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ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ, ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ И ЛЕЧЕНИЯ IgG_4-СКЛЕРОЗИРУЮЩЕГО ХОЛАНГИТА

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Clinical Features, Differential Diagnosis and Treatment of IgG_4-Related Sclerosing Cholangitis

Резюме

Цель обзора: представить современный взгляд на особенности клинического течения, дифференциальной диагностики и лечения IgG_4-склерозирующего холангита. **Основные положения**. IgG_4-склерозирующих холангит — фиброзно-воспалительное заболевание, при котором поражаются внутрипеченочные и внепеченочные желчные протоки. Проявления IgG_4-склерозирующего холангита схожи с изменениями при первичном склерозирующем холангите, опухолях желчных протоков и поджелудочной железы, в связи с чем, более трети пациентов с IgG_4-склерозирующим холангитом подвергаются оперативным вмешательствам. На данный момент отсутствуют специфичные и чувствительные методы диагностики данного заболевания. Повышение уровня сывороточного IgG_4 наблюдается при многих других заболеваниях. Четырёхкратное повышение IgG_4 в сыворотке крови является более надежным маркером для диагностики IgG_4-склерозирующего холангита, однако такое значение наблюдается лишь у небольшой доли пациентов. При визуализации желчных протоков выявляются сегментарные или протяженные стриктуры с престенотическим расширением и утолщением стенок. Глюкокортикостероиды остаются первой линией терапии для индукции и поддержания ремиссии заболевания. Рецидив наблюдается более чем у половины пациентов. Некоторые исследования также указывают на повышенный риск развития злокачественных опухолей. В данном обзоре освещены клинические и лабораторно-инструментальные проявления IgG_4-склерозирующего холангита, проведена сравнительная характеристика с первичным склерозирующим холангитом и холангиокарциномой, а также представлены возможности терапии, прогноз и исходы заболевания. **Заключение.** IgG_4-склерозирующий холангит — редкое и сложно диагностируемое заболевание, требующее проведения тщательной дифференциальной диагностики с первичным склерозирующим холангитом, раком желчных протоков и поджелудочной железы. Несмотря на относительно благоприятное течение и эффективность глюкокортикостероидов, заболевание часто рецидивирует и имеет неизвестный долгосрочный прогноз. Особое внимание уделяется риску развития злокачественных новообразований у данной группы пациентов, что подчеркивает необходимость пожизненного наблюдения за пациентами.

Ключевые слова: *IgG_4-склерозирующий холангит, первичный склерозирующий холангит, холангиокарцинома, иммуноглобулин IgG_4, аутоиммунный панкреатит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The aim: To present the state-of-the-art of clinical features, differential diagnosis and treatment of IgG_4-related sclerosing cholangitis. **Key points:** IgG_4-sclerosing cholangitis is a fibrotic inflammatory disease affecting the intrahepatic and extrahepatic bile ducts. The clinical features of IgG_4-sclerosing cholangitis are similar to those of primary sclerosing cholangitis, bile duct cancer and pancreatic cancer. More than one third of patients with IgG_4-sclerosing cholangitis undergo surgery. Currently, there are no specific and sensitive methods to diagnose this disease. Increased serum IgG_4 levels are observed in many other diseases. A fourfold increase in serum IgG_4 levels is a more reliable marker, but this feature is found in only a small percentage of patients. The imaging of bile ducts usually reveals segmental or extended strictures with prestenotic dilatation and wall thickening. Glucocorticosteroids are the first-line therapy for induction and maintenance of disease remission. More than a half of patients develop relapses. Several studies have found an increased risk of malignant tumors. This review describes the clinical, laboratory, and instrumental features of IgG_4-sclerosing cholangitis. Comparative evaluation of diseases manifestations versus primary sclerosing cholangitis and cholangiocarcinoma is presented along with options of therapy, prognosis and outcomes of the disease. **Conclusion:** IgG_4-sclerosing cholangitis is a rare and difficult to diagnose disease that requires careful differential diagnosis with primary sclerosing cholangitis, bile duct cancer and pancreatic cancer. Despite its relatively benign course and efficacy of glucocorticosteroid therapy, the disease recurs frequently and has an unknown long-term outcome. Special attention is paid to the risk of malignant neoplasms in this group of patients, emphasizing the need for lifelong follow-up.

