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Case Report

Effects of Steroid Therapy on Pancreatic Endocrine Function in IgG4-related AIP: Evaluation by Arginine Stimulation Test

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Abstract

IgG4-related diseases are fibroinflammatory disorders affecting multiple organs, with autoimmune pancreatitis (AIP) being a common manifestation. Steroid therapy is effective in inducing remission but has complex effects on glucose metabolism. Diabetes occurs in 40% to 80% of AIP patients, and steroids can worsen glucose tolerance, although some studies suggest they may improve pancreatic endocrine function. An 81-year-old man with elevated IgG4 levels and imaging findings consistent with AIP initially declined treatment. His condition worsened, leading to poor glycemic management and referral to our hospital. Imaging confirmed AIP and tests showed impaired insulin and glucagon secretion. He was diagnosed with pancreatic diabetes secondary to IgG4-related AIP. Initially, intensive insulin therapy was administered, but within 3 months, both insulin and glucagon secretion declined significantly in the arginine-stimulation test, necessitating steroid therapy with prednisolone (35 mg/day) for the AIP. The high dose of steroid treatment enhanced both insulin and glucagon secretion capacities but gradually declined with dose tapering. On the other hand, although steroid therapy poses a temporary risk of hyperglycemia, it likely prevented further deterioration of pancreatic endocrine function.

Key Words: IgG4-related diseases, autoimmune pancreatitis, pancreatic diabetes, arginine-stimulation test, pancreatic endocrine function, steroid

Introduction

IgG4-related diseases (IgG4RD) are fibroinflammatory diseases that affect various organs throughout the body [1]. Among them, autoimmune pancreatitis (AIP) is the most common manifestation. AIP is more prevalent in older males and presents with a sausage-like enlargement of the pancreas and irregular narrowing of the pancreatic ducts or localized enlargement and mass lesions of the pancreas. It has been reported that between 40% and 80% of patients with AIP have diabetes as a consequence of impaired pancreatic endocrine function [2]. Steroid therapy has been shown to be effective for the treatment of IgG4RD. The efficacy of steroid therapy for AIP has already been demonstrated in previous studies: 98% of patients with AIP responded to steroid therapy, 80% exhibited improvement in pancreatic enlargement on imaging, and IgG4 levels decreased in all patients [3]. Although the remission rate of AIP is 98%, relapse occurs in 30% to 60% of the cases. To prevent relapse, 1 to 3 years of maintenance therapy with steroids is recommended. Given its role to prevent relapse and the long-term prognosis of pancreatic function, steroid therapy remains the gold standard treatment for AIP [3].

However, it is widely recognized that steroid therapy may exacerbate diabetes. Conversely, some reports indicate that steroid therapy has been shown to enhance pancreatic endocrine function and glucose tolerance [3-5]. The effect of steroid therapy in AIP on blood glucose levels remains inconclusive but a case report suggests a potential correlation between fluctuations in blood glucose levels in response to steroid administration and steroid-induced alterations in α-cell function [6].

In light of these findings, we sought to examine the effect of steroid therapy for IgG4-related AIP on pancreatic endocrine function over time using the arginine-stimulation test (AST).

Case Presentation

An 81-year-old man visited his previous physician 6 years before the referral to our hospital because of dyspnea and facial edema. He had no significant medical history. His family history was notable only for his mother having diabetes. Upon examination, he was found to have pleural effusion and pericardial effusion. After further examination, although the cause was unknown, he was initiated on treatment with azosemide 60 mg for idiopathic constrictive pericarditis. Hepatobiliary enzymes were also elevated, and he received a diagnosis of congestive liver. At the same time, he was diagnosed with diabetes with a fasting blood glucose level of 156 mg/dL (8.7 mmol/L) (reference range, 70-109 mg/dL; 3.9-6.1 mmol/L) and glycated hemoglobin A1c (HbA1c) of 6.9% (52 mmol/mol) (reference range, 4.6-6.2%; 22-44 mmol/mol). Under the guidance of his physician, he initially managed his blood glucose levels through lifestyle intervention with diet and exercise. However, his HbA1c deteriorated, necessitating the initiation of medication 3 years later.

