ORIGINAL ARTICLE

Immunoglobulin G4–related sclerosing disease: experience with this novel entity in a local hospital

TL Ng 吳芷琳
IS Leong 梁延信
WL Tang 鄧偉倫
KF Chan 陳鉅發
YW Luk 陸耀榮
WC Lao 勞偉祥
CM Leung 梁志文
SY Liu 廖崇瑜
CS Kho 許紫珊
KL Lee 李嘉麗
KK Chan 陳國強
Michael KW Li 李家驊

Objective To review the site of involvement, clinical presentation, and treatment outcome of patients having immunoglobulin G4–related sclerosing disease in a local regional hospital.

Design Retrospective case series.

Setting Pamela Youde Nethersole Eastern Hospital, Hong Kong.

Patients All patients with a diagnosis of immunoglobulin G4–related sclerosing disease in the hospital diagnosed in the period from April 2008 to March 2010.

Results A total of 12 patients with involvement of various organs were identified. There was a male predominance (male-to-female ratio=5:1). The mean age at diagnosis was 65 years. The salivary glands, biliary tract, pancreas, and cervical lymph nodes were the commonest involved sites. The immunoglobulin G4 level was elevated in 83% of the patients. Patients usually appeared to respond well to steroid treatment.

Conclusion Immunoglobulin G4–related sclerosing disease is a systemic disease and can involve various systems.

New knowledge added by this study

- As in other Asian and western countries, immunoglobulin G4 (IgG4)–related sclerosing disease can affect various systems in our local population, predominantly in males. The response to steroid therapy is usually good.

Implications for clinical practice or policy

- IgG4-related sclerosing disease is important as it is a multi-system disease. Differentiating it from pancreaticobiliary carcinoma is important as it is usually steroid responsive and major surgery can be avoided.

Introduction

Immunoglobulin G4 (IgG4)–related sclerosing disease is a novel clinicopathological entity characterised by intense fibrosis and lymphoplasmacytic infiltration of tissue.[1,2] It manifests as sclerosing mass lesions which invariably show increased numbers of IgG4-positive plasma cells and is usually associated with a raised serum IgG4 level. At first it was mostly described in patients with autoimmune pancreatitis (AIP),[3] but over the past decade IgG4-related involvement of various organs is being increasingly reported, suggesting that it is a systemic disorder.[1,4,5] Given the increased recognition of such a disease entity, we report our hospital's experience of IgG4-related diseases encountered over the past 2 years.

Methods

All patients with a serum IgG4 assay ordered in our hospital, or a histology report compatible with IgG4-related sclerosing disease from our histology laboratory encountered over the period April 2008 to March 2010, were reviewed. A diagnosis of IgG4-related sclerosing pancreatitis was made by Mayo Clinic Diagnostic Criteria.[6] Extrapancreatic IgG4-related sclerosing disease was made by high percentage of IgG4+/IgG+ cells or abundant IgG4+ cells by histology in at least one site of involvement. Demographic data, sites of clinical involvement, clinical manifestations, investigation results, and treatment responses were reviewed.

Results

Twelve patients were diagnosed to suffer from an IgG4-related sclerosing disease; their mean age was 65 years, and male-to-female ratio was 5:1.

Key words
Autoimmune diseases; Immunoglobulin G; Lymph nodes; Pancreatitis, chronic; Sclerosis

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Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong:
Department of Medicine
TL Ng, MB, BS, FHKCP
IS Leong, FRCP, FHKAM (Medicine)
YW Luk, FRCP, FHKAM (Medicine)
WC Lao, FRCP, FHKAM (Medicine)
CM Leung, FRCP, FHKAM (Medicine)
SY Liu, FRCP, FHKAM (Medicine)
CS Kho, FHKCP, FHKAM (Medicine)
KL Lee, FHKCP, FHKAM (Medicine)
KK Chan, FRCP, FHKAM (Medicine)
Department of Pathology
WL Tang, MB, ChB, FHKAM (Pathology)
KF Chan, MB, ChB, FHKAM (Pathology)
Department of Surgery
MKW Li, MB, BS, FRCS

Correspondence to: Dr IS Leong
Email: leongls@ha.org.hk

Demographic data, presenting symptoms, and sites of involvement

Demographic data, clinical presentations, and sites of involvement in these patients are summarised in Table 1. Sites of involvement were defined by histology, imaging, clinical history, or response to steroid treatment. In our series, salivary glands, the biliary tract (including gallbladder), the pancreas and cervical lymph nodes were the commonest involved sites, accounting for 50%, 42%, 33% and 25% of the patients, respectively. Two patients had prostatic and pericardial involvement, in which the sites have been rarely reported in the literature. Patients with involvement of salivary glands usually presented with corresponding glandular swelling, whereas orbital swelling was the complaint if the lacrimal gland was affected. In those with hepatobiliary or pancreatic disease, obstructive jaundice was the most frequent presenting symptom. Fever was an unusual presentation, which manifested in only one of our patients. Weight loss was also rare and reported by only one patient.