Key words: *IgG_4-related sclerosing cholangitis, primary sclerosing cholangitis, cholangiocarcinoma, immunoglobulin IgG_4, autoimmune pancreatitis*

Conflict of interests

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AIP — autoimmune pancreatitis, GCS — glucocorticosteroids, MNP — malignant neoplasms, CT — computer tomography, MRI — magnetic resonance imaging, PSC — primary sclerosing cholangitis, US examination — ultrasound examination, CC — cholangiocarcinoma, AMA — anti-mitochondrial antibodies, ANA — anti-nuclear antibodies, ANCA — antineutrophil cytoplasmic antibodies, ASMA — anti-smooth muscle antibody, HLA — human leukocyte antigen, IgG_1 — immunoglobulin G_1, IgG_2 — immunoglobulin G_2, IgG_4 — immunoglobulin G_4, IgG_4-AD, immunoglobulin G_4-associated disease, IgG_4-SC — immunoglobulin G_4– associated sclerosing cholangitis, SIR — standardised incidence ratio

Introduction

Immunoglobulin G_4-associated sclerosing cholangitis (IgG_4-SC) is a biliary manifestation of systemic IgG_4-associated disease (IgG_4-AD) [1, 2]. IgG_4-SC manifests as diffuse or focal inflammatory infiltration with IgG_4-positive plasma cells of intrahepatic and extrahepatic bile ducts, development of moire fibrosis, often with type 1 autoimmune pancreatitis, and rapid response to glucocorticosteroid therapy [3]. Due to similar clinical and instrumental manifestations of this condition and primary sclerosing cholangitis (PCS), bile duct and pancreatic cancer, over a third of patients undergo various surgeries [4]. The outcome and prognosis of this disease are understudied; however, more and more information suggests a higher risk of malignant neoplasms (MNOs) in patients with IgG_4-SC [1, 5, 6]. Glucocorticosteroids (GCS) are used as an induction and maintenance therapy for disease remission [3]. Nevertheless, according to various studies, 30–50 % of patients experience relapses within 6 months after glucocorticosteroid discontinuation[7, 8]. This review presents current information on clinical course, differential diagnosis and therapy of IgG_4-associated sclerosing cholangitis.

Epidemiology

According to the literature, the incidence of IgG_4-SC is 2 cases per 100,000 people [9]. IgG_4-SC affects primarily men (the ratio of 4 : 1) over 60 years of age (median age: 66.2 years old) [10, 11]. However, according to the studies, where the condition was observed in patients of 23 to 83 years of age, it can affect younger patients [7, 11].

Aetiology and Pathogenesis

Aetiology and pathogenesis of IgG_4-SC are understudied [12]. The impact of genetic factors has been discussed, e.g. a genome-wide association study (GWAS), which enrolled 835 patients from Japan with various variants of IgG_4-AD, established that genes HLA-DRB1 and FCGR2B are associated with a higher risk of IgG_4-AD [13]. A majority of studies conclude that an autoimmune inflammation has a role to play in the disease pathogenesis. Patients with IgG_4-SC had antibodies to galectin-3, laminin 511-E8, prohibitin 1, and annexin A11 [14–17]. However, no specific autoantibodies have been found. There is an evidence of a possible contribution by allergic mechanisms in IgG_4-AD. Increased serum IgE levels are observed in 30 % of patients with type 1 autoimmune pancreatitis (AIP), and every fifth patient has a history of allergic diseases, such as bronchial asthma, drug-induced allergy or chronic rhinosinusitis [17]. The possible role of changed microbiota in IgG_4-SC development has been studied. An examination of faeces of patients with PSC, IgG_4-SC and controls demonstrated reduced alpha diversity and changes in microbiota composition in the study groups vs. controls [18]. Besides, significant

