

# Ophthalmological Findings in Cases of Autoimmune Pancreatitis: Changes in Long-term Corticosteroid Therapy

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## ABSTRACT

**Background & Aims:** Patients with autoimmune pancreatitis (AIP) sometimes show characteristic ophthalmologic findings, such as dacryoadenitis and dry eye. However, the ocular findings in AIP patients thus far have not fully been analyzed, especially in patients treated long term with corticosteroids (CS). We aimed to study the current and previous history of ocular diseases in AIP patients and changes of the common ophthalmologic findings during the CS treatment.

**Methods:** We retrospectively analyzed the history of ophthalmologic diseases in 105 AIP patients and further examined the changes in the ophthalmologic findings and associated factors occurring during CS treatment in 63 patients.

**Results:** Several common ophthalmic diseases, including cataract (33.3%) and glaucoma (6.3%), were recognized in approximately one-third of the AIP patients at their initial diagnosis. Behcet uveitis was seen in the past histories of two AIP patients. During 70 months of CS treatment, exacerbation of cataract was recognized in 31.7%, and new onset of glaucoma in 7.9%. Univariate and multivariate analyses demonstrated the cumulative CS amount as a significant risk of cataract exacerbation ( $p < 0.05$ ) and diffuse pancreatic swelling at the initial diagnosis as a risk of Mikulicz's disease ( $p < 0.01$ ).

**Conclusions:** An ophthalmologic check at the initial diagnosis and monitoring during CS treatment is required for patients with AIP. Promising steroid-sparing agents are expected to lessen the adverse ophthalmologic events caused by CS.

**Key words:** autoimmune pancreatitis – ophthalmologic finding – corticosteroid – cataract – glaucoma.

**Abbreviations:** AIP: autoimmune pancreatitis; CS: corticosteroid; AIH: autoimmune hepatitis; PBC: primary biliary cirrhosis; IOP: intraocular pressure; OR: odd's ratio; RR: relative risk.

## INTRODUCTION

Autoimmune pancreatitis (AIP) is a systemic disease associated with focal or diffuse pancreatic swelling, the involvement of several other organs, and a high response rate to corticosteroid (CS) therapy. Today, CS [1] are the sole drug approved by the Japanese national health insurance system for the treatment of AIP and are indicated for patients with AIP symptoms, such as obstructive jaundice, abdominal pain, and hydronephrosis [2]. Steroid treatment is effective in almost

all patients with AIP [2, 3] and positive responses can be seen in clinical images within two weeks to one month [2, 4]. Subsequent maintenance treatment with low-dose corticosteroids is recommended to reduce the relapse rate [2, 5]. However, the long-term administration of CS remains controversial because of chronic, adverse CS-associated events, such as diabetes mellitus and osteoporosis [5-8].

Several ocular findings, including cataract [8] and glaucoma [9], have also been reported as adverse effects of long-term CS. Diabetes, which is frequently a complication of AIP, also increases the risk of ophthalmologic disorders, including glaucoma, cataract, and retinopathy [10, 11], when it is prolonged. The majority of AIP patients are male and may have lifestyle habits that include smoking [12] and drinking [13], which are also possible risks for these ocular diseases. However, to date, the ophthalmologic findings in patients with AIP treated with long-term CS have seldom been reported.

Some ophthalmologic findings are also associated with many systemic autoimmune diseases, such as retinal cotton-wool patches in systemic lupus erythematosus, scleritis in rheumatoid arthritis, and HLA-B27-associated uveitis in ankylosing spondylitis [14]. To date, dacryoadenitis associated with dry eye, also known as Mikulicz disease [15-17], is the only ocular disease specifically reported in patients with AIP. This disease is associated with typical IgG4-related pathological findings in the lacrimal glands and usually responds well to CS. However, some autoimmune diseases, such as Evans syndrome (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura) and AIH-PBC overlap syndrome (autoimmune hepatitis and primary biliary cirrhosis) [18, 19], can overlap simultaneously or metachronously in a single patient. Similarly, ocular diseases other than dacryoadenitis may develop in cases of AIP; however, at present, any overlap of these other autoimmune-associated ophthalmologic diseases has rarely been reported.

The aims of the current study were to investigate the ocular diseases occurring in patients with AIP and to analyze the ophthalmologic findings before and after CS treatment and their associated factors.

## METHODS

The institutional review board (IRB) of the Shizuoka Cancer Center Ethical Committee approved this study (IRB no. 2025-4863).

The past histories of ocular diseases were analyzed in 105 AIP patients initially diagnosed in the Shizuoka Cancer Center between April 2004 and February 2024, based on the Japanese Diagnostic Criteria for AIP (2018) [20]. Recorded data were age, gender, history of ophthalmological disorders and their treatment, smoking and alcohol habits, comorbidities, the serum IgG4 level at the initial diagnosis, the management for AIP. The diagnoses were definitive AIP (95 cases), probable AIP (5 cases) and possible AIP (5 cases). Corticosteroid treatment was administered in a generally recommended manner [2] for a median of 70 months.

