA complicated by Crohn's disease (Figs. 9.1 and 9.2). The patient was an 18-year-old male with concomitant GI manifestations, increased carotid artery thickness (Fig. 9.1a), and fever. Because of stenosis of the ascending colon (Fig. 9.1b), the patient underwent partial colectomy. Afterward, the patient began immunosuppressive therapy of subcutaneous adalimumab injection and oral mesalamine and since achieved remission.

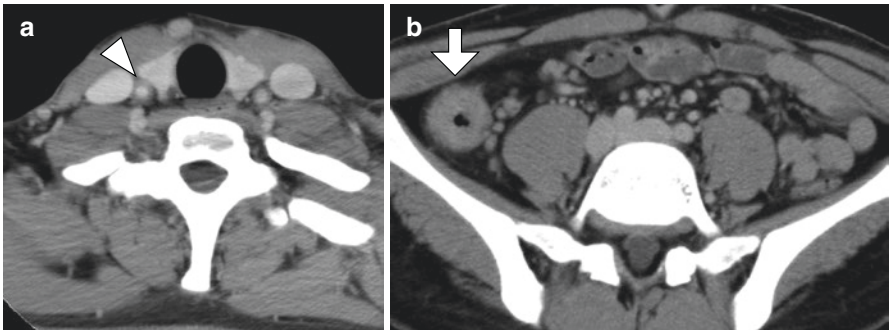

Fig. 9.1 Enhanced computed tomography (CT) images in a patient with Takayasu arteritis complicated by Crohn's disease. (**a**) Wall thickness of the right carotid artery is shown (arrowhead). (**b**) Ascending colon shows wall thickness due to inflammation from Crohn's disease (arrow)

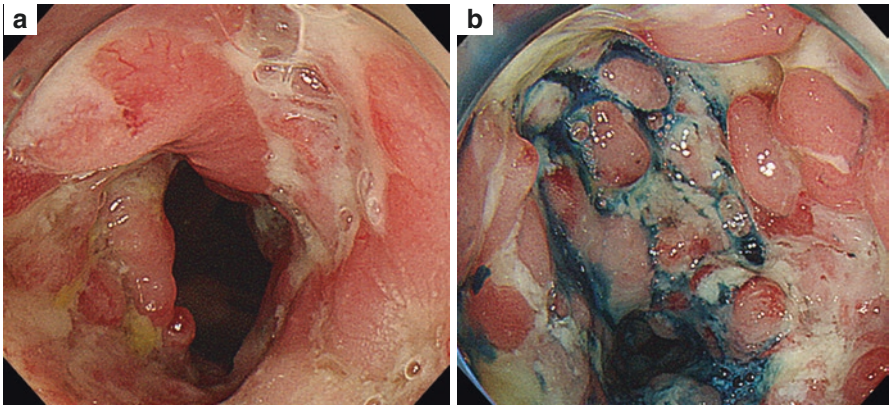

Fig. 9.2 Colonoscopy findings in this patient. Longitudinal ulcers (**a**) and cobblestone appearance with indigo carmine dye staining (**b**) are shown

9.2.1.2 Treatment of TA

Treatment with glucocorticoids (GCs) at a dose of 0.5–1.0 mg/kg of body weight per day, a prednisolone equivalent, is used initially to treat active TA. However, relapses are common when tapering GCs [16]. Immunosuppressants, such as methotrexate (MTX) (6–25 mg per week), cyclophosphamide (CYP) (intravenous pulse of 7.5–15 mg/body weight monthly, or 2 mg per day orally), and mycophenolate mofetil (MMF) (1–3 g per day), are used for refractory cases [17, 18]. Anti-TNF agents for refractory TA, especially infliximab (IFX) and adalimumab (ADA), have also been used [19]. Recently, the efficacy of tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody (162 mg subcutaneous injection per week), has been reported in a randomized, placebo-controlled, phase 3 trial in Japan (the TAKT study) [20]. TCZ treatment resulted prolonged time to relapse of TA compared to placebo. Therefore, TCZ is a desirable biologic agent for the treatment of TA. In contrast, abatacept (CTLA-4 Ig) has limited effects on TA, because Lanford et al. reported that abatacept administration to TA did not prolong the duration of remission compared to placebo [21]. Open surgery and endovascular treatments are sometimes warranted, such as in cases of symptomatic celiac or mesenteric artery stenosis. Unfortunately, vascular surgery may have a high risk of restenosis; one study showed a recurrence rate of 30–70% in 5–10 years after angioplasty [22].

9.2.2 Giant Cell Arteritis

GCA affects the aorta and/or its major branches, including the carotid, subclavian, and vertebral arteries. Temporal arteritis is a well-known clinical phenotype [1, 2, 23]. Aortitis can occur in 10–25% of GCA patients [2]. GCA most commonly occurs in Western countries (annual incidence rates, higher than 17 per 100,000 in Europe) and can occur in patients >50 years, with peak incidence of 70–80 years [24].

9.2.2.1 GI Manifestations of GCA

GCA rarely affects the mesenteric vessels. However, a systematic review of the literature found 12 GCA cases—75% with a positive temporal artery biopsy result—resulting in small intestine infarction [25]. Infarctions of the colon have also been described [26]. Some patients suffer abdominal pain derived from abdominal aortic aneurysms or even dissection, which are most likely to occur 6–7 years from GCA onset to diagnosis [27]. Therefore, routine screening of the aorta should be performed. One-third to one-half of GCA patients show asymptomatic liver enzyme elevation, including alkaline phosphatase and transaminase levels; these abnormalities might result from bile duct epithelial cell injury due to adjacent arteritis [2, 28].

9.2.2.2 Treatment of GCA

Similar to TA, GCs are the main agents used to treat GCA. Immunosuppressants and surgery are also considered [2]. Since GCA mainly develops in older patients, morbidity and mortality are relatively high [29]. MTX is sometimes used as an immunosuppressant, but the steroid-sparing effect is limited [30]. Recently, the addition of TCZ has been reported to be effective for GCA patients in a randomized, double-blind, placebo-controlled, phase 3 clinical trial called the Giant-Cell Arteritis Actemra (GiACTA) trial [31]. Abatacept has also been investigated and may be effective for reducing relapse of GCA [32].

9.3 Medium-Sized Vessel Vasculitides

9.3.1 Polyarteritis Nodosa

PN is a medium-sized muscular artery vasculitis. Patients with PN have narrow, tapered arteries along with saccular or fusiform microaneurysms in renal, hepatic, and mesenteric arteries on abdominal arteriography, computed tomography, or magnetic resonance angiographies [1, 2]. Previously, a diagnosis of PN included HBV-associated PN [1, 33], but PN now refers only to a noninfectious entity. HBV-associated PN is now categorized as a vasculitis associated with probable etiology in the most recent 2012 CHCC [1]. Because HBV infection rates have decreased and antiviral treatments have progressed, the incidence of HBV-related PN has decreased [33]. The annual incidence of PN was 0–8 cases per million in European countries in the early 2000s [2, 34].

9.3.1.1 GI Manifestations of PN

GI involvement in PN is more frequent in HBV-associated vasculitis than non-HBV PN [33]. Abdominal pain is commonly seen (35–95%) [35, 36] and is thought to derive from transmural necrotizing inflammation of the mesenteric vessels, most commonly seen in the small intestine [2, 3]. Other symptoms, such as vomiting, diarrhea, hematochezia, melena, and hematemesis, are also seen. GI or intra-abdominal bleeding can result from ischemic mucosal ulcerations, bowel infarctions, perforations, or intraperitoneal rupture of aneurysms or microaneurysms in hepatic, splenic, or renal vessels [1–3]. Pagnoux et al. reported GI ulcers in 37% (14/38) of PN patients, with gastroduodenal ulcers as the predominant type [33]. Segmental liver or spleen infarcts and hepatic vein occlusions (Budd-Chiari syndrome with antiphospholipid syndrome) have also been reported, secondary to hepatosplenic vessel involvement [37].

9.3.1.2 Treatment of PN

The FFS can be used to assess treatment strategy for non-HBV-associated PN [5]. Fortunately, 5-year survival is greater than 80% [36]. For severe cases, including GI manifestations (FFS ≥ 1), CYP and high-dose GCs (plus intravenous pulses of methylprednisolone for 3 days) are used for remission induction, followed by azathioprine (AZP) (2 mg/kg body weight per day) or MTX for maintenance therapy [38]. For patients with non-severe forms (FFS 0), GCs alone can be considered. AZP is used for maintenance therapy; however, in one study, the systematic addition of AZP to GCs as a first-line treatment failed to reduce treatment failure or relapse of PN [39]. The treatment of HBV-associated vasculitis relies on antiviral drugs (lamivudine, entecavir, tenofovir, adefovir dipivoxil, or telbivudine). For severe disease or rapid control of clinical manifestations, antiviral drugs can be combined with GCs and plasma exchange [40].

9.3.2 Kawasaki Disease

KD is a mucocutaneous lymph node syndrome associated with medium artery involvement, such as coronary arteries, in up to 25% of untreated cases [1]. KD mostly occurs in young children, with over 80% cases occurring between 6 months and 4 years old. KD is prevalent in Asian populations, especially in Japan, where annual incidence is 265 cases per 100,000 children <5 years old [41]. In contrast, in North America, Australia, and Europe, the incidence is 4–25 cases per 100,000 children <5 years old [42]. Adults are rarely affected, and adult-onset KD often manifests as an incomplete form of the disease [43].

9.3.2.1 GI Manifestations of KD

Baker et al. reported that 61% of patients with KD had GI symptoms (abdominal pain, nausea, and vomiting) in the 10 days prior to KD diagnosis [44]. In another series of 219 children with KD, 10 (4.6%) presented with more severe abdominal symptoms (acute abdomen): gallbladder mucocele (hydrops), paralytic ileus, appendicular vasculitis, and/or hemorrhagic duodenitis [45]. In that study, coronary aneurysms developed in half of the children despite early administration of intravenous immunoglobulins. Gallbladder mucocele is thought to be secondary to gallbladder wall vasculitis [2]. In adult KD, abdominal pain and jaundice are the most common GI manifestations [43].

9.3.2.2 Treatment of KD

Aspirin and intravenous immunoglobulins (2 g/kg body weight) are used to treat KD, which reduces the risk of coronary artery aneurysms from 20–25 to 2–4% [46]. For patients resistant to initial therapy, repeat intravenous immunoglobulin should

be administered [47]. GCs are also recommended for refractory disease. IFX, IL-1 antagonists, plasma exchange, and CYP have also been used as rescue therapies for severe KD in a few case reports [2, 48].

9.4 Small-Vessel Vasculitides

9.4.1 ANCA-Associated Vasculitis

AAV involves fibrinoid, necrotizing inflammatory, leukocytoclastic, systemic small-vessel vasculitides with few or no immune deposits. AAV include EGPA, GPA, and MPA. ANCAs are specific autoantibodies for antigens in cytoplasmic granules of neutrophils and monocyte lysosomes, such as myeloperoxidase (MPO) or proteinase 3 (PR3) [4, 49]. ANCAs are associated with the pathogenesis of vasculitis (pauci-immune necrotizing glomerulonephritis) [49]. MPO-ANCA is predominantly seen in MPA (90%) and less so in EGPA (40%). PR3-ANCA is mainly detected in GPA patients (90%). However, PR3-ANCA positivity in GPA patients is relatively lower in Japan than in European countries [50, 51]. Elderly-onset AAV (75 years or older) has a relatively lower 1-year survival rate than AAV in younger patients [51].

9.4.1.1 Microscopic Polyangiitis

MPA mainly affects the kidney (pauci-immune glomerulonephritis) and lung (interstitial lung disease and alveolar hemorrhage). MPO-ANCA is associated with the pathogenesis of MPA [49]. The annual incidence of MPA is 1–10 cases per million [52]. MPA is common in Asian populations (18.2 per million in Japan) [53]. In contrast, the annual incidence of MPA in the United Kingdom is lower than Japan (6.5 per million). Watts et al. have reported that the peak age of MPA onset is 65–74 years old [54].

GI Manifestations of MPA

GI symptoms occur in 5–30% of MPA patients and include abdominal pain, nausea, vomiting, and diarrhea. Severe GI manifestations are rare and include colonic ischemic ulcers, peritonitis, and intestinal perforations [2, 33, 55]. Involvement of the liver rarely occurs in MPA; however, fibrinoid degeneration of interlobular arterioles, necrotizing arteritis, and lymphocytic infiltration of portal tracts has been observed [56].

