

Case Report: A Rare Case of Hepatoid Adenocarcinoma in Stomach and Duodenum Simultaneously

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Abstract: HAC is a rare extrahepatic malignancy histologically resembling hepatocellular carcinoma which can occur in many organs. Especially for cases carrying HAC within the stomach or duodenum, we found that typically HAC only happened in either of them and there was no case exhibiting HAC in both sites. Here, we presented a case having HAC in both sites and to our knowledge, this is the first report presenting HAC in these two distinct organs simultaneously. Firstly, a 57-year-old male was tested for increased serum alpha-fetoprotein level. Following PET-CT images showed strengthened FDG uptake in the gastric antrum and proximal duodenum. Esophagogastroduodenoscopy also revealed an irregular lump at the gastric antrum and a deep ulceration at the duodenum bulb. Next, an immunohistochemistry panel confirmed the diagnosis of HAC. Finally, genetic tests were performed on this patient after the clinical diagnosis of HAC to reveal the molecular etiology.

Keywords: HAC, case report, AFP, SALL4, endoscopy, NGS

Introduction

Hepatoid adenocarcinoma (HAC) refers to a scarce extrahepatic malignant neoplasm with the characteristics of hepatocellular differentiation. The higher the percentage of the HAC cell component in a tumor, the more alpha-fetoprotein (AFP) is secreted.¹ HAC arises mostly in the stomach² and also in other sites including esophagus,³ duodenum,⁴ jejunum,⁵ colon,⁶ peritoneum,⁷ pancreas,⁸ and ovary.⁹ Based on the reported cases for HAC, it only happens in a single organ and patients suffering from HAC typically undergo a poor prognosis due to the aggressive phenotypes of HAC containing various primary lesion sites, advanced tumor stages and early metastasis, thus early diagnosis becomes the most urgent issue for HAC patients.

To date, the diagnosis of HAC still heavily depends on the histology and immunohistochemistry (IHC) tests. Histological examination reveals large, polygonal cells with abundant eosinophilic cytoplasm in both trabecular and glandular structures.⁴ In addition to histological tests, HAC can be confirmed by several biomarkers such as Sal-like protein 4 (SALL4), AFP, hepatocyte and glypican 3 (GPC3)¹⁰ in which AFP and *SALL4* are the most commonly used ones. AFP, as an oncogenic glycoprotein, is widely used in clinical practice to screen HCC. Elevated serum AFP had also been found in different kinds of cancers and one of which is AFP-positive gastric cancer (AFPGC). From empirical viewpoint, serum AFP level of AFPGC patients is only slightly higher than that in patients with the other common gastric cancers. The other commonly used biomarker, *SALL4*, is an oncofetal protein with unique expression pattern which is found to be expressed in the fetal liver but silenced in the adult liver. It could be detected in 94.7% of stomach HAC patients,¹ but we could not find any article reporting the correlation between the expression level of *SALL4* and HAC progression or patients' prognosis.

In this report, we present the first case report about a patient who was diagnosed as HAC in our hospital and had HAC in both the stomach and duodenum.

Case Presentation

The patient was a 57-year-old male patient with a 30-year medical history of chronic hepatitis B virus (HBV) infection, and he was admitted to our department simply because of a significantly elevated serum level of AFP at 6998 IU/mL detected by routine serum test for tumor markers, but some other commonly used tumor markers including CA125, CA199 and CA724 were tested to be in the normal range. The patients did not have any uncomfortable symptoms and we did a physical examination for this patient where no positive sign could be found. Other laboratory tests showed that most of the clinical indexes related to blood cell count and liver function were still in the normal range. HBV surface antigen (HBsAg) was tested as seropositive whereas serum HBV- DNA was shown to be lower than the prescribed minimum of the test. Based on these results, originally, he was highly suspected to have primary HCC and to confirm our initial diagnosis, he underwent computerized tomography (CT) and magnetic resonance imaging (MRI) examinations which showed that no tumor mass could be found in the liver area. Although we did not find any tumor within the liver, we did discover a diffuse, uneven thickening and abnormal enhancement in the pyloric area which was approximately 22×24 mm in diameter under CT scan (Figure 1A). Cancerous thrombi were detected in the hepatic portal vein and left gastric vein by CT scan (Figure 1B and C). MRI scan also showed the same results in the left gastric vein and hepatic portal vein, respectively (Figure 1D and E). Compared to Figure 1B and C, Figure 1F represented the CT scan results for this patient finishing four months/four cycles of therapy after the initial AFP test which will be discussed in detail later. To get a more comprehensive understanding about the primary sites, PET-CT was performed, and the results illustrated

