Clinical Features

5

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Introduction

The diagnosis of IgG4-SC requires a high index of suspicion and understanding of clinical features is the first step of suspicion. Early recognition of IgG4-SC may lead to proper management with corticosteroids and can eventually prevent organ failure that could possibly result from a delayed diagnosis. On the contrary, a misdiagnosis of IgG4-SC as other types of sclerosing cholangitis or cholangiocarcinoma may delay the optimal treatment or result in unnecessary operation. This chapter discusses various clinical features of IgG4-SC and compares with those of other disorders causing biliary strictures.

Demographics

IgG4-SC patients have a male preponderance and typically present in the sixth and seventh decades of life. In 2008, Ghazale et al. analyzed the large database of AIP patients at Mayo Clinic and described the clinical profiles and response to therapy of 53 patients with IgG4-SC [1]. The mean patient age was 62.2 years (range, 14–85 years) and 83% were older than age 50. The majority of patients were men (85%).

In 2015, Japanese nationwide survey was conducted regarding primary sclerosing cholangitis (PSC) and IgG4-SC, which enrolled all patients with IgG4-SC, irrespective of the presence or absence of AIP, with the largest case series of IgG4-SC patients reported to date [2]. This nationwide survey consisted of a questionnaire-based, multicenter, retrospective study. The male/female ratio was 436/91 (83%/17%), indicating male dominance in this disease. The median age was 66.2 years (range, 23.0–88.5 years), and the age distribution indicated that patients in their 60s had the highest risk for developing IgG4-SC (Fig. 5.1).

Clinical Presentation

The clinical presentation depends on the location, disease activity and the distribution of organs involved. Patients with IgG4-SC often present with obstructive jaundice (35–80%), pruritus, weight loss, abdominal pain, and cholangitis [1, 2] (Fig. 5.2). Abdominal pain usually does not require narcotics. It is extremely rare for patients with IgG4-SC to present with symptoms of decompensated cirrhosis [1]. However, no specific symptoms enable reliable differentiation of IgG4-SC from other causes of biliary obstruction. This fact is fundamentally important given

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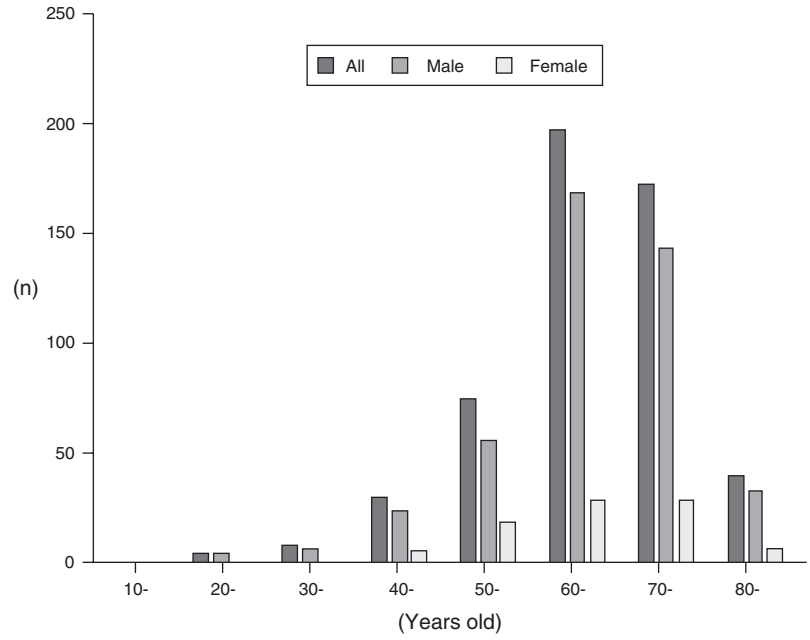

Fig. 5.1 Distribution of age at presentation, for patients with IgG4-related sclerosing cholangitis (Ref. [2])