9.4.1.2 Granulomatosis with Polyangiitis

GPA mainly involves the upper and lower respiratory tracts with granulomatous lesions and kidneys (glomerulonephritis). GPA is closely associated with PR3-ANCA. The global annual incidence is estimated to be 2–15 cases per million [2].

In Japan, the incidence of GPA is lower than in Western countries (2.1 cases in Japan versus 14.3 cases per million in the United Kingdom). GPA onset peaks at 55–65 years old [54].

GI Manifestations of GPA

GI symptoms occur in 5–11% of GPA cases [2, 33]. Autopsy studies have reported that 24% of cases have histological evidence of GI vasculitis [57]. Any part of the GI tract can be involved; however, lesions in the small intestine and colon are most common. GI symptoms are nonspecific, ranging from transient abdominal pain and ulcerations to bloody stool and intestinal perforations [2, 32]. Endoscopic studies show ulcerations—sometimes described as granulomatous—and ischemic changes [2, 58]. Ulcers seen in GPA are relatively shallow and transversely oriented compared with those seen in Crohn's disease, but the distinction is quite difficult because GPA cases can co-occur with Crohn's disease or ulcerative colitis [59]. Biopsy for diagnosis is not recommended because of low sensitivity and a high risk of perforation [2, 33]. Granulomatous cholecystitis, a granulomatous pancreatic mass, has also been reported in GPA, which can mimic malignancy on imaging [60].

9.4.1.3 Eosinophilic Granulomatosis with Polyangiitis

Patients with EGPA have late-onset asthma and eosinophilia, with vasculitis manifestations such as skin purpura or mononeuritis multiplex. ANCAs are positive in only 30–40% of patients and are mainly MPO-ANCAs. Cardiac involvement is the main concern for mortality [61]. The annual incidence is 0.8–2.8 cases per million, and the main age at EGPA diagnosis is 34–54 years [2, 62].

GI Manifestations of EGPA

GI symptoms are seen in 30–50% of patients. Symptoms are nonspecific and include abdominal pain (91%), diarrhea (45%), melena or hematochezia (19–36%), nausea and vomiting (18%), and acute abdomen needing surgery (6–36%) [2, 63]. Mesenteric artery vasculitis is the most common explanation for these manifestations and can lead to bowel infarction. Mucosal infiltration of eosinophils in the GI tract can also cause abdominal pain, motility disorders, obstructive symptoms, and diarrhea. Eosinophilic, granulomatous mucosal ulcers can be a potential source of GI bleeding, and acalculous cholecystitis, omental nodules, and hematomas have also been reported [33]. In addition, EGPA with concurrent IBD has been reported [12].

Treatment of AAV

AAV patients with severe GI manifestations must promptly receive GCs combined with another potent immunosuppressant, such as CYP or rituximab (RTX). RTX (375/m^2 body area, weekly for 4 consecutive weeks), a chimeric CD20 B-cell-targeting antibody, is an alternative to CYP in AAV, especially in severe MPA and GPA [64]. In EGPA, mepolizumab, an anti-IL-5 monoclonal biologic agent, has been used for refractory cases [65]. Recently, positive results have been reported after using mepolizumab to treat for EGPA in a multicenter, double-blind, parallel group, phase 3 trial [66]. However, in urgent situations, surgery is sometimes required [33]. If AAV relapses, different treatment approaches with immunosuppressive agents can be considered [67].

9.4.2 IgA Vasculitis

IgA vasculitis (formerly Henoch-Schonlein purpura) can develop at any age but most commonly occurs in childhood (3–10 years old) [68]. The incidence is 2–3 cases per 100,000 children and 0.1–0.8 cases per 100,000 in adults. No ethnic predominance exists; however, the disease is rare in black populations [69].

9.4.2.1 GI Manifestations of IgA Vasculitis

In IgA vasculitis, 50–75% of patients have GI manifestations [70]. GI bleeding related to mucosal and submucosal vasculitis occurs in 18–52% of patients. About 20% of patients suffer abdominal pain [70]. Endoscopic findings can show petechial lesions, diffuse mucosal redness, and hemorrhagic erosions [71]. Esophageal involvement such as ulcers or strictures is rare. Most GI manifestations are self-limited; however, 5% of patients show bowel wall edema, infarction, necrosis, perforations (usually ileum), or intussusception, which may cause perforation of the ileum [2, 70]. The extent of skin purpura on the upper extremities is associated with the degree of risk for GI bleeding [2]. Protein-losing enteropathy, pancreatitis, cholecystitis, and appendicitis have also been reported [72]. Chao et al. have described hepatobiliary involvement by IgA vasculitis, in which 8.8% (20/228) of children with IgA vasculitis showed right upper quadrant pain (80%), elevated circulating transaminase levels (75%), elevated gamma-glutamyl transpeptidase (30%), hepatomegaly (75%) on abdominal ultrasonography, and gallbladder wall thickening (25%) [73]. In our institute, we had a case of IgA vasculitis complicated by abdominal pain and hematochezia. A 51-year-old male was admitted to our hospital for GI symptoms with purpura on his lower legs. Enhanced CT and colonoscopy findings are shown in Figs. 9.3 and 9.4. Steroid pulse therapy and oral prednisolone therapy ameliorated his symptoms, and prednisolone doses were successfully tapered.

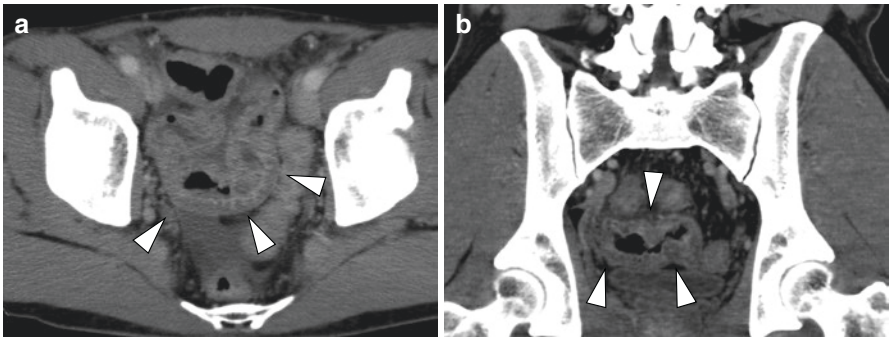

Fig. 9.3 Enhanced CT images in a patient with IgA vasculitis. (**a**, **b**) Wall thickness of the terminal ileum is shown (arrowheads)

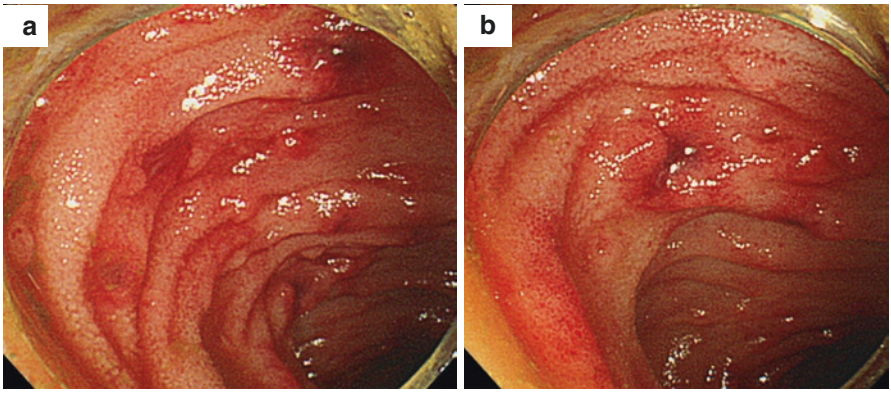

Fig. 9.4 Colonoscopy findings in a patient with IgA vasculitis. (**a**, **b**) Diffuse mucosal redness and hemorrhagic erosions/ulcers in the terminal ileum are shown

9.4.2.2 Treatment of IgA Vasculitis

IgA vasculitis is often self-limiting and is over in a few weeks [68]. IgA vasculitis with renal involvement is more likely to recur. For abdominal manifestations, GCs should be used. In severe cases, MMF or RTX can be used to achieve remission those who do not respond well to GCs [2, 74]. In contrast, CYP administration had no clear benefit [75]. Laparotomies may be required for intussusception, perforations, or uncontrolled bleeding (5–12% of patients) [2].

9.4.3 Cryoglobulinemic Vasculitis

Cryoglobulins are circulating immunoglobulins that precipitate at temperatures below 37 °C and dissolve upon rewarming. Cryoglobulins consist of three subtypes: type I refers to a single monoclonal immunoglobulin, usually in relation to an

underlying lymphoproliferative disorder; type II is composed of both polyclonal IgG and monoclonal immunoglobulin; and type III refers to polyclonal immunoglobulins. A low C4 complement fraction (with normal C3 fraction) and a positive rheumatoid factor strongly suggest the presence of cryoglobulins [2]. Cryoglobulinemic vasculitis mainly manifests with type II and III cryoglobulins and can affect the skin, kidneys, or peripheral nerves [1]. Cryoglobulinemic vasculitis is most common in patients in their mid-50s and is more common in males (3:1 ratio). HCV infection is the main cause of mixed cryoglobulinemia (98%). Approximately half of the patients with HCV infection have circulating cryoglobulins; however, only 5–10% of patients develop vasculitis [76]. Other causes of cryoglobulinemia include HBV and HIV infection, autoimmune disorders such as Sjogren syndrome, and lymphoproliferative disorders [77].

9.4.3.1 GI Manifestations of Cryoglobulinemic Vasculitis

GI involvement of cryoglobulinemic vasculitis is uncommon, but when it occurs, it is often life-threating [78]. GI manifestations range from abdominal pain and bloody stool to intestinal perforations, intestinal ischemia, acute cholecystitis, and pancreatitis. Severe GI manifestations are associated with poor prognosis [79]. Liver involvement is common in HCV-infected patients with cryoglobulinemic vasculitis (60%), and 25% of patients show progression to liver cirrhosis. Hepatocellular carcinoma occurs less frequently in HCV-infected patients with cryoglobulinemic vasculitis than in those without [2].

9.4.3.2 Treatment of Cryoglobulinemic Vasculitis

The therapeutic management should be individualized according to the underlying disorder (HCV infection, autoimmune disease, or lymphoma) and the severity of vasculitis. In severe systemic disease, aggressive therapy with high-dose GCs; immunosuppressants, mainly CYP and RTX; or plasmapheresis can be considered [80]. New antiviral therapies are desirable for treatment of virus-associated cryoglobulinemic vasculitis [81]. In addition, RTX can also be used with antiviral agents to induce remission in patients with severe vasculitis, including GI manifestations [82].

9.4.4 Others

Single-organ vasculitis (SOV) is a form of vasculitis restricted to a single organ or organ system [83]. SOV of digestive organs, including the esophagus, stomach, omentum, small intestine, colon, appendix, gallbladder, and pancreas, has been reported [2, 83, 84]. Although SOV is rare, it is associated with significant morbidity and mortality [2]. Approximately two-thirds of SOV patients suffer from

acute abdomen. Since SOV patients are usually diagnosed based on histological findings after surgery, diagnostic bias may exist [2, 83]. Resection of inflammatory lesions alone may be sufficient in some patients; however, systemic therapies such as GCs and immunosuppressive agents are usually required to ameliorate the disease [84]. The progression to systemic vasculitis is uncommon, affecting 0–25% of patients with GI manifestations after 5 years [2, 84]. Nevertheless, diagnostic workup is needed to assess GI findings suggestive of systemic vasculitis in SOV patients [2].

Cogan's syndrome is a very rare variable-vessel vasculitis that mainly affects the inner ear (Meniere-like symptoms, hearing loss), eyes (e.g., interstitial keratitis, eye redness, photophobia, and eye pain), and aorta (aortitis) [85]. Cogan's syndrome mostly occurs in young adult Caucasian patients of either sex. GI manifestations of Cogan's syndrome are extremely rare, but IBD may co-occur [86]. Early diagnosis and prompt intervention with GCs is important to protect ear function [85, 86]. Other immunosuppressants, including cyclosporine, MTX, and anti-TNF inhibitors, can be used.

Other variable-vessel vasculitides, including Behcet disease, and vasculitides with systemic diseases, including systemic lupus erythematosus and rheumatoid arthritis, will be described in other chapters.