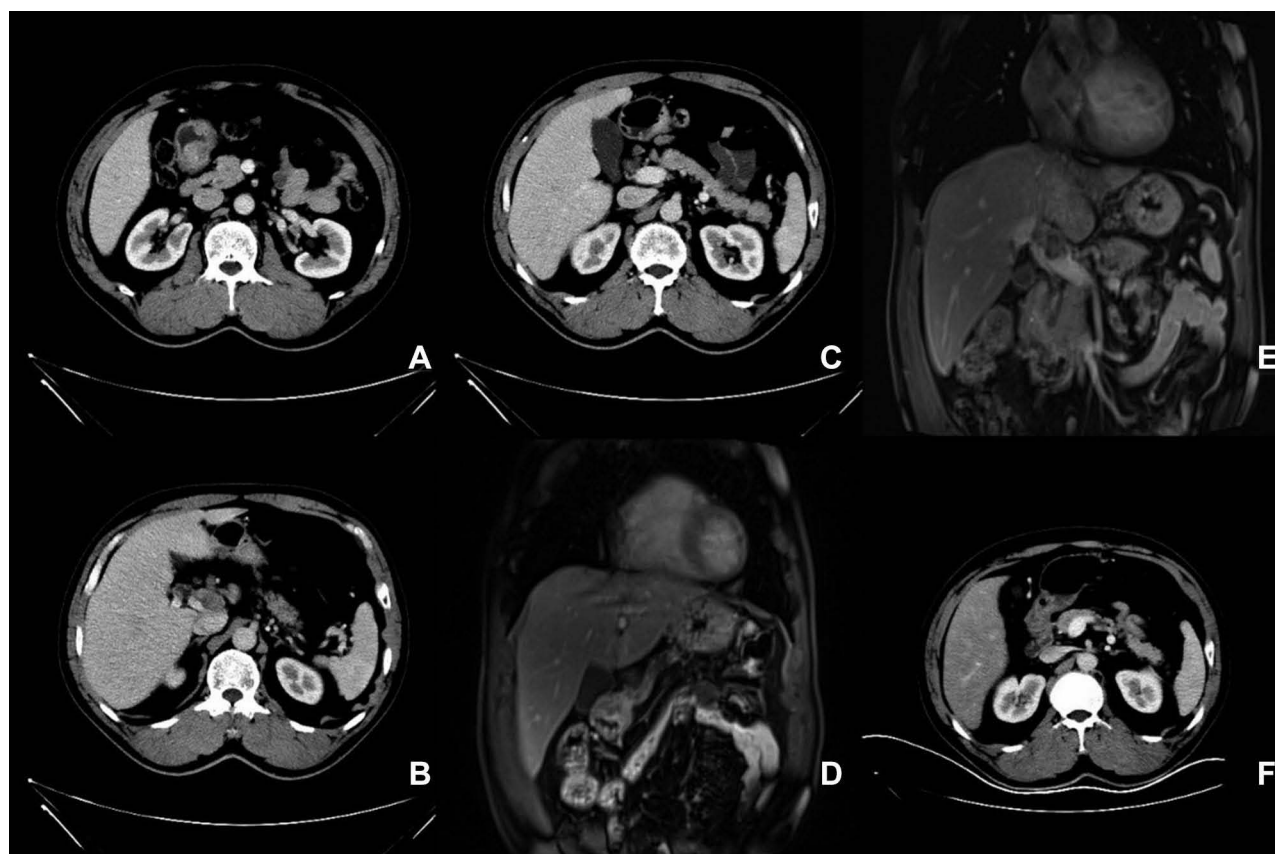


Figure 1 CT and MRI scan results for the patient before treatment (A–E) and after treatment (F). (A) There was a diffuse, uneven thickening and abnormal enhancement in pyloric area which was approximately 22×24 mm in diameter under CT scan. (B–E) Cancerous thrombi were detected in hepatic portal vein (CT and MRI, respectively). (C and D) Cancerous thrombi were detected in left gastric vein (CT and MRI, respectively). (F) CT scan result after treatment.

