



Two families with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): case reports and literature review

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Background: Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), a hereditary gastric polyposis syndrome that presents with fundic gastric polyposis, is associated with an increased risk of gastric adenocarcinoma. The four patterns of point mutation in the *adenomatous polyposis coli* (*APC*) promoter 1B region have been identified as the cause of GAPPS. GAPPS was first reported in 2012, and only 33 families with GAPPS have been reported worldwide to date. Therefore, the clinical management for GAPPS are still controversial. We herein report two unrelated GAPPS families with the same point mutation site.

Case Description: Total seven patients of two families had >100 carpeting polyps in the gastric body and fundus, and one of them (69-year-old female) had gastric adenocarcinoma. As a result of germline analysis, both families harbored a point mutation (c.-192A>G) in *APC* promoter 1B region, previously reported in only one family. Three of seven patients underwent total gastrectomy, and others were followed-up with regular esophagogastroduodenoscopy (EGD) and biopsy every 6 months. To summarize the reported cases, total 42 patients of 35 families have developed gastric adenocarcinoma.

Conclusions: This report may contribute to determining the appropriate guidelines for the clinical practice of GAPPS. When EGD reveals gastric polyposis localized to the gastric body and fundus, it is important to obtain a detailed family history and perform germline mutational analysis. And more, point mutation type of our family cases was a rare pattern, suggested that c.-192A>G pattern might be a pathogenic variant.

Keywords: Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS); point mutation in *adenomatous polyposis coli* promoter 1B (point mutation in *APC* promoter 1B); fundic gland polyposis (FGPs); case report

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Introduction

It has been reported that familial adenomatous polyposis (FAP) is caused by a germline mutation of the *adenomatous polyposis coli* (*APC*) gene (1). Patients with FAP mainly present with colorectal lesions, but some cases may also present with gastric polyps in the fundic gland area (2). Most sporadic gastric polyps are histologically benign. However, fundic gland polyposis (FGPs) associated with FAP frequently develops into gastric cancer (GC) (3). Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), a subtype of FAP, is characterized by polyposis localized to the gastric body and fundus, with a significant risk of GC. GAPPS was first reported by Worthley *et al.* (4). GAPPS is an autosomal dominant syndrome caused by point mutations in the *APC* promoter 1B region (5). Most GAPPS cases were reported in Western countries in the 2010's; however, recently, GAPPS cases have been reported in Asian countries (6-10). The diagnostic criteria for GAPPS are as follows: (I) gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; (II) over 100 polyps carpeting the proximal stomach in the index case or over 30 polyps in a first-degree relative of another case; (III) predominantly fundic gland polyps, some having regions of dysplasia (or a family member with either dysplastic

fundic gland polyps or gastric adenocarcinoma); (IV) an autosomal dominant pattern; and (V) exclusions include other hereditary gastric polyposis syndromes and the medication of the proton pump inhibitor (PPI) because PPI has been considered to be associated with the onset of gastric fundus polyposis (4). Because GAPPS is a relatively rare disease, appropriate guidelines for the treatment of GAPPS have not been reported. Since the first report by Worthley *et al.*, a total of 33 families have been reported (4-19) (Table 1). The accumulation of further cases may be useful for obtaining an adequate consensus regarding GAPPS. Herein, we report a literature review of 35 GAPPS cases, including our two families with GAPPS. We present this article in accordance with the CARE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-564/rc>).

Case presentation

Family #34 (Figure 1 and Table 1)

Figure 1A shows the pedigree of family #34. The proband (case 1) was a 71-year-old male diagnosed with gastric polyposis by esophagogastroduodenoscopy (EGD) in his 30's. The patient was followed-up with regular EGD every year and two to five biopsies were collected in each endoscopy. As the number of polyps increased annually, despite no malignant findings, he was referred to our hospital for therapeutic management and germline analysis in his 60's. Both of his parents had undergone surgery for GC, while his mother had no gastric polyposis, and the man's cousin on the paternal side died due to GC at 55 years of age. He had no symptoms or medication, including the use of PPI. EGD revealed >100 carpeting gastric polyps localized in the proximal stomach (Figure 1B). Carpeting polyps measured 1–10 mm. Histological examination confirmed fundic gland hyperplasia without malignancy.