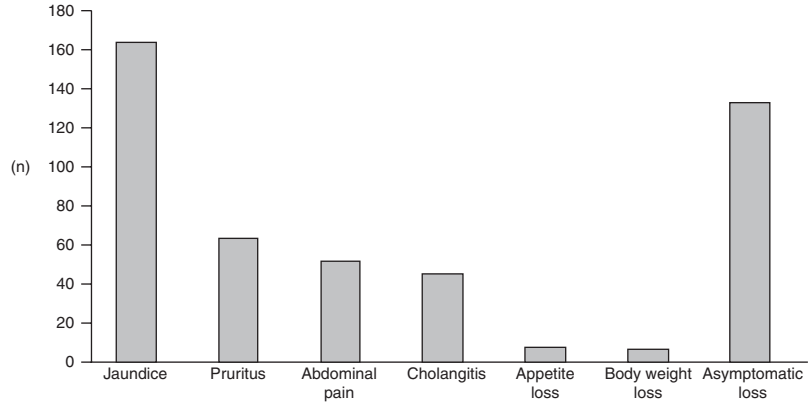

Fig. 5.2 Symptoms at presentation, for patients with IgG4-related sclerosing cholangitis (Ref. [2])

the serious consequences of misdiagnosis, which include surgical resection for presumed malignancy and inappropriate medical therapy [1, 3].

One-quarter of patients with IgG4-SC are asymptomatic or have nonspecific symptoms [2]. This finding suggests that, in the course of IgG4-SC, there is a latent phase without apparent symptoms before presentation. In such patients, IgG4-SC can be detected during the investigation of nonspecific symptoms or in the setting of abnormal liver function test results. IgG4-SC can also be found incidentally on cross-sectional imaging performed for other reasons.

IgG4-SC is included in the spectrum of IgG4-related disease, and some patients present with symptoms related to other organs affected by IgG4-RD. Other organ involvement is an important clue to the diagnosis of IgG4-SC. More than 90% of IgG4-SC patients have other organ involvements of IgG4-RD [1, 2]. The pancreas is most commonly involved. The presence of unexplained pancreatic disease in patients with biliary strictures should raise the suspicion for IgG4-SC. According to the literature, AIP was associated with 72–95% of the IgG4-SC patient population [1, 2, 4, 5]. Those with concomitant

AIP can present with symptomatic pancreatic exocrine and endocrine insufficiency such as steatorrhea and new-onset diabetes mellitus [1]. The different rate of association with AIP is most likely because of the different population of IgG4-SC whether isolated CBD stricture is included or not. Although pancreatic disease is present in the majority of IgG4-SC, patients who have no obvious pancreatic disease by clinical manifestations or image findings should not be excluded in the differential diagnosis. Attention should also be given to other organs that can be involved such as the salivary glands (sialoadenitis), retroperitoneum (retroperitoneal fibrosis), lymph nodes (mediastinal and axillary), or renal involvements.

In Japanese study, development of cholangiocarcinoma was reported in 0.8% [2]. In these patients, cholangiocarcinoma was diagnosed approximately at the same time as IgG4-SC (in two cases), or later (4 months and 4 years, respectively). Malignancies other than cholangiocarcinoma were detected in 21 patients, including lung cancer in 5, gastric cancer in 3, and duodenum cancer in 3. Overall, malignant diseases including cholangiocarcinoma were found in 25 patients with IgG4-SC (4.7%). However, the causal relationship between IgG4-SC and cholangiocarcinoma has not been documented.

Clinical Differences Between IgG4-SC and PSC

IgG4-SC should be differentiated from all disorders causing biliary strictures including PSC and cholangiocarcinoma because these conditions have entirely different therapeutic and prognostic implications. Classic PSC is generally refractory to steroid therapy, and liver transplantation is ultimately required due to liver failure, while cholangiocarcinoma generally requires surgical resection or chemotherapy. In contrast, IgG4-SC dramatically responds to steroid. Since various cholangiographic features of IgG4-SC are similar to those of PSC and cholangiocarcinoma, it is often difficult to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone. Therefore, multidisciplinary approach is very important in order to avoid the misdiagnosis of PSC and malignant diseases [1, 6, 7].

In particular, differential diagnosis between IgG4-SC and PSC can be confusing because of their similar manifestations, such as male predominance, cholestatic liver dysfunction of unknown etiology, and frequent stenosis of both the intrahepatic and extrahepatic bile ducts. Men appear to be more commonly affected by IgG4-SC same as PSC. However, no sex differences in incidence were noted in the PSC group in Japanese study [8]. Patient's age at clinical onset is around two decades older in IgG4-SC than in PSC. Very few cases have been reported in young adults less than 40 years of age (0–10%) [1, 4, 9]. In contrast, PSC tends to be a disease of young adults and middle-aged persons. The median age at diagnosis for PSC ranged from 35 to 41 years in Western countries [10, 11]. Interestingly, a Japanese nationwide survey for PSC demonstrated two unique peaks in age distribution (the first at 35–40 years and the second at 65–70 years) [12]. The age distribution of Korean patients with PSC corresponded to that of the Western population, rather than the Japanese population, as patients had a median age of 34 years and showed no second peak at older age. One plausible explanation for this discrepancy between Japan and Korea is that many older patients diagnosed with PSC in Japan might actually represent IgG4-SC patients, because the nationwide survey included various gastroenterologists with varying experience in PSC/IgG4-SC [4].

