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NOTE

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Application of a novel carboxymethyl cellulose-based Mohs sol–gel on malignant wounds in three dogs

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ABSTRACT. The preparation of modified Mohs paste, commonly used for malignant wounds, requires time and effort. Moreover, metal-containing liquid waste is generated when malignant wounds are scrubbed. Therefore, we previously changed the base material of the modified Mohs paste from zinc oxide starch powder to carboxymethyl cellulose (CMC). The novel modified Mohs paste based on CMC (moM-CMC sol) may reduce these disadvantages. In the present study, the moM-CMC sol was applied to malignant tumors in three dogs to manage bleeding and malodor. The moM-CMC sol transitioned into a gel on the tumors within an hour of application and could be easily removed. The symptoms resolved in all cases. The moM-CMC sol could be beneficial for dogs with malignant wounds.

KEY WORDS: carboxymethyl cellulose, dog, malignant wound, Mohs paste, zinc chloride

Malignant wounds, also referred to as fungating wounds, ulcerating tumors, or neoplastic (new growth) lesions, present a particularly challenging clinical scenario owing to the difficulty in achieving successful treatment outcomes [11]. The common symptoms associated with malignant wounds, namely pain, copious exudate, malodor, and hemorrhage, can cause extreme distress in patients with advanced cancer [2, 11].

The original Mohs paste is composed of saturated zinc chloride solution, stibnite, and *Sanguinaria canadensis* [8]. Stibnite and *S. canadensis* were not available in Japan; therefore, a modified Mohs paste with zinc oxide starch powder was developed [13]. The modified Mohs paste has been successfully used to treat malignant wounds in humans [3, 15]. The key component of the modified Mohs paste is zinc chloride [8, 13]. Zinc chloride enables adherence of the paste on tissues as observed by microscopy, makes the paste controllable in terms of penetration depth and is safe to handle since it has relatively little effect on intact skin [8]. The modified Mohs paste is beneficial in reducing hemorrhage and malodor in dogs and cats with malignant wounds [1]. Moreover, it reportedly reduced degenerated hyperplastic tissue in an Indian elephant with chronic pododermatitis [4].

The disadvantages of the modified Mohs paste are as follows. i) It takes time and effort to prepare the paste, as it has to be prepared before each treatment since the properties of Mohs paste change immediately after component mixing [12, 15]. ii) It is not easy to handle; to limit the modified Mohs paste to a specific region petroleum jelly should be applied to the skin [1, 3, 13, 15]. iii) A metal (zinc)-containing liquid waste is generated when malignant wounds are scrubbed [1, 3, 15] and when the mortar used to prepare the gel is washed [1, 3, 12, 14, 15]. Researchers have attempted to alter the modified Mohs paste using D-sorbitol [14], microcrystalline cellulose [14], hydrophilic ointment [12], and macrogol ointment [14], to maintain its properties for subsequent applications. However, these modified pastes require a mortar for preparation, and the malignant wound should be scrubbed before application.

Carboxymethyl cellulose (CMC) is used as a thickener in food industry [6]. The base material of the modified Mohs paste was changed from zinc oxide starch powder to CMC in our preliminary study (unpublished data). This sol could be easily prepared using a disposable cup. The modified Mohs paste based on CMC (moM-CMC sol) transitioned into a gel (moM-CMC gel) when applied to chicken breast meat and could be removed without scrubbing. Moreover, it did not generate any metal-containing liquid waste. Therefore, the moM-CMC sol could overcome the disadvantages of the modified Mohs paste.

The purpose of this case series was to elucidate the properties of the moM-CMC sol and to perform a pilot usage of moM-CMC for 3 dogs with malignant wounds.

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The moM-CMC sol was composed of 1 g of CMC, 2 ml of saturated zinc chloride water, and 1–1.5 ml of purified water. The mixture was transparent, and therefore, it was difficult to identify any unintentionally applied or dropped sol. Green is the complementary color of red (blood) or brown (hair). Therefore, 5.5 g of green food-coloring agent (Kyoritsu food dye green; Kyoritsu Foods, Tokyo, Japan) was mixed with 500 g of CMC powder (CMC Sodium Salt; FUJIFILM Wako Pure Chemical Co., Osaka, Japan) in advance. The premixed CMC (1 g) was mixed with saturated zinc chloride (FUJIFILM Wako Pure Chemical Co.) water (2 ml; moM-CMC liquid) in an unbranded disposable cup (Fig. 1). Purified water (1.5 ml) was then gradually added to the moM-CMC liquid with constant stirring. The viscosity of the sample increased with the addition of water, and the liquid transitioned to the moM-CMC sol. The moM-CMC sol then transitioned to moM-CMC gel over time (Fig. 1B). The apparatus used for the preparation was appropriately discarded. These processes were performed wearing disposable gloves.