63 of the 105 patients who were treated with CS for more than 6 months and who underwent ophthalmologic tests at least twice were analyzed for changes in ocular findings during the course of their CS treatment. To avoid a deviation in indications for CS treatment, the ophthalmologic past histories were analyzed at the initial diagnosis of AIP in all 105 patients. Of these 63 patients, 30 were followed exclusively in the ophthalmologic division of the Shizuoka Cancer Center, 2 patients were followed only at nearby hospitals or clinics, and 31 patients were followed at both the Shizuoka Cancer Center and nearby hospitals.

The incidences of optic findings and factors associated with the exacerbation of cataract, glaucoma, and Mikulicz's disease were retrospectively analyzed in the 63 cases that underwent CS treatment.

The ophthalmologic check included examinations for cataract and glaucoma [including intraocular pressure (IOP)], as well as examinations of the retina and cornea. The patients were usually followed at 3–6 months intervals by the ophthalmologists in charge, and the ophthalmologic

information was gathered at appropriate times for cases visiting nearby institutes. The levels of cataract and glaucoma were categorized as mild (manageable with eye drops alone) and severe (requiring surgery and/or laser treatment). These levels were compared at the time of steroid initiation and during the subsequent course. Exacerbation was defined as either a newly recognized cataract or glaucoma or an increase from a mild to a severe level. Common ophthalmic disorders, such as amblyopia and astigmatism, were also checked; however, the data were excluded from the analysis in the current study.

To determine the risk of deterioration due to ophthalmic diseases during CS treatment, we listed factors associated with demographics, AIP-related findings, and CS treatment, and we compared positive and negative effects on deterioration. Demographic factors, such as age [11, 21], smoking [12], drinking [13], diabetes [11, 22-24], body mass index [25], and CS treatment [26-29] were examined, as they have been reported to impose risks for cataract and glaucoma.

## Statistical Analysis

Factors possibly associated with the exacerbation of ocular findings were analyzed using univariate and multivariate tests. For univariate analysis, the levels of continuous variables were compared using the Mann–Whitney *U* test. The incidence of binary variables was compared using Fisher's exact test. Multivariate analysis was conducted using logistic regression and the R statistical software (ver. 4.3.1). Two-tailed analysis was done, and a probability value less than 0.05 was deemed statistically significant.

## RESULTS

105 patients (80 males and 25 females) with a median age of 69 years (range: 45–84) included 95 cases with definitive AIP, 5 cases with probable AIP, and 5 cases with possible AIP. Among these patients were 72 cases with focal-type AIPs and 33 cases with diffuse-type AIPs (Table I). At the initial diagnosis, the median serum IgG4 level was 313.5 mg/dL (range: 4–3440 mg/dL). Other organ involvements, as defined in the Japanese criteria [20], were recognized in 39 patients (37.1%).

In the 105 patients with AIP, a past history of ocular diseases was identified in 29.5% (31 cases), including cataract in 21.9% (11 mild and 12 severe cases), mild glaucoma in 5.7% (6 cases), macular degeneration in 3.8% (4), dry eye in 2.9% (3), Behcet's disease-associated uveitis in 1.9% (2), Mikulicz disease in 1.9% (2), floaters in 1.9% (2), serous retinal detachment in 1.0% (1), diabetic retinopathy in 1.0% (1), epimacular membrane in 1.0% (1), retinal break in 0.9% (1), and strabismus in 0.9% (1) (Table I).

Corticosteroid treatment was administered in a generally recommended manner [2] for a median of 70 months, with a cumulative amount of CS of 5213 mg (range: 840–36,894 mg).

In total, 63 patients with AIP were treated with CS for more than 6 months and underwent ophthalmologic tests at least twice (Table II) and were analyzed for changes in ocular findings during their CS treatment. These AIP patients consisted of 45 males and 18 females, with a median age of 67 years (range: 45–84). Of these 63 patients, 41 cases (65.1%) had a history of smoking, 13 cases (20.6%) had a history of drinking (>200 g of alcohol intake/week), and 13

cases (20.6%) had diabetes. The categories of AIP included 59 definitive AIPs, 1 probable AIP, and 3 possible AIPs (macroscopic classification: 40 focal-type and 23 diffuse-type). The median serum IgG4 level at initial diagnosis was 296 mg/dL in (range: 22-3,440 mg/dL). Other organ involvement [20] was recognized in 28 cases (44.4%) (Table I).

The past histories of the 63 CS-treated AIP cases showed similar incidences to those of the total 105 cases (Table I). Their initial ophthalmologic checks revealed new diagnoses, including four additional cases of mild cataract (a total of 21 cases of cataract including past history), two cases of dry eye, 2 cases of optic nerve pit, 1 case of coloboma, 1 case of conjunctival melanosis, and 1 case of retinal arteriosclerosis. During the 70 months of CS treatment, the incidence of cataract increased from 21 cases (33.3%) to 37 cases (58.7%), whereas cataract decreased in 20 cases (31.7%). Similarly, a mild level of glaucoma developed in 5 cases (7.9%), Mikulicz's disease in 5 cases (7.9%), fundal hemorrhage in 1 case (1.6%), and serous retinal detachment in 1 case (1.6%) (Table II).

