Clinical characteristics and risk factors analysis for the recurrence of pelvic endodermal sinus tumors

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Abstract
This study investigated the clinicopathological characteristics and factors influencing the recurrence of pelvic endodermal sinus tumor (PEST). 54 cases were retrospectively analyzed from at the Zhejiang Cancer Hospital. Progression-free survival (PFS) and related factors on disease recurrence were evaluated. Six patients had extragonadal endodermal sinus tumor, and four had histological features of endodermal sinus tumor (EST) combined with embryonal carcinoma (EC). 39 patients underwent fertility-preserving surgery, 18 patients had a childbearing history, and eight patients had residual tumor after initial treatment as surgery or chemotherapy. 26 patients had a tumor diameter of more than 15 cm, and 30 patients had a serum α-fetoprotein (AFP) level greater than 10,000 ng/mL before initial management. The median follow-up was 47.5 months (range, 14–212 months). During follow-up, 15 patients experience recurrence, with a recurrence rate of 27.8% and a 5-year PFS rate of 61.1%. In univariate analysis, the FIGO (International Federation of Gynecology and Obstetrics) stage (stage III–IV vs. I–II; hazard ratio (HR) = 9.73, p < 0.001), residual tumor (yes vs. no for the first surgery; HR = 4.86, p = 0.001), histological features (EST combined with EC vs. EST; HR = 4.08, p = 0.017), and use of platinum-based chemotherapy (courses ≥3 vs. courses <3; HR = 0.19, p = 0.004) were independent factors influencing recurrence. In multivariate analysis, only stage was an independent risk factor for PFS (stage III–IV vs. I–II; HR = 6.92, p = 0.02). Stage is a prognostic factor for recurrence of PEST. The aim of the initial surgery is to maximally debulk all grossly visible tumor and the post-operative treatment should include a sufficient dose and full course of platinum-based chemotherapy, which may reduce the recurrence rate. Maybe some gene expression that could be associate with PEST.

Keywords
Pelvic endodermal sinus tumor; Yolk sac tumor; Embryonal carcinoma; FIGO stage; Residual tumor; Platinum-based chemotherapy

1. Introduction
Endodermal sinus tumor (EST), also known as yolk sac tumor, is rare and highly malignant neoplasm. It usually occurs in infants, adolescents, and women. It is named because its histological structure is very similar to the endodermal sinus of rat placenta and is histopathologically characterized by the Schiller-Duval bodies [1]. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) often indicates of a large pelvic or abdominal mass (See Fig. 1). The sites of occurrence can be divided into gonads (ovaries, testes) and non-gonads (sacroccocygeal, mediastinal, retroperitoneal, lung, oral cavity, pineal gland and vagina) [2–4]. According to literature reports, extragonadal germ cell tumors account for approximately 1%–5% of all germ cell tumors [1, 5, 6].

The pelvic endodermal sinus tumor (PEST) is defined as an EST that occurs in the pelvic cavity (See Fig. 2). Patients with PEST usually present with a pelvic mass accompanied by abdominal pain, abdominal distension and vaginal bleeding.

PESTs are sensitive to chemotherapy and had a high mortality rate until the development of effective chemotherapy drugs. Since the 1980s, the use of platinum-based chemotherapy has greatly improved the prognosis of this disease [7]. However, tumor recurrence still occurs frequently.

PESTs are extremely rare, and little information is known about their clinical features and treatment outcomes. Moreover, there is currently a lack of studies about PEST with large sample sizes, so there has been no accurate conclusion about the factors related to recurrence in patients with PEST. If we can determine the relevant factors that affect the clinical recurrence of PEST, treatment will vastly improve. By clarifying the appropriate treatments for PEST, we can utilize medical resources with greater efficiency to treat patients.
2. Methods

2.1 Data collection

We retrospectively reviewed the clinical data of patients with PEST from January 2000 to December 2019 in the Cancer Hospital of the University of Chinese Academy of Sciences. The following data were collected: age, childbearing history, residual tumor, histological features (EST with or without embryonal carcinoma (EC)), growth site of EST, fertility-preserving surgery, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, courses of platinum-based chemotherapy, α-fetoprotein (AFP) level before the initial treatment, surgical approach and method, and recurrence.