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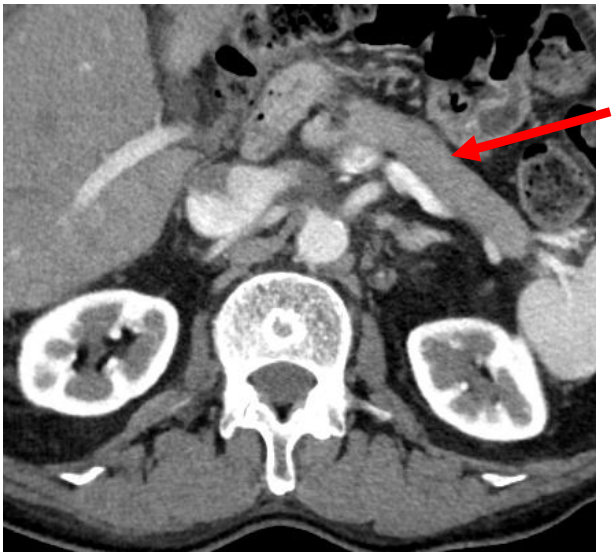

Figure 1. Axial view of pancreatic dynamic contrast-enhanced CT. The arrow indicates diffuse enlargement of the pancreas.

Table 1. Results of the meal tolerance test at the diagnosis and 3 months after

	0 minutes	120 minutes	Reference range (0 minutes)
At the diagnosis			
Plasma glucose	121 mg/dL (6.72 mmol/L)	271 mg/dL (15.06 mmol/L)	70-109 mg/dL (3.9 mmol/L −6.0 mmol/L)
Serum C-peptide	1.58 ng/mL (0.523 nmol/L)	2.76 ng/mL (0.914 nmol/L)	0.61-2.09 ng/mL (0.20 −0.69 nmol/L)
Just before the start of steroid (3 months after diagnosis)			
Plasma glucose	161 mg/dL (8.94 mmol/L)	228 mg/dL (12.67 mmol/L)	70-109 mg/dL (3.9-6.0 mmol/L)
Serum C-peptide	0.69 ng/mL (0.228 nmol/L)	0.97 ng/mL (0.321 nmol/L)	0.61-2.09 ng/mL (0.20-0.69 nmol/L)

Values in parentheses are International System of Units (SI). A generally accepted reference range for the postload data of meal tolerance test has not been established.

He had been on diuretics continuously for 6 years, successfully reducing pleural and pericardial effusions. However, because there was no improvement in liver dysfunction, the previous physician conducted a thorough evaluation 1 year before the referral to our hospital. The level of IgG4 was elevated at 690 mg/dL (6.90 g/L) (reference range, 11-121 mg/dL; 0.11-1.21 g/L), and computed tomography (CT), magnetic resonance cholangiopancreatography, and endoscopic ultrasonography showed findings indicative of AIP, including diffuse pancreatic enlargement and irregular stenosis of the main pancreatic duct. The possibility of IgG4RD was pointed out to the patient, but he had no subjective symptoms and did not wish to undergo further examination, which led him to leave without any subsequent examination or treatment.