For cataract, the median amount of predonine administered to the patients who showed exacerbated cataract was significantly larger (12,445 mg) than the amount administered to the patients without an onset or exacerbation of cataract (5,515 mg) ( $p = 0.035$ ). Multivariate analysis identified the cumulative predonine amount as an independent risk factor of cataract exacerbation [odds ratio (OR)=3.62, 95% CI: 1.07-12.30,  $p=0.039$ ] (Table III).

None of the listed factors was significant in terms of predicting glaucoma after CS treatment (Supplementary file, Table I), but both univariate analysis (OR=13.76, 95%CI: 1.54-123.28,  $p=0.008$ ) and multivariate analysis (OR=20.30, 95%CI: 1.82-226.00,  $p=0.014$ ) identified diffuse-type AIP (a finding suggestive of high autoimmune activity) as a risk of the onset of Mikulicz's disease. Although not reaching statistical significance, the proportion of female patients was 57% in the Mikulicz's disease group, whereas the non-Mikulicz's disease group had a male predominance (75%) (Supplemental file, Table II). Mikulicz's disease was detected at the initial diagnosis of AIP or during the CS-withdrawal period based on a high level of serum IgG4 (746 mg/dL) (Table IV); however, the patients responded well to restarted CS treatment.

#### AIP Patients Accompanied with Behcet's Disease

Among the 105 AIP patients, 2 patients had a history of Behcet's disease. In one male patient, Behcet's disease had developed into bilateral uveitis at the age of 30 years, and he had been treated with CS implants and oral cyclosporine (100–200 mg/day). At the age of 57 years, enhanced computed tomography performed during his post-surgical follow-up for lung cancer accidentally revealed a swollen pancreatic tail. Subsequent magnetic resonance cholangiopancreatography showed a narrowing of the main pancreatic duct, and subsequent endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and measurement of an elevated level of serum IgG4 (351 mg/dL; normal range, 4.5-117 mg/dL) led to the diagnosis of probable type 1 AIP [20].

**Table I.** Demographic and clinical characteristics of autoimmune pancreatitis (AIP) at the initial diagnosis

Factors	Total AIP cases (n=105)	AIP cases with CS therapy and ophthalmologic follow up (n=63)
Gender (male): n, (%)	80 (76.2)	45 (71.4)
Age, median (range), y.o.	69 (45 - 84)	67 (45 - 84)
Diabetic findings*, n, (%)	52 (49.5)	26 (41.3)
Past history: n, (%)		
Smoking	76 (72.4)	41 (65.1)
Drinking**	18 (17.1)	13 (20.6)
Diabetes	29 (27.6)	13 (20.6)
Ophthalmologic diseases, n (%)		
Any	31 (29.5)	21 (33.3)
Cataract	23 (21.9)	17 (27)
Glaucoma	6 (5.7)	4 (6.3)
Uveitis	2 (1.9)***	1 (1.6)
Others	14 (13.3)	10 (15.9)
AIP-related findings at the initial diagnosis		
Diagnostic level#	definitive: 95, probable: 5, possible: 5	definitive: 59, probable: 1, possible: 3
Macroscopic type	focal-type: 72, diffuse-type: 33	focal-type: 40, diffuse-type: 23
Serum IgG4: median (range), mg/dL	313.5 (4 - 3,440)	296 (22 - 3,440)
Other organ involvement†, n, (%)	39 (37.1)	28 (44.4)
Mikulicz disease, n (%)	2 (1.9)	2 (3.2)

AIP: autoimmune pancreatitis; y.o.: years old; CS: corticosteroid; mo: month; \*positive for either findings within diabetic drug intake, serum HbA1c over 6.2%, or urinary glucose; \*\* $\geq 200$ g of habitual alcohol intake per week; \*\*\*uveitis associated with Behcet's disease and already treated by drugs;# Diagnosis of AIP was based on the Japanese Diagnostic Criteria of AIP (2018); †: macular degeneration (4), dry eye (3), floaters (2), serous retinal detachment (1), diabetic retinopathy (1), macular epiretinal membrane (1), retinal break (1), strabismus (1) in 105 patients.

**Table II.** Changes of ophthalmologic findings in cases with AIP between at CS initiation and at last CS treatment period (n=63)

Factor	At CS initiation*	At last CS treatment
Age: median (range), y.o.	68 (45-84)	73 (48-89)
CS treatment *		
Duration, median (range), mo	-	70 (6-204)
Cumulative CS amount, median (range), mg	-	5,213 (840-36,894)
Ophthalmologic finding/disease, n (%)		
Cataract		
none	42 (66.7)	26 (41.3)
mild	13 (20.6)	18 (28.6)
severe	8 (12.7)	19 (30.2)
exacerbated after CS initiation	-	20 (31.7)
Glaucoma		
none	59 (93.7)	54 (85.7)
mild	4 (6.3)	9 (14.3)
severe	0 (0)	0 (0)
exacerbated after CS initiation	-	5 (7.9)
Miculcz's disease	1 (3.2) (treated by CS)	5 (7.9)(new onset during or after withdrawal of CS)
Other newly recognized findings (n)	dry eye (2), optic nerve pit (2), coloboma (1), conjunctival melanosis (1), retinal arteriosclerosis (1)	fundus hemorrhage (1), retinal detachment (1)

\*ophthalmologic findings recognized at the CS initiation. For the rest of abbreviations see Table I.