Investigation results

Investigation results of these 12 patients at presentation are shown in Table 2. The serum IgG4 level was elevated in 10/12 (83%) of the patients. Among these patients, in 11 of them relevant histology revealed a large number IgG4-positive plasma cells and/or a high ratio of IgG4-to-IgG–positive plasma

IgG4相關硬化性病：本地醫院對此新型病症的經驗

目的 探討一所本地分區醫院中，IgG4相關硬化性病患者的受影響部位、臨床徵狀和治療結果。

設計 病例回顧。

安排 香港東區尤德夫人那打素醫院。

患者 2008年4月至2010年3月期間所有在本院確診患上IgG4相關硬化性病的病人。

結果 共有12位IgG4相關硬化性病患者，平均確診年齡為65歲。患者以男性居多，男女比例為5:1。他們受影響的部位各有不同，最常見牽涉的器官為唾液腺、膽管、胰臟和頸部淋巴結。有83%患者的IgG4水平偏高。一般來說，患者對於類固醇治療反應良好。

結論 IgG4相關硬化性疾病是一種全身性疾病，可牽涉不同的器官。

TABLE 1. Demographic data, presentation, and sites of involvement*

Patient No.	Age (years)	Sex	Presentation	Sites of involvement		
				By histology	By imaging	By treatment response or history alone†
1	48	M	Jaundice	GB	Pancreas	Pancreas
2	51	M	Jaundice, fever	GB, biliary tract	-	-
3	50	M	Jaundice	Pancreas, GB, biliary tract, intra-abdominal LNs	-	-
4	72	M	Jaundice	-	Pancreas, biliary tract, intra-abdominal LNs	Pancreas, biliary tract, intra-abdominal LNs
5	50	M	Jaundice, swollen eyelids, salivary gland swellings, cervical lymphadenopathy	Salivary glands	Pancreas, biliary tract	Lacrimal glands, salivary glands, cervical LNs, pancreas, biliary tract
6	80	F	Pancreatic mass and splenic vein thrombosis	Pancreas	-	-
7	67	M	Salivary gland swellings, CHF	Pericardium	-	Salivary glands†
8	55	M	Bilateral orbital swelling, cervical lymphadenopathy, salivary gland swelling	Cervical LNs	Lacrimal glands, salivary glands	Lacrimal glands, salivary glands
9	83	M	Salivary gland swellings, obstructive uropathy	Salivary glands, prostate	-	-
10	71	M	Left submandibular gland swelling	Salivary glands	-	-
11	74	M	Salivary gland swellings, cervical lymphadenopathy, anaemia and weight loss	Salivary glands	Cervical LNs	Cervical LNs
12	77	F	ARF due to obstructive uropathy	Retroperitoneal tissue	-	-

* GB denotes gallbladder, LN lymph node, CHF congestive heart failure, and ARF acute renal failure

† Patient 7 had right submandibular mass with excision done 6 years before presentation showed chronic inflammation and sclerosis

TABLE 2. Histology and laboratory results*

Results		Patient No.											
		1	2	3	4	5	6	7	8	9	10	11	12
Histology													
No. of IgG4+ cells per high power field		240	141	-	-	190	60	150	106	127	-	99	64
IgG4/IgG (%)		90	37	90	-	~100	65	-	-	-	40	-	50
Laboratory	Reference range												
IgG4 (mg/dL)	0-291	340	200	800	920	1450	300	1250	400	3450	480	3150	110
IgG (g/L)	7.5-15.6	14.4	22.4	24.3	48.8	22.0	14.9	28.5	35.6	77.5	-	45.2	14.0
IgA (g/L)	0.82-4.53	2.31	5.18	3.49	2.57	-	2.13	2.86	1.10	0.92	-	0.87	3.35
IgM (g/L)	0.46-3.04	1.46	0.75	1.21	1.49	-	0.43	0.40	0.45	0.52	-	0.54	0.94
CA 19.9 (IU/L)	<37	120	219	17	196	23	80	-	-	-	-	-	-
Creatinine (μmol/L)	62-115	60	61	68	102	84	68	95	106	320	121	81	737
Albumin (g/L)	35-50	36	34	40	33	32	34	42	35	37	40	36	40
Globulin (g/L)	31-37	37	42	47	52	64	36	42	62	96	34	50	28
Bilirubin (μmol/L)	3.4-20.5	300	147	320	82.2	81	3.4	311	7	9	8.6	10	7.1
Alkaline phosphatase (IU/L)	53-128	692	437	507	470	549	172	64	58	70	74	61	47
Alanine transaminase (IU/L)	<41	332	295	922	174	550	82	20	15	22	53	10	13