Table 2. Arginine-stimulation test at the diagnosis

	0 minutes	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes	90 minutes	120 minutes	Reference range (0 minutes)
Plasma glucose	158 mg/dL (8.77 mmol/L)	161 mg/dL (8.94 mmol/L)	162 mg/dL (9.00 mmol/L)	164 mg/dL (9.11 mmol/L)	164 mg/dL (9.11 mmol/L)	167 mg/dL (9.28 mmol/L)	164 mg/dL (9.11 mmol/L)	165 mg/dL (9.17 mmol/L)	162 mg/dL (9.00 mmol/L)	70-109 mg/dL (3.9-6.0 mmol/L)
Serum insulin	3.4 μU/mL (23.6 pmol/L)	8.0 μU/mL (55.6 pmol/L)	6.8 μU/mL (47.2 pmol/L)	6.3 μU/mL (43.8 pmol/L)	6.1 μU/mL (42.4 pmol/L)	6.0 μU/mL (41.6 pmol/L)	5.3 μU/mL (36.8 pmol/L)	4.7 μU/mL (32.8 pmol/L)	5.2 μU/mL (36.1 pmol/L)	1.84-12.2 μU/mL (12.7-84.7 pmol/L)
Serum C-peptide	1.22 ng/mL (0.40 nmol/L)	1.63 ng/mL (0.54 nmol/L)	1.43 ng/mL (0.47 nmol/L)	1.61 ng/mL (0.53 nmol/L)	1.62 ng/mL (0.54 nmol/L)	1.45 ng/mL (0.48 nmol/L)	1.58 ng/mL (0.52 nmol/L)	1.71 ng/mL (0.57 nmol/L)	1.73 ng/mL (0.57 nmol/L)	0.61-2.09 ng/mL (0.20-0.69 nmol/L)
Plasma glucagon	20.2 pg/mL (5.9 pmol/L)	57.8 pg/mL (16.9 pmol/L)	75.4 pg/mL (22.0 pmol/L)	83.9 pg/mL (24.5 pmol/L)	79.1 pg/mL (23.1 pmol/L)	62.0 pg/mL (18.1 pmol/L)	53.5 pg/mL (15.6 pmol/L)	42.6 pg/mL (12.4 pmol/L)	44.8 pg/mL (13.0 pmol/L)	5.4-55.0 pg/mL (1.6-16.9 pmol/L)

Values in parentheses are International System of Units (SI). A generally accepted reference range for the arginine-stimulation test has not been established; reference data regarding patients with type 2 diabetes and pancreatic diabetes can be found in the Diagnostic Assessment section of the manuscript.

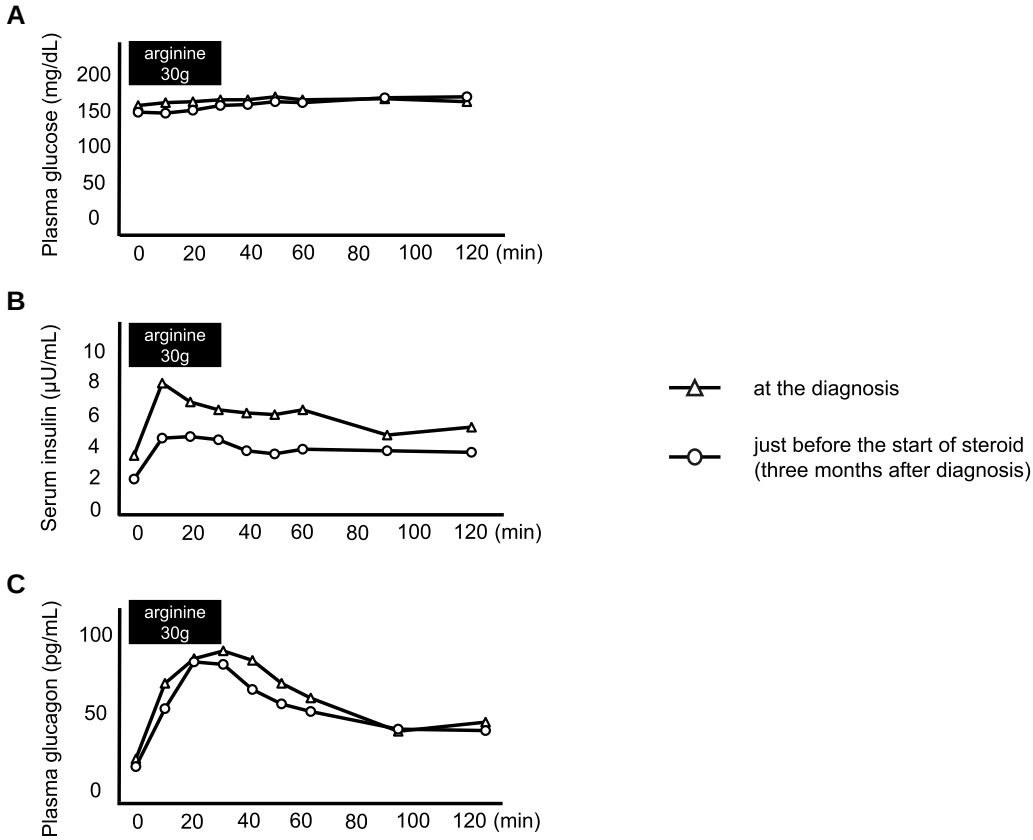

Figure 2. Arginine-stimulation test for assessing pancreatic endocrine capacity. The graph shows the result of AST of at the diagnosis (white triangle) and just before the start of steroid (white circle). (A) Plasma glucose. (B) The secretion of serum insulin. (C) The secretion of plasma glucagon.