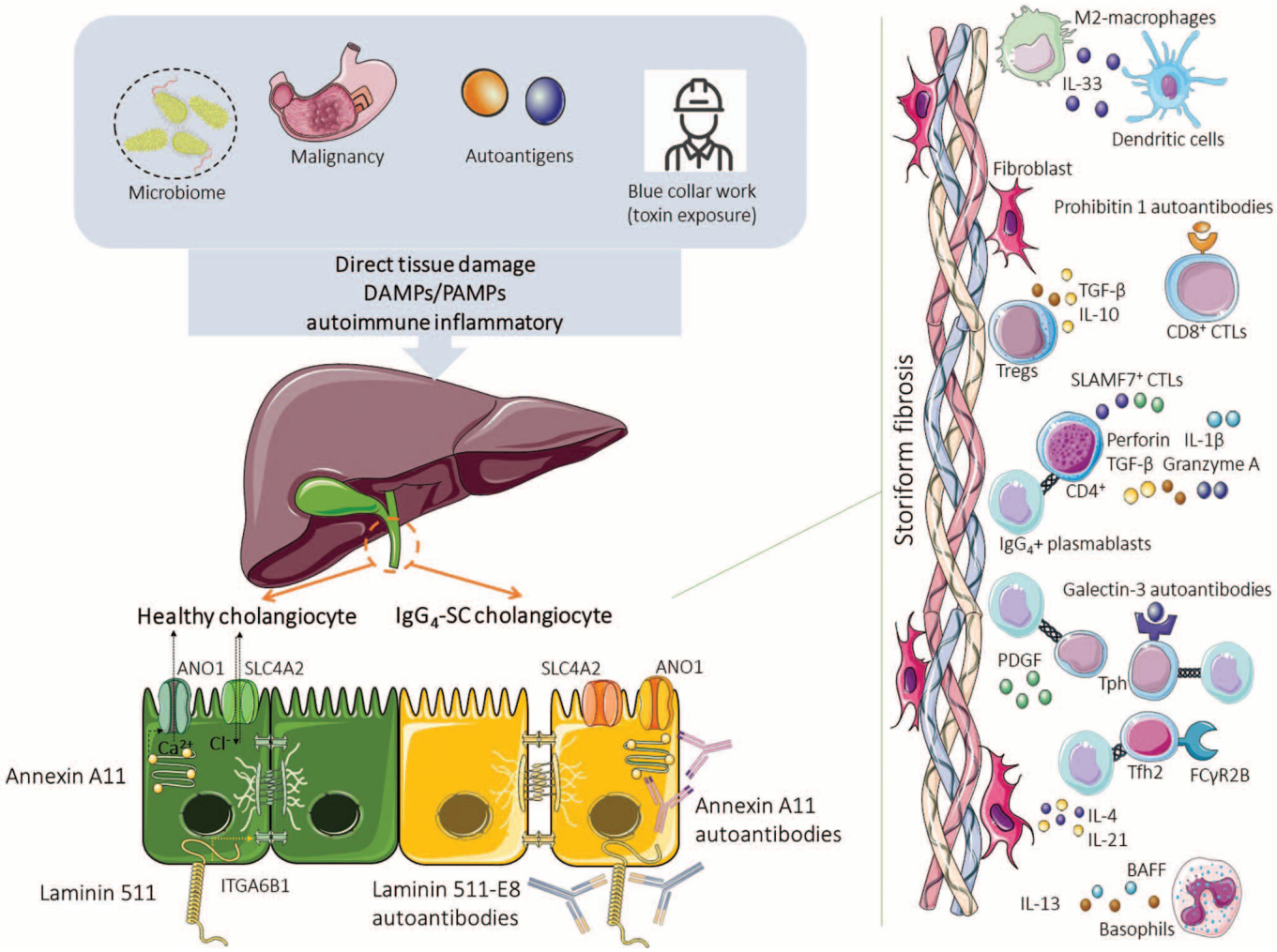

Figure 1. *Proposed pathogenesis of IgG_4-related sclerosing cholangitis*

Note: Exposure to autoantigens, DAMPs/PAMPs (produced by altered microbiome/malignant tumors) and hazardous industrial factors, through molecular mechanisms of mimicry, are possible causes of IgG_4-CX development. Activation of the innate immune system leads to disruption of the adaptive immune system. IgG_1 and IgG_4 plasmablasts produce autoantibodies against annexin A11, laminin 511-E8, galectin-3, and progibitin 1. Antibodies against annexin A11 disrupt Cl^- and Ca^{2+} transport via ANO1 to the apical membrane of cholangiocytes. Antibodies against laminin 511-E8 block binding to membrane receptors (ITGA6B1), impairing cholangiocellular barrier function. Antibodies to galectin-3 and progibitin-1 affect B- and T-cell activation. Oligoclonal IgG_4 plasmoblasts support immune dysregulation through stimulation and reactivation of oligoclonal CD4 SLAMF7 cytotoxic T cells. In addition, due to PDGF secretion they contribute to the formation of storiform fibrosis.

