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Evaluation of antiseizure medications including zonisamide in feline idiopathic epilepsy at a referral hospital in Japan

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Abstract
Background: Idiopathic epilepsy in cats is a more common disease than previously thought, but little information is available about the medical treatment of feline idiopathic epilepsy.
Aim: To assess the therapeutic efficacy and safety of antiseizure medication (ASM) for a minimum of 6 months, including zonisamide (ZNS), in feline idiopathic epilepsy at a referral hospital in Japan.
Methods: Twenty cats diagnosed with idiopathic epilepsy treated with ASMs were retrospectively included.
Results: Nine cats that were finally treated with phenobarbital (PB) monotherapy reached the primary goal (the seizure frequency after the treatment intervention was less than one seizure every 3 months). Three cats were treated with ZNS monotherapy and two reached the primary goal. Eight cats finally received combination therapy. Two of the three cats receiving PB and ZNS therapy achieved the primary goal, but one was considered no responder. Five cats [PB + diazepam (DZP), ZNS + DZP, and ZNS + levetiracetam + DZP] decreased the seizure frequency and reached the primary goal in all but one cat reached the secondary goal. Adverse events were observed in eight patients, but these were curable. Two patients had vomiting after ZNS monotherapy, one had diarrhea, and another was an increase in sleeping hours.
Conclusion: PB was frequently used and seemed effective as both monotherapy and combination therapy. Some cats were treated with ASM protocols containing ZNS. ZNS may be available to treat idiopathic epilepsy in cats. However, ZNS administration may cause adverse events, such as gastrointestinal toxicity, in cats.
Keywords: Antiseizure medication, Feline, Idiopathic epilepsy, Zonisamide, Seizure.

Introduction

Epileptic seizures are characterized by abnormal excessive or synchronous neuronal activity in the brain (Coates and O'Brien, 2017). In veterinary practice, the incidence of epileptic seizures has been reported to be 2.1% among cats presenting to the hospital for any reason (Schriefl *et al.*, 2008).

Idiopathic epilepsy is defined as "recurring seizure syndrome with no detectable underlying abnormalities" (Platt and Risio, 2014). They are generally presumed to be genetic, but the pattern of inheritance is unknown in cats. At present, seizures without detectable cause are also referred to as idiopathic epilepsy in cats. In a study of cats presented to a veterinary neurology referral hospital in Japan, feline idiopathic epilepsy was diagnosed in 29% of the cats visiting the hospital because of brain disorders (Nakamoto *et al.*, 2019). Magnetic resonance imaging (MRI) is now widely used in veterinary practice and is a powerful tool for detecting structural abnormalities that may cause seizures. Thus, the increasing use of MRI helps the differentiation between idiopathic and structural epilepsy.

In veterinary medicine, epileptic seizures frequently require treatment with antiseizure medications (ASMs) depending on the frequency and severity of events. In cats, phenobarbital (PB), imepitoin, and levetiracetam (LEV) are often used to treat epilepsy (Charalambous *et al.*, 2018). However, imepitoin is not on the market and is not easily available in Japan. LEV is recommended as a second line ASMs for cats with epilepsy, but it is more expensive than other ASMs and needs administration three times daily, frequent administration of drugs is stressful for cats. Therefore, the other choice for ASMs should be evaluated for feline epilepsy. Zonisamide (ZNS) is licensed to treat canine epilepsy in Japan and is often used to treat dogs

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with recurrent seizures. In one survey, ZNS is the most frequently held ASMs in Japanese veterinary hospitals, and Japanese clinicians prescribe ZNS second most often, even in feline epilepsy (Mizuno *et al.*, 2022). However, no study has evaluated the efficacy and safety of ZNS in clinical feline cases and ZNS has not been strongly recommended for the treatment of feline epilepsy in a systematic review (Charalambous *et al.*, 2018). Moreover, the follow-up periods of almost all previous studies about ASMs were shorter than 6 months (Charalambous *et al.*, 2018), and the efficacy and safety information has not been clear enough. Therefore, more information on the use of ASMs, including ZNS, is needed to treat feline idiopathic epilepsy. This study used the medical records for at least 6 months in the Veterinary Medical Center (VMC) of the University of Tokyo to evaluate the efficacy and safety of ASMs, including ZNS, for treating feline idiopathic epilepsy.

