DOI: 10.34108/eujhs.1307531

SAĞLIK BİLİMLERİ DERGİSİ
JOURNAL OF HEALTH SCIENCES
Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü Yayın Organıdır

Olgu Sunumu 2023; 32(Supplement): 57-62

3-YEAR FOLLOW-UP OF REGENERATIVE ENDODONTIC TREATMENTS WITH THE APPLICATION OF CONCENTRATED GROWTH FACTOR AS SCAFFOLD: NINE CASES*
KONSANTRE BÜYÜME FAKTÖRÜ KULLANILARAK YAPILAN REJENERATİF ENDODONTİK TEDAVİLERİN ÜÇ YILLIK TAKİBİ: DOKUZ ADET OLGU

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ABSTRACT

The aim of this case series is to present Three year clinical and radiographic follow-ups of nine regenerative endodontic treatment cases using concentrated growth factor in necrotic immature permanent teeth. Nine patients aged 8-21 years were referred to our clinic. According to clinical and radiographic examinations, it was decided to perform RET. After the working length determination, teeth were irrigated with 2.5% NaOCl and activated with Endo Activator. Root canals were instrumented with XP-endo Finisher-R file. 20 mL of 17% EDTA was used as final irrigation, and calcium hydroxide and temporary fillings were placed. Two weeks later, roots were irrigated with 17% EDTA and five mL distilled water and dried with paper points. Bleeding was induced into the coronal part of the root canal. Concentrated growth factor (obtained from the patient's blood) was placed into the root canals. Biodentine was placed on the blood clot and permanent restorations were made with resin composite. At three-year follow-up, clinical and radiographic healing was observed in five patients. In the other four patients, persistent infection and sinus-tract formation were detected at different time periods. Although RET is a promising treatment that aims to preserve teeth vitally, more randomized clinical research is needed due to its unpredictable results.

Keywords: Concentrated growth factor, immature necrotic permanent tooth, regenerative endodontic treatment

ÖZ

Bu olgu serisinin amacı, apeksi açık nekrotik daimi dişlerde konsantre büyüme faktörü kullanılarak gerçekleştirilen dokuz adet rejeneratif endodontik tedavi olgusunun üç yıllık klinik ve radyografik takiplerini sunmaktır. Yaşları 8-21 arasında değişen dokuz hasta kliniğimize başvurdu. Yapılan klinik ve radyografik muayeneler sonucunda rejeneratif endodontik tedavi (RET) yapılmasına karar verildi. Çalışma boyu tespitinden sonra dişler 20 mL %2,5 NaOCl ile irige edildi ve Endo Activator ile aktive edildi. Kök kanalları XP-endo Finisher-R eğesi ile enstrümante edildi. Final irrigasyonu olarak 20 mL %17 EDTA kullanıldı, ardından kalsiyum hidroksit ve geçici dolguları yerleştirildi. İki hafta sonra kökler 20 mL %17 EDTA ve beş mL distile su ile irige edildi ve kağıt konlar ile kurutuldu. Kök kanallarının koronal kısmına kadar kanama gerçekleştirildi. Hastadan kan alınarak elde edilen konsantre büyüme faktörü kök kanallarına yerleştirildi. Oluşan kan pıhtısının üzerine Biodentine yerleştirildi ve rezinkompozit ile daimi restorasyonları yapıldı. üç yıllık takipte beş hastada klinik ve radyografik iyileşme gözlendi. Diğer dört hastada farklı zaman dilimlerinde persiste enfeksiyon ve sinüs yolu oluşumu saptandı. Rejeneratif endodontik tedaviler dişleri canlı olarak korumayı amaçlayan ve gelecek vadeden tedaviler olsa da öngörülemeyen sonuçları nedeni ile daha fazla randomize klinik araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Konsantre büyüme faktörü, apeksi açık daimi nekrotik diş, rejeneratif endodontik tedavi

*This article was presented as an oral presentation at the "2nd Erciyes University International Dentistry Congress" 23-26 February 2023, Kayseri, Turkiye

Makale Geliş Tarihi : 31.05.2023
Makale Kabul Tarihi: 18.09.2023

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INTRODUCTION

Dental trauma, caries, or congenital anomalies may cause periapical periodontitis of immature permanent teeth (1). Apexification is the traditional treatment for these teeth that creates an apical hard tissue barrier with an apical plug with calcium hydroxide or calcium silicate cement (2). Recently, regenerative endodontic treatments (RETs) have become popular as biologically based procedures designed to replace damaged structuresof the pulp dentin complex (3), and studies have reported that RETs have emerged as a promising treatment with successful results for necrotic immature permanent teeth (4-6).