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Chapter 10
Gastrointestinal Involvement of Behçet's Disease

Tomoyuki Asano, Shuzo Sato, and Kiyoshi Migita

Abstract Behçet's disease (BD) is a chronic inflammatory disease of unknown origin, featuring recurrent aphthous ulcers in the oral mucosa, uveitis, skin symptoms, and vulvar ulcers. Its inflammation can involve important organs such as the gastrointestinal tract, central nervous system, and vascular system. BD with gastrointestinal lesions is called intestinal BD, which is more common in Japan and Korea than elsewhere. Although ulcers at the ileocecal site are representative of intestinal BD, any part of the gastrointestinal tract can be involved. Therefore, the symptoms of intestinal BD are diverse and nonspecific. There are no specific markers for diagnosing this condition, and establishing the diagnosis of intestinal BD still remains a challenge. In the differential diagnosis of intestinal BD, Crohn's disease and intestinal tuberculosis often need to be ruled out. Glucocorticoids and antitumor necrosis factor-α antibodies are the key agents for the treatment of intestinal BD. Many patients experience disease flare-up, and they sometimes follow a severe clinical course.

Keywords Inflammatory bowel disease · Intestinal Behçet's disease · HLA-B51 · Diagnosis · Glucocorticoids · Anti-TNF-α monoclonal antibody · Infliximab · Adalimumab

10.1 Introduction

Behçet's disease (BD) is a systemic inflammatory disease characterized by recurrent aphthous ulcers in the oral mucosa, uveitis, skin symptoms, and vulvar ulcers. It is complicated by gastrointestinal, central nervous system, or vascular manifestations, which often affect the patient's prognosis. The gastrointestinal manifestation of BD, called intestinal BD, is common and is associated with serious

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morbidity and mortality [1]. Approximately 3–16% of patients with BD have gastrointestinal manifestations, which require differentiation from inflammatory bowel disease and infection [2]. This section reviews intestinal BD and provides case presentations.

10.2 Epidemiology

Several genetic factors are thought to contribute to BD, a representative example of which is human leukocyte antigen (HLA)-B51. The geographic location of patients with BD is extremely specific, with cases accumulating along the Silk Road from Japan to the Mediterranean coast; this generally coincides with the region inhabited by those with a high frequency of HLA-B51 [3]. However, in Alaskan Eskimos, few case reports of BD have been published, despite the high rate of HLA-B51 in that population (28.8%) [3]. It has also been suggested that consideration of the rate of BD among migrants to or from high-BD regions could be informative. For example, there are few cases of BD among Japanese immigrants in Hawaii [4]. Moreover, the incidence of BD among Turkish immigrants in Berlin is higher than that of Germans [5]. These findings suggest that both genetic and environmental factors are related to the onset of BD. However, in another study on residents of Paris, the incidences of BD among North African and Asian immigrants were higher than that of Europeans but were similar to the frequencies in their countries of origin [6]. This would suggest that the onset of BD is due mainly to genetic factors. Interestingly, intestinal BD is not so common in the Mediterranean but is more prevalent in East Asia, such as Japan and Korea [7–9]. However, little is known about why this is the case.

10.3 Etiology

In recent meta-analyses, it has been reported that the odds ratio of developing BD with HLA-B51 positivity is 5.78 (95% CI 5.00–6.67) compared with HLA-B51-negative cases [10]. Furthermore, genome-wide association studies (GWASs) focused on Japanese and Turkish people have progressed, revealing the disease susceptibility genes. For example, in 2010, independent research groups reported that *HLA-A* (*HLA-A26* in Japanese, unknown in Turkish), *IL (interleukin)-10*, and *IL-23R-IL12RB2* correlate with BD [11, 12]. Subsequently, *ERAP1* (*endoplasmic reticulum aminopeptidase 1*), *STAT4* (*signal transducer and activator of transcription 4*), *CCR1* (*chemokine [C-C motif] receptor 1*), and *KLRC4* (*killer cell lectin-like receptor subfamily C, member 4*) were identified from GWAS on groups of Turkish and Japanese in 2013 [13].

In addition, *MEFV*, a gene causative of familial Mediterranean fever, was identified as a disease susceptibility gene for BD in the Turkish population [14]. Although less frequently identified than the above-mentioned genes, pattern recognition receptors such as Toll-like receptor (TLR) 4 and nucleotide-binding oligomerization domain-containing protein (NOD) 2 have also been mentioned as having an association with BD, and some results suggest that innate immunity is involved in its pathology [15]. Interestingly, familial onset of BD due to a single genetic abnormality of A20 haplotype deficiency was recently reported [16].

Although immunological abnormality in BD has been demonstrated, the mechanism behind the onset of BD has not been elucidated. One suggested hypothesis is that it is associated with persistent bacterial or viral infections as a causative environmental factor. It has also been suggested to be associated with periodontal disease, and it is reported that the hygiene of the oral cavity is related to the severity of BD [17]. Among bacterial infections, an association with *Streptococcus* spp., particularly *Streptococcus sanguinis*, is suspected, and *S. sanguinis* is detected from the oral cavity in BD patients at a high rate compared with that in healthy controls [18].

In the active phase of BD, neutrophil-dominant cell infiltration into the acute inflammatory site has been observed [19]. In addition, the infiltration into inflammatory sites of cells involved in innate immunity, such as γδ T cells, has also been observed in patients with BD [20]. Helper T (Th)17 cells produce IL-17, and abnormalities of Th17 cells have been found to be important in the activation of neutrophils. Increased production of IL-17 and IL-23 has been reported in active BD patients, and serum IL-23 is known to correlate with uveitis activity [21]. It is known that Th1-dominant cytokine production (IL-12, IL-18, interferon-γ) is elevated in the peripheral blood of BD patients [22]. Th1 cells are differentiated and induced by IL-12, and its action is suppressed by IL-10. IL-10 and STAT4 were reported to be disease susceptibility genes from the results of GWAS described above.

10.4 Symptoms

The main symptoms of intestinal BD are abdominal pain, nausea, vomiting, diarrhea, melena, and sometimes perforation [23]. However, intestinal BD can cause inflammatory disorders at any site from the esophagus to the rectum, so the symptoms can vary. (The symptoms are described for each region in Sect. 10.5.) Oral ulcers are usually considered separately from intestinal BD because they are a major and particularly problematic symptom of BD [2]. They can cause intense pain and may result in difficulty eating, drinking, swallowing, speaking, and performing routine oral hygiene [4, 7].

10.5 Regions of Involvement in the Gastrointestinal Tract

10.5.1 Involvement of the Esophagus

Esophageal involvement in BD is rare. Bayraktar et al. reported that the incidence of esophageal involvement is between 2 and 11% [24]. The main symptom is chest pain, and dysphagia, odynophagia, melena, and hematochezia occasionally occur [25, 26]. Patients with intestinal BD sometimes experience serious complications such as stenosis [27] and perforation [28, 29]. The endoscopic findings of esophageal ulceration of BD are diverse and nonspecific: single or multiple, shallow or deep, small or large, or clearly or unevenly marginated [25]. Reports on the histological findings describe that acute or chronic nonspecific infiltrates and granulation tissue and fibroblasts are typically seen at the base of ulceration [25]. Routine endoscopy is not recommended for all BD patients, but the introduction of upper endoscopy may be appropriate if the patients complain of some upper gastrointestinal symptoms [26]. Compared with those in age-matched controls, both median lower esophageal pressure (LES) and LES relaxation in the BD patient group are significantly lower [30].

10.5.2 Involvement of the Stomach and Duodenum

The stomach and duodenum are the least affected regions in patients with intestinal BD. However, Ning-Sheng et al. reported a high frequency of gastroduodenal involvement of BD patients in Taiwan [31]. The common symptoms are dyspepsia and epigastralgia, and endoscopic findings include single or combined gastroduodenal ulcers [31]. As further rare complications, cases of Dieulafoy's ulcer [32], gastric non-Hodgkin's lymphoma [33], pyloric stenosis [34], and gastroparesis [35] have also been reported. Although the prevalence of *Helicobacter pylori* does not appear to be increased in patients with BD, 18.8% of patients treated with eradication therapy demonstrated a statistically significant decrease in oral ulcers and genital ulcers; this suggested unknown etiological roles of *H. pylori* infection in BD [36].

10.5.3 Involvement of the Jejunum, Ileum, and Colon

According to studies using capsule endoscopy, intestinal BD can result in the formation of ulcers along the whole of the small intestine, as well as in other parts of the digestive tract [37, 38]. Lee et al. reported that the typical intestinal BD manifestations are as follows: larger than 1 cm, round/oval, deep, and having discrete margins in the ileocecal lesion [39]. Almost 96% of patients with intestinal BD have involvement of the ileocecal region; 67% of patients have a single ulcer, and the rest have multiple ulcers [39]. The existence of a multi-segmental and diffuse distribution

of lesions is uncommon, with a rate of 6%. The mean diameter of the ulcers is large, at 2.9 cm. Deep ulcers are more common than superficial ones, with rates of 68% and 38%, respectively [39]. Additionally, rectal involvement of patients with BD is extremely rare, occurring in less than 1% of them [23].

10.5.4 Other Extra-Gastrointestinal Involvement

Some patients with BD exhibit involvement of the pancreas or liver, but this is extremely rare [24]. In addition, very few cases of pancreatitis associated with BD have been reported [40, 41]. An autopsy series of 170 BD patients from Japan suggested that 2.9% of such patients feature involvement of the pancreas [42]. The question why this inflammatory lesions occur in the pancreas of BD patients has been considered to be involved in vasculitis from the histological findings; this is further supported by findings of other vasculitic diseases such as granulomatosis with polyangiitis, which has also been associated with pancreatitis [43]. Budd–Chiari syndrome (BCS) is the most common manifestation of BD in the liver. BCS is associated with a high mortality rate. The mechanisms behind this have been proposed to involve venous thrombosis secondary to endothelial dysfunction complicated by vasculitis in BD [44]. In studies on BCS in BD, it was reported that the rate of BCS among BD cases was 1.3–3.2% [45–47]. The prevalence of this condition is higher in males than in females, and its symptoms include right hypochondralgia, hepatosplenomegaly, ascites, lower extremity edema, esophageal varices, and liver failure [48, 49]. Acute BCS is sometimes associated with a poor prognosis [50], so it has been suggested that ultrasonography should be performed for screening patients with BD [45]. In rare cases, intestinal BD can even be complicated by amyloidosis. The most common tissue associated with amyloidosis in BD is the kidney, but we have also reported on colon amyloidosis in patients with intestinal BD. In previous reports, only five cases with the complication of amyloidosis in intestinal BD have been described [51].

10.6 Diagnosis

The diagnosis of BD should be performed clinically after excluding other differential diagnoses because there are no universally recognized pathognomonic laboratory tests for BD. Various diagnostic criteria are used, most of which are dependent on mucocutaneous lesions, especially oral aphtha, genital ulcers, cutaneous vascular lesions, and skin pathergy test result [4, 52, 53]. In Japan, Mizushima et al. reported recent research on such criteria in Japanese BD patients, which are among the most sensitive, specific, and commonly used sets of criteria, especially in East Asia [54]. They include major symptoms (oral ulcers, skin lesions, uveitis, and genital ulcers) along with minor ones (arthritis, intestinal ulcers, vascular disease,

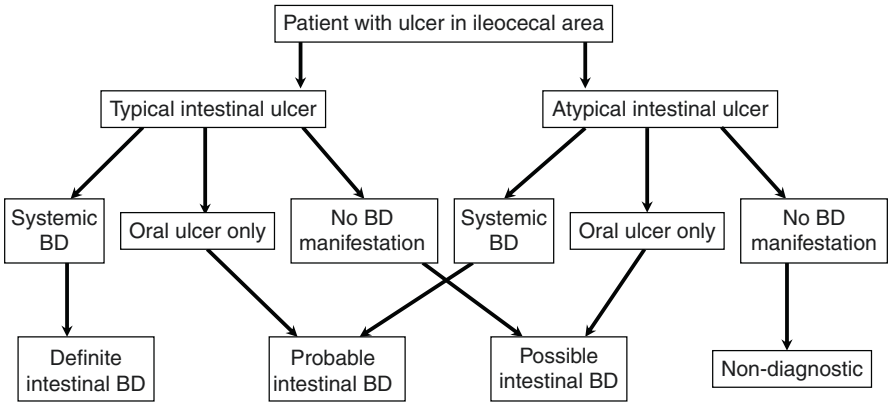

Fig. 10.1 Algorithm for the diagnosis of intestinal Behçet's disease (BD). Typical: large, ovoid, deep ulcers with discrete margins located in the ileocecal region. Atypical: several tiny, shallow aphthous ulcers. Adapted from Cheon et al. [55]

neuropsychiatric disorders, and epididymitis). Intestinal BD is characterized by the presence of deep and round punched-out ulcers, commonly in the ileocecal area. However, establishing a diagnosis of intestinal BD remains a challenge because not all patients with BD have "typical" ulcers at the time of endoscopy; this often leads to misdiagnosis. Against this background, Cheon et al. [55] proposed an algorithm for the diagnosis of intestinal BD (Fig. 10.1).