that no more abnormal fluorodeoxyglucose (FDG) uptake could be detected other than the gastric antrum, proximal duodenum, left gastric vein and hepatic portal vein. In detail, maximum intensity projection (MIP)-FDG PET-CT image revealed an strengthened FDG activity at the gastric antrum and proximal duodenum (Figure 2A upper arrow: gastric antrum and proximal duodenum, lower arrow: tumor thrombus of the portal vein) and transverse views of the PET-CT image showed strengthened tracer uptake in gastric antrum (Figure 2B), left gastric vein (Figure 2C) and hepatic portal vein (Figure 2D) accompanying with standardized uptake values (SUV) as 4.1, 5.7, and 6.7, respectively. Meanwhile, esophagogastroduodenoscopy (EGD) showed a large irregular lump at the gastric antrum (Figure 3A) and a deeply ulcerating mass at the duodenum bulb (Figure 3B). Finally, pathological examinations for these two lesions revealed that both belonged to poorly differentiated adenocarcinoma. Figure 3C and D illustrated the hematoxylin and eosin (H&E) staining results for the tumor residing in gastric antrum and duodenum. Immunohistochemically, the tumor cells were demonstrated to be positive for *SALL4* (Figure 3E and F: gastric antrum and duodenum), AFP (Figure 3G and H: gastric antrum and duodenum) and hepatocyte (Supplementary Figure 1A and B: gastric antrum and duodenum). Whereas GPC3 was shown to be positive in the tumor from gastric antrum (Supplementary Figure 1C) but barely positive in the tumor from duodenum (Supplementary Figure 1D). On the contrary, caudal-type homeobox 2 (*CDX2*) which is thought to be a highly sensitive and specific marker for adenocarcinomas of intestinal origin¹¹ was negative in the tumor from the gastric antrum (Supplementary Figure 1E) but positive in the tumor from the duodenum (Supplementary Figure 1F) which met

