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CASE REPORT

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IgG4-related disease presenting with cholangitis mimicking cholangiocarcinoma: a case report with a literature review

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ABSTRACT

Introduction. IgG4-related disease (IgG4-RD) is currently known as a unique progressive immune-mediated disease creating tumor-like fibrotic masses in different organs of the human body.

Case presentation. We report a 23-year-old woman who presented with acute abdominal pain, icterus, and fever. A biliary stricture aroused suspicion of cholangiocarcinoma. In addition, some colon masses were observed, which were suspected to be mucinous carcinoma with appendix origin. The patient underwent a major surgery consisting of cholecystectomy, hepaticojejunostomy, and right hemicolectomy. The post-surgical pathology report for all the lesions and masses was IgG4-RD.

Conclusion. The biliary lesion was IgG4-related sclerosing cholangitis. We concluded that IgG4-RD was a rare but important differential diagnosis for solitary or multiple masses and biliary lesions.

Key words: IgG4-related disease, cholangiocarcinoma, colon mass, sclerosing cholangitis

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Introduction

IgG4-related disease (IgG4-RD) has been known as a unique disease entity since 2003. From the pathophysiological point of view, it is a progressive immune-mediated disease creating tumor-like fibrotic masses in different organs of the human body [1]. The immunological mechanism of IgG4-RD is not completely understood. It seems that B cells — the antibody-producing cells — have a variety of dysfunctions consisting of disturbed subpopulations and abnormal expression of key signaling, co-stimulatory, and inflammatory molecules [2].

Since IgG4-RD can involve many different organs, it can mimic some other diseases or have unspecific manifestations and also have overlap or association with other diseases including tuberculosis infection [3], pericarditis [4], Castleman's disease [5], osteomyelitis [6], Crohn's disease [7], malignancies [8], and so on. Among the mentioned diseases, IgG4-RD association with cancers is notable. It is hypothesized that some common pathophysiological themes are involved. For instance, numerous studies have mentioned that M2 macrophages are activated in IgG4-RD [9–12]; on the other hand, M2 macrophages help cancer cell survival [13].

Sclerosing cholangitis can be a presentation of IgG4-RD [14], and also IgG4-RD can mimic cholangiocarcinoma [15]. In the present study, we report a case of IgG4-RD presenting with cholangitis mimicking cholangiocarcinoma and review the data in the literature.

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Case presentation

A 23-year-old woman was referred to Bu Ali hospital, Hamadan, Iran (2021) with acute abdominal pain, icterus, and fever (cholangitis triad). The patient did not have any positive past medical history, familial history, or alcohol or substance use. Her medication history consisted of only pantoprazole. In the emergency ward, she had elevated liver enzymes in the aspartate aminotransferase (AST) test: 139 IU and alanine aminotransferase (ALT): 221 IU, along with total bilirubin 4.7 mg/dL.

After the patient became stable thanks to intravenous fluid resuscitation and antibiotics, endoscopic retrograde cholangiopancreatography (ERCP) was performed. During the procedure, strictures were observed, and a stent was placed. The report of ERCP was "suspicion of sclerosing cholangitis". She was referred to Firoozgar hospital, Tehran, Iran to be diagnosed and treated further. ERCP was performed again, and the stent was removed. The report of ERCP was "suspicion of cholangiocarcinoma, IgG4-related disease should be considered", and the report of brush cytology was "negative for malignant cells". Thereafter, endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) of lymph nodes was performed. The report of EUS was "highly suspicious for hilar cholangiocarcinoma", and the cytology report was again "negative for malignant cells".

Since inflammatory bowel disease (IBD) has a correlation with primary sclerosing cholangitis (PSC), a colonoscopy was performed. A large irregular fold was observed in the cecum, and the pathology of colon biopsy was negative for IBD. Abdominal computed tomography (CT) scan was also performed, and large masses in the cecum lateral wall and ascending colon with peritoneal seeding were seen (suggestive of a mucinous tumor with an appendix source).

