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Review

Inflammatory Bowel Disease and Primary Sclerosing Cholangitis

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Abstract

Primary sclerosing cholangitis is a progressive and chronic disease in which biliary tract damage develops with patchy inflammation, fibrosis, and destruction in the bile ducts. Inflammatory bowel disease is a chronic inflammatory disease which affects the gastrointestinal tract. Although it seems like 2 separate diseases, primary sclerosing cholangitis is mostly seen together with inflammatory bowel disease. Although it seems like two seperate diseases, PSC is mostly seen together with IBD. Many of the genes that genetically predispose to primary sclerosing cholangitis are also associated with ınflammatory bowel disease. The relationship between the development of primary sclerosing cholangitis and the gut, genetic predisposition, common immunity cells, and pathways suggested the relationship of these 2 disesases, although it cannot be clearly demonstrated. Because of this close relationship, primary sclerosing cholangitis should be considered when cholestatic enzyme elevation is present in patients with ulcerative colitis, and every patient diagnosed with primary sclerosing cholangitis should be screened for inflammatory bowel disease with colonoscopy and random biopsies, regardless of symptoms. Concomitant inflammatory bowel disease is often ulcerative colitis. Symptoms of the bowel are often milder than ulcerative colitis alone. The most important point in the co-existence of these 2 diseases is the increased risk of colon cancer. Patients should definitely undergo an annual colonoscopic control, and if possible, they should be evaluated with chromoendoscopy and random biopsies should be taken. If primary sclerosing cholangitis–inflammatory bowel disease patients had cancer, high-grade dysplasia, and unresectable low grade dysplasia (LGD), colectomy should be considered. It should be kept in mind that the risk of colon cancer continues even after liver transplantation, and annual screening should be continued.

Keywords: Inflammatory bowel disease, primary sclerosing cholangitis, ulcerative colitis

INFLAMMATORY BOWEL DISEASE AND PRIMARY SCLEROSING CHOLANGITIS

Inflammatory bowel disease (IBD) is a chronic inflammatory disease group that develops on the basis of genetic and environmental triggers and affects the gastrointestinal tract. The disease often presents with symptoms such as diarrhea, abdominal pain, weight loss, and sometimes bloody diarrhea. The main cause of the symptoms is inflammation. Ulcerative colitis (UC) is a chronic disease limited to colon involvement, starting from the rectum and making diffuse involvement limited to the mucosa only. Crohn's disease is a chronic disease that can affect all parts of the gastrointestinal tract from the mouth to anus, with patchy and full-thickness mucosal involvement. Extraintestinal manifestations such as fistula and rectal lesions often accompany Crohn's disease.[1] However, primary sclerosing cholangitis (PSC) is often accompanied by UC.

Primary sclerosing cholangitis is a progressive and chronic disease in which biliary tract damage develops with patchy inflammation, fibrosis, and destruction in the microscopic and macroscopic bile ducts. In the later stages of the disease, narrowing and dilation of the bile ducts occur, which causes cholestasis, cirrhosis, hepatic failure and its complications, and even cholangiocarcinoma.[2]

The adult human liver has approximately 2-3 km of bile ductules and ducts.[3] The microscopic bile ducts begin with bile canaliculi and Hering ducts (<20 µm) and finish with segmental canals (400-800 µm). The macroscopic biliary tract consists of the common hepatic duct formed by the union of the lober bile ducts, and Choledoch and Wirsung ducts. Bile acid production is a complex process involving hepatocyte and cholangiocytes. Bile production begins at the level of the bile canaliculus, the smallest branch of the biliary tract. Receptors and transport proteins along this pathway mediate the transport and regulation of bile.[4] In the pathogenesis of PSC, there is cholestasis that develops as a result of damage to this pathway in the bile ducts and hepatocytes. Primary sclerosing cholangitis usually develops from macroscopic bile ducts. The most common cause of extrahepatic cholestasis in the macroscopic bilayer tract is choledocholithiasis. In addition, benign bile ducts strictures, ischemic bile ducts strictures (after cholecystectomy and liver transplantation), chronic pancreatitis, pseudocysts, parasites (complicated hydatic cysts, fasciola, ascaris, etc), portal vein thrombosis (cavernos hemangiomas), biliary atresia, choledoc cysts, cancers (cholangiocarcinoma, periampullary tumors, and Hodgkin disease) may also be the cause.

