Local suture ligation-assisted percutaneous sclerotherapy for Kasabach-Merritt phenomenon-associated kaposiform haemangioendothelioma

XIAO LI*, MING-ZHE WEN*, LI-XIN SU, XI-TAO YANG, YI-FENG HAN and XIN-DONG FAN

Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Stomatology and Shanghai Research Institute of Stomatology, Shanghai 200011, P.R. China

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Abstract. Kaposiform haemangioendotheliomas (KHEs) complicated by the Kasabach-Merritt phenomenon (KMP) are rare and severe neoplastic lesions often associated with locally aggressive disease, consumption coagulopathy and high mortality rates. Current regimens have yet to achieve a satisfactory therapeutic effect. Thus, an effective and minimally invasive approach for treating complex KHE/KMP cases is necessary for clinical management. The present case series describes patients with KHE/KMP who underwent local suture ligation-assisted percutaneous sclerotherapy to minimise surgical trauma and ensure effective treatment. Between September 2015 and September 2017, 3 consecutive patients with KHE/KMP underwent staged local suture ligation-assisted percutaneous sclerotherapy. Of these patients, 2 presented with medical histories of corticosteroid treatment with unsatisfactory outcomes. The patients underwent a stepwise synthetic serial therapy programme consisting of percutaneous sclerotherapy and adjunctive pharmacotherapy accompanied by a suture ligation procedure. Clinical, radiological, pathological and laboratory data were analysed to evaluate the outcomes of the therapy. All patients were successfully managed with the proposed procedure. Significant relief of clinical symptoms and improvements in haematological indicators were achieved. No recurrence or complications were observed during regular follow-up (4, 19 and 28 months). In conclusion, local suture ligation-assisted percutaneous sclerotherapy was demonstrated to be a safe and effective treatment for KHE/KMP, being minimally invasive, involving simple manipulation and providing a clear treatment benefit in certain cases. Further studies involving larger sample sizes are required to thoroughly evaluate the procedure, which can potentially be used as a novel therapeutic option for KHE/KMP treatment.

Introduction

Kaposiform haemangioendotheliomas (KHEs) were first described in 1993 by Zukerberg et al (1) as rare soft-tissue neoplastic lesions often associated with locally aggressive disease, lymphangiomatosis and the Kasabach-Merritt phenomenon (KMP). According to Croteau et al (2), the prevalence in Massachusetts is ~0.91 cases per 100,000 individuals. First reported by Kasabach and Merritt in 1940 (3), KMP is a haemangioendothelioma-producing condition that occasionally causes microangiopathic haemolytic anaemia, thrombocytopenia and consumption coagulopathy. Untreated or recurrent KHE/KMP can be a life-threatening condition that occasionally causes microangiopathic haemolytic anaemia, thrombocytopenia and consumption coagulopathy. Untreated or recurrent KHE/KMP can be a life-threatening condition that occasionally causes microangiopathic haemolytic anaemia, thrombocytopenia and consumption coagulopathy.
treatment, pharmacological management, which has been the focus of numerous studies, is regarded as one of the most important non-invasive treatments. However, according to a previous study (6), the non-selective β-adrenergic antagonist propranolol is partially effective, with only 36% of cases responding to treatment. Systemic corticosteroid therapy, as a conventional treatment option for patients with KHE, is associated with limited therapeutic efficacy and relatively higher rates of side effects (7,8). Alternative treatments have recently emerged. A meta-analysis by Liu et al (9) showed that corticosteroids were considerably less effective and had higher complication rates compared with vincristine; however, several side effects of the latter cannot be ignored, with constipation, peripheral neuropathy and syndrome of inappropriate antidiuretic hormone secretion being reported (10-12). In addition, another study described a patient who partially responded to paclitaxel chemotherapy and subsequent treatments (prednisone, doxorubicin, interferon-α, gemcitabine and ifosfamide), but succumbed to severe KMP and major gastrointestinal bleeding (13).