Stimulation of bleeding and intracanal blood clot formation is a current procedure to provide a three-dimensional scaffold for pulp-dentin regeneration that traps undifferentiated stem cells and promotes new tissue growth in RET (7). However, it is not always possible to induce periapical bleeding into the canal space, which will be inadequate to provide asufficient scaffold (8). To overcome this, the use of autologous platelet concentrates has been advocated (9). Autologous platelet concentrates release growth factors and cytokines required for tissue regeneration (10). Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are second-generationautologous platelet concentrates and have been successfully used in RETs (4).

Concentrated growth factor (CGF) is the latest generation platelet concentrate product (11) and unlike PRF, it does not contain bovine thrombin and anticoagulants (12). The structure of CGF is relatively stiffer, so it is more similar to natural fibrin. It contains large amounts of growth factors and proteins derived from autologous platelets and leukocytes (13). CGF has been investigated as a scaffold for endodontic regeneration in a few case reports and showed promising clinical and radiographic outcomes (14-15). To the best of our knowledge, there is no case series reporting RET results with the application of CGF. Therefore, the aim of this case series is to present long-term follow-up of RETs using CGF in necrotic immature permanent teeth

CASE PRESENTATION

The treatment protocol of each case of this case series followed the clinical guidelines proposed by Banchs and Trope (16) and the American Association of Endodontists' position statements regarding regenerative endodontic procedures (3). The treatments were carried out by the same operator (T.G.) between August 2019, and January 2023, at the Department of Endodontics of Fırat University, Elazıg, Turkiye. Before the treatment, informed consent forms were obtained from the patients that the treatment-related information and data could be used in scientific research. Case-specific items of the teeth treated with a regenerative endodontic procedure are shown in Table I.

The diagnosis of RET was based on history, clinical and radiographic examination findings. The tooth sensibility testing was performed by using an electric pulp tester (Digitest II; Parkell, NY, USA) and thermal testing with cold spray (Endo-Frost; Roeko, Langenau, Germany). The same procedure was applied in all cases as follows;

Treatment procedures (interventions)

First visit

The tooth was anesthetized with a carpule of maxicaine (80 mg/2 mL) (Vem, Istanbul, Turkiye) using infiltration technique and then isolated witha rubber dam.The tooth surface was disinfected with 2% chlorhexidine (Microvem, Sakarya, Turkiye) and an access cavity was prepared. The working length was determined clinically using an electronic apex locator (Propex Pixi; (Dentsply Maillefer, Ballaigues, Switzerland) and then confirmed with a periapical radiograph. Root canals were irrigated with sodium hypochlorite (20-mL 2.5%) and activated with Endo Activator (Dentsply Maillefer) (Figure Ia). XP -endo Finisher-R instrument (FKG Dentaire, La Chaux-de-Fonds, Switzerland) was used for the instrumentation of root canals, which has non-cutting and non-active tip, to eliminate the residual biofilm layer (Figure Ib). EDTA (17% 20-mL) (Prime Dental Product, Mumbai, India) was used as final irrigation. After drying the root canal with sterile paper points (Figure Ic), calcium-

Table I. Case-specific items of the teeth treated with a regenerative endodontic procedure