Abbreviations: ANO1 — anoctamin 1; **BAFF** — B-cell activation factor; **CD4** — cluster of differentiation 4; **CTLs** — cytotoxic T lymphocytes; **DAMPs** — damage-associated molecular patterns; **PAMPs** — pathogen-associated molecular patterns; **FCγR2B** — Fc γ receptor 2B; **ITGA6B1 —** integrin α6β1; **SLAMF7** — signaling lymphocytic activation molecule family member 7; **PDGF —** platelet-derived growth factor; **SLC4A2 —** solute carrier family 4 member 2; **Tfh** — follicular T helper 2 cells; **TGF-β** — Transforming growth factor-β; **Tph** — peripheral T helper cells; **Tregs —** regulatory T cells.

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differences in microbiota composition in patients with PSC and IgG_4-SC [21] have been noted. The study of unfavourable environmental factors is also of great importance. A study of 101 patients with IgG_4-SC and autoimmune pancreatitis (AIP) showed that 68 % of them were blue-collar-workers, i.e. those who were manual industrial labourers exposed to industrial solvents and gases [19]. This value was far higher than in controls, where blue-collar-workers accounted for 39 % (OR = 3.66; 95 % CI: 2.18–6.13; n = 404; $p < 0.0001$). Moreover, it has been found out that prolonged contact with industrial gases, dust and organic substances, such as asbestos, for over a year is associated with a higher risk of IgG_4-SC and AIP (OR = 2.14; 95 % CI: 1.26–3.16; $p < 0.001$, and OR = 2.95; 95 % CI: 1.78–4.90; $p < 0.001$, respectively) [19]. Figure 1 shows key concepts of possible pathogenesis of IgG_4-SC.

Clinical Presentation

Approximately 25 % of IgG_4-SC cases are asymptomatic [11]. Most common manifestations of IgG_4-SC are obstructive jaundice (35–80 %), sharp weight loss, moderate abdominal pain, rarely — skin itching (13 %) [11]. Often, patients who underwent bile duct treatment and diagnostic procedures experienced signs of infectious cholangitis, such as fever [20]. According to various sources, 72–95 % of IgG_4-SC patients had concomitant type 1 AIP [11, 21, 22]. Such cases presented with manifestations associated with the development of exocrine and endocrine deficiency of pancreas (53 % and 37 %, respectively) [7]. Also, in numerous cases, IgG_4-SC was concomitant to other IgG_4-associated diseases, such as tubulo-interstitial nephritis (5 %), dacryoadenitis (15 %), salivary adenitis (26 %), retroperitoneal fibrosis (5 %), mediastinal and axillary lymphoadenopathy (8 %) [10].

Laboratory Diagnostics

Blood samples of patients with IgG_4-SC demonstrate higher cholestasis marker levels: alkaline phosphatase, gamma-glutamyltranspeptidase, total bilirubin, mainly due to direct fraction [3, 23]. Increased serum IgG_4 levels of > 1.35 g/L were observed in 75–90 % of patients with IgG_4-SC [22, 24, 25]. Studies showed that a 4-fold increase in blood IgG_4 levels was highly specific and had positive prognostic value (100 %); however, sensitivity was significantly reduced and made 42 % (95 % CI: 31–55) [3, 24, 26]. Also, there are cases of moderately increased serum IgG_4 levels in patients with PSC (9–22 %) and cholangiocarcinoma (CC) (8–14 %)[22, 27, 28]. Table 1 shows average serum IgG_4 levels in IgG_4-SC and other diseases. According to a Japanese study, the threshold value of serum IgG_4 of 2.07 g/L can be a useful additional tool to differentiate types 3 and 4 IgG_4-SC and CC [22]. In order to differentiate IgG_4-SC and PSC, the threshold value of serum IgG_4 was 1.77 g/L, with the sensitivity and specificity being 91.5 % and 87.6 %, respectively [22]. A study

Table 1. *Mean serum IgG_4 levels in IgG_4-sclerosing cholangitis, primary sclerosing cholangitis, cholangiocarcinoma and pancreatic cancer*

Disease	Serum IgG_4 (M±SD)			
	Hirano et al. 2006[33]	Ohara et al. 2013 [22]	Nakazawa et al. 2012[34]	Oseini et al. 2011[35]
IgG_4-SC	-	6,46±6,62	-	2,771±0,552**
IgG_4-SC type 1 vs PCa	-	6,13±6,18* **vs** 0,593±0,659*	5,48±7,71* **vs** 0,49±0,73*	-
IgG_4-SC type 2 vs PSC	-	7,99±8* **vs** 0,687±0,86*	8,84±8,54* **vs** 0,5±0,45*	-
IgG_4-SC types 3,4 vs CC	-	6,46±7,11* **vs** 0,523±0,468*	5,14±5,42* **vs** 0,64±0,59*	-
PSC	1,86±2,41	-	-	-
CC	0,624±0,378	-	-	0,646±0,063**
PCa	66±3,8	-	-	-