Materials and Methods

Inclusion criteria of idiopathic epilepsy

Cats were included retrospectively if they were referred to the VMC of the University of Tokyo between 2013 and 2019 and were diagnosed with idiopathic epilepsy or presumptive idiopathic epilepsy by the following criteria: two or more unprovoked seizures at least 24 hours apart; no neurological abnormality in the interictal period; neither no complaints indicating intoxication nor blood test abnormalities that may cause reactive seizures (Kwiatkowska *et al.*, 2019); no structural abnormalities which can cause seizures identified on MRI scan (Risio *et al.*, 2015; Stanciu *et al.*, 2017).

Signalment

Medical information collected included breed, sex, body weight at the first visit, age at seizure onset, type of seizures, presence of cluster seizures and status epilepticus, and results of physical and neurological examinations, blood test results including complete blood cell count and serum biochemistry profile (sodium, potassium, chloride, calcium, alanine aminotransferase, alkaline phosphatase, total bilirubin, urea, creatinine, glucose, and ammonia) (Kwiatkowska *et al.*, 2019) and MRI findings.

In some cases, several examination data, such as urinalysis and cerebrospinal fluid analysis, were lacking but diagnosed as idiopathic epilepsy by clinicians as "presumptive idiopathic epilepsy." The viral status was examined when viral infection was especially suspected. None of the cats performed electroencephalography.

Definitions of terms and efficacy assessment

The types of seizures were classified based on the International veterinary epilepsy task force consensus statement (Berendt *et al.*, 2015) as generalized epileptic seizures, focal epileptic seizures evolving into generalized epileptic seizures, and focal epileptic seizures. Cluster seizures were defined as two or more seizures within 24 hours. Status epilepticus was clinically defined as (a) greater than 5 minutes of continuous epileptic seizures or (b) two or more discrete epileptic seizures separated by incomplete recovery of consciousness (for generalized convulsive seizures). Each seizure was counted individually and when cluster seizures were noted in a day, the seizure frequency was calculated as one seizure event. To evaluate the efficacy and adverse events of ASMs, information related to the treatment, such as used ASMs, the dosages of these ASMs, adverse events during the treatment, blood concentration of ASMs if available, the frequency of seizures at the diagnosis and before changing ASMs in VMC (before referral), frequency of seizures at 6 months after referral, and presence of cluster seizures and status epilepticus before and after 6 months of treatment, was collected.

Seizure frequency was calculated based on the owner's report. Patients in which the seizure frequency after the treatment intervention was less than one seizure every 3 months were defined as reaching the "primary goal". Patients showing more than a 50% reduction in the frequency of seizures or preventing cluster seizures or status epilepticus were considered to reach the "secondary goal" (Potschka *et al.*, 2015). Patients that did not reach the primary nor the secondary were considered as "no responders".

Ethical approval

This work involved using non-experimental animals only (including only owned animals and data from retrospective studies). Established internationally recognized high standards ("best practice") of individual veterinary clinical patient care were followed. The owner agreed with the informed consent for academic purposes.

Results

Animals and classification of seizures

Sixty-three cats were diagnosed with idiopathic epilepsy (including presumptive) at the VMC of the University of Tokyo between 2013 and 2019. Among those cases, information on follow-up after 6 months was available for 20 cats treated with ASMs, which was included in this study. Exclusions (n = 43) were as follows; inadequate records for treatment (n = 26), no treatment due to a low frequency of seizures and acceptable for the owner (n = 11), withdrawal of treatment (n = 2), the presence of sudden behavioral changes such as aggression as the primary symptom, which precluded accurate assessments from determining whether the patient had epilepsy or behavioral problems (n = 3), MRI scan was not performed (n = 1).

Information about the 20 cats suited for treatment evaluation was described in Table 1. Of these 20 cats, nine were males (one sexually intact and eight castrated) and 11 were females (three sexually intact and eight spayed). At the first onset of an epileptic seizure, the patient's ages ranged from 4.0 months to 13 years (median, 2.8 years). The body weight ranged from 1.8 to 6.1 kg, and the median weight was 3.5 kg. Breeds included were as follows; domestic shorthair (n = 10), American short hair, Scottish fold, and Munchkin (n =

Table 1. Information about the patients included in the 6-month evaluation.