Primary sclerosing cholangitis is a chronic, inflammatory, segmental, progressive, fibrotic biliary tract disease. It is often seen in men, in the third and fourth decades of life, and in patients with UC. The prevalence of the disease is 0.2-14 cases per 100, 000.[5]

The etiology and pathogenesis of PSC remain poorly understood. But PSC represents an ımmunologic reaction that develops in some people with a genetic predisposition who are exposed to environmental or toxic triggers, such as infection, drugs or another factor. The other theory of PSC

pathogenesis is that it should be together with IBD especially ulserative colitis. The relationship between the 2 diseases shows us that pathogenesis affects the intestinal tract and liver, as well as the role of nutrients, bile acids, immune cells, and microboata. In recent studies, over 20 risk genes have been identified for PSC.[6] The effect of these genes on the disease is currently 10%. The majority of identified loci of genes have been associated with UC and Crohn's disease. There are some conflicting theories of etiology. Primary sclerosing cholangitis, like other autoimmune diseases, causes destruction in the target tissue with specific antigens. However, immunosuppressive drugs are not effective in the treatment of the disease. In the histopathologic examinations, in addition to concentric fibrosis of cholangiocyte in the bile ducts (onion skin), which have a typical PSC, intense T lymphocyte, as well as macrophage and neutrophil accumulation draws attention.[7] Anti-neutrophil cytoplasmic antibodies (ANCA) which are frequently found in PSC suggest that B lymphocytes also have a role in the pathogenesis. The B lymphocytes are probably developing in response to antigens of gut origin.[8] Another issue is the progression of PSC even after colectomy. Studies have shown that adhesion molecules and chemokine receptors, which are normally found in the gut, are also found in PSC liver. It leads to the accumulation of the lymphocytes of intestinal origin.[9] In some mouse studies, it has been shown that, lipopolysaccaride and the other bacterial commonents trigger to innate immunity by passing into the portal circulation with the gut leakage and cause cholangiopathy like findings.[10] Human studies showing the effect of microbiota are still limited. Although genetic evidence and failure of UDCA using to prevent progression in some patient does not support a role for bile as an initiator of PSC, some evidence suggest that bile is important to progression in PSC. Bile is a complex structure containing bile acids, cholesterol, bilirubin, phospholipids, and various proteins. Any imbalance in this content can reduce bile fluidity, increase pressure, and cause harmful effects. In a healthy cholangiocyte, there are mechanisms to protect against the toxic effects of bile. The most important protective factor is the bicarbonate umbrella, which provides dilution and alkalinization with several channel systems in biliary epithelial cells.[11] The most important canal is cystic fibrosis transmembrane conductance regulator (CFTR). The TGR5 receptor in the biliary epithelium provides a protective bicarbonate layer by the regulation of the CFTR canal.[12] Since the disorder in the bile balance is thought to be the basis of the disease, the treatment target is also aimed at this step (e.g., UDCA). As a result of all these etiological factors, hypotheses, and genetic predisposition, the fibrosis process starts with the participation of hepatic stellate cells, portal myofibroblasts, and cholangiocytes. This biliary fibrosis is the reason for the typical histological findings of onion skin. Due to its progressive process, biliary tract strictures, liver cirrhosis and its complications, and cholangiocarcinoma can be observed during the setting of the disease.

CLINICAL, LABORATORY, AND IMAGING FEATURES

Primary Sclerosing Cholangitis and Inflammatory Bowel Disease

Primary sclerosing cholangitis and IBD are seen together in 60%-80% of patients. Inflammatory bowel disease presents earlier in patients with PSC than in those who do not have PSC. While ulserative colitis accompanies 80%, Crohn disease is seen less than 20% (13). Ulserative colitis often occurs before PSC, but in some patients; UC may develop even after PSC associated liver transplantation.