Case number	Age/Sex	Tooth	Nolla stage	Etiology	Pulpal status	Signs/Symptoms	Periapical lesion	Follow-up (mo)	Cause of failure
1	12/M	31	8	Trauma (2.5 years ago)	Necrosis	Vestibular sinus tract	Yes	36	-
2	13/F	41	9	Trauma (3 years ago)	Necrosis	No signs	Yes	36	-
3	21/F	34	8	Trauma (10 years ago)	Necrosis	No signs	Yes	36	-
4	8/F	11	8	Trauma (1.5 months ago)	Necrosis	Gingival swelling	Yes	36	-
5	8/F	21	9	Trauma (2 weeks ago)	Necrosis	No signs	No	36/failed	Persistent infection/ Vestibular swelling
6	11/M	14	9	Unknown	Necrosis	Gingival swelling, vestibular sinus tract	Yes	9/failed	Persistent infection/ Vestibular sinus tract
7*	7/F	11	8	Trauma (3 months ago)	Necrosis	Vestibular sinus tract	No	3/failed	Persistent infection/ Vestibular sinus tract
8*	7/F	21	8	Trauma (3 months ago)	Necrosis	No signs	No	36	-
9	10/F	11	8	Trauma (1 years ago)	Necrosis	Vestibular sinus tract	Yes	30/failed	Persistent infection/ Vestibular sinus tract

*Cases 7 and 8 belong to the same patient.

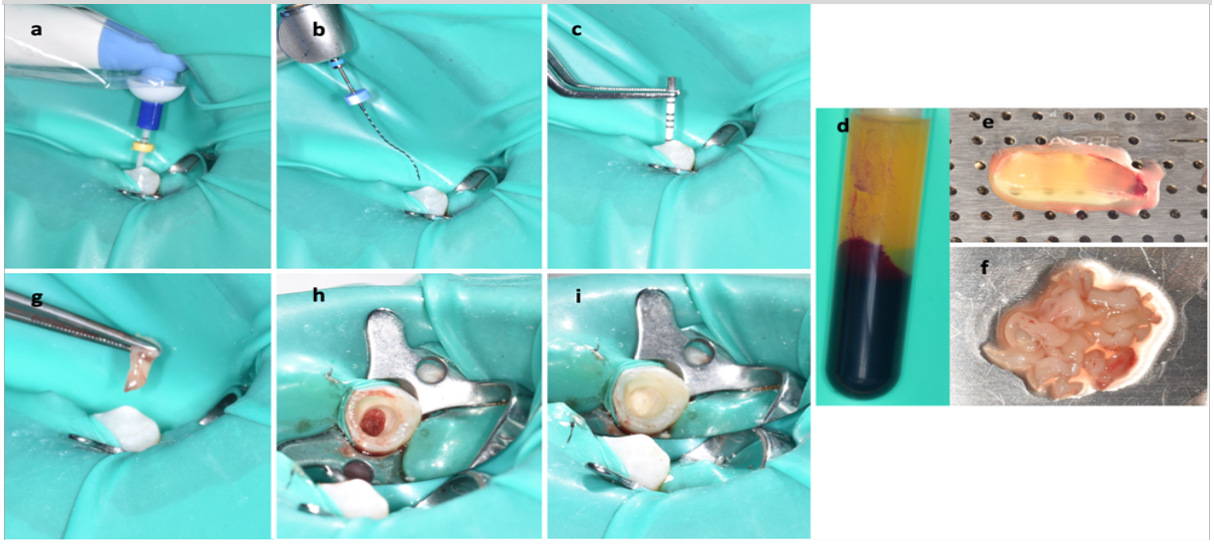

Figure I. Representative images of the RET procedure. (a) Activating the irrigation solution with Endoactivator, (b) using XP-endo Finisher R file to disrupt the biofilm structure on root canal walls, (c) drying with paper point, (d) the blood sampleafter centrifuging, (e) separated CGF layer, (f) fragmentation of CGF, (g) placement of CGF fragments to the root canal, (h) after placement of CGF to the whole root canal space, (i) placement of Biodentine.

hydroxide (Metapaste; Meta Biomed Co Ltd, Chungbuk, Korea) was placed and temporarily sealed with glass ionomer (Ionoseal; VOCO GmbH, Cuxhaven, Germany).