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma; PCa — pancreatic cancer.
* $p < 0.05$
**M±SEM

by Boonstra K. et al. established that, if IgG_4 levels are up to two normal values, it is recommended to measure the IgG_4/IgG_1 ratio, which in IgG_4-SC was ≥ 0.24, with the sensitivity and specificity being 86 % and 95 %, respectively [26]. Similar results were obtained by Liming Tan et al. (2019), who analysed blood levels of IgG_4, CA19-9, autoantibodies (ANA, ASMA, AMA, ANCA) in 45 patients with IgG_4-SC, 80 — with PSC, 41 — with biliary duct tumour, 52 — with pancreatic cancer, and 48 healthy volunteers [29]. The study demonstrated that a higher serum IgG_4 level was observed in patients with IgG_4-SC (86.67 %) vs. controls ($p < 0.01$) [29]. Serum IgG_4 levels were also elevated in patients with PSC (25 %), bile duct cancer (7.32 %) and pancreatic cancer (9.62 %) [29]. Positive ANAs were observed in patients with IgG_4-SC and PSC (40 % and 32.5 %, respectively); however, the difference was not statistically significant [29]. The rate of ANCA, ASMA and AMA in patients with IgG_4-SC was significantly lower than in patients with PSC ($p < 0.01$) [29]. Positive ANCAs were observed more often in patients with PCS as compared to patients with IgG_4-SC (61.25 % and 6.67 %, respectively) ($p < 0.01$)[29]. CA19-9 levels were higher in over a half of patients with IgG_4-SC (51.11 %) and in a majority of patients with bile duct adenocarcinoma and pancreatic cancer (92.68 % and 90.38 %, respectively) [29]. Significant changes in CA19-9 levels reduced in the presence of jaundice. Also, there are published data on increased bile IgG_4 levels in patients with IgG_4-SC. The threshold value of 0.038 g/L allowed differentiating IgG_4-SC and patients with PSC and CC, with sensitivity and specificity being 100 % and 77 %, respectively [30]. However, in order to implement this method in the wide clinical practice, additional studies are required. Patients with IgG_4-SC and AIP had higher IgG_2 values as compared to patients with isolated autoimmune pancreatitis or primary sclerosing cholangitis, with high specificity (97 %) and positive prognostic value (91 %) [38]. High IgG_1 levels (8.2 ± 2.6 g/L) indicated primary sclerosing cholangitis [31]. Also, it has been established that the IgG_4/IgG ratio of > 0.129 was more often indicative of IgG_4-AD (OR 31.25; 95 % CI: 15.31–63.79; $p < 0.001$) [32].

Classification

In 2004, Nakazawa et al. proposed an IgG_4-SC classification taking into account the cholengiography pattern [36]. ***Type 1*** (64 %) is associated with narrowing of the distal section of the choledochous duct. Isolation of this type is disputable, because some experts believe that duct narrowing is a result of compression of an enlarged pancreatic head [37]. However, is some cases, type 1 IgG_4-SC is not associated with autoimmune pancreatitis [38]. This type should be differentiated from pancreatic head tumour, pancreatic pseudotumor and cholangiocarcinoma. ***Type 2*** is characterised by involvement of intrahepatic and extrahepatic bile ducts. This type is further subdivided into type 2a (5 %) and type 2b (8 %). Type 2a presents with narrowing of intrahepatic bile ducts and prestenotic enlargement. In type 2b, narrowing of intrahepatic bile ducts is combined with reduction in the number of side ducts, however, without prestenotic enlargement. In this type, differential diagnosis is with PSC. ***Type 3*** of IgG_4-SC (10 %) is characterised by narrowing of the distal section of the choledochous duct and confluence area. ***Type 4*** (10 %) manifests only with duct narrowing near the hepatic hilum. Types 3 and 4 of IgG_4-SC mimic changes typical of CC, therefore, morphological verification is essential in order to rule out tumour. If changes on a cholangiogram do not correspond to any of these types, the condition should be classified as an unidentified type. Comparison of IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma is presented in Table 2.