His pancreatic lesion went into remission during the next six months, with only continuous cyclosporine intake.

Another female patient with Behcet's disease, who had a history of uveitis at age 43 and who had lost vision in her left eye, developed AIP at age 73. She tested positive for HLA antigen types A26 and B51. Her serum IgG4 level

was within the normal range, but her pancreas was diffusely swollen. Histology of the FNA tissue, her steroid response, and her imaging findings led to a diagnosis of definitive type 1 AIP [20]. Her CS therapy was discontinued 22 months after initiation, and her pancreas stayed well, without relapse, for 18 months. However, at the fifth month after CS withdrawal,

**Table III.** Factors associated with the exacerbation of cataract after CS initiation (n=63)

Factor	Exacerbation of cataract		Univariate analysis		Multivariate analysis	
	(+), n=20	(-), n=43	Odd's ratio (95%CI)	p	Odd's ratio (95%CI)	p
Gender (male), n (%)	16 (80)	29 (67.4)	1.93 (0.54-6.86)	0.379		
History						
Smoking: %(n)	16 (80)	25 (58.1)	2.24 (0.63-8.03)	0.247		
Drinking#: %(n)	2 (10)	11 (25.6)	0.32 (0.06-1.62)	0.196		
Diabetes: %(n)	4 (20)	9 (20.9)	0.94 (0.25-3.53)	1		
At the diagnosis of AIP						
Age: median (range), y.o.	66 (50-77)	69 (45-84)	-	0.522		
Diabetes*, n (%)	8 (40)	18 (41.9)	0.93 (0.31-2.73)	1		
BMI, median (range)	22.1 (19.0-28.6)	21.3 (16.1-32.3)	-	0.374		
AIP-related findings						
Serum IgG4, mg/dL	295 (78-1080)	299 (22-3440)	-	0.337		
Macroscopic type** (diffuse type), n (%)	9 (45)	14 (32.6)	1.69 (0.57-5.03)	0.405		
Other organ involvement: %(n)	11 (55)	17 (39.5)	1.87 (0.64-5.46)	0.286		
At the last CS intake						
Age: median (range), y.o.	76 (62-80)	73 (52-89)	-	0.447		
Cumulative amount of predonine, median (range), mg	12,445 (1990-43760)	5,515 (1347-32168)	-	0.035	3.62 (1.07-12.30)	0.039

#habitual alcohol intake over 200g/week, \*positive if serum HbA1c is >6.2%, positive urinary glucosa or diabetic drugs are used, \*\*macroscopic type of AIP is consisted of focal-type and diffuse-type. For the rest of abbreviations see Table I.

**Table IV.** Clinical findings at the onset of Mikulicz's disease (n=7)

Gender (male), n (%)	3 (42.9)
Age: median (range), y.o.	61 (52-80)
Onset of Mikulicz's disease at the initial diagnosis of AIP, (after withdrawal of CS)	2 (5)
CS intake, n (%)	0 (0)
Serum IgG4, median (range), mg/dL	746 (76-1,240)#
OOI other than pancreas, parotid gland, and submandibular gland, n (%)	1 (14.3), hilar bile duct at the initial diagnosis
Recurrence of AIP, n (%)	0 (0)

OOI: other organ involvement, \*All seven cases developed Mikulicz's disease at the initial diagnosis of AIP or after the withdrawal of corticosteroids. #P = 0.08 (vs. Mikulicz's disease (-) group by Mann-Whitney U test). For the rest of abbreviations see Table I.

she developed elbow pain and intermittent fever ( $\leq 38^{\circ}\text{C}$ ). Her serum IgG4 was still within the normal range, but her serum C-reactive protein was elevated (3.8-7.2 mg/dL; normal:  $\leq 0.3$  mg/dL). She was diagnosed with a recurrence of Behcet's disease with arthritis, and she responded well after restarting low-dose CS and colchicine.

## DISCUSSION

So far, ophthalmologic changes after long-term CS therapy have not been reported in patients with AIP. Besides, Mikulicz disease [15-17] is the only ocular disease specifically reported in patients with AIP. Our current study demonstrated the alterations of ocular findings after the long CS treatment, and especially focused on the factors associated with the new onset or exacerbation of cataract, glaucoma and Mikulicz's disease. In 105 patients with AIP, two patients demonstrated a history of Behcet's uveitis, possibly suggesting a spectrum of autoimmune disorder, as in association with Mikulicz's disease.

The past histories of ophthalmologic diseases were analyzed in 105 patients with AIP. The changes over time in the ophthalmologic findings and the factors associated with the onset and exacerbation of cataract (Table III), glaucoma (Supplemental file, Table 1), and Mikulicz's disease (Supplemental file, Table 2) were also investigated in 63 of the 105 patients who were undergoing CS therapy. Prior to the onset of AIP, at the diagnosis of AIP, and during the treatment course of AIP, various ophthalmologic disorders were identified, suggesting the need for ophthalmologic consultation in cases of AIP.