The colitis is usually pancolitis, but symptoms might be mild, often with no rectal bleeding and inflammation (rectal sparing), and characterized by prolonged remissions. Inflammation is seen more commonly in the right colon than in the left, and colon cancer in patients with IBD who also have PSC is typically right-sided.[14,15] In some patients, the terminal ileum is slightly inflamed (backwash ileitis), but by definition does not show features of Crohn's ileitis. In addition, PSC cases with proctocolectomy and ileo-anal pouch anastomosis have a higher frequency of pouchitis.[13]

Some asymptomatic IBD patients may have just histological changes and may develop colitis subsequently.[16] Therefore, endoscopic examination and random biopsies of colonic mucosa are recommended in all patients with a new diagnosis of PSC.

Symptoms and Physical Examination

Primary sclerosing cholangitis remains asymptomatic for a long time. Fifty percent of patients are found incidentally with routine laboratory tests. The most common symptoms at the time of presentation include pruritus, fatigue, jaundice, and pain. Some patients at the beginning of the disease may present with symptoms such as abdominal distension, confusion, clouding of consciousness, hematemesis, and dyspnea which are complications related to liver failure. The other symptoms are fever, vomiting, night sweats, and weight loss.[17]

Physical examination may be normal in asymptomatic PSC patients. The most common examination abnormalities include jaundice, splenomegaly, and excoriations resulting from pruritis. If there is an obliteration in the bile duct, we can examine abdominal pain of the right upper side and fever. As the liver disease progresses and cirrhosis develops, spider telangiectasias, edema, ascites, muscular atrophy, abdominal distension, and the other signs of advanced liver disease may appear.[17]

Laboratory Tests

Cholestatic enzyme elevation is seen at the forefront. It may be accompanied by elevated transaminases. When the elevation of transaminases is predominant, the association of autoimmune hepatitis should be considered. Bilirubin levels may be normal or fluctuate. In the case of cholangitis associated with stenosis, acute phase reactants elevation can be seen.

Prolonged prothrombin time and reduced albumin platelet level may reflect advanced liver disease and hepatic synthesis dysfunction.

The level of IgG4 may increase. The increase does not always suggest IgG4-related disease. However, if the level is more than 4 times the upper limit of normal, the diagnosis should be considered more as an Ig4-related disease.[18] Perinuclear ANCA are detected in 65-88% of patients.[19] Cancer antigen 19-9 (CA 19-9) elevation should not always suggest cholangiocarcinoma cancer, but it must be excluded.

Especially in ulserative colitis patients, if cholestatic enzym elevation is detected, they should be examined for PSC.

Imaging

Transabdominal ultrasound is rarely useful in the diagnosis of PSC but may be helpful in excluding other causes of biliary obstruction. The best imaging is cholangiography which by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) or percutaneous transhepatic cholangiography.[20] Endoscopic retrograde cholangiopancreatography is the gold standard method. But ERCP has some limitations, such as follows: it is invasive, is more expensive than MRI, and depends on user experience. So MRCP can be stated as more useful than ERCP. Multifocal annular

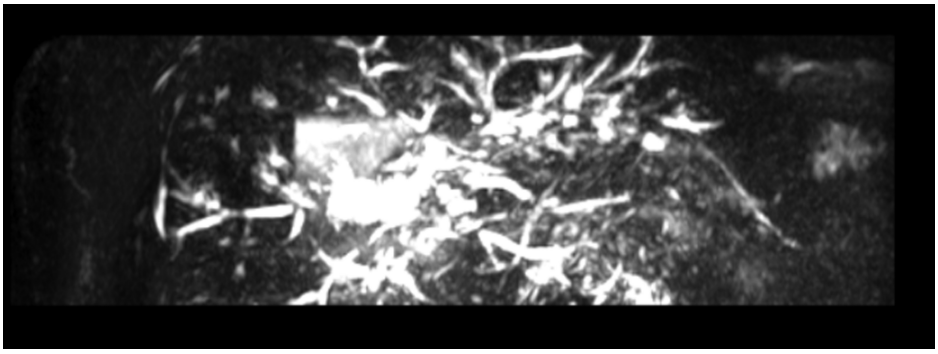

Figure 1. MR image of a patient with PSC (from Istanbul Medicine Faculty Hospital Gastroenterohepatology department archive, to be taken with the consent of the patient). PSC, primary sclerosing cholangitis.

narrowing and normal or dilated segments of intra/extrahepatic bile ducts is the classic imaging finding which is called "beaded appereance"[21] (Figure 1). Typically, there is diffuse involvement. However, more than 25% of patients have only intrahepatic disease.[22] Isolated involvement of the extrahepatic biliary tract is rarer.