The patient was referred to a primary care physician for further care.

Despite the monitoring of his diabetes by his primary care physician, the patient's fasting blood glucose remained elevated at 159 mg/dL (8.8 mmol/L) and his HbA1c at 9.8% (83.5 mmol/mol) with the administration of 5 mg of linagliptin and 0.5 mg of repaglinide twice per day before breakfast and dinner. For further examination and treatment, he was admitted to our hospital.

Diagnostic Assessment

Serum IgG4 levels were elevated at 676 mg/dL (6.76 g/L), and pancreatic dynamic contrast-enhanced CT (Fig. 1) and endoscopic ultrasonography showed diffuse enlargement of the pancreas and irregular stenosis of the main pancreatic duct. Following the Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2018 [7], he was diagnosed with definite AIP.

We surmised that the patient had pancreatic diabetes resulting from IgG4-related AIP, as diabetes was diagnosed concurrently with pericarditis without a history and any significant changes in lifestyle. The 24-hour urinary C-peptide excretion was slightly decreased at 64.8 μg/day (21.58 nmol/day) (reference range, 29.2-167 μg/day; 9.72—55.61 nmol/day), and the C-peptide response to the meal tolerance test also showed a reduced response, indicating that insulin secretion was moderately impaired (Table 1). To assess pancreatic endocrine function, we performed AST. AST was conducted by infusing 30 g of L-arginine hydrochloride over 30 minutes, and blood glucose, insulin, C-peptide, and glucagon levels were measured at 0, 10, 20, 30, 45, 60, 90, and 120 minutes.

Although there is some ambiguity in the mechanism on the stimulation of insulin secretion, it is widely accepted that AST is one of the standard tests to evaluate insulin secretion capacity. In addition, AST has an additional benefit of being able to evaluate glucagon secretion. In certain types of diabetes, including pancreatic diabetes, AST has been used to evaluate the decrease in glucagon secretion caused by damage to α cells [8]. In patients with type 2 diabetes, AST reportedly indicates a C-peptide apical value of approximately 3 to 4 ng/mL (1.0-1.3 nmol/L). In contrast, patients with pancreatic diabetes exhibits a lower C-peptide apical value of approximately 1 to 2 ng/mL (0.33-0.67 nmol/L) along with a diminished insulin secretory capacity [8]. This case showed a decrease in insulin secretion with a C-peptide apical value of 1.73 ng/mL (0.58 nmol/L) during AST (Table 2). Regarding glucagon secretion, Takeshima et al [6] reported that the difference between the peak and basal values of glucagon secretion during AST in a patient with reduced pancreatic endocrine capacity because of AIP was approximately 50 pg/mL (50 ng/L), which was comparable to the observation in this case (Table 2).

We further performed a pancreatic function diagnostic test to evaluate pancreatic exocrine function, which involves the oral administration of a reagent followed by measuring the excretion of its metabolites in the urine to assess the pancreatic exocrine function. The 6-hour excretion rate was found to be 39.3% (reference range, 73.4%-90.4%), indicating a decrease in pancreatic exocrine function. We diagnosed the patient with pancreatic diabetes resulting from AIP associated with IgG4RD based on the findings of reduced insulin and glucagon secretion as well as pancreatic exocrine function.