Prior to the initial diagnosis, the patients with AIP, who had a median age of 69 years, had histories of cataract in 20%, glaucoma in 6%, uveitis in 2%, Mikulicz disease in 1%, and various other eye diseases in smaller fractions (Table I). Known risk factors for cataract and glaucoma, such as histories of diabetes (49.5%) [11] and smoking (72.4%) [12], were frequently recognized at the initial diagnosis of current AIP cases as indications for a requirement for eye checks among patients being considered for CS treatment, which is also a risk for these eye diseases [26-28]. The Japanese Ophthalmological Society advocates determining the risk for IOP elevation and recommends that doctors perform regular IOP tests in patients undergoing CS treatment ([https://www.gankaikai.or.jp/info/20250401\\_steroid.pdf](https://www.gankaikai.or.jp/info/20250401_steroid.pdf)).

The most characteristic ophthalmologic disease in cases of type 1 AIP is Mikulicz's disease, which is a common phenotype associated with IgG4-related diseases [30], with symptoms that include swelling of the lachrymal gland, submandibular gland, and parotid gland. Histologically, the disease appears as IgG4-positive lymphoplasmacytic aggregation. When associated with type 1 AIP, patients with Mikulicz's disease often demonstrate markedly elevated serum IgG4 (970-1253 mg/dL) [17, 31], diffuse pancreatic swelling (80%) [17], and other organ involvements (73%) [31]. The cases with Mikulicz's disease in the current study also demonstrated higher disease activities than were observed in the patients without Mikulicz's disease (Supplemental file, Table 2), and five cases developed the disease after CS withdrawal, showing high serum IgG4, but without pancreatic recurrence (Table IV). Typically, nearly 80% of AIP cases are male [6], but fewer males were found among the cases with Mikulicz's disease in the current study (43%, 3/7) and in a study reported by Kubota et al. (20%, 1/5) [17]. Kuruma et al. [31] also reported a marked predominance of females in cases with only Mikulicz's disease (79%, 11/14), but found a male predominance in AIP cases with the onset of Mikulicz's disease (73%, 11/15). A retrospective study from 9 Japanese ophthalmic divisions demonstrated nearly equal gender balance (155 male vs. 170 female) in patients with IgG4-related lacrimal gland lesions [32]. Women's cosmetic consciousness may result in female predominance in ophthalmic cohorts [32], and in contrast, the proportion can be deviated toward male in an AIP cohort [31], so that true gender ratio is difficult to be determined in Mikulicz's disease.

Several autoimmune diseases, such as AIH-PBC overlap syndrome (autoimmune hepatitis and primary biliary cirrhosis) [33], Evans syndrome (immune thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia) [34], and many other patterns [35], may concomitantly or subsequently overlap multiple autoimmune disorders [35]. Within our 105 cases of AIP, 2 cases had a history of Behcet's disease (Table I). One case had controlled the disease activity by taking an immunosuppressant, and the other case, who experienced a relapse of Behcet's disease with multiple joint pain after the withdrawal of CS, restarted the intake of predonine and colchicine. Although rare, overlap can occur between IgG4-related diseases (including type 1 AIP) and several other autoimmune diseases (including rheumatic diseases [36] and systemic lupus erythematosus [37]). Doctors

need to remain aware of relapse, not only of AIP but also of the previous autoimmune disease, because of possible exacerbation of autoimmune activity due to administration and withdrawal of CS.

Corticosteroid-induced glaucoma was also a concern raised by the current findings. The global incidence of glaucoma has been reported to be roughly 3.5% (open-angle glaucoma: 3.1% and angle-closure glaucoma: 0.5%) in people aged 40–80 years; however, this rate varies due to subtle differences in ethnicity [38] and recently increasing incidences (e.g. 1.29% in East Asia and 0.15% in Eastern Europe during the past two decades) [21]. The incidence of glaucoma in Japanese people over 40 years of age has been reported to be even higher (5.0–7.6%) [22, 39], and is almost comparable to the current incidence (6%) (Table I). To date, modest risks for glaucoma have been reported due to aging [38], diabetes [11, 38] and CS intake [29]; however, we were unable to establish risk factors that were significantly associated with glaucoma (Supplemental file, Table 1).

During the median 70 months of CS treatment, 7.9% (5/63) of our patients developed mild glaucoma and required eye drop treatments, but not surgery or laser therapy (Table II). In general, about 5% of the population are high-steroid responders and develop an IOP elevation >15 mmHg above baseline [28]. Close monitoring of high-risk patients is recommended, and withdrawal or use of steroid-sparing drugs should be considered if IOP elevation is recognized. The IOP usually returns to normal within 2–4 weeks after stopping steroid use, but about 1–5% of the cases do not respond to medical therapy and need surgery [28]. The prevalence and seriousness of this condition lead us to support the recommendation of regular eye checks for glaucoma in patients undergoing CS treatment [28, 29].