Methods of Instrumental Diagnostics

Images of bile ducts in IgG_4-SC patients demonstrate segmental or extensive stenosis of bile ducts, with prestenotic enlargement and wall thickening [49]. PSC is characterised by short, moniliform stenosis, with diverticula-like duct protrusion [36]. According to another study, typical signs of IgG_4-sclerosing cholangitis seen during intraduct ultrasound were circular symmetric thickening of bile duct wall with even external and internal edges, as well as wall thickening up to > 0.8 mm outside the stenosis area [50]. This threshold wall thickness was highly sensitive (95–100 %) and specific (91 %) for differentiation from CC [50]. Comparison of changes seen during intraduct ultrasound is presented in Table 3. According to studies, CT signs of IgG_4-SC include: circular duct wall thickening with an even external and internal contour; uniform contrast accumulation in arterial phase; involvement of the intrapancreatic section of the bile duct; discontinuity of involvement; concomitant changes in pancreas; visible lumen; funnel-like narrowing of the proximal section of the common bile duct; extended bile ducts proximal to stenosis to 9 mm [51]. A comparative study by Yata

Table 2. *Comparative characterization of IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma*

Parameter	IgG_4-SC	PSC	CC
Prevalence	2/100.000[9]	1-16/100.000[39]	5,9/100.000[40]
Age (years)	50–60[24]	25–45[41]	50–70[42]
Gender (m:f)	4–8:1[23]	2:1[43]	1.5:1[44]
Clinical features	jaundice, significant weight loss, epigastric pain [24]	up to 50 % asymptomatic, jaundice, pruritus [45]	asymptomatic in early stages, especially in intrahepatic CC; painless jaundice in 90 % of patients with extrahepatic CC [46]
Other organ involvement	type 1 AIP (up to 90 %), generalized lymphadenopathy, sialoadenitis, retroperitoneal fibrosis [24]	50–80 % IBD [45] (85–90 % — UC; 10–15 % -CD)	metastases
Elevated serum IgG_4 level	74–90 %[26]	9–22 %[27]	8–22 %[22,28]
CA-19-9	51 % 153–292 U/ml[29]	12 % 47–97 U/ml[29]	93 % 329–384 U/ml[29]
pANCA	7 %[29]	61 %[29]	-
Histology	lymphoplasmacellular infiltrate (>10 IgG_4+ plasma cell, IgG_4/IgG>0,40), storiform fibrosis, obliterative phlebitis[47]	periportal sclerosis, onion-skin fibrosis[47]	dysplasia, biliary neoplasia, atypical cells[47]
Immunohistochemistry: IgG_4+ plasma cell	50–90 %[24]	5–25 %[27]	25 % (n=4)[48]
Immunohistochemistry: IgG_4+:IgG+ plasma cell ratio	>0.40[24]	-	-
Response to GS	rapid, distinct in the early stages[3,23]	no[39]	-
Prognosis	favorable[23,24]	progressive disease, depends on the response to UDCA [41]	at 5 years after diagnosis, survival rates range from 7 % to 20 %[40]

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma; GS — glucocorticoids; UDCA — ursodeoxycholic acid

M. et al. (2016) demonstrated that a combination of the above CT signs was sensitive (80 %) and specific for differentiation from CC [51]. Besides, a double contour see on CT was highly specific for cholangiocarcinoma (90 %), unlike single-layer contrast accumulation in IgG_4-SC [51]. Tokala A. et al. (2014) proposed to use the wall thickness of the common bile duct of > 2.5 mm, seen on MRI, as a diagnostic criterion to differentiate from PSC [49]. In 71.4–100 % of cases, thickened bile duct walls evenly accumulated contrast [49, 52, 53], and were iso- or hyperintense during the portal vein or delayed phase vs. hepatic parenchyma [49, 52, 53].

Morphological Characteristics

Typical morphological changes in IgG_4-SC are lymphoplasmacytic infiltration, moire fibrosis, obliterating phlebitis, sometimes — eosinophilic infiltration [3]. In order to verify IgG_4-SC morphologically, it is required to observe at least 10 IgG_4-positive plasma cell HPF (x400) in the fine-needle aspiration material, or > 50 cells in intraoperative samples, including edge biopsy, and the ratio of IgG_4/IgG-positive cells of at least 40 % [20, 55]. However, IgG_4-positive plasma cells can be observed in PSC and cholangiocarcinoma [9, 28]. Typical morphological changes in IgG_4-SC were usually absent, since the key changes take place in submucosa and deeper [9].Moreover, stenting can cause non-specific changes, such as atypical epithelial cells, epithelial ulceration and inflammatory infiltration, which can facilitate incorrect interpretation as signs of PSC and CC [56, 57]. In fine-needle biopsy of the liver, only 57 % of patients with intrahepatic involvement of hepatic ducts had > 10 IgG_4-positive plasma cells and only in 8 % of cases — with involvement of extrahepatic bile ducts only [58]. Sensitivity and specificity of intraductal biopsy were 52 % and 96 %, respectively [59]. Biopsy of major duodenal papilla ampulla is indicated