2.2 Follow-up protocol

After treatment, the patients were observed every 2–4 months in the first 2 years, every half year in years 3–5, and every year after 5 years. The follow-up included assessment of the physical condition, physical examination, serum tumor marker (AFP), and imaging-related examinations. Patients were observed via outpatient visits or a telephone connection. The follow-up period continued until 28 February 2021, or the tumor recurrence date.

2.3 Evaluation indicator

After the initial treatment, data from the imaging examination and serological examination were collected as the baseline characteristics. Patient health was regularly reviewed by imaging and serological indexes. The imaging and serological indexes of each review were compared with the baseline data. Recurrence was defined as patients were complete remission after initial treatment, increased tumor marker AFP, and/or imaging findings indicating local, regional or distant tumor progression 4 weeks after of treatment. The time points of recurrence were recorded. Progression-free survival (PFS) was defined as time between the initiation of randomization and the occurrence (progression) or death (for any reason) of the tumor.

2.4 Statistical analysis

SPSS 19.0 software (Statistical Product and Service Solutions 19.0 software, International Business Machines Corporation, Armonk, NY, America) was used for statistical analysis. Univariate analysis was performed using the Kaplan-Meier method, and the differences were compared by log-rank tests. A multivariate Cox proportional regression model was used for multivariate linear regression analysis. $p < 0.05$ was regarded as statistically significant.

3. Results

The clinical characteristics of 54 patients with PEST are summarized in Table 1. The median age at initial treatment was 21 years (range, 11–52 years). Thirty-six patients (66.7%) had a childbearing history; the serum AFP level before initial management was $\geq 10,000$ ng/mL in 30 patients (55.6%); six patients had extragonadal EST; and the tumor size was $\geq 15$ cm in 26 patients (48.1%).

All 54 patients underwent open surgery. Forty-two patients (77.8%) chose to preserve fertility. The surgical procedures performed were as follows: lymphadenectomy ($n = 32$, 59.3%), omentectomy ($n = 39$, 72.2%), and unilateral salpingo-oophorectomy (USO; $n = 47$, 87.0%). In addition, five patients (9.3%) underwent bilateral salpingo-oophorectomy (BSO); two patients (3.7%) underwent cystectomy; and 46 patients (85.2%) had no residual tumor.

Among the 42 patients with fertility preservation, USO ($n = 40/42$, 95.2%) and simple adnexectomy ($n = 2/42$, 4.8%) were performed. Thirty-one patients underwent omental resection, and 22 underwent lymphadenectomy.

Of the 12 patients who did not receive fertility-sparing
TABLE 1. Characteristics of 54 patients with PEST.

| Characteristic                  | Total n (%) |
|--------------------------------|-------------|
| **Age (yr)**                   |             |
| Median                         | 21 (11–52)  |
| <18                            | 14 (25.9%)  |
| ≥18                            | 40 (74.1%)  |
| **Childbearing history**       |             |
| No                             | 36 (66.7%)  |
| Yes                            | 18 (33.3%)  |
| **Stage**                      |             |
| I                              | 26 (48.1%)  |
| II                             | 3 (5.6%)    |
| III                            | 22 (40.7%)  |
| IV                             | 3 (5.6%)    |
| **Tumor site**                 |             |
| Ovarian                        | 48 (88.9%)  |
| Extragonadal                   | 6 (11.1%)   |
| **Tumor size (cm)**            |             |
| <15                            | 28 (51.9%)  |
| ≥15                            | 26 (48.1%)  |
| **Histological features**      |             |
| EST without EC                 | 50 (92.6%)  |
| EST + EC                       | 4 (7.4%)    |
| **Course of platinum-based chemotherapy** |          |
| <3                             | 6 (11.1%)   |
| ≥3                             | 48 (88.9%)  |
| **Serum AFP level before initial management (ng/mL)** | |
| <10,000                        | 24 (44.4%)  |
| ≥10,000                        | 30 (55.6%)  |
| **Total**                      | 54          |

EST, endodermal sinus tumor; EC, embryonal carcinoma; AFP, α-fetoprotein.

surgery, five patients underwent total hysterectomy with BSO; six patients underwent radial hysterectomy with USO; one patient underwent subtotal hysterectomy with USO; and 10 patients underwent lymphadenectomy. Omentectomy was performed in eight patients.