Sirolimus was recently proposed as an effective alternative for KHE/KMP (14). Ji et al (15) presented a multicentre retrospective study of 52 patients with KHE and concluded that sirolimus was effective and safe for treating progressive KHE. Despite several studies assessing the therapeutic effect of sirolimus, the side effects of this drug cannot be ignored (16,17). Clinical sirolimus application has been reported to result in the following side effects: Hyperglycaemia, oral sores and signs of immunosuppression (5). Additionally, in a 2017 case report by Triana et al (18), a 4-month-old infant with pancreatic KHE showed no response to sirolimus. As pharmacological treatment of KHE has mostly been demonstrated to reduce rather than to eliminate the tumour mass, a certain risk of non-response and recurrence remains. Furthermore, the relapse of lesions may have lethal consequences (19).

Surgical resection is applied in certain cases of KHE/KMP, although tissue defects are a major source of trauma for these patients. In 2016, Guo et al (20) described the case of a 48-day-old male infant with KMP who did not respond to propranolol or glucocorticoid treatment. The infant recovered subsequent to receiving surgical resection, indicating that surgical approaches may be required despite the associated challenging recovery. In the report by Zahir et al (21), a 24-day-old male neonate received transfusions of platelets (PLTs) and packed red blood cells (RBCs), as well as medical treatments that included oral prednisolone, intravenous methylprednisolone and interferon-α. Despite thrombocytopenia, the PLT count returned to normal following resection. Furthermore, Leung et al (22) described the case of a full-term male baby with pancreatic KHE/KMP who had a PLT count of 23x10^9/l (normal range of PLT: 100-300x10^9/l); the baby underwent resection treatment and recovered with a normal PLT count following surgery. Surgical resection has been reported to be effective in several other cases (23-26). However, postoperative tissue defects may severely impair the structural and functional development of tissues in an infant. Although a less invasive surgical procedure is necessary in certain cases, a consensus regarding comprehensive and sequential therapy for KHE has yet to be established.

The present study reports a novel approach, stepwise local suture ligation-assisted percutaneous sclerotherapy, which is effective and less invasive for the treatment of complex cases of KHEs complicated by KMP, in a limited series. This study aimed to retrospectively review the clinical features and treatment outcomes of stepwise local suture ligation-assisted percutaneous sclerotherapy for the treatment of KHE/KMP.

Patients and methods

Patients. Approval from the Institutional Review Board of Shanghai Ninth People's Hospital was obtained for a retrospective review of patient medical and imaging records, and written informed consent from the legal guardian of the patients was obtained. Inclusion criterions included: i) A definite diagnosis of KHE/KMP confirmed by clinical, pathological and laboratory manifestations; ii) legal guardians agreeing with the treatment plan. The exclusion criterion was if the legal guardians refused the proposed plan. Between September 2015 and September 2017, 3 consecutive patients (2 males, 1 female; mean age, 2.67 months; range, 1-5 months) with KHE/KMP underwent staged treatment, including 2 patients with a medical history of corticosteroid treatment and lesion relapse following treatment. Clinical, radiological, haematological (including PLT, haemoglobin, RBC count, D-Dimer and fibrin degradation product) and pathological features of the cases are recorded (Tables I and II; Figs. 1-3). All diagnoses were based on a combination of medical history, clinical manifestations, imaging findings and pathological data.

Treatment process. The patients underwent a stepwise synthetic serial therapy consisting of percutaneous sclerotherapy and adjunctive pharmacotherapy, accompanied by a suture ligation procedure.

Local suture ligation-assisted percutaneous sclerotherapy was performed under general anaesthesia with a standard aseptic technique. A suspension containing 10 mg/m² (body surface area) bleomycin and 8 ml 0.9% NaCl was injected into the tumour using a 10-ml syringe. Percutaneous punctures were located at several points, including adjacent to, and at the centre of, the lesion. Subsequently, a tight local suture ligation was applied to limit the blood supply of the lesion. A 9x34-mm circular needle and 3-0 absorbable sutures were used. An interrupted suture method was applied to form a grid-like pattern on the surface of local lesions. The spacing between sutures was 2-3 cm and the suture depth was 2-3 cm. Every knot was tight and tensile, and the lesions were covered with wound dressings following the suture ligation procedure. A biopsy was performed during the suture ligation procedure and specimens were used for pathological diagnosis. The suture ligation procedure limited the blood supply to the lesion and reduced intraoperative blood loss during biopsy incision.