Histology

With the development of imaging methods in PSC, the need for biopsy has decreased considerably. Now, apart from the diagnosis of small duct PSC, it is often used in the diagnosis of different diseases that show similar findings such as IgG4-related diseases and overlap syndromes.

Atypical histological findings such as bile duct proliferation, cholangioectasis, ductopenia, chronic inflammatory periportal changes, periportal inflammatory cells infiltrate, and varying degrees of fibrosis and cirrhosis are often seen in PSC. Periductal concentric fibrosis, called the "onion-skin," is a rare typical PSC histological image.[23]

Differential Diagnosis

If the patient with IBD has cholestatic enzyme elevation and typical cross-sectional imaging signs, the diagnosis is often PSC. Before the diagnosis, secondary sclerosing cholangitis causes must be excluded, especially in the absence of IBD. Infection disease and recurrent pyogenic cholangitis, immundeficiency related diseases, cholelithiasis, surgical bile duct trauma, hepatic allograft arteiral insufficiency especially after liver transplantation, chronic pancreatic, Ig-G4 releated disease, portal biliopathy, sarcoidosis, amiloidosis, hypereosinophilic syndrome, Caroli disease should be considered in the differantal diagnosis. More rarely, Langerhans cell histiocytosis, AIDS-related cholangiopathy, and cystic fibrosis cholangiopathy should be considered (Table 1). In addition, the most important in differential diagnosis is malignancies such as cholangiocarcinoma, ampullary, or pancreatic cancer.[5]

The IgG4-related disease can mimic PSC. The main diagnostic criterion is the histological demonstration of IgG4. Ig-G4 serum level higher than four times the upper limit of normal is also helpful for diagnosis. The IgG4-related disease is a fibro-inflammatory systemic disease. Since corticosteroids are the first choice for the treatment, they must be differentiated from PSC.[18]

In addition to all these differential diagnoses, PSC is also accompanied by some diseases. The overlap rate of autoimmune hepatitis (AIH)–PSC is 1.4%-17%.[24] Typically in these patients, in addition to radiologic imaging of PSC, there are elevated transaminases, autoantibody positivity such as anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), liver-kidney microsomal antibody-1 (LKM-1), and histological findings such as interface hepatitis supporting AIH. Due to the effect of steroid therapy, the prognosis of AIH–PSC overlap is better than only PSC.[24] So far, we have talked about the diseases that coexist with PSC. But PSC may be associated with other autoimmune diseases such as Sjogren, Hashimoto thyroiditis, type 1 diabetes mellitus, and autoimmune hemolytic anemia.

Natural History of Primary Sclerosing Cholangitis and Prognostic Models

The natural history of PSC is unpredictable and variable. It is often seen in men, in the third and fourth decades of life. The subclinical phase,

Table 1. Differential Diagnosis of PSC

Infection	Bacterial/parasitic cholangitis
	Recurrent pyogenic cholangitis
Immunodeficiency related	Congenital immunodeficiency
	Acquired immunodeficiency (e.g., HIV)
	Combined immunodeficiency
	Angioimmunoblastic lymphadenopathy
Mechanic/toxic	Cholelithiasis/choledocholithiasis
	Surgical bile duct trauma
	Intra-arterial chemotherapy
Ischemic	Vascular trauma
	Hepatic allograft arterial insufficiency
	Paroxysmal nocturnal hemoglobinuria
Pancreatic disease	Chronic pancreatitis
	IgG4-related systemic disease
Others	Cystic fibrosis cholangiopathy
	ABCB4-associated cholangiopathy
	Sclerosing cholangitis of critical illness
	Hypereosinophilic syndrome
	Sarcoidosis
	Graft-versus-host disease
	Amyloidosis
	Systemic mastocytosis
	Caroli's disease
	Congenital hepatic fibrosis
	Hodgkin's disease
	Cholangitis glandularis proliferans
	Neoplastic/metastatic disease
	Langerhans cell histiocytosis
	Hepatic allograft rejection

PSC, primary sclerosing cholangitis.