Germline mutational analysis revealed a point mutation (c.-192A>G) in *APC* promoter 1B region, and the patient was diagnosed with GAPPS. The patient had a daughter and three sisters (cases 2, 3, 4, and 5; Figure 1A). All four patients were asymptomatic and were not treated with PPI. The four relatives were referred to our Genetic Counseling Unit for further clinical examinations and appropriate genetic counseling for patients and their relatives. Histologic findings of the polyp biopsy specimen showed tubular adenoma in case 2, tubular adenoma in case 3, hyperplasia in case 4, and hyperplasia in case 5. No

Highlight box

Key findings

- Two family cases with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and the discussion of rare *adenomatous polyposis coli* (*APC*) point mutation pattern.

What is known and what is new?

- GAPPS is a hereditary gastric polyposis syndrome with a significant risk of gastric adenocarcinoma. Four pattern of *APC* promoter 1B point mutation type have been identified.
- From literature review with our two cases, we summarized and calculated the prevalence of developed gastric adenocarcinoma.
- c.-192A>G mutation pattern was previously reported in only one family.
- *APC* promoter 1A is physiologically downregulated by hypermethylation in normal fundic gastric mucosa, while *APC* promoter 1B mutations at the germline level may cause a loss of *APC* messenger RNA, resulting in the development of multiple polyps in the gastric fundus.

What is the implication, and what should change now?

- Our two additional cases suggest that the variant pattern c.-192A>G might be a pathogenic mutation.