Pre- and post-adjunctive pharmacotherapy was administered to maintain a relatively acceptable physiological status during hospitalisation. Patients began treatment with intravenous corticosteroids (methylprednisolone, 6 mg/kg/day) from the first day of hospital admission throughout the treatment procedure. Drug dosages were gradually reduced after KMP vanished and PLT returned to normal (normal range of PLT:}
Histological observation. All tumour tissue samples were fixed in 10% neutral buffered formalin solution (24 h at room temperature) for histopathological evaluation. Later, they were

100-300x10^9/l) for three days. Oral administration of prednisone acetate was reduced from 2 to 1.5 mg/kg/day until drug withdrawal.

Table I. Demographics and clinical presentation of patients with Kaposiform haemangioendotheliomas associated with the Kasabach-Merritt phenomenon.

| Patient | Sex | Age, months | Location             | Dimensions, cm | Appearance                                                   |
|---------|-----|-------------|----------------------|----------------|--------------------------------------------------------------|
| 1       | M   | 2           | Left lower abdomen   | 3x5            | Indurated ecchymotic mass with local swelling               |
| 2       | F   | 5           | Left cluneal region  | 10x15           | Indurated ecchymotic mass with local swelling               |
| 3       | M   | 1           | Left shin            | 5x7            | Firm mass without cutaneous changes, limiting ankle extension|

F, female; M, male.
Table II. Initial relevant haematological investigations of patients with Kaposiform haemangioendotheliomas associated with the Kasabach-Merritt phenomenon.

| Patient | PLT, n (x10^9/l) | HGB, g/l | RBC, n (x10^{12} cells/l) | DD, µg/ml | FDP, µg/ml |
|---------|------------------|---------|--------------------------|----------|-----------|
| 1       | 70               | 101     | 3.62                     | 11.13    | 51.0      |
| 2       | 59               | 111     | 4.16                     | 6.96     | 25.6      |
| 3       | 6                | 63      | 2.02                     | 83.86    | 284.0     |

PLT, platelet; HGB, haemoglobin; RBC, red blood cell; DD, D-Dimer; FDP, fibrin degradation product.
Figure 3. Clinical, radiological, pathological and laboratory evaluations of case 3. Pre-treatment image (A) of the patient and (B) a close-up of the affected area. Images obtained at 4 weeks following suture ligation treatment of (C) the patient and (D) a close-up of the affected area. (E) Pre-treatment radiological evaluations. Histopathological examinations including (F) haematoxylin-eosin staining and immunohistochemical staining for (G) cluster of differentiation (CD)34, (H) CD31, (I) podoplanin, (J) prospero homeobox protein 1, (K) glucose transporter 1, (L) proliferation marker protein Ki-67, (N) desmin of the lesion and (M) smooth muscle actin. Original magnification for (F‑N), x200; inset image in (F), x400. (O‑Q) Laboratory evaluations: (O) PLT, (P) HGB and (Q) RBC counts. The arrow indicates the time-point of suture ligation treatment. PLT, platelet; HGB, haemoglobin; RBC, red blood cell.
embedded in paraffin and sectioned at a thickness of 4 µm were prepared from formalin-fixed and paraffin-embedded blocks, deparaffinised in xylene, rehydrated and microwaved for 10 min at 30% power in citrate buffer, pH 6.0 (Poly Scientific, Bay Shore, NY, USA). Endogenous peroxidase activity was blocked using 0.3% hydrogen peroxide in 80% methanol for 5 min at room temperature. The sections were either stained with haematoxylin-eosin (HE) (2 g/l haematoxylin for 5 min followed by 0.5% eosin for 1-3 min, both at room temperature) or incubated with primary antibodies, including cluster of differentiation 34 (CD34), CD31, desmin (Des), podoplanin (D2-40), prospero homeobox protein 1 (Prox-1), factor VIII (FVIII), vascular endothelial growth factor receptor 3, glucose transporter 1 (GLUT-1), proliferating cell nuclear antigen (PCNA), proliferation marker protein Ki-67 (Ki-67) and smooth muscle actin (SMA) overnight at 4˚C subsequent to blocking with 3% bovine serum albumin (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany). Secondary antibodies were applied to the slides for 1 h at room temperature. The primary and secondary antibodies involved in the present study are listed in Table III. Photographs were obtained with an Eclipse Ti-E inverted microscope (Nikon Corporation, Tokyo, Japan; magnification, x200 and x400) and a Nikon E600 camera.