Second Visit

After ensuring the patients were asymptomatic, the local anesthetic without vasoconstrictor was administered (Safecaine; Vem). The tooth was isolated with a rubber dam and the tooth surface was disinfected with chlorhexidine. After removing the temporary filling, the root canal was irrigated with EDTA (17% 20-mL) with sonic activation. The root was rinsed with distilled water (5-mL) and dried with sterile paper points. Bleeding was inducted into the coronal part of the root canal by over instrumentation of a sterile #25 spreader 2–3 mm beyond the apex and waited for 10-15 minutes until clot formation (only for case 1, probably depending on the size of the lesion, the bleeding was achieved up to the middle of the root canal, while adequate bleeding was achieved for the other cases). 10 ml of intravenous blood sample was taken from the patient, placed in centrifuge tubes without anticoagulant and immediately centrifuged with the following programs; 30 seconds accelerated; centrifuged at 2700 rpm for 2 minutes, at 2400 rpm for 4 minutes, at 2700 rpm for 4 minutes, at 3000 rpm for 3 minutes; and slowed down by 36 seconds to stop (14). Three layers were observed at the end of the procedure (serum layer, buffy coat (CGF) and red blood cell layer) (Figure I d). CGF clot was obtained from the middle layer (Figure I e) and divided into small pieces (Figure I f) and placed into the root canal with the help of a plugger (Figure I g, h). Biodentine (Septodont, Saint-Maur-des-Fossés, France) was placed approximately 3 mm below the cementoenamel junction (Figure I i) and permanent restorations were made with resin composite. Patients were scheduled for clinical and radiographic examination.

Clinical and Radiographic Follow-up

At the 3-year follow-up, five teeth showed clinical and radiographic healing (Case 1, 2, 3, 4 and 8) (Figure II, III and tooth number 21 of Figure V). Intracanal calcifications were observed in cases 1, 2 and 4 (Figure II d, Figure II j, Figure III h). In the other four patients, vestibular sinus-tract formation, vestibular swelling and persistent infection were detected at different time periods, as summarized in Table I (Figure IV and tooth number 11 of Figure V). Apexification treatment was performed with Biodentine forfailed cases 5, 6 and 7. Case 8 continued her treatment in another centre. Although an increase in dentin thickness was observed in healed cases, apical closure was not observed in any of them.

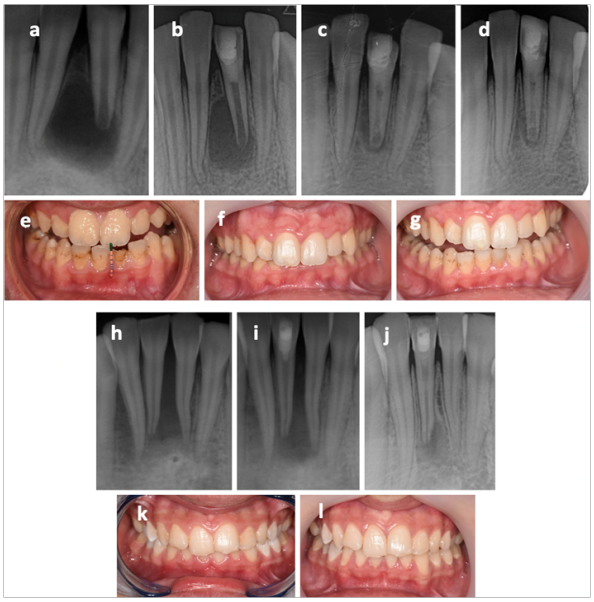

Figure II. Images of Case 1/tooth number 31 (a-g) and Case 2/tooth number 41 (h-l). (a)The preoperative periapical radiograph of Case 1, (b) 6-month follow-up radiograph, (c) 12-month follow-up radiograph, (d) 3-year follow-up radiograph, (e) preoperative intraoral photograph of Case 1, (f,g) 3-year follow-up photographs. (h) The preoperative periapical radiograph of Case 2, (i) 6-month follow-up radiograph, (j) 3-year follow-up radiograph, (k) preoperative intraoral photograph of Case 2, (l) 3-year follow-up photograph.