Table 3. Comparative characterization of intraductal ultrasound findings in patients with IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma

Parameter	Naitoh I., et al., 2009[50]			Kubota K., et al., 2011[6]			Naitoh I., et al., 2015[54]	
	IgG_4-SC		*CC* (n=11)	*IgG_4-SC* (n=6)	*CC* (n=12)	*PSC* (n=10)	*IgG_4-SC* (n=35)	*PSC* (n=15)
	intrahepatic biliary ducts (n=16)	extrahepatic biliary ducts (n=9)						
Wall thickness (mm) *M±SD* *Me(IQR)*	2,3±0,4	2,6±0,3	3,3±1,2	3,7±0,9	2,8±0,6	2,6±0,9	2.5 (2.2–2.9)	2.4 (1.8–3.0)
Wall thickness (n): symmetric:asymmetric	11:4[1]	6:3[2]	1:9	6:0*	1:11*	2:8*	27:6*	1:14*
Outer margin (n): clear: unclear	15:0	9:0[2]	2:9	-	-	-	33:0*	2:13*
Inner margin (n):								
- smooth:irregular	15:0	9:0[2]	0:9	6:0*	1:11*	1:9*	33:0*	0:15*
- papillary	0	0	2	-	-	-	-	-
- diverticulum-like outpouching	-	-	-	-	-	-	0*	10*
Internal echo (n): homogeneous:heterogeneous	15:0[1]	9:0[2]	1:10	-	-	-	33:0*	7:8*
Extrinsic compression	1	0	0	-	-	-	2	0
Three layers structure (n): - preservation:disappearance	-	-	-	-	-	-	33:0*	0:15*

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma.
[1]p <0.01 IgG_4-SC with intrahepatic biliary duct involvement vs CC
[2]p <0.01 IgG_4-SC with extrahepatic biliary duct involvement vs CC
*p <0.05

for patients with IgG_4-SC and concomitant type 1 AIP; however, this procedure was associated with a high risk of complications, such as pancreatitis, recurrent Hayem-Widal syndrome and papillitis [59].

Treatment

GCSs are a first-line therapy for remission induction in IgG_4-SC. A recommended GCS dose is 0.5–0.8 mg/kg/day per os (a standard starter prednisolone dose is 30–40 mg/kg/day) for 4 weeks with subsequent dose reduction by 5 mg once every 1–2 weeks [3, 45]. Results show that the average prednisolone dose (0.5–0.6 mg/kg) was as efficient as the high dose (0.8–1 mg/kg) for remission [60]. Given a high rate of relapses after GCS discontinuation (> 50 %) [24], studies recommend using a maintenance low-dose therapy with GCS (2.5–7.5 mg/day), for one to three years [61]. According to a retrospective analysis, maintenance therapy with low-dose prednisolone for over three years improved survival rates of patients with IgG_4-SC [62]. In case of insufficient response to GCS therapy or disease relapse, it is recommended to use immunosuppressants as a send-line therapy for remission maintenance [3]. This group of drugs includes thiopurines (azathioprine, 6-mercaptopurine), mycophenolate mofetil, methotrexate and calcineurin inhibitors (tacrolimus, cyclosporin A) [63–65]. A retrospective analysis to compare cyclophosphamide and mycophenolate mofetil did not demonstrate any superiority of one drug over the other in terms of remission induction [66]. Rituximab was prescribed to induce and maintain remission if GCS and steroid-sparing drugs were contraindicated, or if these agents were inefficient [67, 68]. According to a meta-analysis, complete response in 6 months was observed in 88.9 % (95 % CI 80.5–93.9), the rate of relapses was 21 % (95 % CI 10.5–40.3), median time to relapse was 10 months [67]. A higher relapse rate of 35.9 % (95 % CI 17.3–60.1) was recorded in patients with multisystemic damages (in addition to pancreas and/or bile ducts) [67]. Adverse events were observed in 25 % of patients: infusion reactions (8 patients), infectious complications (9 patients), hypogammaglobulimenia (1 patient), gall bladder cancer (1 patient) [67]. The rate of relapses after rituximab induction was

still high; the drug should be used with caution in IgG_4-SC, given the potential risk of infectious complications, such as bacterial cholangitis, cholecystitis and hepatic abscesses [12].