### Results

#### Clinical outcomes

The proposed local suture ligation-assisted percutaneous sclerotherapy strategy was effective in all patients, with notable relief of clinical symptoms and improvement of haematological indicators. Pre- and post-treatment clinical, radiological, pathological and laboratory evaluations are presented in Figs. 1-3.

Regarding clinical manifestations, the tumour mass was reduced, local swelling was diminished, the tendencies for ecchymosis and bleeding were weakened, and the overall health status was largely improved in all patients. Furthermore, in one patient (presented in Fig. 3) who had suffered from limited range of motion in ankle joint due to KHE in his left lower limb, no difference in the range of motion in bilateral lower limbs was detected through post-treatment clinical examination. More importantly, none of the patients experienced tissue defects or local dysfunction. The entire treatment process was successful without any adverse effects. At the time of writing the present study, the patients were undergoing regular follow-ups (28-, 19- and 4-month follow-ups for cases 1, 2 and 3, respectively). Following operating local suture ligation-assisted percutaneous

| Primary antigen | Source (cat. no.) | Clone | Dilution | Secondary antigen, source, cat. no., dilution |
|-----------------|-------------------|-------|----------|-----------------------------------------------|
| CD34 | CST\(^a\) (3569S) | ICO0115 | 1:30 | Peroxidase AffiniPure Donkey Anti-Mouse IgG (H+L), Jackson\(^b\), 715-035-150, 1:500-1:5,000 |
| Des | R&D\(^c\) (AF3844) | DES | 5-15 µg/ml | AffiniPure Bovine Anti-Goat IgG (H+L), Jackson\(^b\), 805-035-180, 1:500-1:5,000 |
| D2-40 | Abcam\(^d\) (ab77854) | D2-40 | 1:40 | Peroxidase AffiniPure Donkey Anti-Mouse IgG (H+L), Jackson\(^b\), 715-035-150, 1:500-1:5,000 |
| CD31 | CST\(^a\) (3528S) | PECAM-1'89C2 | 1/1,600 | Peroxidase AffiniPure Donkey Anti-Mouse IgG (H+L), Jackson\(^b\), 715-035-150, 1:500-1:5,000 |
| FVIII | Novus\(^e\) (NB100-91761) | F8 | 1:50-1:200 | Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L), Jackson\(^b\), 711-035-152, 1:500-1:5,000 |
| GLUT-1 | Novus\(^e\) (NB110-39113) | SLC2A1 | 1:200 | Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L), Jackson\(^b\), 711-035-152, 1:500-1:5,000 |
| Ki-67 | CST\(^a\) (9449S) | 8D5 | 1:400 | Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L), Jackson\(^b\), 711-035-152, 1:500-1:5,000 |
| PCNA | CST\(^a\) (13110S) | D3H8P | 1:8,000 | Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L), Jackson\(^b\), 711-035-152, 1:500-1:5,000 |
| Prox-1 | CST\(^a\) (14963S) | D2J6J | 1:500 | Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L), Jackson\(^b\), 711-035-152, 1:500-1:5,000 |
| SMA | R&D\(^c\) (MAB1420) | 1A4 | 8-25 µg/ml | Peroxidase AffiniPure Donkey Anti-Mouse IgG (H+L), Jackson\(^b\), 715-035-150, 1:500-1:5,000 |
| VEGFR-3 | R&D\(^c\) (AF349) | FLT4 | 5-15 µg/ml | Peroxidase AffiniPure Donkey Anti-Goat IgG (H+L), Jackson\(^b\), 805-035-180, 1:500-1:5,000 |

\(^a\)Cell Signaling Technology, Boston, MA, USA; \(^b\)Jackson ImmunoResearch Laboratories, West Grove, PA, USA; \(^c\)R&D Systems, Minneapolis, MN, USA; \(^d\)Abcam, Cambridge, UK; \(^e\)Novus, Littleton, CO, USA, CD, cluster of differentiation; Des, desmin; D2-40, podoplanin; FVIII, factor VIII; GLUT-1, glucose transporter 1; Ki-67, proliferation marker protein Ki-67; PCNA, proliferating cell nuclear antigen; Prox-1, prospero homeobox protein 1; SMA, smooth muscle actin; VEGFR-3, vascular endothelial growth factor receptor 3.
sclerotherapy there were eunemia and no signs of recurrence in all cases.