Table 1 Characteristics of reported 33 family cases and our two cases

Family number	Author	Year	APC mutation	FGPs cases/all family members examined [†]	Youngest age diagnosed with FGPs in family	Patients with GC/all family members examined	Youngest age diagnosed with GC
1	Worthley <i>et al.</i> (4)	2012	c.-195A>C, c.-125delA	31/50	10 y.o.	2/50	33 y.o.
2	Worthley <i>et al.</i> (4)	2012	c.-191T>C	6/9	23 y.o.	2/9	49 y.o.
3	Worthley <i>et al.</i> (4)	2012	c.-192A>G	3/9	33 y.o.	2/6	34 y.o.
4	Yanaru-Fujisawa <i>et al.</i> (11)	2012	NR	6/8	56 y.o.	1/8	56 y.o.
5	Yanaru-Fujisawa <i>et al.</i> (11)	2012	NR	4/10	42 y.o.	2/10	42 y.o.
6	Li <i>et al.</i> (5)	2016	c.-191T>C	2/5	NR	0/5	NA
7	Li <i>et al.</i> (5)	2016	c.-191T>C	2/2	NR	0/2	NA
8	Li <i>et al.</i> (5)	2016	c.-191T>C	4/6	NR	2/6	NR
9	Repak <i>et al.</i> (12)	2016	c.-191T>C	5/10	23 y.o.	5/10	23 y.o.
10	McDuffie <i>et al.</i> (13)	2016	NR	3/NR	45 y.o.	2/NR	55 y.o.
11	McDuffie <i>et al.</i> (13)	2016	NR	9/NR	21 y.o.	4/NR	50 y.o.
12	Beer <i>et al.</i> (14)	2017	c.-191T>C	1/NR	38 y.o.	0/NR	NA
13	Mitsui <i>et al.</i> (6)	2018	c.-191T>C	3/4	18 y.o.	1/4	NA
14	Foretová <i>et al.</i> (15)	2019	c.-191T>C	2/4	30 y.o.	1/4	NA
15	Foretová <i>et al.</i> (15)	2019	c.-191T>C	5/9	29 y.o.	3/9	29 y.o.
16	Foretová <i>et al.</i> (15)	2019	c.-191T>C	2/8	41 y.o.	0/8	NA
17	Foretová <i>et al.</i> (15)	2019	c.-191T>C	2/3	28 y.o.	1/3	28 y.o.
18	Foretová <i>et al.</i> (15)	2019	c.-191T>C	7/13	22 y.o.	1/13	40 y.o.
19	Foretová <i>et al.</i> (15)	2019	c.-191T>C	2/3	36 y.o.	0/3	NA
20	Foretová <i>et al.</i> (15)	2019	c.-191T>C	1/5	27 y.o.	0/5	NA
21	Foretová <i>et al.</i> (15)	2019	c.-191T>C	3/3	34 y.o.	0/3	NA
22	Kunovsky <i>et al.</i> (16)	2019	NR	2/NR	43 y.o.	0/NR	NA
23	Powers <i>et al.</i> (17)	2021	c.-191T>C	1/NR	60 y.o.	1/NR	60 y.o.
24	Kanemitsu <i>et al.</i> (7)	2021	c.-191T>C	4/6	37 y.o.	4/6	37 y.o.
25	Kanemitsu <i>et al.</i> (7)	2021	c.-191T>C	6/7	24 y.o.	2/7	24 y.o.
26	Ako <i>et al.</i> (8)	2022	NR	3/NR	29 y.o.	0/NR	NA
27	Matsumoto <i>et al.</i> (9)	2022	NR	4/NR	41 y.o.	1/NR	41 y.o.
28	Grossman <i>et al.</i> (18)	2022	c.-195A>C	2/4	8 y.o.	0/4	NA
29	Iwakawa <i>et al.</i> (10)	2022	NR	4/NR	40's	1/NR	NR
30	Iwakawa <i>et al.</i> (10)	2022	NR	1/NR	30's	1/NR	30's
31	Iwakawa <i>et al.</i> (10)	2022	NR	1/NR	40's	1/NR	40's
32	Iwakawa <i>et al.</i> (10)	2022	NR	3/NR	20's	1/NR	NR
33	Salami <i>et al.</i> (19)	2022	c.-191T>C	3/5	36 y.o.	0/5	NA
34	Our cases	2023	c.-192A>G	6/6	39 y.o.	1/6	69 y.o.
35	Our cases	2023	c.-192A>G	1/1	30 y.o.	0/1	NA
Total				112/190 (58.9%)		42/190 (22.1%)	

[†], evaluated cases were only counted in all family members. APC, *adenomatous polyposis coli*; FGPs, fundic gland polyposis; GC, gastric cancer; y.o., years old; NR, not reported; NA, not available.