* Ig denotes immunoglobulin, and CA cancer antigen

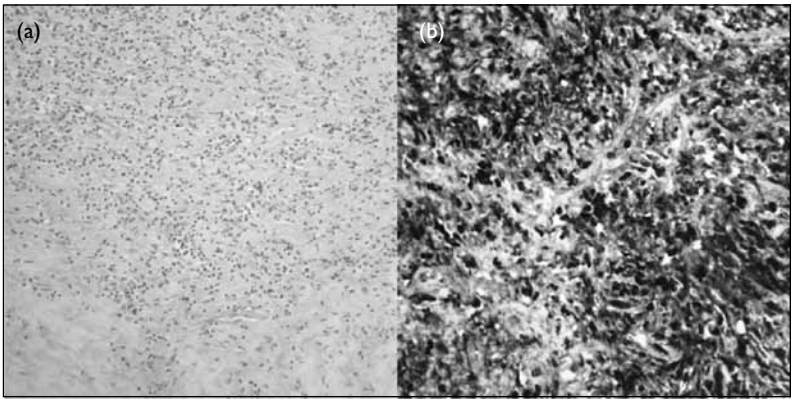

FIG 1. (a) Immunoglobulin G staining in the pericardium of patient 7 (original magnification, x 200). (b) Immunohistochemical staining of immunoglobulin G4 in prostatic tissue of patient 9 (original magnification, x 400)

cells, which confirmed the diagnosis of IgG4-related sclerosing disease. Patient 4 with pancreaticobiliary disease was diagnosed by Mayo Clinic Diagnostic Criteria. Interestingly, the total IgG levels were also elevated in eight of our 12 patients. Moreover, nine of them had a reversed A/G ratio. Among patients with biliary tract involvement (patients 1 to 5), serum alanine transaminase and alkaline phosphatase levels were elevated. Figure 1 shows immunological staining of IgG4-positive plasma cells in some of the patients. Positron emission tomography (PET)–computed tomographic scans were performed in four patients, which all showed increased metabolic activity in the involved areas.

Treatment outcome

Details of treatment and treatment responses are summarised in Table 3. In all patients with biliary tract involvement, endoscopic retrograde cholangiopancreatography (ERCP) was performed to enable temporary biliary drainage. Owing to lack of knowledge about this disease and the possibility of malignancy, the first two of these patients underwent surgical resection. However, we offered a trial of steroid therapy to patients 3 to 5, but the former preferred surgery. Patients 4 and 5 were successfully treated with steroid therapy alone. Figure 2 shows paired ERCP films of patient 4 before and after steroid treatment. Patients 2 and 3 relapsed after tapering off or cessation of the steroid therapy, they were managed by increasing the dose or adding immunosuppressive therapy. Patients with salivary gland and lymph node involvement usually responded well to steroid therapy. Patient 9 died of necrotising fasciitis during steroid treatment. Patients 6, 10 and 12 did not receive steroid therapy as they were relatively asymptomatic after surgical resection. Five patients had serum IgG4 levels checked after steroid treatment; in two patients the level had normalised, and in the other three they were lower.