Case	Breed	Sex	BW (kg)	Age at onset (year)	Seizure type classification	First treatment	Second treatment after protocol change	Blood concentration	Seizure frequency per month (before referral)	Seizure frequency per month (after 6 months)	Reduction of seizure frequency	CS/SE (before referral)	CS/SE (after 6 months)	Response evaluation	Adverse effects
#1	ASH	SF	3.4	1.9	Focal epileptic seizures evolving into generalized epileptic seizures	PB 1.5 kg/ kg BID	PB 2.3 mg/ kg BID	PB 19 µg/ml (2nd)	10.0	0	100%	none	none	primary goal	none
#2	Chartreux	CM	4.8	8.4	Generalized	PB 1.6 mg/ kg BID	PB 1.5 mg/ kg BID	N/A	1.7	0	100%	none	none	primary goal	none
#3	DSH	SF	3.1	3.9	Focal	PB 1.7 mg// kg BID	PB 2 mg/kg BID	N/A	1.2	0	100%	none	none	primary goal	none
#4	DSH	CM	3.9	0.3	Generalized	PB 2 mg/kg BID	PB 2 mg/kg BID	N/A	6.7	0	100%	CS	none	primary goal	none
#5	DSH	CM	3.2	2.4	Generalized	PB 2.4 mg/ kg BID	PB 2.4 mg/ kg BID	PB 24.3 µg/ml (1st and 2nd)	0.5	0	100%	CS	none	primary goal	none
#6	DSH	CM	3.5	3.2	Generalized	PB 2.8 mg/ kg BID	PB 2 mg/kg BID	N/A	30.0	0	100%	CS	none	primary goal	none
#7	DSH	F	3.0	12.7	Generalized	PB 3 mg/kg BID	PB 3 mg/kg BID	N/A	30.0	0.5	98%	CS	none	secondary goal	none
#8	Munchkin	SF	3.2	3.1	Generalized	PB 6 mg/kg SID	PB 6 mg/kg SID	N/A	6.7	0	100%	CS	none	primary goal	Depressed proprioception of hind limbs
#9	Scottish fold	SF	4.1	3.8	Generalized	ZNS 6 mg/ kg BID	PB 2 mg/kg BID	N/A	3.0	0	100%	none	none	primary goal	Persistent diarrhea (ZNS)
#10	DSH	SF	3.2	0.4	Generalized	PB 5 mg/kg BID	PB 7.5 mg/ kg BID and DZP 0.5 mg/kg BID	N/A	3.8	2	48%	CS	none	secondary goal	Dullness (PB ~ PB + DZP)
#11	DSH	CM	6.1	4.2	Generalized	PB 2.6 mg/ kg BID and DZP 0.08 mg/kg SID	PB 2.6 mg/ kg BID and DZP 0.08 mg/kg SID	PB 29.8 µg/ml (1st and 2nd)	N/A	0	100%	none	none	primary goal	Elevation of liver enzyme (PB + DZP)
#12	Russian blue	F	2.3	1.2	Focal	PB 3 mg/kg BID	PB 2 mg/kg BID ZNS 7.4 mg/ kg BID	N/A	8.6	5	42%	none	none	no responder	Elevation of liver enzyme (PB + ZNS)