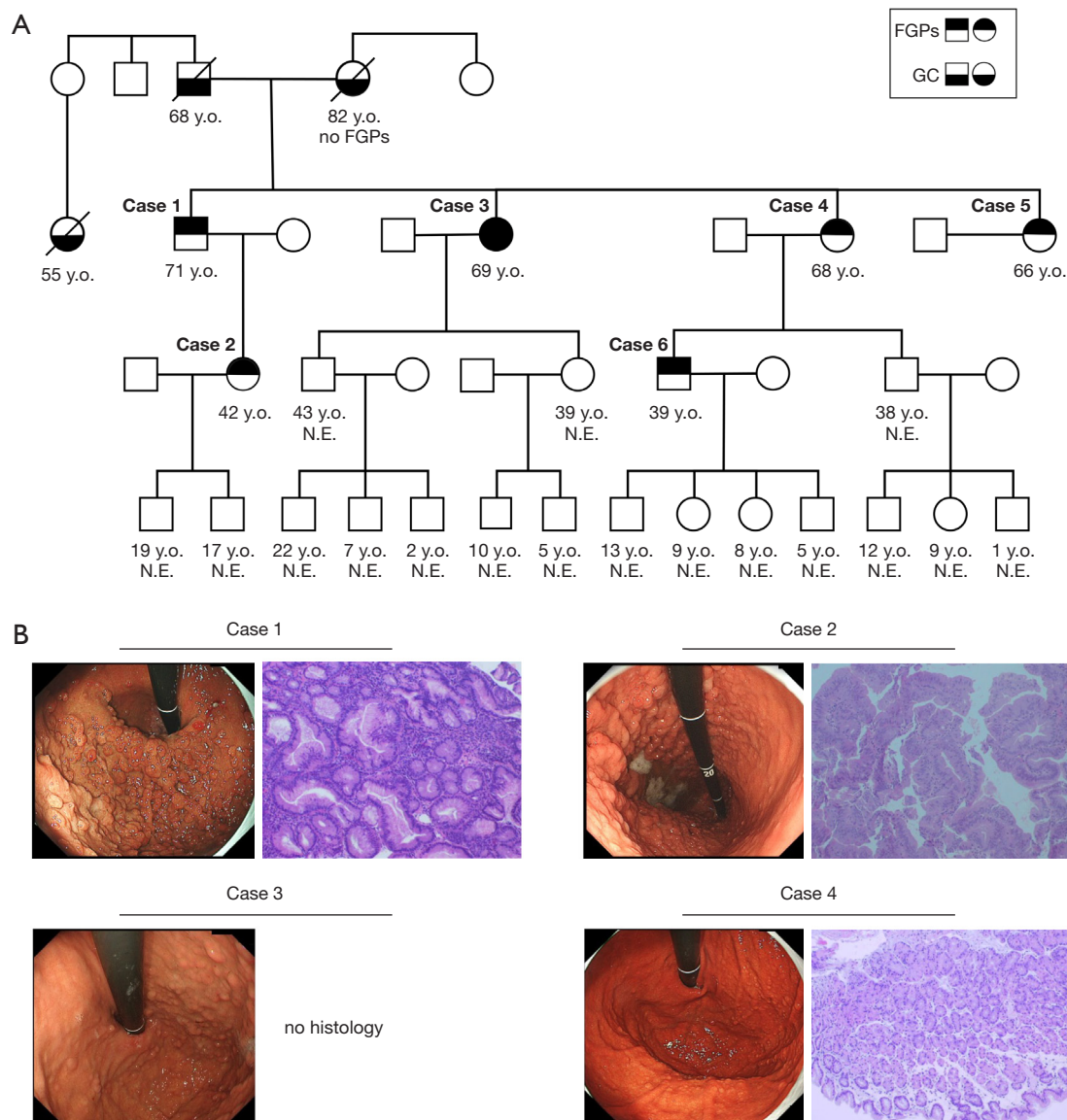


Figure 1 Family #34. (A) The pedigree of family #34. Case 1, a 71-year-old male, was proband. (B) Upper gastrointestinal endoscopy findings in family #34. All four patients (cases 1, 2, 3, and 4) demonstrated carpeting fundic gland polyps in the gastric body and fundus but no malignancy in histology by biopsy, with hematoxylin and eosin staining in original magnification, $\times 200$. In case 3, macroscopic finding of EGD suggesting dysplasia, and histologically diagnosed as tubular adenoma. FGPs, fundic gland polyposis; GC, gastric cancer; y.o., years old; N.E., not evaluated; EGD, esophagogastroduodenoscopy.

malignancies were observed in these patients. Germline mutational analysis revealed that all four patients had the same point mutation in the *APC* promoter 1B region (c.-192A>G) as in case 1 and were diagnosed with GAPPs (Figure 1B). The proband's niece (case 6), a 39-year-old female, was identified as having FGPs, but germline mutation analysis of *APC* promoter 1B region was not

performed in this case. GAPPs has been identified in two generations of this family. None of the patients had GC or dysplasia. Three patients (cases 1, 2, and 3) underwent prophylactic total gastrectomy at another hospital, and case 3 was histologically diagnosed with gastric adenocarcinoma. Cases 4 and 5 did not undergo surgical treatment and were followed-up with regular EGD and