10.7 Differential Diagnosis

It is important to distinguish intestinal BD from infectious enterocolitis including tuberculosis, inflammatory bowel disease, and other diseases that cause gastrointestinal ulcers.

In particular, Crohn's disease (CD) often appears to be similar to intestinal BD. Both diseases commonly occur at a young age and have nonspecific gastrointestinal symptoms, similar extra-intestinal manifestations and complications, and disease courses that wax and wane over time [23]. CD is a chronic, relapsing, transmural inflammatory bowel disease, which often affects the entire gastrointestinal tract. Regarding the endoscopic findings in CD, typical irregular, longitudinal ulcers with a cobblestone appearance and aphthous lesions are common [39]. Strictures, fistulae, and abscesses are common complications in CD [23]. Additionally, Lee et al. reported differences between BD and CD: a round ulcer shape, focal distribution, the presence of fewer than six ulcers, the absence of aphthous lesions, and the lack of a cobblestone appearance are more commonly seen in BD than in CD [56].

In terms of clinical and endoscopic findings, intestinal tuberculosis (TB) is also a difficult disease to distinguish from intestinal BD. Patients with intestinal TB

Table 10.1 Differences among intestinal BD, Crohn's disease, and intestinal tuberculosis

	Crohn's disease	Intestinal tuberculosis	Intestinal BD
Onset age	Young age	High age	Age of 20–40
Spontaneous site	All digestive tracts	Duodenum, jejunum, ileum, and colon	Common at ileocecal area
Continuity	Segmental (skip lesion) or diffuse	Segmental	Segmental
Clinical course	Repeat relapse and remission	Primary infection in the intestinal or secondary to pulmonary tuberculosis	Repeat relapse and remission
Main symptoms	Diarrhea, melena, abdominal pain, fever, loss of body weight, general fatigue	Diarrhea, abdominal pain, melena	Diarrhea, nausea, melena, abdominal pain
Intestinal complications	Perianal fistula, abscess, stenosis, perforation, malnutrition	Stenosis, fistula, perforation	Perforation Perianal fistula and abscess are less common but possible
Endoscopic findings	Irregular, longitudinal ulcers with cobblestone appearance may have aphthous lesions	Annular or band-like, stenosis or ulcer	Round- or oval-shaped, punched-out lesions with discrete margins, >1 cm, focal distribution, <5 ulcers No aphthous lesions
Histopathology	Noncaseating epithelioid granuloma	Caseating granulomas, circumferential inflammation	Nonspecific neutrophilic or lymphocytic phlebitis with or without aortitis

BD Behçet's disease

often complain of fever, intermittent tight lower abdominal pain, and weight loss [24]. T-SPOT.TB, an interferon-γ release assay for detecting *Mycobacterium tuberculosis* infection, is useful for diagnosing intestinal TB [57]. Although the sites of ulcers can overlap between intestinal BD and intestinal TB, their treatments are completely different [58]. Biopsies obtained during endoscopy for culture and polymerase chain reaction testing for *M. tuberculosis* can help to make the appropriate diagnosis [23]. Table 10.1 demonstrates the key differences among intestinal BD, CD, and intestinal TB [39, 56, 59–61].

10.8 Treatment

At present, there are no established guidelines for the treatment of intestinal BD, so previous experience obtained from treating CD has been applied to BD [62]. Sulfasalazine (1–4 g/day) and 5-aminosalicylates (5-ASAs) (2–4 g/day) are often

used on patients with intestinal BD, similar to the case in CD [63]. However, 5-ASAs should be used to treat intestinal BD if it is evaluated as mild [63].

Glucocorticoids (GCs) are the main group of agents used to treat not only intestinal BD but also systemic BD [63]. The dosage of oral GCs depends on the severity of the lesion and ranges from 0.5 to 1.0 mg/kg prednisolone per day for 1–2 weeks, followed by tapering of 5 mg weekly until discontinuation [64]. Patients with high activity and who have been hospitalized often require intravenous methylprednisolone therapy [23]. It was proposed that intravenous methylprednisolone therapy of 1 g/day be administered, followed by the tapering of oral prednisolone [65]. However, monoclonal antibody or immunosuppressive agents are required for patients who are steroid-dependent or steroid-resistant.

Some case reports of the use of tumor necrosis factor (TNF) inhibitors against intestinal BD have been published [66, 67]. Recently, it was described in a Japanese case report that infliximab (IFX), a chimeric monoclonal antibody against TNF-α, was administered to patients with active intestinal BD; the effective rate 10 weeks later and the clinical remission rate were 80% and 53%, respectively [68]. Intestinal BD was also successfully treated with adalimumab (ADA), a fully humanized IgG1 monoclonal antibody that binds to TNF-α [69]. Clinical trials of ADA for intestinal BD were performed in Japan, and the complete remission rate and remarkable remission rate at 24 weeks after administration were 20% and 45%, respectively [70].

Azathioprine (AZA) is often used for patients with steroid-dependent cases. Treatment with AZA is begun at 25–50 mg/day, after testing for mutations in the gene encoding thiopurine methyltransferase, with gradual titration every 2–4 weeks to 2.0–2.5 mg/kg [64]. In addition, AZA can be used for the maintenance therapy of intestinal BD patients who have achieved remission after IFX or ADA therapy [71].

Patients with severe abdominal pain, persistent bleeding, or perforation may require surgery [23]. Other indications for surgery include fistulae, obstruction, abdominal mass, and failure to respond to medical therapy [72].

10.9 Prognosis

Although it was believed that the prognosis of intestinal BD is worse than that of CD, a recent retrospective study showed no difference in the cumulative probability of disease-dependent surgery and hospitalization [59]. However, despite the lack of a significant long-term difference in outcome in comparison with that in CD, surgical rates in intestinal BD are high [73].

Poor prognostic factors of intestinal BD include young age, “volcano-shaped” ulcers, high levels of CRP, a history of postoperative GC therapy, and the presence of intestinal perforation among the pathological findings [72, 74]. Cases of mortality

due to intestinal BD are uncommon because disease-specific mortality in BD is mainly due to vessel disease or neurological involvement [75].

10.10 Case Presentation

10.10.1 Case 1: Intestinal BD Treated with IFX

A 34-year-old female was admitted to our department for fever, arthralgia, and oral aphthous ulcers. Laboratory findings showed positivity for HLA-A24, but B51 was negative. Upper endoscopy was undertaken and a "volcano-like" ulcer was found in the middle esophagus (Fig. 10.2a). Colonoscopy also showed

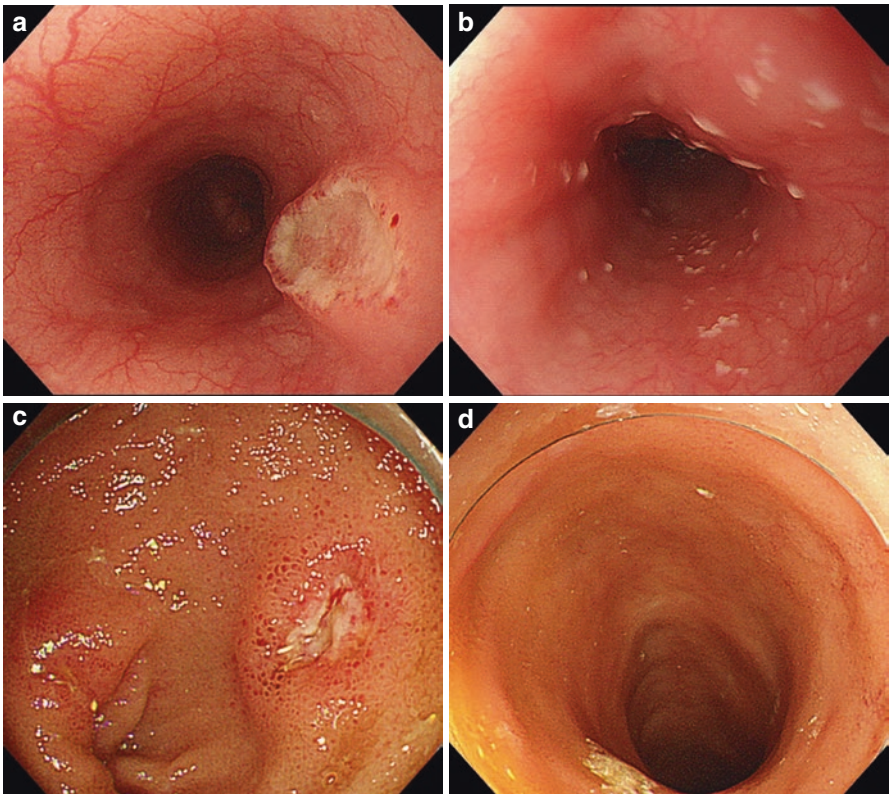

Fig. 10.2 Upper endoscopy and colonoscopy findings treated with infliximab (IFX). (**a**) "Volcano-like" ulcer at the middle esophagus. (**b**) Small, multiple punched-out ulcers at the terminal ileum. (**c**) The same lesion at the esophagus after IFX therapy. (**d**) The same lesion at the terminal ileum after IFX therapy

multiple small ulcers at the terminal ileum (Fig. 10.2b). The patient was diagnosed with intestinal BD and treated with IFX. After IFX therapy, the ulcers at the esophagus and ileum disappeared (Fig. 10.2c, d).

10.10.2 Case 2: Intestinal BD Treated with ADA

A 46-year-old female was referred to our hospital for acne-like papules, oral aphthous ulcers, and melena. Laboratory data showed positivity for HLA-B51. Colonoscopy showed a large ulcer at the cecum (Fig. 10.3a) and terminal ileum (Fig. 10.3b). Subcutaneous injection therapy of ADA was administered. After 4 months of this therapy, the ulcers at the cecum had completely disappeared (Fig. 10.3c, d).

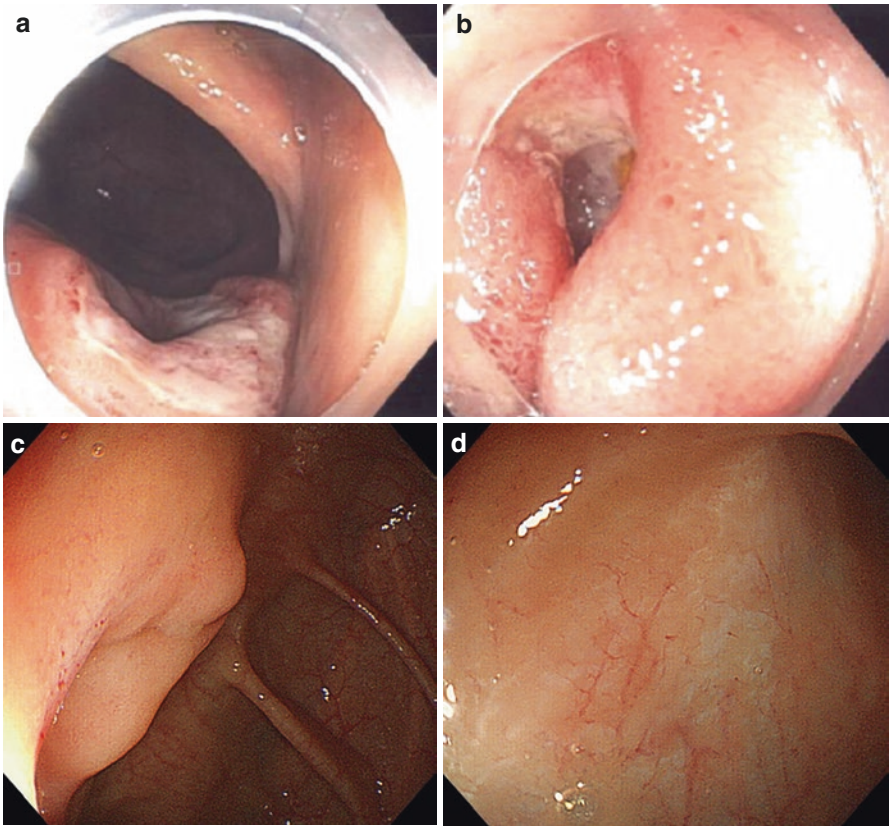

Fig. 10.3 Colonoscopy findings of intestinal Behçet's disease treated with adalimumab (ADA). (**a**) Large oval ulcers at the cecum and (**b**) edematous mucosa of the terminal ileum with punched-out ulcers, before ADA therapy. After ADA therapy, the ulcers disappeared, leaving only scars (**c**, **d**)