According to the pathological and stage criteria, the numbers of patients by stage were 26 in stage I, three in stage II, 22 in stage III, and three in stage IV.

When it came to chemotherapy, the median course of postoperative platinum-containing chemotherapy was four courses (range, 0–7 courses) in 54 patients, of which two patients did not receive adjuvant therapy. Fifty-two patients received platinum (cisplatin or carboplatin) chemotherapy. Among them, 46 patients received bleomycin + etoposide + cisplatin (BEP) chemotherapy; three patients received BEP and etoposide + cisplatin (EP) chemotherapy; one patient received BEP with cisplatin intraperitoneal perfusion (IP) chemotherapy; one patient received paclitaxel + carboplatin chemotherapy; and one patient received vindesine + carboplatin + ifosfamide, vindesine + pirarubicin + cisplatin, and cisplatin IP chemotherapy at different times (Table 2).

Fifteen of 54 patients experienced recurrence and had an average recurrence time of 13.1 months (Details of evidence of recurrence see Table 3). Of these 15, two patients had FIGO stage I, 10 patients had FIGO stage III, and three patients had FIGO stage IV. Two patients who did not receive chemotherapy experienced recurrence after primary surgery, and one patient with recurrence had only received platinum-containing chemotherapy twice after the initial treatment. The histological features of three patients with recurrent PEST were EST with EC. Six patients with recurrence had residual tumor after the first surgery.

After univariate analysis, the significant risk factors for PFS in patients with PEST included the course of platinum-based chemotherapy, the FIGO stage, the histological features (EST combined with EC), and the presence of residual tumor (p < 0.05). Age, childbearing history, tumor site, fertility-preserving surgery, tumor size, and serum AFP level before initial management did not affect PFS (p > 0.05; Table 4, Figs. 3,4,5,6). Only FIGO stage was an independent risk factor for PFS after multivariate analysis (Table 5).

4. Discussion

EST is the second most common ovarian germ cell malignancy [8] and is characterized by varied and diverse histological patterns [9]. Most ESTs synthesize AFP, so elevation of this tumor marker can support a diagnosis. Fifty percent of ESTs are mixed and contain other germ cell elements, including EC, teratoma, germinoma, and choriocarcinoma [5].

Our study included a large sample size from a single center for the retrospective study of PEST. The study included 48 patients with ovarian EST and six with extragonadal EST—a rare representation in the existing literature.

With regard to risk factors for the EST recurrence, multiple researchers have attempted to determine accurate markers. Yang et al. [10, 11] believed that the size of postoperative residual tumor affected the prognosis of ovarian EST. Minimal residual tumor reflected a better prognosis. Kawai et al. [12] reported that the 5-year survival rate of patients with residual tumors larger than 2 cm (36%) was significantly lower than that of patients with residual tumors smaller than 2 cm (82%; p < 0.05). Nawa et al. [13] and Wang et al. [14] also reported that patients with small residual tumors after initial surgery had better prognoses. However, Nasioudis et al. [15] found no significant correlation between residual tumor and prognosis. Cicin et al. [16] reviewed the surgical data of 32 patients with ovarian EST: 10 patients underwent hysterectomy and BSO, 18 patients underwent USO, two patients underwent BSO, and two patients underwent cystectomy. The results showed no significant difference in efficacy between fertility-preserving surgery and radical surgery. Zhao et al. [17] retrospectively analyzed the data of 130 patients with malignant ovarian germ cell tumor. The results showed no significant difference in OS (overall survival: Time from randomization to death (for any reason)) and DFS (disease-free survival: Time from...
TABLE 2. Platinum-based chemotherapy of 54 patients with PEST.