Laboratory evaluations. Pre-treatment haematological data of the cases were presented in Table II, which indicated KMP through evaluation of PLT, haemoglobin, RBC, D-Dimer and fibrin degradation products. According to laboratory and haematological evaluations, immediate and notable improvements in PLT, RBC and haemoglobin measurements were observed in all patients on the first day after suture ligation treatment. In cases 1 and 2, the PLT continued to increase until reaching normal thresholds and showed similar plateau trends that remained stable within normal range (normal range: 100-300x10^9/l) for 22 and 60 days, respectively, according to haematological evaluations. However, in case 3, although the relevant indicators remained at subnormal levels several days after suture ligation, a marked and rapid increase in PLT levels was observed between days 13 and 21, which reached a plateau of ~300x10^9/l after the 21st day.

Histological findings. Histological analysis by HE staining showed that the lesions were characterised by irregular sheets of spindle-shaped endothelial cells and characteristic slit-like vascular channels, confirming the diagnosis of KHE by pathology. In all cases, immunohistochemical staining results were positive for vascular markers (CD31, CD34 and FVIII) and proliferation markers (PCNA), and a population of parietal cells was partially positive for lymphatic markers D2-40 and Prox-1, ~5% positive for Ki-67 staining, and negative for GLUT-1 and Des. Muscular marker staining of SMA revealed a negative result in case 1, and positive results in cases 2 and 3 (Figs. 1-3).

Discussion

KHE/KMP is a type of haemangioma characterised by consumption coagulopathy and potentially high mortality rates; it is usually located in the extremities and retroperitoneum (10). In the present study, a stepwise synthetic serial treatment for patients with KHE was explored, particularly for those who failed to respond to, or tolerate, conventional treatment. The clinical results showed that severe KHE/KMP responded to the proposed treatment, local suture ligation-assisted percutaneous sclerotherapy, in a limited series. This therapy is particularly adaptable to lesions on the trunk and extremities.

Previous studies have demonstrated that a definitive diagnosis is essential in the management of KHE/KMP (16,27-30). KHE presents during early childhood and manifests as violaceous subcutaneous masses with ill-defined borders and a purpuric, bruised appearance, located on the extremities and trunk in ~75% of cases (27). KMP, a thrombocytopenic coagulopathy often associated with more aggressive KHEs (28,29), is one of the most dangerous and life-threatening clinical conditions, with a 30-40% mortality rate due to uncontrollable haemorrhage (16). The present cases showed clinical features consistent with KMP located in the extremities and trunk. Radiological evaluations provided supporting images of the lesions. More importantly, pathological diagnosis is widely accepted as the gold standard for KHE. Pathologically, the features of KHE resemble a capillary haemangioma and Kaposi's sarcoma. Infiltrating sheets composed of slit-like vascular channels and irregularly shaped spindle endothelial cells are characteristic features of KHEs (30). Regarding pathological findings, all cases in the present study showed classic features that confirmed the pathological diagnosis of KHE.