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Chapter 11
Gastrointestinal Involvement in IgG4-Related Disease

Mitsuru Sugimoto, Erina Suzuki, Kazuhiro Tasaki, Yuko Hashimoto, and Hiromasa Ohira

Abstract IgG4-related disease (IgG4-RD) is characterized by increased serum IgG4 and swelling of several organs or nodules by infiltration of IgG4-positive plasma cells and lymphocytes, as well as fibrosis observed throughout the body. In the gastrointestinal area, autoimmune pancreatitis (AIP) and IgG4-related sclerosing cholangitis (IgG4-SC) are primarily observed. In 2010, the International Consensus Diagnostic Criteria (ICDC) for AIP were proposed, and in 2012, clinical diagnostic criteria for IgG4-SC were proposed. Nevertheless, the aetiology of IgG4-RD remains unknown, and histological diagnosis of gastrointestinal IgG4-RD remains difficult. Differentiation between gastrointestinal IgG4-RD and malignant pancreaticobiliary diseases is difficult. Steroids have become the established therapy for IgG4-RD; however, predictive relapse factors are controversial. In this chapter, we introduce the history, diagnosis and treatment of gastrointestinal IgG4-RD, as well as several challenges to ameliorating the difficulties mentioned above.

Keywords IgG4-related disease · Autoimmune pancreatitis · IgG4-related sclerosing cholangitis

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11.1 Introduction

IgG4-related disease (IgG4-RD) was first reported by Suzuki et al. in 1993 [1]. IgG4-RD is characterized by increased serum IgG4 accompanied by swelling of several organs or nodules infiltrated by IgG4-positive plasma cells and lymphocytes, and fibroses are observed throughout the body [2, 3]. IgG4-RD is a multiple organ disorder, including retroperitoneal fibrosis [4, 5], Riedel's thyroiditis [6], tubulointerstitial nephritis [7–9], Mukulicz's disease [10, 11] and Küttner's tumour [12–16]. In the gastroenterological field, autoimmune pancreatitis (AIP) [17, 18] and IgG4-related sclerosing cholangitis (IgG4-SC) [19–21] are primarily observed.

11.2 Aetiology

IgG4-RD has been increasingly reported; however, the causes of IgG4-RD and the role of IgG4 remain unknown. Regarding AIP and Mukulicz's disease, several mechanisms have been predicted. Okazaki et al. have hypothesized that IgG4 is related to regulatory T cells and interleukin-10; thus, IgG4-RD is established through several processes [22]. Hubers et al. reported the detection of annexin A11 (a calcium-dependent phospholipid-binding protein)-specific IgG4 and IgG1 in the serum of IgG4-RD patients [23]. In that study, IgG4 was reported to play an anti-inflammatory role, preventing IgG1-mediated proinflammatory autoreactivity against annexin A11 in IgG4-RD patients. On the other hand, in 2018, Shiokawa et al. identified laminin-511 as a target antigen in AIP patients [24]. In that report, anti-laminin-511-E8 IgG (a truncated form of laminin-511) was observed in 26 of 51 AIP patients (51.0%); however, IgG was observed in only 2 of 122 controls (1.6%).

In addition, a relationship between complement and IgG4-RD has been reported. Originally, IgG4 was reported not to bind C1q and not to activate the classical complement pathway [25–28]. However, it was reported that hypocomplementemia was observed in some IgG4-RD. Muraki et al. reported 44 AIP patients, 36% of whom showed low C3 and C4 and 17% of whom showed low CH50 [29]. Kawano et al. reported 41 IgG4-related kidney disease patients, 22 of whom showed hypocomplementemia and 16 of whom showed low C3, C4 and CH50 [9]. In regard to this finding, Muraki et al. reported that IgG1 immune complex (IC) activated the classical complement pathway in AIP patients [29]. In that report, AIP patients were divided into two groups according to the value of circulating IC binding C1q. The high circulating IC group showed lower C4 and lower IgG1. Sugimoto and Watanabe et al. proved that IgG4 IC of IgG4-RD patients with hypocomplementemia connected C1q and the IgG4 IC-activated classical complement pathway [30]. Subsequently, Konno and Watanabe et al. reported that fucosylation of IgG4 may be related to complement activation in IgG4-RD patients with hypocomplementemia [31]. In IgG4-RD patients with hypocomplementemia, complement activation may be related to pathology.

11.3 AIP

11.3.1 History of AIP

AIP was defined by Yoshida et al. as pancreatitis caused by pancreatic swelling, irregular narrowing of the pancreatic duct, or infiltration and fibrillation of lymphocytes, with such events related to autoimmune mechanisms [32]. Hamano et al. reported rising levels of serum IgG4 in patients with AIP [17]. The 2010 International Consensus Diagnostic Criteria (ICDC) for AIP defined pancreatitis as "type 1" when there was elevated serum IgG4, other organ involvement was present and lymphoplasmacytic sclerosing pancreatitis (LPSP) was the histological characteristic; "type 2" was defined when elevated serum IgG4 was not present, and symptoms accompanying inflammatory bowel disease, idiopathic duct-centric chronic pancreatitis (IDCP) or granulocytic epithelial lesion (GEL) were the distinguishing histological characteristics [33]. AIP type 1 is IgG4-RD; therefore, here, we treat AIP type 1 as "AIP".

11.3.2 Diagnoses of AIP

The ICDC are shown in Tables 11.1 and 11.2 [33]. AIP is diagnosed according to the criteria (Table 11.2) using level 1 or level 2 findings (Table 11.1). We showed a representative AIP patient who was diagnosed by endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) (Fig. 11.1).

Table 11.1 Level 1 and level 2 criteria for AIP type 1 (quoted from [33])

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical:	Indeterminate (including atypical):
		Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
		Multiple strictures without marked upstream dilatation	
S	Serology	IgG4 >2 × upper limit of normal value a or b	IgG4 >1–2 × upper limit of normal value a or b
O	Other organ involvement	(a) Histology of extrapancreatic organs	(a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct

(continued)

Table 11.1 (continued)

	Criterion	Level 1	Level 2
		Any three of the following:	Both of the following:
		(1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	(1) Marked lymphoplasmacytic infiltration without granulocytic infiltration
		(2) Storiform fibrosis	(2) Abundant (>10 cells/HPF) IgG4-positive cells
		(3) Obliterative phlebitis	
		(4) Abundant (>10 cells/HPF) IgG4-positive cells	
		(b) Typical radiological evidence	(b) Physical or radiological evidence
		At least one of the following:	At least one of the following:
		(1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture	(1) Symmetrically enlarged salivary/lachrymal glands
		(2) Retroperitoneal fibrosis	(2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection)	LPSP (core biopsy)
		At least three of the following:	Any two of the following:
		(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
		(2) Obliterative phlebitis	(2) Obliterative phlebitis
		(3) Storiform fibrosis	(3) Storiform fibrosis
		(4) Abundant (>10 cells/HPF) IgG4-positive cells	(4) Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)		Diagnostic steroid trial	
		Rapid (≤2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

Table 11.2 Diagnosis of definitive and probable AIP type 1 (quoted from [33])

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI + Rt

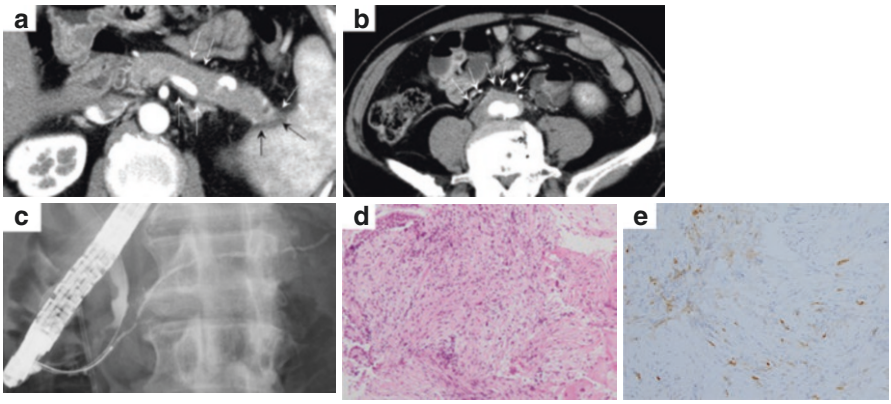

Fig. 11.1 A case of autoimmune pancreatitis. A 65-year-old man had elevated serum IgG4 (212 mg/dL). He underwent endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), and he was diagnosed with lymphoplasmacytic sclerosing pancreatitis. (**a**) Abdominal CT: diffuse pancreatic swelling with capsule-like rim sign (arrow) was observed. (**b**) Abdominal CT: retroperitoneal fibrosis (arrow) was seen. (**c**) ERP: full length of main pancreatic duct became thinner. (**d**) Specimen acquired by EUS-FNA (HE ×200): storiform fibrosis with inflammatory cells was observed. (**e**) Specimen acquired by EUS-FNA (IgG4 ×200): IgG4-positive plasma cells were observed

11.3.2.1 Imaging Diagnoses

Contrast-enhanced CT is useful for diagnosing AIP. AIP appears as diffuse pancreatic swelling with a capsule-like rim sign (Fig. 11.1a) [34]. The capsule-like rim sign is membranous structure surrounding the swollen pancreatic part and is efficient for distinguishing AIP from pancreatic cancer [35–37]. The CT findings of AIP include many things, including sausage-like appearance, delayed homogeneous enhancement, capsule-like rim, irregular narrowing of the main pancreatic duct, dotted enhancement, duct penetrating sign, enhanced duct sign, absence of biliary duct or pancreatic duct dilatation and low-attenuation halo [35–38]. The combination of these findings contributes to distinguishing AIP from pancreatic cancer. In addition, Sun et al. reported that CT attenuation values were useful for diagnosing AIP [35].

On MRI, AIP appears as low-intensity (T1-weighted image) diffuse or focal pancreatic swelling [39]; however, this is not characteristic for AIP. A capsule-like rim sign could be recognized in AIP patients on MRI [40–42]. Diffusion-weighted MRI was reported as useful for distinguishing AIP from pancreatic cancer [43–47]. Concise evaluation of pancreatic duct is reported to be difficult by magnetic resonance cholangiopancreatography (MRCP); therefore, the pancreatic duct evaluation by MRCP is not involved in ICDC [33]. Nevertheless, several recent reports described the efficacy of MRCP for evaluating the main pancreatic duct of AIP [42, 48–50]. In some of these

reports, 3T MRI and three-dimensional MRCP were used; therefore, it is hoped that the evaluation of pancreatic duct can be performed noninvasively with MRI machine improvement. In addition, it was reported that MRI was useful for observing pancreatic volume reduction after steroid therapy initiation as with CT [41].

Regarding FDG-PET, FDG accumulation was observed both in AIP and in pancreatic cancer [51–58]. Nevertheless, it was useful for detecting extra pancreatic lesions of AIP [52–54, 57–60]. In addition, FDG-PET was useful for differentiating AIP from pancreatic cancer by several findings using SUV_{max} [52, 53]. FDG accumulation disappears after steroid therapy [59–61].

Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) is used to differentiate AIP from pancreatic cancer. In CH-EUS, AIP appears as a homogeneous hyper- to iso-enhancement lesion, while pancreatic cancer appears as a heterogeneous hypo-enhanced lesion [62, 63]. In addition, time-intensity curve or eFLOW colour mode using CH-EUS was reported to be useful to distinguish between AIP and pancreatic cancer [64, 65].