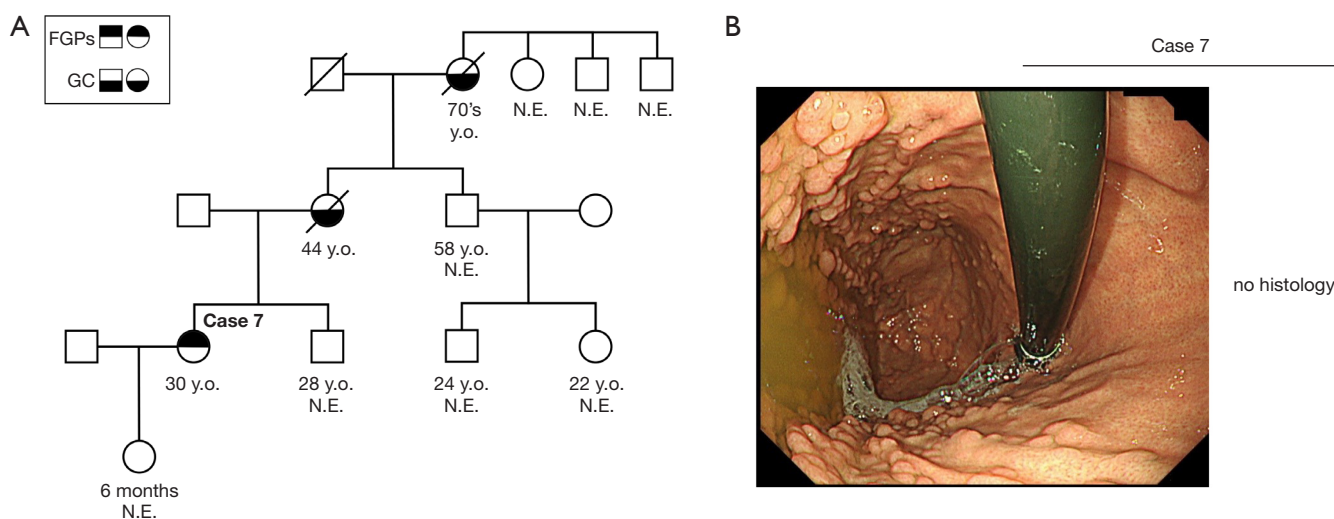


Figure 2 Family #35. (A) The pedigree of family #35. Case 7, a 30-year-old female, was proband. (B) The finding of upper gastrointestinal endoscopy of case 7 in family #35. Carpeting gastric polyps in the proximal stomach were detected but histology indicated no malignancy, with hematoxylin and eosin staining in original magnification, $\times 200$. FGPs, fundic gland polyposis; GC, gastric cancer; y.o., years old; N.E., not evaluated.

biopsy every 6 months.

Family #35 (Figure 2 and Table 1)

The pedigree of family #35 is shown in *Figure 2A*. The proband (case 7) is a 30-year-old female. Her mother and grandmother died of GC, but detailed information regarding the gastric polyps was not obtained. EGD screening revealed gastric polyposis, and she was referred to our department for therapeutic management and germline mutation analysis. She had no symptoms, PPI medication, or history of *Helicobacter pylori* (*H. pylori*). EGD revealed >100 carpeting polyps in the gastric body and fundus (*Figure 2B*). Histological examination revealed a tubular adenoma without malignancy. Germline mutational analysis identified a point mutation (c.-192A>G) in the *APC* promoter 1B region, which was diagnosed as GAPPSS. No relationship was found with family #34. The patient decided not to undergo surgical treatment and was referred to another hospital for a second opinion. The other family members did not undergo EGD or mutational analyses.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written

consent is available for review by the editorial office of this journal.

Discussion

Here, we report two new GAPPSS families with *APC* germline mutation in promoter 1B, c.-192A>G. Our cases showed that both FGPs and c.-192A>G mutations at the germline level were present in six cases examined. As GAPPSS is recognized as an autosomal dominant disease (4), the morbidity rate was calculated to be 50%. Our review indicated that the prevalence of FGPs was 58.9% (112 patients of 190 all family members examined). Our patients may have occasionally had a high morbidity rate.