| Chemotherapy regimen          | Schema                                         | Total n |
|-------------------------------|------------------------------------------------|---------|
| BEP                           |                                               |         |
| Bleomycin (15 mg, days 1, 8 and 15) |                                               |         |
| Etoposide (100 mg/m², days 1–5) |                                               |         |
| Cisplatin (20 mg/m², days 1–5)  |                                               |         |
| **Every 3 weeks for 1–7 cycles** |                                               | 46      |
| **BEP + EP**                  |                                               |         |
| Bleomycin (15 mg, days 1, 8 and 15) |                                               |         |
| Etoposide (100 mg/m², days 1–5) |                                               |         |
| Cisplatin (20 mg/m², days 1–5)  |                                               |         |
| Etoposide (100 mg/m², days 1–5) |                                               |         |
| Cisplatin (20 mg/m², days 1–5)  |                                               |         |
| **BEP every 3 weeks for 2–3 cycles; EP every 3 weeks for 1–3 cycles** | | 3       |
| **TC**                        |                                               |         |
| Paclitaxel (100 mg/m², day 1)  |                                               |         |
| Carboplatin (AUC = 5, day 1)   |                                               |         |
| **Every 3 weeks for 4 cycles** |                                               | 1       |
| **BEP + cisplatin (IP)**      |                                               |         |
| Bleomycin (15 mg, days 1, 8 and 15) |                                               |         |
| Etoposide (100 mg/m², days 1–5) |                                               |         |
| Cisplatin (20 mg/m², days 1–5)  |                                               |         |
| Cisplatin (IP) (60 mg/m²², day 1)|                                               |         |
| **BEP for 1 cycle; cisplatin (IP) for 1 cycle** | | 1       |
| **VCI + VAP + cisplatin (IP)** |                                               |         |
| Vindesine (3 mg/m², day 1)     |                                               |         |
| Carboptalin (AUC = 5, day 1)   |                                               |         |
| Ifofamide (1.5 mg/m², day 1)   |                                               |         |
| Vindesine (3 mg/m², day 1)     |                                               |         |
| Pirarubicin (30 mg/m², day 1)  |                                               |         |
| Cisplatin (65 mg/m², day 1)    |                                               |         |
| Cisplatin (IP) (60 mg/m²², day 1)|                                               |         |
| **VCI every 3 weeks for 4 cycles; VAP every 3 weeks for 2 cycles; cisplatin (IP) for 1 cycle** | | 1       |

*BEP, bleomycin + etoposide + cisplatin; EP, etoposide + cisplatin; TC, paclitaxel + carboplatin; AUC, area under the curve; IP, intraperitoneal perfusion; VCI, vindesine + carboplatin + ifosfamide; VAP, vindesine + pirarubicin + cisplatin.*

TABLE 3. Details of evidence of recurrence in fifteen patients.

| Patient number | AFP elevated | Metastasis of imaging                  |
|----------------|--------------|----------------------------------------|
| 1⁴             | Yes          | Omentum                                |
| 2              | Yes          | NK                                     |
| 3⁴             | Yes          | Pelvic                                 |
| 4              | Yes          | Diaphragm                              |
| 5⁴             | Yes          | Liver and spleen                       |
| 6              | Yes          | Diaphragm and abdominal cavity         |
| 7              | Yes          | Brain                                  |
| 8              | Yes          | Brain                                  |
| 9              | Yes          | NK                                     |
| 10             | Yes          | Pelvic                                 |
| 11             | Yes          | NK                                     |
| 12             | Yes          | NK                                     |
| 13             | Yes          | Liver and abdominal cavity             |
| 14             | Yes          | NK                                     |
| 15             | Yes          | Liver and bone                         |

⁴: Patient 1, 3 and 5 were extragonadal EST; NK, not known.
Table 4. Univariate analysis factor analysis for recurrence of PEST.

| Factors                                      | $p$ value | PFS             |
|----------------------------------------------|-----------|-----------------|
| Factors                                      |           |                 |
| Age                                          |           |                 |
| <18                                          | 0.556     | 0.72 (0.25–2.12) |
| $\geq$18                                     |           |                 |
| Childbearing history                         | 0.078     | 0.29 (0.07–1.28) |
| No                                           |           |                 |
| Yes                                          |           |                 |
| Histological features (EST + EC)             | 0.017     | 4.08 (0.47–35.74) |
| No                                           |           |                 |
| Yes                                          |           |                 |
| Extragonal EST                               | 0.642     | 1.43 (0.32–6.34) |
| No                                           |           |                 |
| Yes                                          |           |                 |
| Stage                                        | 0.642     | 1.43 (0.32–6.34) |
| I–II                                         | $<0.001$  | 9.73 (3.47–27.34) |
| III–IV                                       |           |                 |
| Fertility-sparing surgery                    | 0.32      | 2.11 (0.48–9.34) |
| No                                           |           |                 |
| Yes                                          |           |                 |
| Tumor size (cm)                              | 0.529     | 0.72 (0.26–2.03) |
| $<15$                                        |           |                 |
| $\geq$15                                     |           |                 |
| Residual tumor                               | 0.001     | 4.86 (1.03–23.01) |
| No                                           |           |                 |
| Yes                                          |           |                 |
| Course of platinum-based chemotherapy        | 0.004     | 0.19 (0.02–2.16) |
| $<3$                                         |           |                 |
| $\geq$3                                      |           |                 |
| Serum AFP level before initial management ($\geq$10,000 ng/mL) | 0.973 | 1.02 (0.37–2.81) |
| No                                           |           |                 |
| Yes                                          |           |                 |