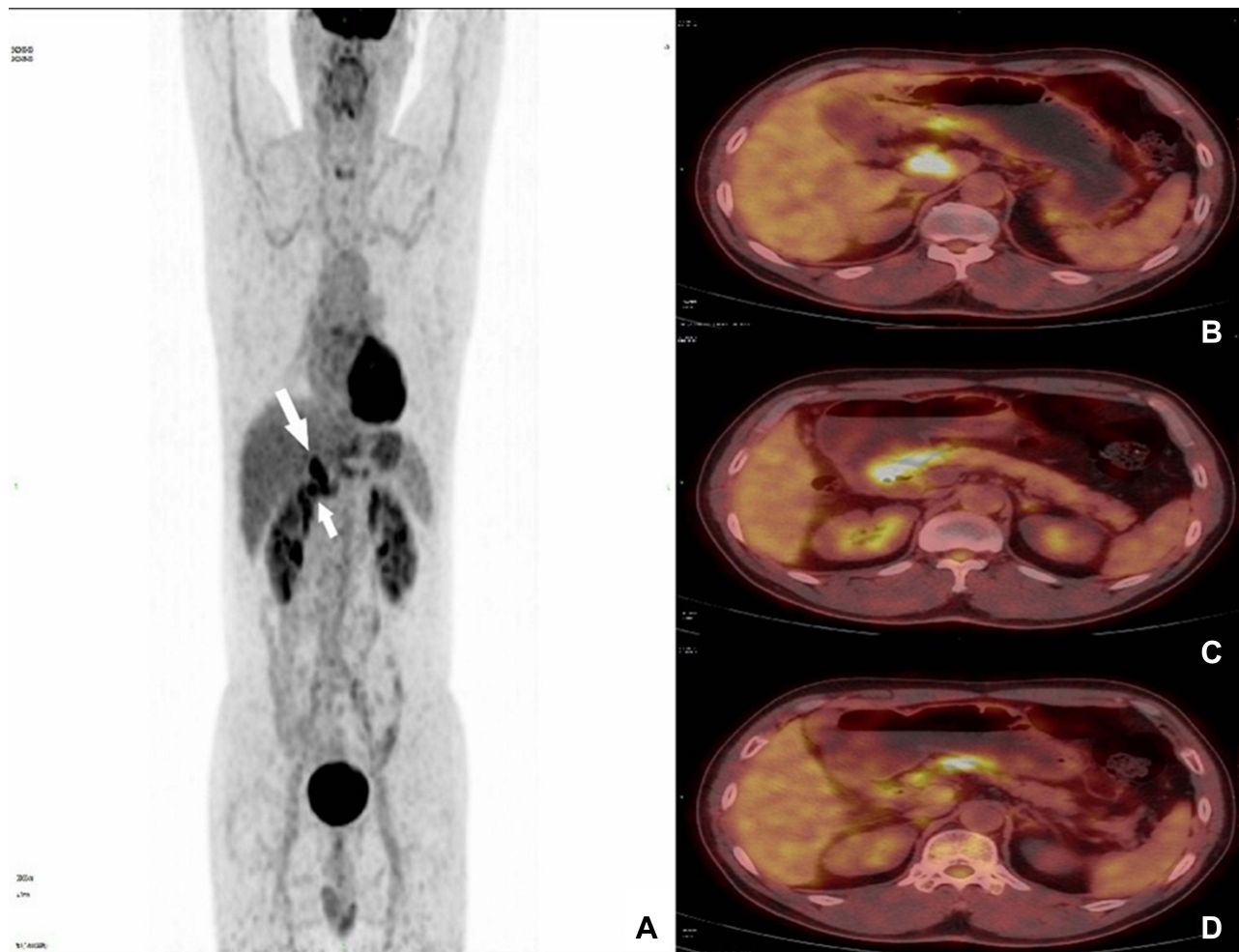


Figure 2 PET-CT scan results for the patients before treatment. (A) There existed strengthened FDG activity at the gastric antrum and proximal duodenum (upper arrow: gastric antrum and proximal duodenum, lower arrow: tumor thrombus of the portal vein). (B–D) Transverse views of the PET-CT image indicated strengthened tracer uptake in gastric antrum (B), left gastric vein (C) and hepatic portal vein (D).

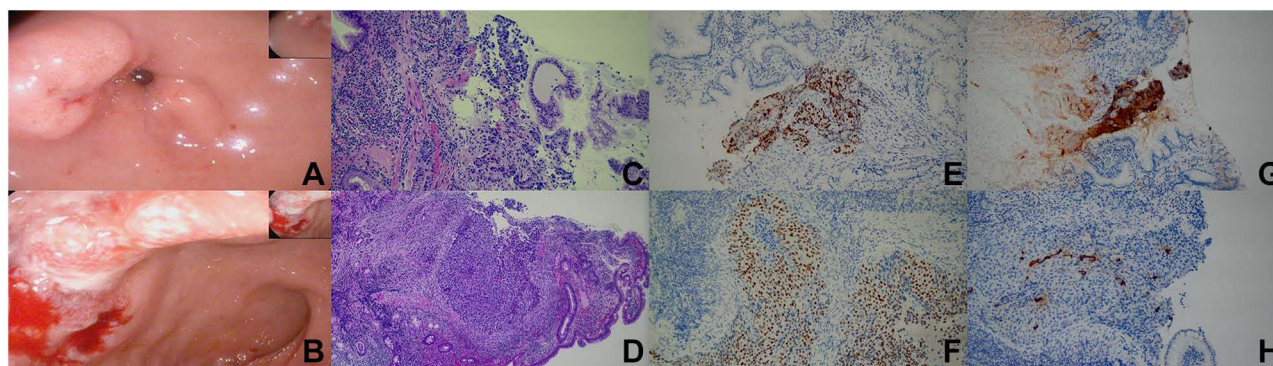


Figure 3 EGD (A and B), HE (C and D) and IHC (E–H) results for the patient. (A and B) EGD showed a large irregular lump at the gastric antrum (A) and a deeply ulcerating mass at the duodenum bulb (B). (C and D) H&E staining results for the tumor residing in the gastric antrum and duodenum. (E and F) SALL4 staining results for gastric antrum (E) and duodenum (F). (G and H) AFP staining results for gastric antrum (G) and duodenum (H).

the diagnostic criteria for HAC precisely. To this stage, all the data suggested that the final diagnosis for this patient should be HAC rather than HCC.