Continued

Case	Breed	Sex	BW (kg)	Age at onset (year)	Seizure type classification	First treatment	Second treatment after protocol change	Blood concentration	Seizure frequency per month (before referral)	Seizure frequency per month (after 6 months)	Reduction of seizure frequency	CS/SE (before referral)	CS/SE (after 6 months)	Response evaluation	Adverse effects
#13	DSH	CM	4.4	0.6	Generalized	PB 1.7 mg/kg BID and ZNS 9 mg/kg BID	PB 6 mg/kg BID and ZNS 1.5 mg/kg BID	N/A	1.9	0	100%	SE	none	primary goal	none
#14	Scottish fold	F	3.2	1.7	Generalized	ZNS 2.2 mg/kg BID	PB 1.2 mg/kg BID and ZNS 7.3 mg/kg BID	PB 24 µg/ml and ZNS 36.9 µg/ml (2nd)	6.4	0	100%	none	none	primary goal	none
#15	Chinchilla	SF	1.8	13.5	Generalized	ZNS 5.4 mg/kg BID	ZNS 7.2 mg/kg BID	ZNS 28.9 µg/ml (2nd)	5.0	0	100%	none	none	primary goal	none
#16	Siberian	M	5.3	0.8	Generalized	ZNS 10 mg/kg BID	ZNS 6.5 mg/kg BID	ZNS 86.4 µg/dl (1st)	2.0	2	0%	CS	none	secondary goal	Increase in sleeping hours (ZNS)
#17	ASH	SF	5.1	12.8	Generalized	ZNS 12 mg/kg BID	ZNS 10 mg/kg BID	ZNS 29.2 µg/ml (2nd)	18.8	0	100%	SE	none	primary goal	none
#18	DSH	CM	2.4	0.4	Generalized	ZNS 5.3 mg/kg BID and DZP 0.53 mg/kg BID	ZNS 7.8 mg/kg BID DZP 0.78 mg/kg BID	N/A	6.6	0	100%	CS	none	primary goal	none
#19	Munchkin	SF	4.5	3.2	Focal	ZNS 5.5 mg/kg BID and LEV 20 mg/kg TID	ZNS 5.5 mg/kg BID and DZP 0.25 mg/kg BID	ZNS 39.3 µg/ml (2nd)	30.0	0	100%	none	none	primary goal	Vomiting (ZNS + LEV); ataxia (PB + ZNS)
#20	DSH	CM	4.8	0.7	Generalized	ZNS 8 mg/kg SID	LEV 25 mg/kg TID, ZNS 4 mg/kg BID and DZP 0.23 mg/kg BID	N/A	10.0	0	100%	CS	none	primary goal	Vomiting (ZNS)

(BW): body weight; (ASH): American short hair; (DSH): Domestic short hair; (SF): Spayed female; (CM): casted male; (F): intact female; (PB): phenobarbital; (ZNS): zonisamide; (DZP): diazepam; (LEV): levetiracetam; (CS): cluster seizures; (SE): status epilepticus.

2, respectively), Russian Blue, Chartreux, Siberian, and Chinchilla (n = 1, respectively). The median duration of seizure history of each cat before inclusion in the study was 65 days (range, 8–334 days).****

Among these 20 cats, 16 exhibited generalized epileptic seizures, one exhibited focal epileptic seizures evolving into generalized epileptic seizures, and the remaining three showed focal seizures. Plasma biochemical analysis was conducted in all patients, but some biochemical parameters, such as plasma total protein, albumin, and phosphate levels could not be described for four cats. Twelve cats were tested for retroviral status, and all showed negative findings for both FeLV and FIV. MRI examinations using a 0.3-Tesla unit (AIRIS; Hitachi, Tokyo, Japan) were performed for 16 cats, and MRI examinations using a 3-Tesla unit (Vantage Galan3T SaturnX; Canon, Tokyo, Japan) were conducted for 4 cats, and T1-weighted (T1W), T2-weighted, fluid-attenuated inversion recovery, and postcontrast-T1W images were acquired. Three cats showed structural abnormalities that were not considered the causative lesions: otitis media in the left ear in one cat, ventricular enlargement in one cat, and cranium dysplasia in one cat. CSF was collected from four cats, and there were no remarkable findings. CSF was not collected in the other 16 cats because of the owner's intention.

ASMs and efficacy

For first-line therapy, 10 cats were treated with PB. Among these cats, one subsequently received additional diazepam (DZP) and one received additional ZNS because of the insufficient efficacy. In this study, eight cats, including one changed from ZNS, finally received PB monotherapy with a median dosage of 2 mg/kg q12hr (range, 1.5–3 mg/kg q12 hr), and one was treated with PB 6 mg/kg q24 hr. Eight cats achieved the primary goal in PB monotherapy, and the remaining cat achieved the secondary goal. Blood concentration of PB was available for only two cats (19.0 and 24.3 µg/ml, respectively; reference range 15–30 µg/ml) and both reached the primary goal.

Six cats were treated with ZNS as first-line therapy and then three underwent treatment changes subsequently; one was treated with PB because of an adverse event, one cat received additional PB, and one was treated with a combination of ZNS, LEV, and DZP. The remaining three cats continued ZNS monotherapy, with dosages of 6.5, 7.2, and 10 mg/kg q12hr. Finally, two cats achieved the primary goal, and one reached the secondary goal because of the prevention of cluster seizures. Blood concentration of ZNS was available for two cats; 28.9 and 29.2 µg/ml, respectively; reference range 10–30 µg/ml. Both cats reached the primary goal. The blood concentration in the cat did not achieve the primary goal was not available.