The prevalence of GC was 42 cases (37.5%) of 112 FGPs cases. A previous report by Kim *et al.* indicated that 13–25% of patients with GAPPSS had a lifetime risk of developing GC (20). While the penetrance of FAP has been reported to be almost 100% that of cancer (21), that of GAPPSS seems to be less than that of FAP. It has been suggested that there may be a critical difference in the penetration rate of germline mutation types of *APC* between the promoter 1B region and the open reading frame.

The appropriate timing for EGD surveillance and surgical management of GAPPSS remains controversial (18). The youngest case with FGPs was an 8-year-old patient (18) and that with GC was 23-year-old (12). In fact, a man's cousin

on the paternal side of case 1 died due to GC at 55 years of age, and the mother of case 7 died due to GC at 40 years of age. While the information on FGPs was unclear in these two patients, the rapid progression of GAPPS might be speculated. When EGD reveals gastric polyposis localized to the gastric body and fundus, it is crucial to obtain a detailed family history and perform germline mutational analysis.

Total gastrectomy is considered the standard radical treatment for patients with GAPPS, GC, or dysplasia polyposis. Prophylactic total gastrectomy was also performed in patients with GAPPS without malignancy or dysplasia. Prophylactic gastrectomy was performed between 30 and 35 years of age or 5 years earlier than the age at which the youngest family member had GC (22). A previous report indicated that in family #9, the patient showed dysplasia and liver metastases for 5 years, despite the continuous surveillance EGD was performed every 18- to 24-month intervals (12), and another report indicated in family #24, two patients underwent surveillance EGD every 3 months and they were diagnosed gastric adenocarcinoma 1 year after initial EGD (7). GAPPS might show rapid malignant progression of gastric polyps in compared with the common gastric polyps. Avoiding surgical management may require strict follow-up with frequent endoscopic surveillance and biopsies to diagnose malignant transformation to GC in a timely manner. Foretová *et al.* suggested that patients undergo EGD every 6 months if prophylactic gastrectomy is refused (15). In 112 cases with FGPs, 21 cases without dysplasia or cancer underwent prophylactic gastrectomy, and seven cases showed cancer or dysplasia after gastrectomy.

GAPPS is a germline mutation at the *APC* promoter 1B region. *APC*, a tumor suppressor gene, has two promoters, 1A and 1B, which regulate *APC* messenger RNA (mRNA) products and may regulate the expression of *APC* in an organ-specific manner (23,24). Because *APC* promoter 1A is physiologically downregulated by hypermethylation in normal fundic gastric mucosa (22), the germline mutation at c.-192A>G of *APC* promoter 1B in GAPPS suppresses the transcription of *APC* gene by the dysfunction of *APC* promoter 1A and 1B at the proximal gastric mucosa, which resulted in the decrease of APC protein at the proximal gastric mucosa (5). These findings might explain one of the mechanisms responsible for the development of multiple polyps at the proximal gastric lesions in GAPPS.

Four types of mutations in *APC* promoter 1B have been reported in GAPPS at the germline level: c.-191T>C, c.-192A>G, c.-125delA, and c.-195A>C (5). These mutations

are associated with a reduction in the binding of the transcription factor Yin Yang 1, resulting in decreased *APC* mRNA expression (23). Our review indicated that 35 GAPPS families have been reported worldwide (Table 1). The most frequent *APC* mutation type was c.-191T>C, while c.-125delA, and c.-195A>C variant patterns were found in two, and one family, respectively. Although c.-192A>G variant pattern was previously reported in only one family (Table 1, family #3) by Worthley *et al.* (4), our two additional cases (Table 1, family #34 and family #35) suggest that the variant is a pathogenic mutation.

Conclusions

Standard guidelines for GAPPS remain to be established because it is a relatively new disease and is not well known worldwide. Further accumulation of cases is necessary to establish an appropriate therapeutic strategy. This case report may contribute to the determination of appropriate guidelines for the clinical management of GAPPS.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-564/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and

accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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