In endoscopic retrograde cholangiopancreatography (ERCP) in AIP patients, long irregular pancreatic duct strictures without marked upstream dilatation were observed (Fig. 11.1c) [32, 66]. In typical AIP cases, the stricture reaches >1/3 length of the main pancreatic duct [66–70]. In AIP cases with focal pancreatic ductal strictures, the distinction from pancreatic cancer should be made carefully. The presence of multiple skip strictures is effective for distinguishing AIP from pancreatic cancer [68–72]. In addition, Iwasaki et al. have reported that the main pancreatic duct and central bile duct adjacent to the major papilla are useful for diagnosing AIP on ERCP [73].

11.3.2.2 Histological Diagnoses

AIP can be diagnosed by imaging and elevated serum IgG4 or by other methods. However, histological diagnosis of AIP requires level 1 findings of histology of the pancreas. Apart from surgical biopsy, EUS-FNA is the only method used to histologically diagnose AIP. Nevertheless, it is very difficult to obtain a sufficient amount of specimen. Mizuno et al. reported that 50% of AIP patients were diagnosed with LPSP using EUS Tru-Cut biopsy needles [74]. Iwashita et al. reported that performing EUS-FNA with a 19-G needle resulted in diagnosis of AIP in 43% of cases [75], and Ishikawa et al. diagnosed LPSP in 9 of 47 AIP patients using a 22-G needle [76]. In a report by Kanno et al., level 1 and 2 histological findings were observed in 56% and 24% of AIP patients, respectively, by EUS-FNA using 22-G automated spring-loaded PowerShot needles [77]. However, Imai et al. could not histopathologically diagnose AIP using a 22-G needle [78]. Two multicentre studies found that the diagnosability of AIP by EUS-FNA was poor [79, 80]. In ICDC, EUS-FNA was recommended for ruling out malignancy before diagnostic steroid trial [33]. In fact, Sugimoto et al.

reported that clinical characteristics of pancreatic cancer differed from those of AIP and EUS-FNA can be used to rule out malignancy in AIP patients [81]. Recently, the efficacy of EUS-FNA using 22-G SharkCore needle was reported for diagnosis of AIP [82, 83]. Future improvements in AIP diagnosability by EUS-FNA using the new needle are desired.

11.3.3 Treatment of AIP

11.3.3.1 Spontaneous Remission

An international consensus for the treatment of AIP was proposed by the International Association of Pancreatology [84]. Steroid therapy is the standard treatment for AIP patients [85]. However, spontaneous remissions were shown in some AIP patients without steroid treatment [85–93]. In 2018, Kubota et al. reported a multicentre study of AIP patients without steroid treatment [94]. In the report, relapse-free survival rates for AIP patients without steroid treatment were 89.4% within 3 years, 81.8% within 5 years and 50% within 10 years. New-onset diabetes mellitus and the presence of extensive multi-organ involvement were reported to be risk factors of relapse in AIP patients without steroid treatment. Thus, follow-up without steroids is appropriate in asymptomatic patients.

11.3.3.2 Initial Dose of Steroid Therapy

The initial dose of corticosteroid varied depending on the report (30–75 mg/day or 0.5 mg/kg/day) [17, 86, 95–100]. A multicentre study by Kamisawa et al. reported that the recommended initial oral prednisolone (PSL) dose was 0.6 mg/kg/day with gradual tapering after 2–4 weeks [87]. Steroid effects should be monitored by blood tests or imaging 1–2 weeks after starting steroid treatment [93].

11.3.3.3 Tapering of Steroids

The initial dose of steroid therapy should be continued for 2–4 weeks. The dose of PSL is tapered by 5–10 mg every 1–2 weeks until reaching a daily dosage of 20 mg [93], or the dose is tapered by 5 mg every 1–2 weeks for 2–3 months [101]. Tapering was monitored with blood tests (serum IgG or IgG4 levels and hepatobiliary enzyme) or imaging (US, CT, MRCP and ERCP). Another recommended regimen by international consensus is 40 mg/day for 4 weeks followed by taper by 5 mg/week until discontinuation [84].

11.3.3.4 Maintenance Therapy

Steroid therapy is standard treatment; however, relapse was reported in 10–53% of cases [85–87, 89, 91, 102, 103]. To prevent relapse of AIP, maintenance steroid therapy should be given. A retrospective Japanese multicentre study (n = 459) reported that 82% of AIP patients were given steroid maintenance therapy (2.5–7.5 mg/day) [87]. Wakabayashi et al. reported that the relapse rate in the maintenance group was lower than that of the non-maintenance group (23% vs. 33%, $p < 0.05$). In the Japanese consensus guidelines for AIP 2013, 2.5–7.5 mg/day glucocorticoid therapy for 3 years was recommended. After 3 years maintenance therapy, discontinuation of maintenance therapy should be considered with confirmation of radiological and serological improvement [93]. In 2017, Kubota et al. reported a Japanese multicentre analysis of 510 AIP patients. In that report, maintenance therapy at 5 mg/day for 2 (total 4625 mg) to 3 years (total 6425 mg) were recommended as effective and safe regimen to maintain the relapse rate <30%. Furthermore, Masamune et al. reported a randomized controlled trial of maintenance corticosteroid therapy. In that report, maintenance therapy consisted of PSL 5–7.5 mg/day, and it was continued for 3 years. It was reported that the relapse rate after 3 years was significantly lower in the maintenance group than in the cessation group.

From these reports, it appears that maintenance therapy is effective in some patients. Nevertheless, relapse occurs in some patients with maintenance steroid therapy. Maintenance therapy should be given with evaluation of disease activity by blood tests or imaging (CT, MRI, EUS).

11.3.3.5 Steroid Pulse Therapy

Steroid pulse therapy is effective for intestinal pneumonia, systemic lupus erythematosus and several autoimmune diseases, producing local immunosuppression after organ transplantation [104–106]. However, steroid pulse therapy has not become established therapy for AIP.

There have been few reports regarding steroid pulse therapy for AIP. Matsushita et al. reported weekly two courses of steroid pulse therapy (methylprednisolone (mPSL) 500 mg/day for 3 days) [107]. They suggested that steroid pulse therapy would be useful for improvement of lower biliary stricture in AIP without a long period drug tapering and that steroid pulse therapy would be useful for ruling out malignancy. If the pancreatic swelling was malignant, surgery could be performed without a long period of steroid tapering.

In 2011, Tomiyama et al. reported significant improvements of glycosylated haemoglobin at 7 months after steroid pulse therapy, in ALT at 2 and 8 weeks and in γ-GTP at 2 weeks after therapy [108]. In that report, the initial dose of mPSL was 500 mg/day for 3 days each week with 2 weekly courses, and oral 20 mg/day PSL with tapering was prescribed.

In 2015, Sugimoto et al. reported that steroid pulse therapy significantly reduced the relapse rate in AIP patients with diffuse pancreatic swelling [109]. In this report, the initial dose of mPSL was 125 or 250 mg/day, and oral 20 mg/day PSL with tapering was prescribed.

Though more future studies are needed, steroid pulse therapy without long period tapering could be useful for denying malignancy, and steroid pulse therapy followed with oral steroid therapy could contribute to the prognoses of AIP patients.

11.3.4 Predictive Risk Factors of AIP Relapse

Several predictive risk factors of AIP relapse have been described. In an international consensus on the treatment of AIP [84], continuous elevated serum IgG4 after steroid treatment [33, 87, 110], diffuse pancreatic swelling, existence of other organ involvement (OOI) including IgG4-SC with obstructive jaundice [87, 111, 112], re-elevation of serum IgG4 levels before relapse [87] and circulating immune complexes [113] were proposed. In 2016, Ohno et al. proposed that pancreatic volume >50 cm^3 after steroid treatment and a reduction of pancreatic volume of <35% before and after steroid treatment were significant steroid relapse factors [114]. Shimizu et al. reported that the rate of decrease of serum IgG4 level was a useful predictive factor of AIP relapse [115].

The predictive risk factors for AIP relapse remain unknown and require more studies in the future. However, the described factors should be noted in routine medical care of AIP.

11.4 IgG4-SC

11.4.1 History of IgG4-SC

IgG4-SC shows diffuse or focal strictures of intra- or extrahepatic biliary ducts with elevated serum IgG4 [17]. On histopathological findings, lymphoplasmacytic infiltration with fibrosis, IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis are observed [19, 116].

Historically, several reports of sclerosing cholangitis with OOI have been described over the last several decades. Waldram et al. reported two cases with chronic pancreatitis, sclerosing cholangitis and sicca complex in 1975 [117]. In 1979, Sjögren et al. described a case of primary sclerosing cholangitis (PSC) associated with fibrosis of the submandibular glands and pancreas [118]. In 1991, Kawaguchi et al. reported a variant of PSC with LPSP [119]. Subsequently, the disease was identified as atypical PSC that responded to steroid therapy and exhibited a better prognosis than typical PSC [99, 120, 121]. Currently, the sclerosing

cholangitis described above was recognized as IgG4-SC that was common in old men and was associated with other IgG4-RDs (AIP, retroperitoneal fibrosis and sialadenitis) [99, 120–127]. In an International Symposium on IgG4-RD held in Boston, Massachusetts, October 4–7, 2011, biliary lesions of IgG4-RD were proposed to be termed "IgG4-related sclerosing cholangitis" [128].

11.4.2 Diagnoses of IgG4-SC

In 2008, diagnostic criteria for IgG4-SC, HISORt criteria for IgG4-associated cholangitis (IAC), were proposed [123] (Table 11.3). In 2012, clinical diagnostic criteria for IgG4-SC were proposed in Japan [129] (Table 11.4). The criteria included (1) characteristic imaging of the biliary tract; (2) elevated serum IgG4; (3) OOI; and (4) characteristic histopathological findings. However, it is difficult to obtain sufficient biliary tract specimens of IgG4-SC by biopsy [21, 130]. Therefore, effectiveness of steroid therapy is an additional tool used to correctly diagnose IgG4-SC [131].

Table 11.3 Diagnostic criteria for IAC: HISORt criteria for IAC (quoted from [123])

Feature	Characteristics
Histology of bile duct	Lymphoplasmacytic sclerosing cholangitis on resection specimens (lymphoplasmacytic infiltrate with >10 IgG4-positive cells/hpf within and around bile ducts with associated obliterative phlebitis and storiform fibrosis)[a]
Imaging of bile duct	One or more strictures involving intrahepatic, proximal extrahepatic or intrahepatic bile ducts Fleeting/migrating biliary strictures
Serology	Increased levels of serum IgG4
Other organ involvement[b,c]	Pancreas: classic features of AIP on imaging or histology[d]; suggestive pancreatic imaging findings: focal pancreatic mass/enlargement without pancreatic duct dilatation, pancreatic atrophy Retroperitoneal fibrosis Renal lesions: single or multiple parenchymal low-attenuation lesions (round, wedge-shaped or diffuse patchy) Salivary/lacrimal gland enlargement
Response to steroid therapy	Normalization of liver enzyme levels of resolution of stricture[e]

[a]Bile duct biopsy specimen often do not provide sufficient tissue for a definitive diagnosis. In such specimens, IgG4 immunostaining showing >10 IgG4-positive cells/hpf is suggestive of IAC; however, the specificity of this finding is not known

[b]IgG4 immunostaining of involved organs show ≥10 IgG4-positive cell/hpf

[c]The presence of IBD suggests PSC rather than IAC; however, the absence of IBD does not help diagnose IAC in an individual patient

[d]Diffusely enlarged pancreas with delayed enhancement and capsule-like rim. Diffusely irregular, attenuated main pancreatic duct or multiple strictures or long stricture without upstream dilatation

[e]Complete resolution of stricture may not be seen in all patients, especially those early in the course of treatment (<6 weeks) or with predominantly fibrotic strictures

Table 11.4 Clinical diagnostic criteria IgG4-related sclerosing cholangitis 2012 (quoted from [129])

Diagnostic items
(1) Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
(2) Haematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL)
(3) Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis or IgG4-related retroperitoneal fibrosis
(4) Histopathological examination shows:
(a) Marked lymphocytic and plasmacyte infiltration and fibrosis
(b) Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
(c) Storiform fibrosis
(d) Obliterative phlebitis
Option: effectiveness of steroid therapy A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out
Diagnosis
Definite diagnosis
(1) + (3)
(1) + (2) + (4) a, b
(4) a, b, c
(4) a, b, d
Probable diagnosis
(1) + (2) + option
Possible diagnosis
(1) + (2)
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility

11.4.2.1 Biliary Tract Imaging

Although abdominal US, CT and MRI are useful for detecting the dilation or thickening of the bile duct, ERCP is needed to evaluate the bile duct precisely in IgG4-SC.