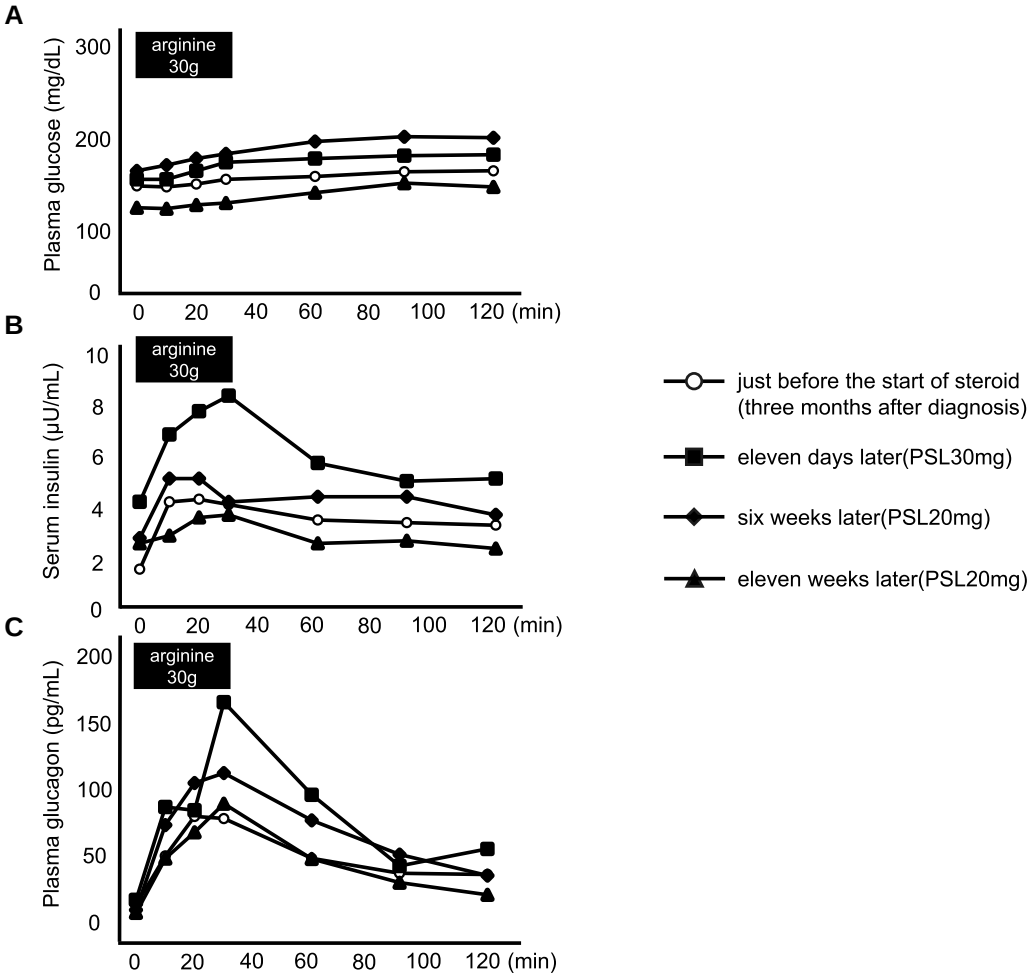

Figure 3. Arginine-stimulation test for assessing pancreatic endocrine capacity during steroid treatment. Results of AST just before the start of steroid (white circle), at 11 days (PSL 30 mg orally: black square), 6 weeks (PSL 20 mg orally: black diamond), and 11 weeks (PSL 20 mg orally: black triangle) after the start of steroid. (A) Plasma glucose. (B) The secretion of serum insulin. (C) The secretion of plasma glucagon.

Treatment

We started intensive insulin therapy for the pancreatic diabetes, which posed risk of further deterioration of the insulin secretion because of AIP. We opted to observe the course of AIP for a period because of the patient's advanced age and performed a meal tolerance test (Table 1) and an AST (Fig. 2) again after 3 months, which showed further decrease in both insulin and glucagon secretion. In addition, Homeostatic Model Assessment of β-cell function (HOMA-β) was 26.1% (reference range, >30%) at the time of AIP diagnosis, but had decreased to 7.8% 3 months later. The change in HOMA-β indicated that the progression of AIP resulted in a deterioration of pancreatic diabetes. Because of the significant reduction in insulin secretion because of progressing AIP, we initiated steroid therapy with prednisolone (PSL) 35 mg (0.5 mg/kg), expecting to improve pancreatic endocrine function, which would be followed by a gradual tapering of the dosage.