TABLE 3. Treatment and outcome*

Patient No.	Treatment†	Outcome
1	ERCP: temporary biliary drainage Surgery: cholecystectomy and bypass surgery (CJ, GJ, JJ) Prednisolone 40 mg daily gradually tapering down to 5 mg daily in 4 months	Pancreatic mass reduced in size starting from 1 month after treatment and then became minimally prominent at 3 months by CT scan
2	ERCP: temporary biliary drainage Surgery: excision of bile duct, hepatico-jejunostomy Prednisolone 40 mg daily gradually tapering off after 3 months	ALP rebound to nearly 3 times upper limit of normal. Azathioprine and prednisolone were started. ALP was maintained within normal while patient was on azathioprine 175 mg and prednisolone 10 mg daily
3	ERCP: temporary biliary drainage Whipple's operation Prednisolone 30 mg daily gradually tapering down to 5 mg daily after 9 weeks	ALP rebound when prednisolone dose decreased to 5 mg daily. Prednisolone was stepped up back to 15 mg daily and then slowly tapering down to 5 mg daily after 1 year
4	ERCP: temporary biliary drainage Prednisolone 30 mg daily gradually tapering off after 6 months	Bile duct stricture resolved after 3 months of steroid treatment as well as pancreatic mass
5	ERCP: temporary biliary drainage Prednisolone 30 mg daily for 4 months and then gradually tapering down to 5 mg daily after 6 months	Salivary glands and orbital swelling subsided after 2 weeks of treatment. Pancreatic mass markedly decreased in size after 4 months. Bile duct stricture resolved after 6 months of treatment
6	Distal pancreatectomy and splenectomy	Remained asymptomatic after surgery
7	Tricuspid valvular annuloplasty Prednisolone 40 mg daily gradually tapering down to 5 mg daily after 10 months	Remained asymptomatic
8	Prednisolone 30 mg daily gradually tapering down to 5 mg daily after 6 months	Salivary glands and orbital swelling subsided after 1 month of steroid treatment
9	TURP Prednisolone 30 mg daily for salivary gland swelling	RFT normalised after TURP Died of infection during prednisolone therapy
10	Submandibular sialoadenectomy	Remained asymptomatic after surgery
11	Prednisolone 30 mg daily gradually tapering off after 6 months	Salivary glands and lymph nodes swelling subsided completely after 3 months of treatment
12	Ureterolysis and adhesiolysis	RFT normalised after surgery

* ALP denotes alkaline phosphatase, CJ choledochojejunostomy, CT computed tomography, ERCP endoscopic retrograde cholangiopancreatography, GJ gastrojejunostomy, JJ jejunojejunostomy, RFT renal function test, and TURP transurethral resection of the prostate

† Treatments were listed according to chronological order

Discussion

Yoshida et al[3] proposed the concept of AIP in 1995, which is a disease characterised by dense pancreatic infiltration of IgG4-positive plasma cells, and CD4- or CD8-positive T lymphocytes, and fibrosis, in association with elevated serum IgG4 levels and good response to steroid therapy. Recently extrapancreatic involvement such as in peripancreatic retroperitoneal tissue, the biliary tract, the gallbladder, the periportal area of liver, the salivary glands, kidneys, lungs and lymph nodes has been increasingly reported. For which reason IgG4-related sclerosing disease is being increasingly recognised as a unique entity with multi-system involvement. In our series, IgG4-related sclerosing disease was confirmed histologically in the pancreas, gallbladder, bile duct, salivary glands, retroperitoneal tissue, prostate, lymph nodes and even the pericardium.

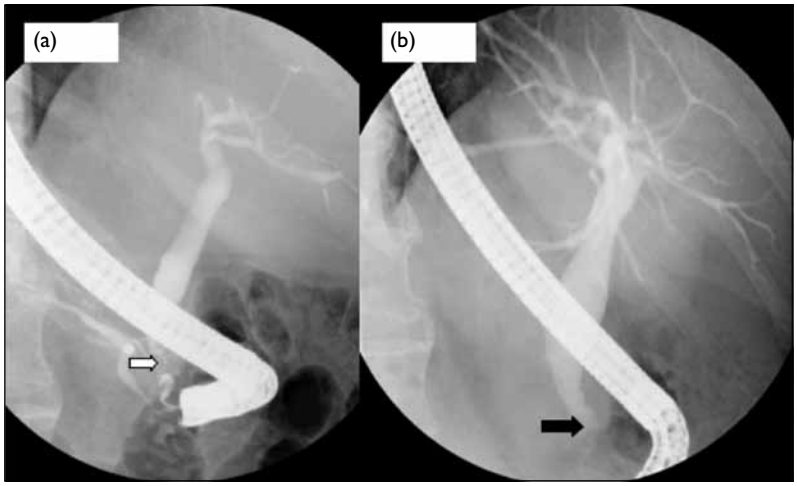

FIG 2. (a) Pretreatment distal common bile duct stricture (white arrow) of patient 4. (b) Distal common bile duct stricture (black arrow) that resolved and filled with contrast after steroid treatment for 3 months