The characteristics of IgG4-SC imaging are divided into four types by stricture region [132] (Fig. 11.2). In a Japanese national survey of IgG4-SC in 2015, the frequency of each type was as follows: type 1, 64%; type 2a, 5%; type 2b, 8%; type 3, 10%; and type 4, 10% [133]. Furthermore, Mo et al. reported the localized intrahepatic IgG4-SC with mass-forming stricture and periductal-infiltrating subtypes [134]. It remains a matter of discussion as to whether type 1 IgG4-SC with stenosis in the lower common bile duct only should be involved in IgG4-SC or not. Lower common bile duct stricture is not frequently seen in

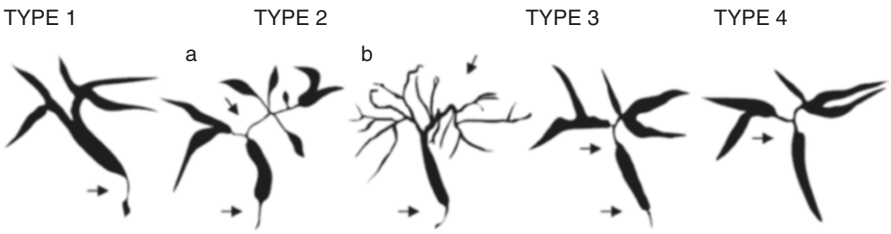

Fig. 11.2 Biliary stricture types of IgG4-related sclerosing cholangitis (quoted from [132]). TYPE 1: only lower common bile duct stricture is observed. TYPE 2: intrahepatic and extrahepatic bile ducts are stenosed. (*2a*) Extended stricture of intrahepatic bile ducts with dilation of upper stream bile ducts. (*2b*) Extended stricture of intrahepatic bile ducts without dilation of upper stream bile ducts and decreased number of bile duct branches. TYPE 3: stricture of both hilar bile duct and lower common bile duct. TYPE 4: only hilar biliary bile duct stricture

AIP patients with pancreatic body or tail swelling. As lower common bile duct stricture is frequently observed in AIP patients with pancreatic head swelling, it may be influenced by AIP [135]. In ICDC, only IgG4-SC with extrapancreatic bile duct stricture was determined as the OOI of AIP [33]. However, it was reported that characteristic IgG4-SC histological findings were observed in lower bile duct strictures [19]. Five cases of type 1 IgG4-SC without AIP were also reported [136].

Characteristic cholangiographic images differ between IgG4-SC and PSC. A pruned-tree appearance, band-like stricture, diverticulum-like outpouching and beaded appearance are observed in PSC [137]. On the other hand, dilatation after confluent stricture is observed in IgG4-RD. Bile duct strictures are comparatively long in IgG4-SC [138, 139].

Intraductal ultrasonography (IDUS) performed after ERC is reported to be useful for diagnosing IgG4-SC. The characteristics of IDUS in bile duct stricture of IgG4-SC were reported as appearing as homogeneous echoes, with symmetrical swelling of the entire circumference of the wall, with smooth inner and lateral margins. Furthermore, the same bile duct wall thickening was reported to be observed in the non-stenotic part of IgG4-SC [21, 140]. On the other hand, the characteristics of IDUS in bile duct strictures of bile duct cancer were reported to be heterogeneous echoes, with asymmetrical swelling of the entire circumference of wall and irregular lateral margins [21, 129, 141–145].

11.4.2.2 Elevated Serum IgG4

Elevated serum IgG4 (>135 mg/dL) is an IgG4-SC diagnostic criterion [17]. As many as 90% of IgG4-SC patients show elevated serum IgG4 (>135 mg/dL) [146, 147]. However, elevated serum IgG4 is observed in PSC of malignant cholangiopancreatic diseases [146–155]. Though the frequency of elevated serum IgG4 in PSC or bile duct cancer is lower than that of IgG4-SC, PSC or bile duct cancer should not be ruled out only by serum IgG4.

11.4.2.3 Coexistence of Other IgG4-Related Diseases

IgG4-SC is complicated by several IgG4-related diseases (sialadenitis, retroperitoneal fibrosis, kidney disease, lung disease, lymph node) [123–127, 133]. Among these, almost all IgG4-SC was associated with AIP [123, 133]. Inflammatory bowel diseases are usually complicated by PSC and are not usually complicated with IgG4-SC [156, 157].

11.4.2.4 Histopathological Examination

For diagnosis of IgG4-SC, bile duct biopsy is important to rule out bile duct cancer. In IgG4-SC, storiform fibrosis and obliterative phlebitis are observed, and lymphocytes and plasma cells infiltrate all layers of the biliary ductal wall, although not in the biliary ductal epithelium. Therefore, histologically proving IgG4-SC by biliary biopsy is very difficult [21, 130, 135, 158]. In 2018, Kato et al. reported that they diagnosed IgG4-SC from cholangiocarcinoma by FISH using biliary biopsy specimens [159]. In that report, no IgG4-SC patients were positive for malignancy by FISH. In some IgG4-SC patients with intrahepatic bile duct strictures, liver biopsy was reported to be useful for diagnosing IgG4-SC histologically [160–164]. On the other hand, Vater's papilla biopsy was reported as a supplemental diagnostic modality for IgG4-SC [165–167]. If infiltration of IgG4-positive plasma cells is seen in Vater's papilla specimen, the findings become helpful for diagnosing AIP and IgG4-SC.

In Fig. 11.3, a representative case diagnosed IgG4-SC is shown.

11.4.2.5 Response to Steroid Therapy

A steroid trial should be performed after all efforts to diagnose IgG4-SC or other IgG4-RD histologically, because malignant lesions advancing after steroid medication should be avoided. The improvement of IgG4-SC should be confirmed by any image (CT or MRCP or ERCP) and blood test 1 or 2 weeks after steroid treatment is initiated [108, 123, 129, 131, 168].

11.4.3 Treatment of IgG4-SC

As mentioned above, asymptomatic AIP patients could be followed up without steroids. However, steroid therapy should be given to IgG4-SC patients because most of them show liver functional failure or obstructive jaundice [101]. Therefore, biliary drainage should be performed before steroid therapy. At that time, investigating malignancy by biliary juice cytology or biliary biopsy should also be performed [85, 87, 93, 145, 169].

If the diagnosis of IgG4-SC is confident (e.g. if IgG4-SC is complicated by AIP and AIP has already been histologically diagnosed), steroid therapy without biliary drainage is efficient for biliary stenosis [131, 170].

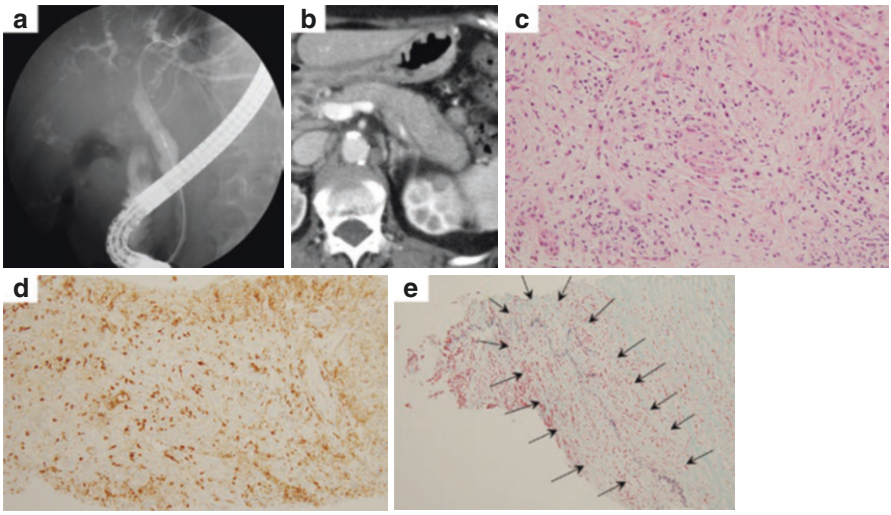

Fig. 11.3 A case of IgG4-related sclerosing cholangitis. An 84-year-old woman had elevated serum IgG4 (568 mg/dL) associated with autoimmune pancreatitis and biliary tract stenosis. (**a**) ERC: lower common bile duct and hilar biliary ducts strictures were observed. (**b**) Abdominal CT: pancreatic tail swollen with capsule-like rim sign. (**c**) Specimen acquired by EUS-FNA (HE ×400): storiform fibrosis with plasma cells was observed. (**d**) Specimen acquired by EUS-FNA (IgG4 ×200): IgG4-positive plasma cells were observed. (**e**) Specimen acquired by EUS-FNA (EM ×200): obliterative phlebitis was observed

The dose of steroid therapy is determined by the steroid therapy of AIP.

11.4.4 Relapse Factors for IgG4-SC

You et al. reported that extrapancreatic and multiple bile duct strictures, less frequent use of maintenance steroid therapy and thicker bile duct walls at initial morbidity were proposed relapse risk factors [110]. Liu et al. reported that multiple organ involvement was associated with poor response to initial steroid therapy [171]. Regarding relapse factors for IgG4-SC with AIP, please see Sect. 11.3.4. More attention should be paid to these relapse factors in routine medical care.

11.5 Conclusion

Recently, increasing data regarding the disease state and treatment of IgG4-RD have been reported. Nevertheless, histological diagnostic methods for AIP and IgG4-SC require more improvement, and the aetiology and predictive relapse factors are not well understood. It is hoped that future studies will clarify these difficulties.

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Chapter 12
Immunosuppressive Agents and Intestinal Involvement

Kyoko Katakura, Kiyoshi Migita, and Hiromasa Ohira

Abstract Infections, including opportunistic infections, are frequently encountered in clinical practice for rheumatic diseases; such infections represent important complications that can affect the prognosis for survival. While steroids, immunosuppressive agents, and other drugs used to treat them increase the risk of infections, the increased incidences of opportunistic infections associated with the use of biologics have recently been posing a grave concern. In the gastrointestinal tract, cytomegalovirus and candida infections are common and can sometimes be fatal; therefore, it is important that the physician engaged in clinical practice for rheumatic diseases endeavor to detect and treat such infections as early as possible and consistently be aware of complications.

Keywords Opportunistic infection · Cytomegalovirus infection · Candida infection · Steroid · Immunosuppressive agent · Biologics

12.1 Introduction

The onset of rheumatic diseases is underlain by autoimmune abnormalities, and it is also accompanied by functional abnormalities in immunocompetent cells responsible for infection immunity and decreased immune responses to pathogenic microorganisms; the overall incidence of infections is higher in patients

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with untreated rheumatoid arthritis or generalized lupus than in healthy persons. Regarding the actual status of infections in rheumatic disease patients, Falagas et al. reviewed 39 infection-related studies and reported that serious infections developed in 1592 (29%) of 5411 patients examined [1]. Infection risk factors include aging, leukocyte (neutrophil) count reductions, high disease activity, and respiratory and diabetic complications, and steroids, antirheumatic drugs, immunosuppressive agents, and the biologics used to treat them primarily also suppress normal immunity [2, 3]. Therefore, it is important that the attending physician should be fully aware of the associations with the use of these drugs. For example, if at least 95% of glucocorticoid receptors including T cells in living organisms are saturated by a large amount of steroid for a length of time, intense immunosuppression will be induced. In addition, cyclophosphamide, methotrexate, leflunomide, and other drugs suppress immunocompetent cells, such as activated T cells, by suppressing cell cycles; cyclosporin, tacrolimus, and other drugs function by controlling the transcription of IL-2; and TNF-α antibodies and the like promote cytokine neutralization. Furthermore, steroid-immunosuppressive agent combination therapies cause even more intensive immunosuppression, used in opportunistic infections, including tuberculosis, with bacteria, fungi, viruses, protozoans, parasites, and other organisms. Respiratory infections account for more than 50% of cases of infections in rheumatoid arthritis, with the next common sites being skin/soft tissues, gastrointestinal tract/abdominal cavity, urinary tract, and bones/joints [4]. Relatively common gastrointestinal opportunistic infections that can be aggravated to become severe conditions include cytomegalovirus (CMV) infections and candidiasis. In this paper, we overview points to note in the clinical care of these conditions and provide some case presentations. Intestinal tuberculosis is also outlined, bearing in mind that there have recently been increasing reports on extrapulmonary tuberculosis during TNF-α inhibitor treatment.