PFS, progression-free survival; HR, hazard ratio; EST, endodermal sinus tumor; EC, embryonal carcinoma; AFP, α-fetoprotein; CI, confidence interval.

Figure 3. Progression-free survival (PFS) according to course of platinum-based chemotherapy. HR, hazard ratio.
Figure 4. Progression-free survival (PFS) according to international federation of gynecology and obstetrics stage. HR, hazard ratio.

Figure 5. Progression-free survival (PFS) according to histological features. HR, hazard ratio; EST, endodermal sinus tumor; EC, embryonal carcinoma.

Figure 6. Progression-free survival (PFS) according to residual tumor. HR, hazard ratio.
randomization to relapse or death (for any reason) between patients with bilateral ovarian germ cell tumor and patients with unilateral ovarian germ cell tumor after 5 years. Mahdi et al. [18] studied the clinical data of 1529 patients with bilateral germ cell tumors, spanning 19 years, from a United States cancer center. The results showed no significant difference in 5-year OS and PFS between patients with bilateral and unilateral ovarian germ cell tumors [18]. Frazier et al. [19], Neeyalavira et al. [20], Chen et al. [21], and Zhang et al. [22] believe that stage is an important factor affecting the prognosis (i.e., earlier stage is associated with better prognosis).

In the univariate analysis of our study, we found that residual tumor (hazard ratio (HR) = 4.86, 95% CI: 1.03–23.01, \( p = 0.001 \)) and stage (HR = 9.73, 95% CI: 3.47–27.34, \( p < 0.001 \)) were risk factors for recurrence of PEST. In addition, in multivariate analysis, we found that stage (HR = 6.92, 95% CI: 1.37–35.03, \( p = 0.019 \)) was an independent risk factor for PFS, whereas tumor size and site and the use of fertility-sparing surgery had no significant effect on the recurrence of PEST.

Interestingly, we found no significant difference in PFS between extragonadal and ovarian EST. This may be due to the following reasons: (1) ESTs at different locations are essentially ESTs, which do not change with location. (2) ESTs at different locations are still sensitive to chemotherapy. Also, extragonadal EST may be treated according to ovarian EST standards.

In the literature, Gershenson et al. [23] reported the treatment of patients who had ovarian EST with BVP (bleomycin + vincristine + cisplatin) chemotherapy. The efficacy of treatment in stage I and II was 95%, and efficacy in stages III and IV was 80% and 60%, respectively. The efficacy of this regimen for patients with recurrence was 40%. Chen et al. [21] noted that a reasonable platinum-containing chemotherapy regimen can benefit patients with ovarian EST. In addition, reports by Nawa et al. [13], Cicin et al. [16] and Mitchell et al. [24] also identified a statistically significant difference in 5-year survival rates between patients with malignant germ cell tumor treated with platinum and those not treated with platinum.

In this study, the course of platinum-containing chemotherapy was a related factor that affected the recurrence of PEST (HR = 0.19, 95% CI: 0.02–2.16, \( p = 0.004 \)). This result might be due to the sensitivity of PEST to platinum-based chemotherapy; if so, a sufficient amount of platinum-based chemotherapy should be given after surgery.

Patients with pure EST have shown better prognoses than patients with other pathological types [19]. Some studies have shown no significant difference in prognosis between pure ovarian EST and germ cell tumor with mixed EST components [16, 25]. However, Chen et al. [21] and Zhang et al. [22] noted that the pathological type is not a factor that affects the prognosis of ovarian EST.