Obstructive jaundice is most frequently observed in patients with IgG4-SC, even when presenting isolated intrahepatic disease, reflecting marked concentric stenosis of the large bile duct. On the other hand, obstructive jaundice is rarely observed at diagnosis in PSC [4, 12].

And also, past history of AIP, concurrent pancreatic lesions, or extrabiliary involvement of other organs unusual for cholangiocarcinoma strongly suggests the possibility of IgG4-SC [1–4, 8, 12]. The majority of PSC patients have concomitant IBD, at a rate of 60–80% in Western countries [13, 14] and 30–50% in Japan [12, 15].

The coexistence of IBD in Korean patients with PSC corresponded to that of the Japanese population, as 41% of PSC patients have IBD [4]. In contrast, IBD is seldom associated with IgG4-SC patients (0–10%) [1, 8]. Backwash ileitis, rectal sparing, and low disease activity seem to be features that characterize IBD when it is associated with PSC [16]. If jaundice is prominent or progressive in patients with PSC, development of benign dominant strictures or cholangiocarcinoma should be considered.

Moon et al. compared patients with IgG4-SC (n = 39) and PSC (n = 76) who had intrahepatic/hilar strictures [4]. Most IgG4-SC patients (87%, 34 of 39) had a previous or concurrent IgG4-related disease; this was most frequently AIP (72%, 28 of 39). Among the five patients with isolated IgG4-SC, four (80%) needed surgical resection for the diagnosis of IgG4-SC. No patient had a history of IBD. PSC patients (41%, 41 of 76) had a history of IBD (30 patients, ulcerative colitis; 1 patient, Crohn's disease). Two patients had a history of diffuse pancreatic enlargement, which was eventually diagnosed as drug-induced acute pancreatitis. The clinical presentations of PSC were as follows: asymptomatic cholestatic liver dysfunction (47%), abdominal pain/discomfort (29%), jaundice (13%), and pruritus (7%).

Clinical Differences Between IgG4-SC and Cholangiocarcinoma

When stenosis develops in the hilar or intrahepatic bile duct, the cholangiographic appearance is similar to that of hilar cholangiocarcinoma. Because IgG4-SC responds well to steroids, but a diagnosis of hilar cholangiocarcinoma leads to hepatectomy, accurate differentiation between IgG4-SC and hilar cholangiocarcinoma is essential. There are few studies on differentiating IgG4-SC from hilar cholangiocarcinoma [17, 18]. IgG4-SC is particularly difficult to differentiate from hilar cholangiocarcinoma when it is not associated with AIP or when the diagnosis of AIP is unclear. Both diseases occurred predominantly in elderly males.

As the initial symptom, differential diagnosis between IgG4-SC and cholangiocarcinoma can be challenging as both diseases share several symptoms and signs [18]. Obstructive jaundice accompanied with skin pruritus, abdominal discomfort, and weight loss have been the most common symptoms in both IgG4-SC and cholangiocarcinoma patients. Obstructive jaundice occurred more frequently in patients with hilar cholangiocarcinoma. Obstructive jaundice may fluctuate during the course of IgG4-SC patients. The median serum total bilirubin levels were significantly higher in the patients with hilar cholangiocarcinoma. The serum CA19-9 levels are found to be significantly higher and more frequently elevate in hilar cholangiocarcinoma patients, but high level of the tumor marker CA 19-9 is also common in patients with IgG4-SC; therefore, CA19-9 levels do not seem to help to distinguish between IgG4-SC and cholangiocarcinoma [19].

Conclusion

Recognition of IgG4-SC requires familiarity with demographic and clinical features because they are the first step of suspicion. However, the diagnosis can be challenging in some patients because of the various presentations of the disease and similar presentations of other disorders causing biliary strictures. Therefore, IgG4-SC should be considered in the differential diagnosis in all patients with unexplained biliary strictures.

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