Cataract is another concern encountered with CS treatment. The data from a Japanese population study in 1995 showed more than mild levels of cataract in 24.3–38.4% persons at age 50, in 42.9–65.3% persons at age 60, and in 65.4–84.6% persons at age 70. Worldwide meta-analyses have identified several mild risk factors, such as radiation exposure among interventional cardiologists [relative risk (RR): 3.21] [40], long-term CS treatment for rheumatoid arthritis (OR: 2.10) [26], diabetes (OR: 1.50–1.97) [23, 24], smoking habit (OR: 1.41–1.47) [12], drinking habit (alcohol consumption: >140 g per week, RR: 1.26) [13], lack of vitamin C (RR: 1.23) [41], vitamin A/E and  $\beta$ -carotene deficiency [12], antidepressant use (OR: 1.12–1.19) [42], and daily sunlight exposure (OR: 1.15)<sup>43</sup>. The current study results demonstrated a similar incidence of cataract (21/63; 33.3%) at the initiation of CS treatment (at 68 years old) and at the last CS treatment (at 73 years old) (37/63; 60%) (Table 2), and CS treatment was the only factor demonstrated to be significantly associated with cataract exacerbation. Although not statistically significant, age and smoking incidence were also higher in the cataract-positive group (Table III).

Lessening the ophthalmologic and other systemic events associated with accumulated steroid intake will require the discovery of steroid-sparing agents. However, to date, CS [1–3] is the only drug approved by the Japanese national insurance for the treatment of AIP. Corticosteroid treatment has been indicated for symptomatic cases, or 82–86% [1] of the total

AIP cases. This treatment leads to clinical remission in 98–99% [1, 2] of patients; however, because up to 92% relapse within 3 years after CS withdrawal [2], a long period of low-dose CS therapy is usually continued [6]. Because immunomodulators (AZA/6-MP and mycophenolate mofetile) and rituximab are available to treat AIP in clinics overseas [3], the development and insurance coverage for steroid-sparing drugs are expected in Japan for the treatment of AIP, especially in cases with high autoimmune activity.

The current study, as a retrospective cohort study, has several limitations. The small number of patients from a single cancer center may prohibit generalization to other cases of AIP (i.e., focal-type AIP was dominant in our patients). Some patients were referred to their nearest ophthalmologist's clinic. Corticosteroid treatment was indicated only for symptomatic patients and was restarted when the disease recurred rather than using immune-modulators or rituximab.

## CONCLUSIONS

The current study analyzed the incidence of and factors associated with the ophthalmologic disorders occurring at the diagnosis of AIP and during CS treatment. Mikulicz's disease, as well as other autoimmune-related diseases, such as Behcet disease, were seen in the patient histories. Common CS-related diseases, such as cataract and glaucoma, were recognized in a proportion of the patients and worsened during the CS treatment course, suggesting that regular ophthalmologic monitoring is needed in patients with AIP.

**Conflicts of interest:** None to declare.

**Authors' contributions:** H.M. performed data acquisition, interpreted the results and drafted and manuscript. H.K. worked on ophthalmologic data acquisition. T.D., H.S., J.S., H.I., T.O., K.S., H.A., K.T., K.I., K.H., S.I., N.K., M.Y., and Y.Y. worked on diagnostic and endoscopic data acquisition, T.S. and K.U. worked on surgical and pathological data acquisition. T.S. and Y.K. performed statistical analyses. H.O. supervised the study. All authors read and approved the final manuscript.

**Supplementary material:** To access the supplementary material visit the online version of the *J Gastrointest Liver Dis* at <http://dx.doi.org/10.15403/jgld-6318>

## REFERENCES

1. Kubota K, Kamisawa T, Nakazawa T, et al. Steroid therapy still plays a crucial role and could serve as a bridge to the next promising treatments in patients with IgG4-related sclerosing cholangitis: Results of a Japanese Nationwide Study. *J Hepatobiliary Pancreat Sci* 2022;29:884–897. doi:10.1002/jhbp.1157
2. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;58:1504–1507. doi:10.1136/gut.2008.172908
3. Okazaki K, Ikeura T, Uchida K. Recent progress on the treatment of type 1 autoimmune pancreatitis and IgG4-related disease. *Mod Rheumatol* 2023;33:237–241. doi:10.1093/mr/roac054