We found that patients in our study with EST + EC were more likely to experience relapse than patients with EST without EC were (HR = 4.08, 95% CI: 0.47–35.74, \( p = 0.017 \)). This finding has been rarely reported in the domestic or international literature.

Our results might be related to the following reasons: First, the degree of malignancy of EST was much higher than that of other types of germ cell tumors, such as dysgerminoma. The biological behavior of tumors associated with PEST combined with EC might be more malignant. Thus, it would be easier for patients whose histological features were EST combined with EC to experience relapse. Second, the chemosensitivity of EC is worse than that of other types of germ cell tumors, which leads to a higher risk of recurrence. However, this study still lacked sufficient sample size, so additional research is needed to verify this conclusion.

Some studies have reported other factors related to ovarian EST. Wang et al. [14] and de la Motte Rouge et al. [26] reported that AFP level affected the recurrence of ovarian EST, whereas Elashry et al. [27] found that AFP did not affect the prognosis of ovarian EST. Solheim et al. [28] reported that the prognosis of patients older than age 50 years was significantly worse than that of patients who were younger than age 50.

| Factors                                      | PFS       | p value |
|----------------------------------------------|-----------|---------|
| Course of platinum-based chemotherapy        |           |         |
| <3                                           | 0.06      | 0.25 (0.06–1.07) |
| \( \geq 3 \)                                 |           |         |
| Stage                                        |           |         |
| I–II                                         | 0.02      | 6.92 (1.37–35.03) |
| III–IV                                       |           |         |
| Histological features (EST + EC)             |           |         |
| No                                           | 0.22      | 2.33 (0.60–8.99) |
| Yes                                          |           |         |
| Residual tumor                               |           |         |
| No                                           | 0.51      | 1.51 (0.44–5.17) |
| Yes                                          |           |         |

*PFS, progression-free survival; HR, hazard ratio; EST, endodermal sinus tumor; EC, embryonal carcinoma; CI, confidence interval.*
years. Bilici et al. [29] also considered age a factor influencing prognosis, but Neeyalavira et al. [20] and Chen et al. [21] did not agree.

In this study, we found that age, childbearing history, and serum AFP level before initial management (≥10,000 ng/mL) were not factors influencing the recurrence of PEST. In addition, a preprint has previously been published [30].

5. Conclusions

We found that stage is a prognostic factor for recurrence of PEST. The aim of the initial surgery is to maximally debulk all grossly visible tumor and the post-operative treatment should include a sufficient dose and full course of platinum-based chemotherapy, which may reduce the recurrence rate. Patients with histological features of EST combined with EC may be more likely to experience relapse.

Some shortcomings to this study still exist. Firstly, maybe some gene expression that could be associate with PEST, unfortunately, these patients have not undergone genetic testing. Secondly, the incidence of PEST is relatively small, and the known cases are limited. To our knowledge, the number of patients with histological features of EST combined with EC is extremely scarce. Therefore, larger sample clinical studies are needed to confirm the conclusions of this study.

This study primarily explored the factors influencing tumor progression in patients with PEST. Stage was a prognostic factor for recurrence of PEST, and the recurrence rate increased with increasing stage. The first surgery for PEST should remove the tumor as completely as possible, and the initial treatment should require sufficient doses and a full course of platinum-based chemotherapy to reduce the recurrence rate. In practice, patients with histological features of EST combined with EC may have an increased susceptibility to recurrence. However, because of the low incidence of PEST and the limited number of known cases, the conclusions need additional validation with large sample studies.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

YLG and HW—contributed equally to this work as first author and co-first author; wrote the manuscript. YLG, TZ and YLZ—conceived and designed the study. YLG, HW, QQL and XC—extracted and analyzed data. TZ and YLZ—were the statisticians who confirmed the analysis of this study. XC and YLZ—critically revised the manuscript. All authors reviewed and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval to review the patients’ medical records and pathological reports was obtained from the institutional review board of Zhejiang Cancer Hospital, Zhejiang, China (IRB-2019-202). Written informed consent was obtained from all patients. Written informed consent was obtained from the patient for publication and accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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