There are various approaches to the matter of bile duct stenting in patients with IgG_4-SC. In their study, Miyazawa M. et al. (2020) emphasise a higher risk of chololithiasis in patients who undergo stenting before GCS initiation [69]. Out of 69 patients with IgG_4-SC, only 41 patients received GCS without stenting and achieved clinical improvements, including 10 patients with obstructive jaundice [69]. The other 28 patients (40.6 %) underwent bile duct stenting before GCS initiation [69]. In this group, after successful GCS therapy, the stent was removed in 13 patients (46.4 %), while 10 patients (35.7 %) experienced spontaneous stent displacement [69]. During the follow-up period, three patients (4.3 %), who underwent stenting, had bile duct stones, while no patients after GCS therapy had this condition ($p = 0.032$) [69]. Another study demonstrated that the incidence of stenting-associated acute cholangitis was significantly lower in patients who had previous steroid therapy as compared to those who did not have any steroids (the incidence of no acute cholangitis in one month): 100 % vs 90 %; log-rank test $p = 0.0278$) [70].

Outcomes and Prognosis

Given the high efficacy of glucocorticosteroids, prognosis for patients with IgG_4-CS is favourable. 10–25 % of patients with IgG_4-SC can experience spontaneous remission [71]. The long-term prognosis is poorly studied; biliary cirrhosis is observed in 4.5–7.5 % of cases [72]; also, there are individual cases of portal hypertension [73] and one case of hepatic decompensation, requiring liver transplant [74]. Kensuke Kubota et al. (2023) conducted a retrospective data analysis of 924 patients with IgG_4-SC [62]. According to the study results, malignant neoplasms were recorded in 15 % (139/924) of patients: before IgG_4-CS developed — 48 cases, simultaneously with the diagnosis of IgG_4-SC or within 3 months after the diagnosis — 18 cases, after IgG_4-SC diagnosis — 83 cases [62]. In patients who had malignant neoplasms diagnosed significantly earlier than IgG_4-SC, it was most commonly localised in colon (27 %; 13 cases out of 48) and urinary system (25 %; 12 cases out of 48) [62]. Where cancer and IgG_4-SC were diagnosed at the same time, the most common malignancy was malignant neoplasm of the upper section of the GI tract (33 %; 6 cases out of 18) [62]. When cancer was diagnosed after the IgG_4-SC diagnosis, the most common cancer was urinary tract cancer (36 %; 30 cases out of 83), stomach and duodenum cancer (34 %; 28 cases out of 83) and colon cancer (28 %; 28 cases out of 83) [62]. Also, eight cases of bile duct cancer and nine cases of pancreatic cancer were diagnosed, all of them, but one, developed after IgG_4-SC. In the majority of cases, pancreatic cancer was diagnosed within 10 years after the diagnosis of IgG_4-SC, while bile duct cancer was diagnosed within two years [62]. Also, a multifactor analysis revealed that an IgG_4-SC relapse is an independent risk factor for malignancy [62]. Relapses were observed in 19.7 % (182/924) of patients [62]. Overall, the standardised incidence ratio (SIR) for MNPs after the diagnosis of IgG_4-SC was 12.68 (6.89–8.79) [62]. SIR values for bile duct and pancreatic cancer were 27.35 (23.39–31.12) and 18.43 (16.44–02.97), respectively [62]. Cumulative survival was statistically higher in patients who had maintenance steroid therapy ($p < 0.001$) [62]. Another retrospective study concluded that patients with IgG_4-SC are at a higher risk of malignancies, including pancreatic and bile duct cancer [5]. SIR for pancreatic and bile duct cancer was 10.30 and 8.88, respectively [5]. The risk of malignancies was high during the first year and five years after the IgG_4-SC diagnosis; SIR was 2.58 and 2.44, respectively [5].

Conclusion

IgG_4-SC is a rare condition which is challenging to diagnose; it can be mistaken for other bile duct diseases, such as PSC and CC. Diagnosis requires a comprehensive assessment of clinical, laboratory and instrumental data and often histological confirmation. In many cases, the condition is diagnosed after an assessment of the efficacy of a trial GCS therapy, usually with fast and positive response. Prognosis is favourable; however, life-long follow-up is required due to a high rate of relapses and a high risk of malignant transformation.

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