The other four cats were treated with combination therapy after diagnosis: one was treated with PB and ZNS, one was treated with PB and DZP, one was treated with ZNS and DZP, and one was treated with ZNS and LEV. As mentioned above, two cats were first treated with PB in the primary doctor switched to combination therapies (one PB and DZP, one PB and ZNS). Two cats with ZNS treatment in the primary were added on PB or LEV and DZP, respectively. One cat that was first treated with a combination (ZNS and LEV) was treated with ZNS and DZP because of the owner's request.

Among the eight cats finally receiving combination therapy, two of the three receiving PB and ZNS therapy achieved the primary goal, while the remaining cat was no responder. Among two cats receiving PB and DZP therapy, one achieved the primary goal, and the other achieved the secondary goal. Two cats treated with a combination of ZNS and DZP achieved the primary goal. Finally, one cat treated with ZNS, LEV, and DZP reached the primary goal.

Adverse events

Adverse events were assessed in 20 cats. Case #11 (PB + DZP) and case #12 (PB + ZNS) showed elevated liver enzyme levels without clinical signs. Transient vomiting was shown in case #19 (ZNS + LEV) and case #20 (ZNS). Plasma ZNS concentrations in these two cats were 10.1 and 33.5 µg/ml, respectively. The former cat also showed ataxia when DZP was added at 0.5 mg/kg per day, which was resolved by dose reduction (DZP 0.25 mg/kg per day). Persistent diarrhea was shown in case#9 (ZNS), resulting in a switch to PB treatment. Case#8 (PB) had transient delayed proprioception of the hind limbs. Case#16 (ZNS) showed an increase in sleeping time when ZNS was administered at 20 mg/kg per day, which was resolved with a dosage reduction of ZNS. Blood concentration at 20 mg/kg per day was 86.4 µg/ml and the concentration after dose reduction was not available. Case#10 (PB) had shown chronic dullness since PB monotherapy, and no treatment had been given.

Discussion

PB is a commonly used ASM to treat feline epilepsy. In a previous study, among cats treated using a protocol that included PB, a 50% reduction in seizure frequency was achieved in 93% of epileptic cats (Finnerty *et al.*, 2014). In the present study, nine cats were treated with PB monotherapy, of which eight were seizure-free and did not experience any adverse events. Thus, PB effectively reduced seizure frequency and was used safely to treat feline idiopathic epilepsy in this study.

In this study, ZNS monotherapy was continued in three-sixths of the cats; two reached the primary goal, and the remaining one achieved the secondary goal. In addition, among the seven cats treated with combination therapy containing ZNS, six were responders during the 6-month assessment period. ZNS is often used to treat canine epilepsy, especially in Japan, because it is licensed for treating canine epilepsy and is inexpensive.

ZNS monotherapy has been reported to show an efficacy of 60% in canine idiopathic epilepsy (Chung *et al.*, 2012), and the effectiveness of ZNS combination therapy in canine idiopathic seizures has been reported to range from 50% to 82% (Klopmann *et al.*, 2007; Dewey *et al.*, 2014). Our research was the first report to use ZNS in spontaneous feline idiopathic epilepsy and show 6-month efficacy in controlling epileptic seizures. The ZNS treatment could become yet another option for feline idiopathic epilepsy.

This study observed adverse events associated with ZNS in4 out of 11 cats. Two cats experienced vomiting, one showed diarrhea, and one showed excessive sleeping behavior. In an experimental study that investigated ZNS toxicity in cats, 50% of the cats were administered 20 mg/kg ZNS per day and showed high blood concentration suffered from adverse reactions, such as anorexia, diarrhea, and vomiting (Hasegawa *et al.*, 2008). However, in our study, most cats treated with ZNS received lower dosages than those used in the previous study and the concentration of ZNS was within the treatment level in dogs (reference range, 10–40 μg/ml). In another cat, ZNS was changed to PB because of persistent diarrhea, even though the ZNS dosage was much lower than 20 mg/kg daily. Thus, our findings indicate that ZNS treatment, even at doses less than 20 mg/kg per day, may cause adverse events, especially gastrointestinal signs, in cats.