Immunoglobulin G4–related sclerosing disease usually presents as a mass lesion. When it involves the pancreas, differentiation from pancreatic carcinoma is a challenge. When it involves the biliary tract, primary sclerosing cholangitis or cholangiocarcinoma enter the differential diagnoses. Patients may be misdiagnosed as Sjögren's syndrome if they present with lacrimal or salivary gland disease. Although it is a benign disease, it can be complicated by the development of malignant lymphoma and possibly carcinoma.[7,8]

The serum IgG4 level is potentially useful in diagnosing this novel disease. Following Hamano et al's landmark study in 2001,[9] serum IgG4 levels were realised to have high specificity (97%) and high sensitivity (95%) for the diagnosis of AIP using a cutoff value of 135 mg/dL. A study in Korea[10] showed similarly high specificity (95%) and sensitivity (73%) using a serum IgG4 cutoff level of 141 mg/dL. Ghazale et al[11] from the United States reported a 93% specificity and 73% sensitivity based on a serum IgG4 cutoff value of 140 mg/dL. In our patients, 83% had elevated serum IgG4 levels, which was slightly higher than previous studies. However, its value as a definitive preoperative diagnostic tool is limited, as it is not elevated in all patients and its turn-around-time is usually longer than 1 month (as in Hong Kong). Serum IgG4 levels decrease in patients who respond to steroids,[12] which was also noted by us. Whether the test can be used to monitor disease relapse remains debatable.

Various imaging modalities were studied as a means of differentiating IgG4-related sclerosing disease from malignancy. Two small-scale studies evaluated the usefulness of PET in AIP and IgG4-related diseases,[13,14] and concluded that it can distinguish between the two. Yet its recognised usefulness is underutilised for monitoring disease activity in IgG4-related sclerosing conditions. From our limited experience, in some cases a diffuse increase in metabolic activity did make radiologists suspect an inflammatory aetiology, rather than a malignant disease.

Histopathological and histochemical demonstration of dense infiltration with IgG4-positive plasma cells and CD4- or CD8-positive T lymphocytes as well as fibrosis in the involved tissue is the gold standard for diagnosis but this renders surgery inevitably.

Immunoglobulin G4–related sclerosing disease usually responds well to steroid therapy. A small Korean study[15] looked into the effectiveness of a 2-week steroid trial in suspected cases of AIP, and noted that they invariably responded; patients who did not respond turned out to have pancreatic cancer. However, this approach needs to be confirmed in further studies.

Steroids remain the standard treatment for IgG4-related sclerosing disease. Most experts suggest a high-dose steroid course for 2 to 3 months, followed by gradual tapering down to a maintenance dose for a further 6 to 12 months.[16] However, the optimal duration for maintenance dosing remains uncertain. For AIP, a 6 to 25% relapse rate had been reported after steroid withdrawal. A recent study by Kamisawa et al[17] found that maintenance with low-dose steroids did not eliminate relapses. Patients with biliary tract involvement seemed to have a higher relapse rate (up to 57%).[9] As the follow-up period of our patients was brief, the post-remission long-term relapse rate remains uncertain. Two of five of our patients relapsed as evidenced by a gradually increasing alkaline phosphatase even as the steroid dose was being tapered down. Azathioprine appears to be an effective means of managing post-steroid treatment relapse.[9] However, the optimal duration of such azathioprine maintenance therapy also remains unknown.

A limitation of our study was that we might have missed some cases of IgG4-related sclerosing disease. If clinicians do not suspect the disease, serum IgG4 assay may not be checked and/or no tissue histology sought. Besides, even when tissue is sent for histology, pathologists may misdiagnose the appearance as 'chronic inflammation'.

In summary, IgG4-related sclerosing disease is a multi-system disease. In our series, salivary glands, the biliary tract, the pancreas and cervical lymph nodes were the commonest involved sites. Serum IgG4 levels and PET imaging have been shown to be useful for non-invasive diagnosis, but have their limitations. This disease is important as it may involve a variety of systems. Major operations can be avoided in patients with pancreatic or biliary IgG4-related sclerosing disease, since it is usually steroid-responsive. We report our limited local experience of this novel entity to increase the awareness of the condition in Hong Kong. Further studies may help to unveil the many unknowns with regard to this new disease entity.

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