Outcome and Follow-up

The level of IgG4 decreased in conjunction with the commencement of steroid therapy, from a pretreatment value of 785 mg/dL (7.85 g/L) to 179 mg/dL (1.79 g/L) at 11 weeks after the initiation of steroid therapy. The results of magnetic resonance cholangiopancreatography demonstrated no worsening of pancreatic morphology.

For diabetes management, bolus insulin was administered 3 times per day before meals throughout the steroid therapy as intensive insulin therapy. No other antidiabetic medications were used. Before starting steroid therapy, a total daily dose (TDD) of 16 units of insulin lispro was administered. However, the initiation of steroid therapy was associated with an increase in insulin requirement, necessitating a TDD of 35 units when 25 mg of steroids were administered, which was the highest TDD during the course of treatment. As steroid dosage tapered, insulin requirements decreased to 24 units at 20 mg of steroids (11 weeks after the initiation of steroid therapy).

Before steroid therapy, the patient's HbA1c level was 8.7% (70.6 mmol/mol). Glycemic management gradually stabilized as the insulin dosage was increased, resulting in an HbA1c range of 7.8% to 8.1% (54.8-61.5 mmol/mol) at 1 month of steroid therapy (PSL 20 mg oral).

To assess the impact of steroid therapy on pancreatic endocrine function, we performed further ASTs at 11 days (PSL 25 mg orally), 6 weeks (PSL 20 mg orally), and 11 weeks (PSL 20 mg orally). There was a significant increase in both insulin and glucagon secretion levels at 11 days after starting steroids compared to the levels observed before the initiation of

steroid therapy (Fig. 3). However, insulin and glucagon secretion gradually decreased along with steroid tapering. In an AST conducted 11 weeks after the start of steroids, insulin secretion appeared to be decreased; however, HOMA-β suggested a slight recovery of insulin secretion capacity (from 7.8% pretreatment to 16.1% at 11 weeks after the initiation of steroid therapy). These results suggest that steroid treatment may have suppressed the inflammation of AIP and halted the progression of β-cell damage.

Discussion

IgG4RD is a steroid-responsive condition, and remission can be achieved in 98% of cases according to a report [3], making steroid therapy the standard treatment for IgG4-related AIP. AIP often causes pancreatic endocrine dysfunction and diabetes, and although steroid therapy can restore β-cell function impaired by AIP, there is also a concern that it may worsen diabetes.

Another group reported that they performed a 75-g oral glucose tolerance test and AST before and 4 weeks after initiating steroid therapy, in which they observed that α-cell function improved more than β-cell function, implying that the predominant restoration of glucagon secretion by steroid therapy for AIP contributed to the deterioration of glucose tolerance [6]. However, in our case, both insulin and glucagon secretion recovered markedly when using high-dose steroids but gradually decreased with steroid tapering to the same levels observed before treatment. There is also a report that glucagon secretion increases when corticosterone is administered under arginine administration in isolated mouse islets [9], suggesting the possibility that the observed increase in insulin and glucagon secretion immediately after starting steroid therapy was not due to the recovery of pancreatic endocrine function but was evoked through the effect of high-dose steroids. Nevertheless, considering the significant decline in pancreatic endocrine function over the 3 months before starting steroid therapy, the therapy may well have been effective in preventing the further deterioration of pancreatic endocrine function due to AIP progression. Indeed, insulin and glucagon secretion were maintained at the same levels as those before the steroid therapy, and HOMA-β was improved.

Learning Points

- The AST can evaluate glucagon secretion capacity in addition to insulin secretion and is therefore useful for the diagnosis of pancreatic diabetes.
- High-dose steroids of approximately 0.5 mg/kg enhance pancreatic endocrine function, likely because of their pharmacological effects.
- The anti-inflammatory effect of steroids may prevent the deterioration of pancreatic endocrine function caused by the progression of AIP.

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Contributors

All authors made individual contributions to authorship. All authors were involved in the diagnosis and management of this patient. M.M. and T.H. were involved in writing the first draft and submission. Y.Y., Y.H., and Y.S. critically revised the manuscript with important intellectual content. All authors reviewed and approved the final draft.

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Disclosures

There are no conflicts of interest to declare.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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