in which the disease is often asymptomatic, just has radiologic signs of disease, and laboratory tests are normal, takes a long time. The asymptomatic phase, in which laboratory tests are elevated, comes after the subclinical phase. After the symptomatic phase, in which symptoms such as pruritus, jaundice, fatigue, weight loss develop, the decompensated cirrhotic phase is seen in the final. Liver transplantation is only curative treatment in this stage. Liver transplantation is the only curative treatment in this stage. If IBD accompanies this whole process, although the clinical course is generally milder, intestinal activity is independent of the disease. Transplantation does not always solve problems completely. Acute cellular rejection, recurrence of the disease, and exacerbation of IBD with cytomegalovirus (CMV) or other infection diseases are among the post-transplant problems.[25]

In general, elder ages of diagnosis, male gender, especially co-existence of UC, and large duct PSC are associated with poor prognosis. These kinds of patients may need transplantation at early age. Small duct PSC is a histologically diagnosed form despite normal cross-sectional imaging. Although PSC is considered in IBD patients, even if the cross-sectional tests are normal, small duct PSC should be excluded by biopsy.[26] Small duct PSC has a better prognosis than classic PSC.

Several prognostic systems have been developed for PSC. The most useful one is the revised Mayo criteria that include age; bilirubin, albumin, and aspartat aminotransferas (AST) levels; and variceal bleeding.[27] This scoring system is used for transplantation time decisions and trials rather than clinical follow-up. The Child–Pugh classification system may also be used to determine survival in PSC patients. The 7-year survival rate of PSC patients with Child A, B, and C cirrhosis is 89.8%, 68%, and 24.9%, respectively. Some evidence suggests that the revised Mayo score might be better in early-stage disease than the Child-Pugh score.[28]

Complications

Cholestasis: In fact, cholestasis may be considered in the pathogenesis of the disease rather than a complication of this disease. But the major cause of pruritis is cholestasis. The accumulation of bile acids in blood and tissue is a potential cause of pruritis.[29] Impaired conjugation of bile acids can also impair the absorption of fat-soluble vitamins (A, D, E, and K). Some problems such as vision and bone-mineral pathologies associated with vitamin deficiencies can occur.[30]

Biliary Stones and Bacterial Cholangitis: Bilirubin pigment stones are seen more frequently in PSC patients than in the normal population. Biliary stasis and strictures may also facilitate this situation. Bacterial cholangitis is a common complication of PSC. If patient had previous biliary instrumentation or stricture, risk of bacterial cholangitis is more higher than non-stricture and non-instrumentation PSC.[31] Previous ERCP and stenting constitute the most important risk factors. The other risk factor is portal bacteremia of active colitis in UC patients.[32] Biliary infection is often polymicrobial. The most commonly isolated microorganisms are *Escherichia coli*, *Klebsiella*, *Enterococcus*, *Pseudomonas*, etc. A common first-line antibiotic for mild episodes is ciprofloxacin. More severe cases are usually treated with a combination of intravenous third-generation cephalosporin and anaerobic-affected antibiotics.[33] Before using antibiotics, blood cultures and, if possible, bile cultures should be taken. Patient with dominant stricture and severe cholangitis require urgent biliary decompression with ERCP. If ERCP is not performed, the death rate will be higher.

Cirrhosis, Portal Hypertension, and Liver Failure: In the later stages of the disease, portal hypertension, chronic liver disease, and related complications such as ascites, variceal bleeding, and hepatic encephalopathy may develop.

Cholangiocarcinoma: Cholangiocarcinoma develops from the biliary epithelium. The prevalence of cholangiocarcinoma is between 5% and 7% over the patients' lifetime. In half of the cases, cancer development occurs within the first year after the diagnosis.[2] While the risk of cholangiocarcinoma is low in small duct PSC, the risk increases in the presence of dominant stricture.[34] It often develops from the common hepatic duct and perihilar region.[35] Most cases are unresectable, and no effective treatments are available when cholangiocarcinoma is diagnosed. Therefore, the combination of MRCP and serum CA 19-9 is very important in screening and surveillance. Positron Emission Tomography (PET) is not routinely recommended. When cancer is suspected, ERCP-based brush cytology, biopsy, and fluorescence in situ hybridization should be used for diagnosis.[36] Liver transplantation is not preferred in these patients because of the poor prognosis and frequent recurrence.[37]