To establish a comprehensive molecular concept of this tumor, we performed next-generation sequencing (NGS) on the 830 genes covering all the exons and parts of introns. The testing provided the reports for all the possible mutation types including point mutations, insertion or deletion mutations, copy number variations (CNV), rearrangement mutations. Besides these mutations, the results also covered tumor mutations burden (TMB) and microsatellite instability (MSI) reports. Surprisingly, common mutations found in *TP53*, *GARD11*, *GEFR*, *FGA*, and *NOTCH3* and *ERBB2* during the progression of HAC¹⁰ were not detected for our patient, which determined that no targeted drug could be used to promote his prognosis (Table 1). Instead of targeted agents, we utilized an empiric therapy consisting of docetaxel, oxaliplatin, tegafur gimeracil, and oteracil potassium capecitabine and the patients received this therapy for six cycles. As we mentioned before, according to a follow-up inspection for this patient (four months/four cycles of therapy after the initial AFP test), the tumor lesion disappeared in the CT scan and the blood AFP level was demonstrated to be lower than the limitation of detection, which suggested that our empiric therapy was effective, at least partly. After six cycles of therapy, the patient received regular follow-up examinations according to our suggestions and to control the tumor growth, the patient received another three cycles during the year of 2021. To date, the patients is still alive, and quality of life is not affected by this disease severely. All the mutated genes were listed in Table 1 and noticeably, most of these

Table 1 Mutations Found by NGS for our Patient

Gene	Nucleotide Changes	Amino Acid Changes	Frequency	Chromosome	Exon	Transcript
<i>CARD11</i>	c.1991C>T	p.Pro664Leu	12.8	7	16/25	NM_032415.4
<i>EGFR</i>	c.286G>T	p.Val96Leu	5.3	7	3/28	NM_005228.3
<i>FGA</i>	c.2159G>C	p.Arg720Thr p.	9.2	4	6/6	NM_000508.3
<i>NOTCH3</i>	c.4669C>T	p.Pro1557Ser	6.6	19	25/33	NM_000435.2
<i>PAK1</i>	c.1474G>C	p.Ala492Pro	11.5	11	14/15	NM_002576.4
<i>PPP4R2</i>	c.248del	p.Met83ArgfsTer6	8.7	3	3/9	NM_174907.3
<i>RAD51C</i>	c.304A>C	p.Thr102Pro	7.2	17	2/2	NM_002876.3
<i>RXRA</i>	c.220C>T	p.Pro74Ser	9.1	9	2/10	NM_002957.5
<i>SPEN</i>	c.9649G>A	p.Val3217Met	6.6	1	11/15	NM_015001.2
<i>USHBP1</i>	c.1831_1832del	p.Leu611AlafsTer132	16.8	19	12/13	NM_031941.3

mutations were firstly reported here to the best of our knowledge. Next, we performed the pathway analysis for these 10 genes using DAVID online tool.¹² Based on [Supplementary Figure 2](#), the most profound pathway for these 10 genes was shown to be Notch signaling pathway which has been extensively studied and proved to play either an oncogenic or a tumor-suppressive role in different kinds of cancers.¹³ [Supplementary Figure 3](#) demonstrated the timeline of events including diagnosis of chronic hepatitis B, date of raised AFP, treatment duration and dates of follow-up scans and tests.