4. Matsubayashi H, Yoneyama M, Nanri K, et al. Determination of steroid response by abdominal ultrasound in cases with autoimmune pancreatitis. *Dig Liver Dis* 2013;45:1034-1040. doi:[10.1016/j.dld.2013.06.006](https://doi.org/10.1016/j.dld.2013.06.006)
5. Masamune A, Nishimori I, Kikuta K, et al. Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis. *Gut* 2017;66:487-494. doi:[10.1136/gutjnl-2016-312049](https://doi.org/10.1136/gutjnl-2016-312049)
6. Kubota K, Kamisawa T, Okazaki K, et al. Low-dose maintenance steroid treatment could reduce the relapse rate in patients with type 1 autoimmune pancreatitis: a long-term Japanese multicenter analysis of 510 patients. *J Gastroenterol* 2017;52:955-964. doi:[10.1007/s00535-016-1302-1](https://doi.org/10.1007/s00535-016-1302-1)
7. Humphrey MB, Russell L, Danila MI, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol* 2023;75:2088-2102. doi:[10.1002/art.42646](https://doi.org/10.1002/art.42646)
8. Rice JB, White AG, Scarpatti LM, et al. Longterm- Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin Ther* 2017;39:2216-2229. doi:[10.1016/j.clinthera.2017.09.011](https://doi.org/10.1016/j.clinthera.2017.09.011)
9. Phulke S, Kaushik S, Kaur S, et al. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. *J Curr Glaucoma Pract* 2017;11:67-72. doi:[10.5005/jp-journals-10028-122610](https://doi.org/10.5005/jp-journals-10028-122610)
10. Wong TY, Sun J, Kawasaki R, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. *Ophthalmology* 2018;125:1608-1622. doi:[10.1016/j.ophtha.2018.04.007](https://doi.org/10.1016/j.ophtha.2018.04.007)
11. Trott M, Smith L, Veronese N, et al. Eye disease and mortality, cognition, disease, and modifiable risk factors: an umbrella review of meta-analyses of observational studies. *Eye (Lond)* 2022;36:369-378. doi:[10.1038/s41433-021-01684-x](https://doi.org/10.1038/s41433-021-01684-x)
12. Kai JY, Zhou M, Li DL, et al. Smoking, dietary factors and major age-related eye disorders: an umbrella review of systematic reviews and meta-analyses. *Br J Ophthalmol* 2023;108:51-57. doi:[10.1136/bjo-2022-322325](https://doi.org/10.1136/bjo-2022-322325)
13. Gong Y, Feng K, Yan N, et al. Different amounts of alcohol consumption and cataract: a meta-analysis. *Optom Vis Sci* 2015;92:471-479. doi:[10.1097/OPX.0000000000000558](https://doi.org/10.1097/OPX.0000000000000558)
14. Nieto-Aristizabal I, Mera JJ, Giraldo JD, et al. From ocular immune privilege to primary autoimmune diseases of the eye. *Autoimmun Rev* 2022;21:103122. doi:[10.1016/j.autrev.2022.103122](https://doi.org/10.1016/j.autrev.2022.103122)
15. Matsubayashi H, Kakushima N, Takizawa K, et al. Diagnosis of autoimmune pancreatitis. *World J Gastroenterol* 2014;20:16559-16569. doi:[10.3748/wjg.v20.i44.16559](https://doi.org/10.3748/wjg.v20.i44.16559)
16. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011;40:352-358. doi:[10.1097/MPA.0b013e3182142fd2](https://doi.org/10.1097/MPA.0b013e3182142fd2)
17. Kubota K, Wada T, Kato S, et al. Highly active state of autoimmune pancreatitis with mikulicz disease. *Pancreas* 2010;39:e6-10. doi:[10.1097/MPA.0b013e3181bc119d](https://doi.org/10.1097/MPA.0b013e3181bc119d)
18. Antonini L, Le Mauff B, Marcelli C, Aouba A, de Boysson H. Rhupus: a systematic literature review. *Autoimmun Rev* 2020;19:102612. doi:[10.1016/j.autrev.2020.102612](https://doi.org/10.1016/j.autrev.2020.102612)
19. Rojas-Feria M, Castro M, Suarez E, et al. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. *World J Gastroenterol* 2013;19:7327-740. doi:[10.3748/wjg.v19.i42.7327](https://doi.org/10.3748/wjg.v19.i42.7327)
20. Kawa S, Kamisawa T, Notohara K, et al. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011. *Pancreas* 2020;49:e13-e14. doi:[10.1097/MPA.0000000000001443](https://doi.org/10.1097/MPA.0000000000001443)
21. Lin Y, Jiang B, Cai Y, et al. The Global Burden of Glaucoma: Findings from the Global Burden of Disease 2019 Study and Predictions by Bayesian Age-Period-Cohort Analysis. *J Clin Med* 2023;12:1828. doi:[10.3390/jcm12051828](https://doi.org/10.3390/jcm12051828)
22. Fujiwara K, Yasuda M, Hata J, et al. Prevalence of Glaucoma and Its Systemic Risk Factors in a General Japanese Population: The Hisayama Study. *Transl Vis Sci Technol* 2022;11:11. doi:[10.1167/tvst.11.11.11](https://doi.org/10.1167/tvst.11.11.11)
23. Khan J, Shaw S. Risk of cataract and glaucoma among older persons with diabetes in India: a cross-sectional study based on LASI, Wave-1. *Sci Rep* 2023;13:11973. doi:[10.1038/s41598-023-38229-z](https://doi.org/10.1038/s41598-023-38229-z)
24. Li L, Wan XH, Zhao GH. Meta-analysis of the risk of cataract in type 2 diabetes. *BMC Ophthalmol* 2014;14:94. doi:[10.1186/1471-2415-14-94](https://doi.org/10.1186/1471-2415-14-94)
25. Chen H, Sun X, Pei L, Wang T. Body mass index influences age-related cataracts: an updated meta-analysis and systemic review. *Arq Bras Oftalmol* 2024;87:e2021. doi:[10.5935/0004-2749.2021-0382](https://doi.org/10.5935/0004-2749.2021-0382)
26. Black RJ, Hill CL, Lester S, et al. The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *PLoS One* 2016;11:e0166468. doi:[10.1371/journal.pone.0166468](https://doi.org/10.1371/journal.pone.0166468)
27. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-955. doi:[10.1001/archinte.159.9.941](https://doi.org/10.1001/archinte.159.9.941)
28. Razeghinejad MR, Katz LJ. Steroid-induced iatrogenic glaucoma. *Ophthalmic Res* 2012;47:66-80. doi:[10.1159/000328630](https://doi.org/10.1159/000328630)
29. Kawabe A, Uesawa Y. Analysis of Corticosteroid-Induced Glaucoma Using the Japanese Adverse Drug Event Reporting Database. *Pharmaceuticals (Basel)* 2023;16:948. doi:[10.3390/ph16070948](https://doi.org/10.3390/ph16070948)
30. Goto H, Ueda SI, Nemoto R, et al. Clinical features and symptoms of IgG4-related ophthalmic disease: a multicenter study. *Jpn J Ophthalmol* 2021;65:651-656. doi:[10.1007/s10384-021-00847-3](https://doi.org/10.1007/s10384-021-00847-3)
31. Kuruma S, Kamisawa T, Tabata T, et al. Clinical Characteristics of Patients with Autoimmune Pancreatitis with or without Mikulicz's Disease and Mikulicz's Disease Alone. *Gut Liver* 2013;7:96-99. doi:[10.5009/gnl.2013.7.1.96](https://doi.org/10.5009/gnl.2013.7.1.96)
32. Goto H, Ueda SI, Nemoto R, et al. Clinical features and symptoms of IgG4-related ophthalmic disease: a multicenter study. *Jpn J Ophthalmol* 2021;65:651-656. doi:[10.1007/s10384-021-00847-3](https://doi.org/10.1007/s10384-021-00847-3)
33. Silveira MG, Talwalkar JA, Angulo P, Lindor KP. Overlap of autoimmune hepatitis and primary biliary cirrhosis: long-term outcomes. *Am J Gastroenterol* 2007;102:1244-1250. doi:[10.1111/j.1572-0241.2007.01136.x](https://doi.org/10.1111/j.1572-0241.2007.01136.x)
34. Fattizzo B, Marchetti M, Michel M, et al. Diagnosis and management of Evans syndrome in adults: first consensus recommendations. *Lancet Haematol* 2024;11:e617-e628. doi:[10.1016/S2352-3026\(24\)00144-3](https://doi.org/10.1016/S2352-3026(24)00144-3)
35. Pepmueller PH. Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. *Mo Med* 2016;113:136-140.
36. Batani V, Lanzillotta M, Mahajne J, et al; Egyptian College of Rheumatology IgG4 Study group. Association of IgG4-related disease and systemic rheumatic disorders. *Eur J Intern Med* 2023;111:63-68. doi:[10.1016/j.ejim.2023.03.015](https://doi.org/10.1016/j.ejim.2023.03.015)
37. El-Saadany H, El-Saadany H, Tharwat S, et al. Discriminative features of immunoglobulin G4-related disease (IgG4-RD) and associated autoimmune rheumatic diseases (ARDs) in a nationwide observational cohort: study from the Egyptian College of Rheumatology. *Clin Rheumatol* 2025;44:747-756. doi:[10.1007/s10067-024-07274-y](https://doi.org/10.1007/s10067-024-07274-y)
38. Jonas JB, Aung T, Bourne RR. Glaucoma. *Lancet* 2017;390:2183-2193. doi:[10.1016/S0140-6736\(17\)31469-1](https://doi.org/10.1016/S0140-6736(17)31469-1)