12.2 Cytomegalovirus Infections

While cytomegalovirus (CMV) occurs as an asymptomatic infection in approximately 90% of adult Japanese people, it can become reactivated in immunosuppressed states and result in a wide variety of organ and tissue disorders. Although CMV is distributed widely in the gastrointestinal tract, it commonly occurs in the large intestine, and it can also be found in the esophagus, stomach, and duodenum. The esophageal CMV lesions are accompanied by odynophagia and the large intestine CMV lesions, by abdominal pain, pyrexia, diarrhea, bloody stools, and other symptoms. The characterization of CMV ulceration is that the ulcer often exhibits a morphology with no surrounding elevation and the ulcer margin abruptly drops onto the ulcer base and is hence the term “punched-out ulcers.” Histologically, intranuclear

inclusion bodies are found in glandular epithelial cells, fibroblasts, and vascular endothelial cells. Because CRP elevations are not always present in the initial stage of CMV infection, a CMV antigenemia (CMV-Ag) method using an antibody against the 65-kd lower-matrix phosphoprotein (pp65), which is a CMV structural protein appearing in the early stage of CMV infection, is useful in diagnosing the disease. To establish the diagnosis of CMV gastroenteritis, it is necessary to take a biopsy from a gastrointestinal ulcer or erosion to demonstrate the presence of the virus in the tissue. It is treated with ganciclovir administered at a dose of 5 mg/kg twice a day for 14 days and then at a maintenance dose of 5 mg/kg in reference to CMV-Ag. This treatment necessitates dose adjustments in patients with impaired renal function.

12.2.1 Patient 1

A woman in her 60s, with rheumatoid arthritis onset at 40 years of age, had been treated with methotrexate and prednisolone 2.5 mg, also anti-TNF-α antibody therapy added 4 years before this admission.

In early February 2014, she experienced pharyngalgia and general malaise and was admitted to a nearby hospital. The lab results showed anemia and thrombocytopenia with a hemoglobin level of 8.8 g/dL and a platelet count of 21,000, as well as an increased inflammatory reaction with a CRP level of 10 mg/dL. The suspected diagnosis was disseminated intravascular coagulation (DIC), and thus she was treated with a protease inhibitor with methylprednisolone (250 mg for 3 days), and then the dose was tapered to prednisolone 30 mg. In late February, tarry stools occurred, and the Hb level decreased to 3.4 g/dL; she was transferred to our hospital for extensive examination and treatment. On admission, the CMV-Ag level was high at 202; thrombocytopenia due to cytomegalovirus infection was suspected, and ganciclovir was started at a dose of 500 mg. Upper gastrointestinal endoscopy detected many large circular punched-out ulcers in the gastric antrum (Fig. 12.1), and an ulcer biopsy revealed a positive test for CMV (Fig. 12.2). Melena was found to be attributable to bleeding from CMV infection ulcer, and anemia was ameliorated after treatment.

12.3 Candida Infections

Candidiasis is normally an endogenous infection with candida occurring commonly in the patient's oral cavity, gastrointestinal tract, vagina, skin, and other parts of the body. In immunosuppressed states associated with collagen disease treatment, esophageal candidiasis and deep candidiasis can develop, causing odynophagia and

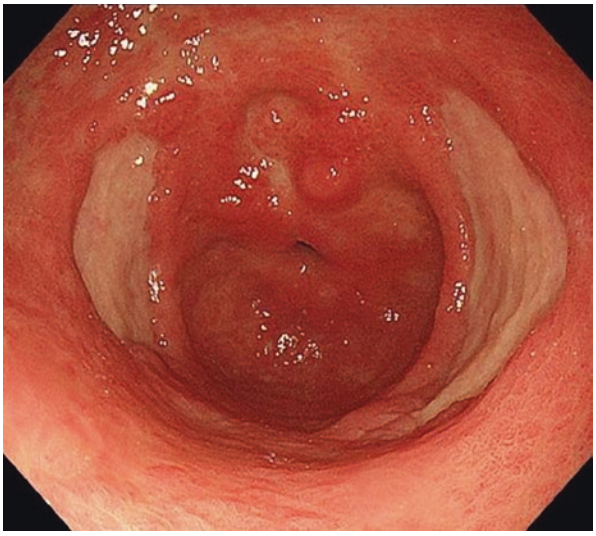

Fig. 12.1 Endoscopy of the stomach. Large clearly margined circular punched-out ulcers are seen in the anterior and posterior walls of the gastric antrum

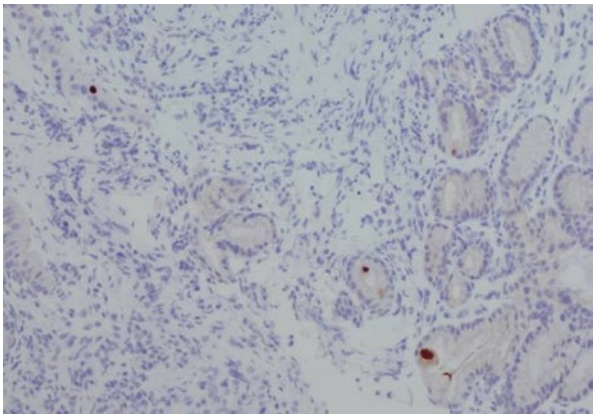

Fig. 12.2 Histopathology of the stomach. Immunological staining of a biopsy from the ulcer base shows the sporadic presence of CMV-positive cells

heartburn. It is known that immediately after steroid pulse therapy, systemic dissemination of fungal infections and acute exacerbation of fungal pneumonia are not rare. Therefore, if the presence of a white film on the tongue, or endoscopically observed gastrointestinal mycosis, or elevated serum β-D glucan levels is noted, administration of antifungal drugs such as itraconazole is desirable. In esophageal candidiasis, endoscopy reveals a millet to rice grain-size white film adhering to the esophagus sporadically or in the form of a band, which cannot be washed off.

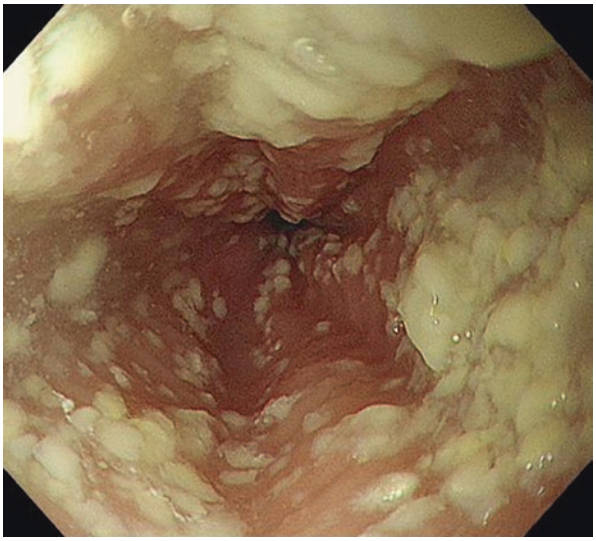

Fig. 12.3 Endoscopy of the esophagus. A thick, slightly elevated, longitudinally fused white film is seen adhering to the esophagus

Although the classification of Kodsi et al. [5] is used for the endoscopic classification, mucosal states are difficult to examine because of extensive coverage by a white film in severe cases. The oral cavity and esophagus can serve as entrances to the host in systemic infections with candida and other fungi, and early treatment initiation is desirable; therefore, for oral candidiasis if noted, treatment with amphotericin B gargling and swallowing is recommended.

12.3.1 Patient 2

A woman in her 60s, who had been diagnosed with dermatomyositis 12 years previously, experienced interstitial pneumonia and started treatment with prednisolone at a dose of 60 mg/day and cyclosporin at 100 mg/day. She experienced repeated recurrences and exacerbations upon steroid dose reductions, which were treated by a switch to steroid pulse therapy and tacrolimus; she was then followed up with Medrol 12 mg and tacrolimus 3 mg.

In early April of 2018, she experienced a strange sensation of the pharynx and epigastric pain and difficulty with oral food intake. Her serum albumin level was 2.1 g/dL, suggesting advanced undernutrition; thus, she was admitted to hospital in mid-May. Upper gastrointestinal endoscopy revealed a thick, slightly elevated, longitudinally fused, white film adhering to the esophagus (Fig. 12.3), showing a finding of candidal esophagitis. In addition, clearly margined circular punched-out

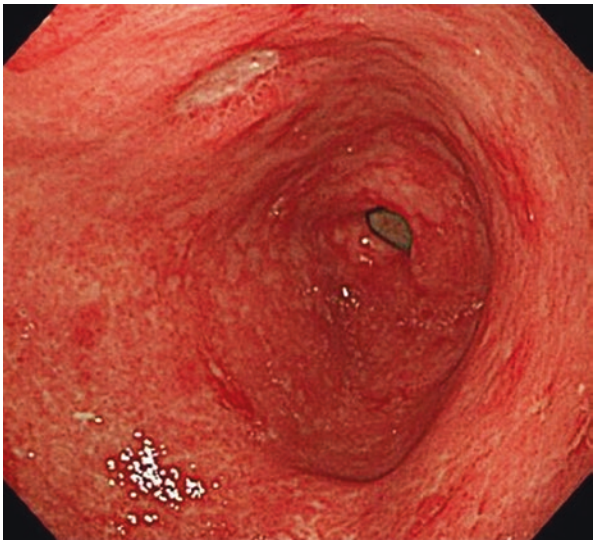

Fig. 12.4 Endoscopy of the stomach. Clearly margined circular punched-out ulcers are seen in the anterior wall of the gastric antrum

ulcers were found in the gastric antrum (Fig. 12.4), and an ulcer biopsy revealed a positive test for CMV. Oral miconazole was started, resulting in gradual amelioration of symptoms.

12.4 Intestinal Tuberculosis

Japan is ranked high in the incidence of tuberculosis among the developed countries; the incidence is more than two times higher, at 20.6 patients per 100,000 people in Japan, than in Europe and the United States (10 patients per 100,000 people). Since the use of TNF inhibitors for rheumatoid arthritis increases the risk of tuberculosis, importance should be placed on screening and prophylaxis when biologics are started. A majority of cases of onset of tuberculosis during TNF inhibitor treatment occur as a result of reactivation of latent tuberculosis infection. It is recommended that a comprehensive judgment be made based on interviews, tuberculin reactions, and interferon-gamma release assays (IGRAs), such as T-SPOT, chest radiography, CT scans, and other findings prior to the start of treatment, and that isoniazid be administered at a dose of 300 mg/day for 6–9 months starting 3 weeks before the start of treatment.

In typical tuberculosis infections, extrapulmonary tuberculosis accounts for not more than 20% of all cases affected; about 50% of patients with tuberculosis developing during TNF inhibitor treatment are affected by extrapulmonary tuberculosis [6], which includes intestinal tuberculosis. Although most cases of

intestinal tuberculosis are considered to be disseminated intraductally by sputum and swallowing containing *Mycobacterium tuberculosis*, the absence of active tuberculosis in the lungs is not rare. The most common site is the ileocecum, followed by the lower part of the jejunum and the ileum. Lesions originate from lymph follicles and form ulcers and can subsequently produce stenosis with the cure of ulcers, which may be accompanied by abdominal pain, diarrhea, abdominal distention, pyrexia, and other symptoms. It is diagnosed if one of the diagnostic criteria is met: (1) demonstration of *M. tuberculosis* or caseating granuloma by open biopsy, (2) demonstration of *M. tuberculosis* by biopsy tissue culture, (3) radiographic/endoscopic findings characteristic of intestinal tuberculosis and amelioration of the findings by antituberculotic therapy, and (4) demonstration of *M. tuberculosis*-specific genome by biopsy tissue PCR. As with pulmonary tuberculosis, the basic treatment comprises a 2-month course of 4-drug treatment with rifampicin, isoniazid, pyrazinamide, and streptomycin, followed by a 4-month course of 2-drug treatment with rifampicin and isoniazid, or a 3-drug treatment with these two drugs and ethambutol.

12.5 Conclusion

Since new biologics have been increasingly approved with indications of rheumatic diseases, countermeasures against opportunistic infections remain important. Since gastrointestinal lesions can help diagnose opportunistic infections and are sometimes fatal due to bleeding and perforations, they must be diagnosed quickly and accurately. To this end, a comprehensive understanding in this field is essential.

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