Discussion

In the last few years, an increasing number of patients have been described with AFP-producing malignant tumors of extrahepatic origin¹⁴ and referred to as HAC due to morphological features similar to HCC.¹⁵ The severity of HAC is highlighted by the fact that they show more aggressive behavior and poorer prognosis than cancers without HCC-like morphology, and 51.2% of patients die within the first 12 months of diagnosis.¹⁶ As we emphasized before, HAC typically only happens in a single site, whereas our case is the first case of HAC in which the tumor exists in both the stomach and duodenum. Then a diagnostic issue was introduced here about the primary site for our case. Apparently, there were three possible mechanisms for our case: (1) the original site was the and then it migrated to duodenum; (2) the original site was the duodenum and then it migrated to stomach; (3) the tumors in both sites were originally formed by themselves. Some clues in our results suggested that both the stomach and duodenal bulb might be the primary sites. The most significant difference was presented by EGD examination in which the morphology of the tumor in the gastric antrum was irregular lumps while the appearance of the tumor at the duodenal bulb was an ulcerative mass. But clearly, we could not generate the final conclusion solely depending on gross appearance. As the second most critical method for differential diagnosis, our IHC staining results showed some differences, but unfortunately, it seemed that we could not obtain a firm conclusion depending on them. The tumor cells from both sites were shown to be positive for common biomarkers for HAC including *SALL4*, AFP and hepatocyte. *GPC3* was shown to be highly expressed by the tumor from the gastric antrum but barely positive in the tumor from the duodenum. Nevertheless, *GPC3* is not a specific marker for either gastric HAC or duodenal HAC. In addition, *CDX2* was positive in the tumor from the duodenum, but negative in the tumor from the gastric antrum. According to some recent studies, *CDX2* was demonstrated to be a sensitive and highly, but incompletely specific marker of intestinal adenocarcinomas.¹¹ Based on our results, the tumor located in the gastric antrum did not show any *CDX2* expression which proved that the tumor in the antrum should be a primary site since it did not show any intestinal characters. Whereas whether the tumor in the duodenal area originated from the tumor in the gastric area or originated by itself remained unclear due to lacking direct evidence from our IHC results.

Currently, no effective chemotherapy approach has been developed for HAC. Platinum-based chemotherapy is the most efficient first-line treatment with a 75% positive response.¹⁷ The combination of chemotherapy regimens with targeted therapy (ie, trastuzumab) in *HER2*-positive tumors seems to be promising, although there lacks robust evidence.¹⁸ More clinical trials are urgently needed for the future treatment for HAC patients. To get a deeper understanding for the molecular mechanism of HAC, numerous NGS related projects were performed, and it turned out that the common mutations were related to *TP53*, *GARD11*, *GEFR*, *FGA*, and *NOTCH3*, suggesting that no matching targeted therapeutic agents could be used for patients' benefits. Our pathway analysis suggested the development and progression of HAC is possibly closely related to Notch signaling pathway and for the future studies, to get a deeper understanding about the role of Notch signaling pathway in HAC might be helpful to reveal the actual pathogenic elements for HAC and provide new therapeutic targets for HAC patients.

In summary, in this report, we presented an extremely rare case of HAC occurring in the stomach and duodenum simultaneously. The diagnosis of HAC was made based on a series of laboratory tests, imaging tests, endoscopic examinations, and pathological confirmation. Moreover, genetic tests provided an overview of the molecular etiology for our case. Although nopractical therapeutic target for our patient existed, based on the genetic tests, the combination of docetaxel, oxaliplatin, tegafur, gimeracil, and oteracil potassium capecitabine eliminated the tumor bulk successfully which was confirmed by CT reexamination and the fact that the serum AFP level was reduced profoundly. From our perspective, the prognosis of HAC patients is dismal since HAC typically exhibits highly aggressive behaviors and early stage lymph node metastases. As a result of insufficient attentions on this disease, unless the patients have some specific clinical manifestations, HAC is prone to delayed diagnosis and management. Hence, at this stage, to increase the clinical

awareness of HAC is an outstanding topic for clinicians. To the best of our knowledge the case we reported here is the first case who had HAC in two distinct sites synchronously and we suggest that in the future, it is worthwhile to be aware that HAC might happen in distinct sites within one single patient. Under this circumstance, comprehensive IHC tests of all the relevant markers we mentioned in the introduction for distinct sites are vital for the diagnosis of HAC and also valuable for resolving the matter of their origin. In addition, NGS tests for all the tumor sites are needed to provide genetic clues for distinguishing the primary sites within distinct tumor sites and molecular proofs for selecting effective targeted drugs.

Ethical Statement

The authors have completed the CARE reporting checklist. All data generated and analyzed during the current study are available from the corresponding author on reasonable request. The authors declare they have no conflict of interest. This study complied with the tenets of the Declaration of Helsinki and was approved by the Ethics Board of the Second Hospital of Dalian Medical University. Case report (CARE) guidelines were followed in this case study. A written consent from the patient was obtained prior to collecting the case material, analyzing the sequencing data, writing the final manuscript and publishing the case report.

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Disclosure

The authors report no conflicts of interest in this work.

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