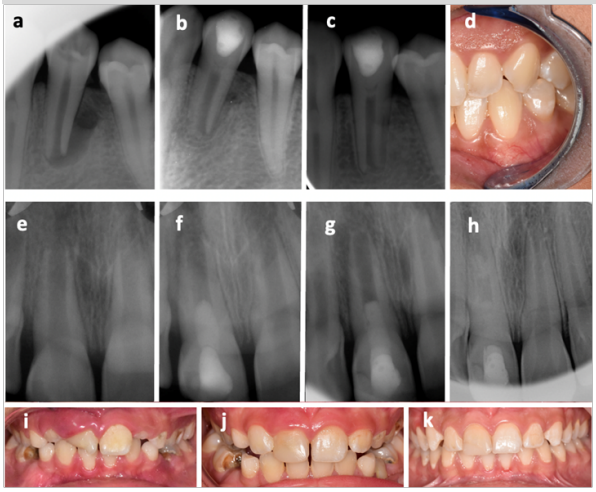

Figure III. Images of Case 3/tooth number 34 (a-d) and Case 4/tooth number 11 (e-k). (a) The preoperative periapical radiograph of Case 3, (b) 12-month follow-up radiograph, (c) 3-year follow-up radiograph, (d) preoperative intraoral photograph of Case 1. (e) The preoperative periapical radiograph of Case 2, (f) 3-month follow-up radiograph, (g) 8-month follow-up radiograph, (h) 3-year follow-up radiograph, (i) preoperative intraoral photograph of Case 4, (j) 8-month follow-up photograph, (j) 3-year follow-up photograph

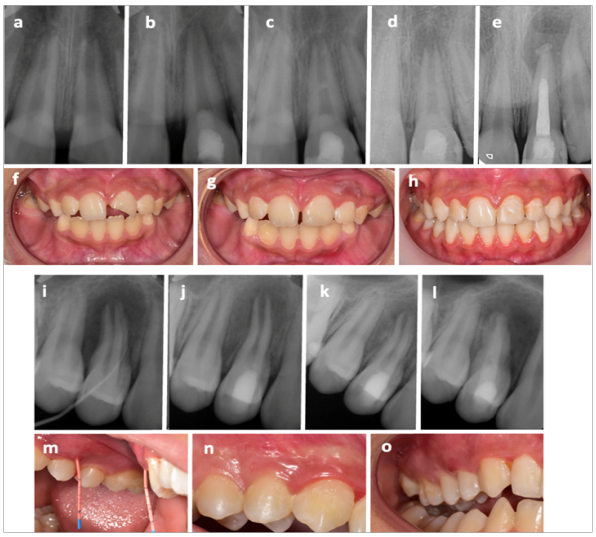

Figure IV. Images of Case 5/tooth number 21 (a-h) and Case 6/tooth number 14 (i-o). (a) The preoperative periapical radiograph of Case 5, (b) 6-month follow-up radiograph, (c) 12-month follow-up radiograph, (d) 3-year follow-up radiograph, (e) radiograph of apexification treatment with calcium silicate cement (f) preoperative intraoral photograph of Case 5, (g) 12-month follow-up photograph, (h) the photograph of after apexification treatment. (i) The preoperative periapical radiograph of Case 6, (j) 3-month follow-up radiograph, (k) 9-month follow-up radiograph, (l) radiograph of apexification treatment with calcium silicate cement, (m) preoperative intraoral photograph of Case 6, (n) 3-month follow-up photograph, (o) 9-month follow-up photograph with vestibular swelling.

DISCUSSION

The present case series aimed to present the clinical and radiographic follow-up of nine RETs using the latest autologous platelet concentrate, CGF, in necrotic immature permanent teeth within the guidelines recommended by the AAE. Five cases showed clinical and radiographic healing in three years of follow-ups, and four cases failed in different follow-up periods.