Finally, after consulting with different services, the patient became a candidate for a major surgery including cholecystectomy, hepaticojejunostomy, and right hemicolectomy. After surgery, the resected gallbladder and resected parts of the colon, including the appendix, cecum, ascending colon, and 22 lymph nodes were sent for pathological evaluation. The report of pathology for the colon masses was "IgG4-related disease", and the report for the resected components of the biliary system was "affected by IgG4-related disease". Immunohistochemistry (IHC) showed positive reactivity for IgG4 and negative for ALK1. All the lymph nodes were reactive. A definite diagnosis of IgG4-RD was made based on the 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD, including clinical and radiologic features (the masses), serological diagnosis (serum IgG4 level >135 mg/dl) and pathological diagnosis (positive IHC) [16]. After surgery and the definite diagnosis of IgG4-RD, she was referred to an internist. The patient was treated with oral corticosteroid therapy and remission was achieved after a 4-week follow-up. Then the corticosteroid tapered off and no relapse occurred up to the time of this report (about one year).

Briefly, the laboratory findings of the patient were as following at the time of admission in Firoozgar hospital: IgG4 level: 148.2 mg/dL [normal (Nl): 11–157 mg/dL]; carcinoembryonic antigen (CEA) level: 1.26 ng/mL (Nl: < 3.0 ng/mL); carbohydrate antigen (CA) 19–9: 13.05 U/mL (Nl: < 37 U/mL) AST: 146 IU; ALT: 225 IU; alkaline phosphatase (ALP): 2208 IU; bilirubin (total/direct): 4.3/2.5 mg/dL; C reactive protein (CRP): 101 mg/L. After surgery, the laboratory findings were as following. AST: 23 IU; ALT: 14 IU; ALP: 201 IU; bilirubin (total/direct): 0.8/0.4 mg/dL.

Discussion

In a descriptive analysis, data for IgG4-related cholangitis from the literature were analyzed. The studies with complete information on the patient age, AST, ALT, ALP, bilirubin, and serum IgG4 were selected from the literature [14, 15, 17, 18]. A summary of the data is shown in Table 1. According to the descriptive statistics, the amounts of ALT, ALP, total bilirubin, and serum IgG4 had wide ranges with abnormal distribution (Tab. 1).

IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-RD. In the present case, IgG4-SC was diagnosed based on the criteria mentioned by Ohara et al. [19] including characteristic biliary imaging findings (here by ERCP), the elevation of serum IgG4 level (here around the upper limit of normal range), presence of IgG4-RD in collateral locations and histopathological features (here positive IHC). In addition, response to steroid therapy was an optional feature that was also clinically achieved in our case [19, 20]. The 2020 RCD criteria for IgG4-RD were fulfilled in this case. In our case, surgery was performed merely due to suspicion of malignancy. Before surgery, IgG4-RD was only a differential diagnosis. However, since the masses were large (up to 5 cm), it seemed that this surgery could be effective for this remission.

The risk factors of IgG4-SC are not currently understood, but it seems that a thicker bile duct wall is a risk factor for relapse and also maintenance therapy with steroids may reduce the risk of relapse [21]. The prevalence of IgG4-SC is estimated to be about 2 cases per 100 000 in the Japanese population. Ten-year disease-free survival for these patients is more than 80% [22].

PSC and cholangiocarcinoma are the most important differential diagnoses of IgG4-SC [23]. IgG4-SC can be with or without hepatic inflammatory pseudotumor (HIP) [24]. In the present study, we had a patient with

Table 1. Individual data for IgG4-related cholangitis

Study	Patient ID	Age	AST	ALT	ALP	Total bilirubin	Serum IgG4
Present study	1	23	146	225	2208	4.3	148.2
Graham et al.	2	59	106	37	260	0.9	56.9
	3	45	62	47	783	1.5	126
	4	76	114	71	1423	1.3	102
	5	56	182	44	95	1.1	Not done
	6	57	180	88	189	0.7	143
	7	73	72	58	242	0.7	63.1
	8	57	37	18	50	0.8	85.3
	9	65	64	55	472	1.5	155
	10	64	114	60	253	1	59
Mizutani et al.	11	59	236	437	998	7.0	110
Rungsakulkij et al.	12	56	59	55	319	16	7223
Hamano et al.	13	50	92	143	1406	8.8	122
	14	56	65	170	488	Normal	119
	15	77	97	117	900	3.1	195
Summary of statistics							
Mean		58.2	108.4	108.33	672.4	3.48	621.96
Standard deviation		13.28	55.79	106.98	616.12	4.40	1900.32
Median		57	97	60	472	1.4	120.5
Interquartile range		56–65	64–146	47–143	242–998	0.9–4.3	85.3–148.2
Minimum		23	37	18	50	0.7	56.9
Maximum		77	236	437	2208	16	7223
Normality p-value		0.092	0.131	< 0.001*	0.024*	< 0.001*	< 0.001*