39. Yamamoto T, Iwase A, Araie M, et al. The Tajimi Study report 2: prevalence of primary angle closure and secondary glaucoma in a Japanese population. *Ophthalmology* 2005;112:1661-1669. doi:[10.1016/j.ophtha.2005.05.012](https://doi.org/10.1016/j.ophtha.2005.05.012)
40. Elmarazy A, Ebraheem Morra M, Tarek Mohammed A, et al. Risk of cataract among interventional cardiologists and catheterization lab staff: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2017;90:1-9. doi:[10.1002/ccd.27114](https://doi.org/10.1002/ccd.27114)
41. Wei L, Liang G, Cai C, et al. Association of vitamin C with the risk of age-related cataract: a meta-analysis. *Acta Ophthalmol* 2016;94:e170-6. doi:[10.1111/aos.12688](https://doi.org/10.1111/aos.12688)
42. Fu Y, Dai Q, Zhu L, et al. Antidepressants use and risk of cataract development: a systematic review and meta-analysis. *BMC Ophthalmol* 2018;18:31. doi:[10.1186/s12886-018-0699-0](https://doi.org/10.1186/s12886-018-0699-0)
43. Li X, Cao X, Yu Y, Bao Y. Correlation of Sunlight Exposure and Different Morphological Types of Age-Related Cataract. *Biomed Res Int* 2021;2021:8748463. doi:[10.1155/2021/8748463](https://doi.org/10.1155/2021/8748463)