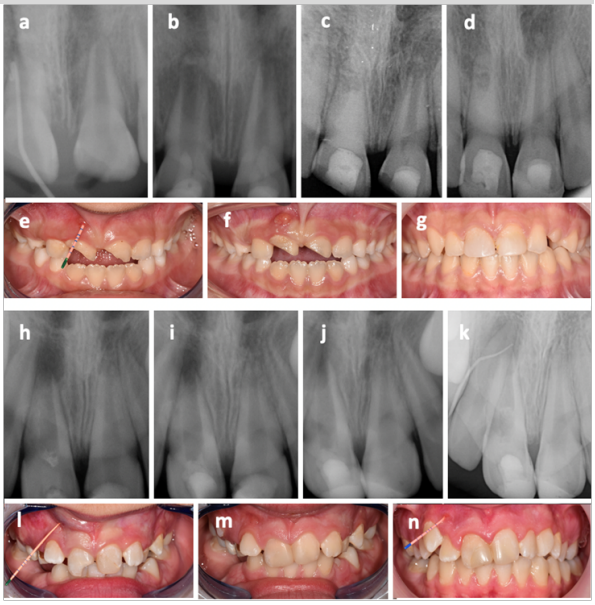

Figure V. Images of Cases7-8/tooth numbers 11-21 (a-g) and Case 9/tooth number 12 (h-n). (a) The preoperative periapical radiograph of Cases 7-8 with vestibular sinus tract of 11, (b) 3-month follow-up radiograph, (c) radiograph of apexification treatment of 11 with calcium silicate cement, (d) 3-year follow-up radiograph, (e) preoperative intraoral photograph of Cases 7-8 with vestibular sinus tract of 11, (f) 3-month follow-up photograph, (g) 3-year follow-up photograph. (h) The preoperative periapical radiograph of Case 9, (i) the radiograph after RET, (j) 3-month follow-up radiograph, (k) 30-month follow-up radiograph with vestibular sinus tract, (l) the preoperative intraoral photograph of Case 9, (m) 3-month follow-up photograph, (o) 30-month follow-up photograph with vestibular sinus tract.

RET is a new treatment modality that has only been introduced in the last 2 decades (16). Despite being routinely administered, outcomes are unpredictable and optimal approaches or procedures are not established. It has been reported that the residual bacteria in root canals has been shown to inhibit complete healing and root maturation significantly (17-18).

Although RET procedures can reduce microbial irritants to levels that allow the successful outcomes of clinical procedures to be more predictable (19), in necrotic root canals, biofilm expands into the dentinal tubules, periapical areaand lateral canals (20-21). Although mechanical preparation of the root canal dentin is clearly not desirable as it will weaken the root dentin structure, it was stated that the recommendation for minimal or no mechanical instrumentation should be reconsidered (19). It has been reported that the application of light filing pressure to the root canal wall disrupts the biofilm structure and allows better penetration of root canal irrigantsor medicaments into the biofilm (19). In this context, irrigation aids such as irrigation activation methods and instrumentation with XP-endo Finisher files have been shown to help disinfect root canals (22). Therefore, Endoactivator and XP-endo Finisher-R file were used in this case series.

Cases with immature roots with large periapical lesion

sizes associated with high bacterial load and the presence of more virulent species have been reported to result in incomplete healing despite inflammation, visible mineralization, and root growth (18,23). In this case series, incomplete healing was observed in cases 1 and 2 with large lesions, although a drastic reduction in the lesion size was observed at a 3-year follow-up. Residual bacteria have been reported to interfere with the release of growth factors from dentin (24). The observation of intracanal mineralization in cases 1, 2 and 4 and the absence of root maturation in all of the healed cases may suggest the presence of residual microorganisms in the root canals.

In a retrospective study evaluating RETs using CGF, cases of developmental dental anomalies in RETs showed a better prognosis than cases of trauma (25). It has been previously reported that trauma can cause detrimental effects on the apical papilla as well as the Hertwig epithelial root sheath, causing root resorption and failure of RETs (26), and damaged areas on the root surfaces of teeth with severe luxation may increase the risk of periodontal healing complications (6). In this case series, the etiologic factors of 8 out of 9 cases were trauma and 4 cases failed, which can be explained by another reason that trauma may have left the teeth more vulnerable to permanent infection.

A previous study has reported that ultrasonic activation increases the release of growth factors in root dentin (27). It has been stated that irrigation activation techniques can be used to increase the effectiveness of disinfection in root canals in regenerative endodontic procedures, and negative pressure irrigation has a beneficial effect on minimizing the risk of irrigant extrusion from the apical foramen (27,28). In this case series, the sonic activation system (Endo Activator) was used to activate the irrigants. Although activation of irrigation was performed 2 mm behind the apical foramen, it may have caused the apical extrusion of the irrigant, which may be causing four cases to fail in addition to other possible causes.

Although RET is a promising treatment for root development and revascularization of the root canal, randomized clinical trials using CGF are needed as the outcomes are unpredictable. The development of methods for the complete removal of residual bacteria that cause persistent infection and inhibit root maturation should be considered. In addition, the apexification treatment with a calcium silicate apical plug, which has a good short to medium-term prognosis, should also be weighed.

Conflict of Interest

The authors deny any conflicts of interest related to this study. Consent was obtained from the patients.

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