The combination of PB and ZNS controlled the frequency of seizures in three cats. From the point of view of pharmacokinetics, PB has been proven to induce cytochrome P-450 (CYP) 3A4 expression in the human liver (Martin *et al.*, 2003), and ZNS can be metabolized and inactivated by CYP3A4 in human medicine. Furthermore, CYP1A, CYP2B, CYP2C, and CYP3A activities are elevated in dogs after 35 consecutive days of PB administration (Hojo *et al.*, 2002). In addition, repeated PB administration has been shown to enhance the clearance of ZNS in dogs, resulting in reduced serum concentration (Orito *et al.*, 2008). However, it is not clear whether continuous PB administration induces CYP activity in cats. The findings of experiments in healthy cats suggest that CYP2C activity may be pretty low in cats compared to that of dogs (Shah *et al.*, 2007) and that PB metabolism did not show significant differences after 21 days of continuous administration (Cochrane *et al.*, 1990). Therefore, it is assumed that cats' CYP-induced auto metabolism and other ASM metabolism may not occur (Risio, 2014). Based on this hypothesis, even if ZNS is used concurrently with PB, alteration of pharmacokinetics may not be considered, and this combination may be a reasonable choice for combination therapy.

Elevation of liver enzyme activity (not otherwise specified) was observed in two cats, of which one received PB and ZNS and the other received PB and DZP. PB sometimes causes elevated alanine transferase levels in cats (Finnerty *et al.*, 2014; Hermans *et al.*, 2022), therefore elevation of liver enzyme observed in this study possibly is explained by the use of PB. ZNS has also been reported to induce elevation of the levels of liver enzymes, especially alkaline phosphatase, in dogs (Klopmann *et al.*, 2007; Boothe and Perkins, 2008; Dewey *et al.*, 2014; Smith *et al.*, 2022) but the exact mechanism of why this elevation of liver enzyme occurs is still undetermined. Experimental administration of ZNS in cats did not induce liver enzyme level elevation (Hasegawa *et al.*, 2008), and cats that received ZNS monotherapy did not experience increased liver enzyme activity in the present study. However, it is premature to conclude that ZNS does not contribute to the elevation of liver enzyme activity in cats.

DZP has been reported to potentially cause idiosyncratic fulminant and lethal liver failure in cats (Center *et al.*, 1996; Hughes *et al.*, 1996). It is hypothesized that it may be due to the lower glucuronidation capacity of cats compared to dogs (Beusekom *et al.*, 2015). Although DZP is occasionally used for feline epilepsy in Japan (Mizuno *et al.*, 2022), the prevalence of this idiosyncratic adverse effect is unknown, and there is only one report after the 2000s from Canada (Park, 2011). Our study also revealed using DZP as an adjunctive ASM in five cats from the medical records. Still, it did not show lethal liver failure, and just one cat that received concurrent ZNS showed elevated liver enzyme levels. A previous report indicated that the level of liver enzymes should be measured before and after starting DZP treatment. Discontinuation of DZP is recommended if any adverse events are observed, especially in the first week (Center *et al.*, 1996). Of course, enough consideration and caution are needed, if no significant adverse events are observed, DZP can be one of the choices for the add-on ASMs of feline idiopathic epilepsy by measuring the concentration of hepatic enzymes frequently.

The main limitation of this study was the small number of cases for each drug, especially ZNS, and the lack of ASM concentration in some cases. Although this seems to be the first report to use ZNS in clinical cases of feline epilepsy, a more extensive study is needed to validate the efficacy of ZNS and identify possible adverse events of ZNS.

In this study, ZNS could be used as monotherapy and combination therapy to treat feline idiopathic epilepsy in a total of nine cats. However, ZNS administration may cause adverse events, such as gastrointestinal adverse effects, in cats.

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Conflict of interest

The authors declared no potential conflicts of interest for this research, authorship, and/or publication of this article.

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Data availability
The entire data substantiating the conclusions of our study is encompassed within this manuscript.

Author contributions
Dr. Yoshida and Dr. Motegi planned this research and collected information and wrote the manuscript. Dr. Maeda and Dr. Yonezawa approved this research. This research also includes the patients that were diagnosed by Dr. Maeda, Dr. Yonezawa, and Dr. Motegi.

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