Colon Cancer: Since the coexistence of PSC and UC, the frequency of colorectal cancer increases approximately 4 times, compared to UC alone.[38] The risk of colorectal cancer in Crohn's disease–PSC is not as high as UC–PSC. But colorectal cancer risk increases with Crohn's disease.[39] Cancers are more commonly right sided than left sided.[38] Colonoscopic screening should be performed at the time of diagnosis of PSC. In case of IBD, it should be done with annual colonoscopic examination and even chromoendoscopy, if possible. Even if the patient has liver transplantation, screening should be continued as the risk continues.[40] Indications for colectomy in PSC–IBD patients include cancer, high-grade dysplasia, and unresectable LGD.[41] Even if there is ileo-anal anastomosis, annual colonoscopic examination should be continued for the risk of malignancy in the pouch.[42]

The Other Cancers: Patients with PSC have an increased risk of gallbladder cancer and hepatocellular cancer (HCC) in cirrhosis. The recommendation is screening with ultrasound annually for gallbladder cancer and with serum alpha fetoprotein (AFP) level and MRI for HCC. Cholecystectomy has been recommended if gallbladder polyps are greater than 0.8 cm.[43]

Treatment

Medical Management: No medical treatment has been shown to reduce disease-free survival and the need for transplantation definitively. The most studied hydrophilic bile acid, UDCA, although it reduces the progression in other biliary tract diseases such as PBC, its effect in PSC has not been clearly demonstrated.[44] Immunosuppressive therapy such as prednisolon, azathioprine, budesonid, tacrolimus, mycophenolate mofetil, has not shown to improvement in classic disease. The combination of UDCA and metronidazole has shown an improvement in liver blood tests but not in disease progression.[45]

Treatment of pruritis is another important issue in this disease. First-line therapy is anion-exchange resins such as cholestyramine, colestipol, or colesevelam.[46] Rifampin and sertraline are the other safe and effective alternatives.

Endoscopic Management: In 1 study, it was shown that the dominant stricture would cause stenosis in 53% of patients at a 5-year follow-up. Before starting the treatment, let us look at what a dominant stricture means. It is a narrowing to less than 1.5 mm in the common bile duct or less than 1 mm in the right and left hepatic ducts.[47] The dominant

stricture prevalence in PSC is 36%-50%.[36,47] The prognosis of PSC with dominant stricture is worse than PSC without stricture. If a patient has a dominant stricture in PSC, ERCP with brush cytology or biopsy should be used to diagnose the process of differentiating benign from malignant strictures. If a patient has symptomatic stenosis, balloon dilatation should be evaluated prior to short-term stenting.[19,20,40] If we use a plastic stent, it should be changed after 3-4 months regularly. Earlier replacement is recommended in cases of elevated ALP levels or clinical findings suggesting stent occlusion. Technological developments and the wider availability of cholangioscopy will probably lead to an increasing role for this procedure in the assessment of strictures in PSC. The use of prophylactic antibiotics is recommended due to the risk of bacterial cholangitis. If there is suspicion of cirrhosis or portal hypertension, endoscopic screening is recommended for the varices.

Finally, total colonoscopy and random mucosal biopsies should be taken in patients diagnosed with PSC. Annual colonoscopic screening should be performed in IBD patients.

Liver Transplantation: Indications for liver transplantation in PSC patients are clearly defined as decompensated liver disease, pruritus unresponsive to medical treatment, and recurrent bacterial cholangitis.[48] Biliary dysplasia is an indication for transplantation in some countries, while cholangiocarcinoma is a contraindication to liver transplantation in most countries. It should also be kept in mind that recurrence is seen in 25% of transplant patients. Identifiable risk factors for the recurrence are male gender, active colitis after transplantation, or presence of an intact colon.[49]

Perhaps the most important message after all of our knowledge: the gold standard in the diagnosis of PSC is MRCP. In the presence of dominant stricture, ERCP and brush cytology should be used for cholangiocarcinoma screening. Balloon dilatation is preferred over stent in strictures. Every PSC patient should be screened for IBD and followed up with colonoscopy. On the other hand, when a patient with IBD has elevated cholestatic enzymes, it should definitely be evaluated for PSC.

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