The laboratory results of our study have been obtained from the primary assessment in Firoozgar center; *Rejection of normal distribution based on the Shapiro-Wilk test at significance level of 0.05; AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase

clinical presentation of cholangitis (abdominal pain, icterus, and fever) and stricture in ERCP (as a manifestation seen in PSC and cholangiocarcinoma). Workup for IBD (PSC) or cholangiocarcinoma did not show a positive result. Nevertheless, since cholangiocarcinoma was highly suspected, and, on the other hand, the colon masses had been observed, we decided on surgery. Finally, the pathology of the resected tissues was reported as IgG4-RD.

Hamano et al. (2005) [18] reported 3 cases of IgG4-SC in the UK. The patients were middle aged or elderly. They had a long segment of narrowing in the bile-duct system mimicking hilar cholangiocarcinoma. One of the patients underwent surgery because of suspicion of malignancy like our case [18]. Naitoh et al. (2009) [25] reported an elderly Japanese patient with IgG4-SC and HIP. Segmental stenosis was seen in the bile-duct system, and a solitary mass was seen in the liver. This patient underwent surgery because of suspicion of malignancy [25]. Mizutani et al. (2012) [17] reported another case of IgG4-SC in Japan. It was a middle-aged patient with a presentation of obstructive jaundice. Graham et al. (2014) [14] reported 9 cases of IgG4-SC in the US. The patients had diffuse irregular thickening in the biliary tree. One of the patients had a history of Crohn's disease. All the patients were middle aged. Like in our study, 8 out of the 9 cases underwent surgical resection [14]. Xiao et al. (2017) [26] reported a middle-aged patient with IgG4-SC in China. This patient underwent surgery and Roux-en-Y anastomosis [26]. Rungsakulkij et al. (2017) [15] reported another middle-aged patient who underwent bile-duct resection. A similar circumstance in our case and the cases reported in the literature was performing surgery because of suspicion of malignancy. The difference between our case and the previous cases was that our patient was young, while the others were middle aged or elderly. It seems that IgG4-SC is rare in young individuals. Interestingly, there was also a case of metastatic cholangiocarcinoma accompanied by IgG4-SC. Therefore, such cases may be misdiagnosed with isolated IgG4-SC [27].

Currently, corticosteroid therapy: 30–40 mg/day of prednisolone is the first-line standard care for symptomatic cases of IgG4-RD or patients with organ dysfunction. Treatment of asymptomatic cases is controversial [28]. In cases of relapse, immunosuppressive and anti-B cell agents may be regarded [1, 28, 29]. Surgery is not recommended for treatment of IgG4-RD. In a European cohort, most of the patients who underwent surgery were suspected of cancer or had cancer. They found no effect on relapse [30]; however, their number of cases was not enough (n = 11) to reach this conclusion. In our case, there were multiple large masses. Although we did not perform surgery for IgG4-RD, we believed that resection of such masses was effective in this remission. The role of surgery in such cases should be studied in the future.

Conclusions

In the present study, we reported a case of a young patient with IgG4-RD mimicking cholangiocarcinoma. This patient underwent surgery due to suspicion of cholangiocarcinoma and also because of the colon masses suspected of mucinous carcinoma with an appendix origin. The serum IgG4 level was around the upper limit of the normal range. After surgery, it was observed that both the bile-duct and colon masses were IgG4-RD. We concluded that IgG4-RD was a rare but important differential diagnosis for solitary or multiple masses and biliary lesions. Closed or open biopsy may help to differentiate IgG4-RD from malignancies.

Conflict of interest

All authors declare no conflicts of interest.

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