In addition to histological features, expression levels and changes in markers revealed by immunohistochemical analysis are essential in assessing KHE and may provide potential guidance for clinical treatment. According to Putra and Gupta (31), as vascular lesions, KHE lesions are immunoreactive to non-specific endothelial markers, including CD31 and CD34, in addition to lymphatic marker immunoreactivity with either Prox-1 or D2-40 within the neoplastic spindle endothelial cells supports the diagnosis of KHE (32). Detailed and systematic evidence of immunohistochemical staining was provided in the present study, showing endothelial cells in the nodules to be positive for vascular markers (CD31, CD34 and FVIII) and proliferation markers (PCNA). In addition, a population of parietal cells was partially positive for lymphatic markers D2-40 and Prox-1, ~5% positive for Ki-67 staining, indicating a relatively low proliferation ability, and negative for GLUT-1; these results facilitate a clear differential diagnosis from infantile haemangioma. Such findings are consistent with those of previous studies and support the pathological diagnosis of KHE. Various therapies for KHE/KMP treatment have long been considered and several methods have been reported in the literature, including oral glucocorticoids, vincristine chemotherapy, interferon therapy and surgical ablation (33,34). However, clinical outcomes have not improved due to limited efficacy, high recurrence possibilities, high risks of adverse reactions and iatrogenic tissue defects (7,35-38). Previously, mesh suture treatment was observed to be effective in the management of KMP (39); however, a more specific association between mesh sutures and KHE was not clearly reported, as only 1 patient in the series was pathologically diagnosed with KHE. In the present study, the reported cases were based on definite pathological KHE diagnoses and were characterised by extremely low PLT levels, partial drug sensitivities, larger tumour types compared with benign lesions, high resection trauma and high potential mortality risks. A local suture ligation procedure was paired with percutaneous sclerotherapy to eliminate the tumour, and patient recovery was achieved through physical and chemical mechanisms. Following this stepwise synthetic serial treatment, which involved a minimally invasive suture ligation procedure supplemented with appropriate pre- and post-treatment medication, all cases presented notable improvement in PLT levels. Indeed, haematological indices rapidly increased and a plateau period indicated a favourable prognosis. All patients recovered and remained stable throughout treatment. Notably, a clear difference in the treatment response times was observed between cases; cases 1 and 2 responded to our treatment 24 h after the suture ligation procedure, while case 3 required 7-8 days prior to presenting an upward trend in his PLT level. The difference in response time may have been associated with the lesion depth; the lesions were subcutaneous in cases 1 and 2, whereas the lesion was within the muscular layer in case 3, which was much deeper and the availability through percutaneous suture ligation...
and sclerotherapy may be limited. However, further investigations with a larger sample size is required to fully elucidate the potential association.

Due to the complex mechanism involved, the true aetiology and pathogenesis of KHE/KMP remain poorly understood. Gruman et al (40) suggested that the severity of thrombocytopenia is associated with the extent of local lesions. Pathological characterisation revealed that local KHE lesions consist of irregular, infiltrating nodules of fascicles of spindle-shaped endothelial cells and slit-like vascular channels (41). Local morphological sites of PLT consumption are characterised by scattered epithelioid or glomeruloid islands featuring endothelium associated with plump α-SMA-positive pericytes, stippled haemosiderin and CD61-positive fibrin thrombi. According to a previous study, such unique architectural features favouring turbulent blood flow and platelet activation likely partially contribute to the association with KMP (10). Such structural features may have been damaged by mechanical pressure from the local suture ligation procedure. Furthermore, PLT consumption may have been interrupted and local PLTs may have been relieved through certain unknown pathways. A second possible explanation for the clinical results is that mechanical pressure may have cut off the supply of nutrient-rich blood to tumours and lead to ischaemia and hypoxia in tumour tissues; a microenvironment of ischaemia and hypoxia may contribute to tumour elimination and disease relief. However, the exact mechanism requires further elucidation. Additionally, only a few studies have focused on the initiation and progression of KHE at the genetic level. Egashira et al (42) performed exome sequencing using DNA from a patient with KHE and identified germline missense single nucleotide variants in the tumour protein p53 and adenomatous polyposis coli genes, and tumour-specific somatic mutations in the integrin subunit β2, interleukin 32 and death inducer-oblitator 1 genes. To provide effective experimental evidence for genetic diagnosis and therapy in patients with KHE/KMP, additional in vivo and in vitro studies are warranted.

The present study is limited by the following: First, it is a retrospective report of a limited number of cases. Larger sample sizes and a prospective study design are required to perform a more precise assessment. Second, the exact mechanisms underlying the physical reactions to local suture ligation-assisted percutaneous sclerotherapy require investigation to obtain a deeper understanding of KHE/KMP.

In conclusion, the outcomes of the present study demonstrate that local suture ligation-assisted percutaneous sclerotherapy is a safe and effective therapy for KHE/KMP, and that it is minimally invasive, involves simple manipulation and results in a clear treatment effect. Therefore, the discussed procedure can be considered as a therapeutic option for treating KHE/KMP.

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Availability of data and materials

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

Authors’ contributions

XDF designed the study and performed the experiments. LXS detailed the study plan. XL and MZW performed the experiments and wrote the manuscript. XTY and YFH analysed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Scientific Research Projects Approval Determination of Independent Ethics Committee of Shanghai Ninth People's Hospital affiliated to Shanghai Jiao Tong University, School of Medicine (approval no. 2017070). Informed consent to participate in the study was obtained in all cases.

Patient consent for publication

The guardians of the patients provided written informed consent for publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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