To elucidate the properties of the moM-CMC sol, two brief experiments were performed. First, the transition period from moM-CMC (purified water 1.0 and 1.5 ml) sol to gel was measured every 10 min in five samples. The different transition states were as follows: solution, sol (best for treatment), hard sol (difficult to fix on the tumor), and gel. The moM-CMC sol with 1.0 ml purified water changed to a solution (5 samples) at 0 min, sol (5) in 10 min, sol (3) and hard sol (2) in 20 min, and gel (5) in 60 min. The moM-CMC sol with 1.5 ml purified water changed to a gel (5) within 10 min. Therefore, moM-CMC with 1.0 ml purified water fixed to the tumor within 10 min. When the sol was soft, a small amount of water was added to adjust its hardness.

Second, water absorption by and zinc chloride release from the moM-CMC sol were evaluated at different sol thicknesses. moM-CMC sol of different thicknesses (range 1.6–14.7 mm) was prepared in eight cups, and then 10 ml of saline solution was poured into the cups (Fig. 1C) for 60 min. After an hour, the saline solution was removed, and its volume was measured. The saline solution was subjected to computed tomography (Asteion (4-slice helical CT scanner); Canon, Tokyo, Japan), and the concentration of zinc chloride released into the saline solution was compared among the moM-CMC sols of different thicknesses. The amount of saline solution absorbed was 1.5 ± 0.1 ml (mean ± SD), and the CT value of the saline solution was 201 ± 26 Hounsfield unit (Fig. 1D). The sol thickness might not affect these findings; therefore, the minimum thickness for the sol to fix to the wound was estimated as 1.6 mm.

The moM-CMC sol was applied to the malignant wounds using cotton swabs. The moM-CMC sol transitioned to a gel, and an hour later, the moM-CMC gel was removed using the hands, gauze, or a needle. The malignant wound was rinsed with saline solution to remove the residual zinc ion solution on the tumor surface on to a pet litter sheet, which was discarded later as a medical waste. All procedures were performed in accordance with the guidelines approved by the Azabu University Animal Experimentation Committee (No. 201030-1).

Here, tumors were classified according to the TNM system (WHO classification) [10], and tumor size was analyzed using the response evaluation criteria for solid tumors (cRECIST v1.0) [9].

Case 1: A 16-year-old spayed female Shetland sheep dog weighing 7.7 kg had a mass with a malignant wound (of diameter 7.6 cm) in the left elbow. The tumor was noted a month before her first presentation to our institute, and it grew rapidly. The owner complained that the dog had an ulcerated tumor, with bleeding and malodor. The dog was diagnosed with sarcoma by cytology, and the tumor was classified as T4N0M0. The packed cell volume (PCV) was 25.1%. The dog's health condition was poor and anorexia and ataxia were noted.

In the first treatment session, the modified Mohs paste [1] was applied without general anesthesia for an hour. The malignant wound, mortar, and pestle were washed with tap water. In total, 2 l of metal-containing liquid waste was generated. Firocoxib (a non-steroidal anti-inflammatory drug; Previcox; Boehringer Ingelheim, Tokyo, Japan) 5 mg/kg was administered once a day during treatment. After 4 days, the bleeding and malodor were reduced (Fig. 2A). To overcome the disadvantages of the modified Mohs paste, moM-CMC was used from the next treatment session.

The second, third, and fourth treatment sessions involved the application of the moM-CMC sol at 3- or 4-day intervals. The scab on the surface was removed using a pair of forceps and scissors. The moM-CMC sol was prepared in the treatment room and applied for an hour (Fig. 2B). The moM-CMC sol transitioned to moM-CMC gel on the tumor, and the gel was removed using hands with gloves (Fig. 2C). The malignant wound was rinsed with a small amount of saline solution on a pet litter sheet, which was later discarded as a medical waste.

In the fifth and sixth treatment sessions, the moM-CMC sol was not removed from the malignant wound after treatment because it was considered that the residual gel was effective in reducing the tumor size. Thus, the malignant wound remained coated with the moM-CMC gel. The fifth treatment session progressed well; however, a skin ulcer was detected under the tumor 3 days after the sixth treatment session. Ten days after the last treatment session with moM-CMC sol, the general health condition of the dog worsened, and its body weight decreased by 6.6 kg. However, the malignant wound did not present bleeding (Fig. 2D). The tumor size was 6.0 cm, and the tumor response was evaluated as partial response (PR). The PCV increased from 25.1 to 32.9% at baseline.

This dog did not require any sedation or general anesthesia during each treatment session. The skin ulcer around the tumor was observed as an adverse event. The dog died 10 days after the last session of treatment.

Case 2: A 6-year-old male castrated West Highland white terrier weighing 8.1 kg was brought to our institute for tumor recurrence after radiotherapy necrosis. The dog was diagnosed with chondrosarcoma and had undergone irradiation by orthovoltage radiotherapy in a local veterinary hospital a year ago. The dorsal side of the muzzle was necrotic, and an enlarged nasal tumor was observed from the dorsal window (Fig. 3A). The malignant wound (characterized by massive bleeding and malodor) in the dog was treated daily using an antibiotic ointment by the owner.

Before a CT scan, general anesthesia was administered to the dog, and its head was held using a bite block-type head

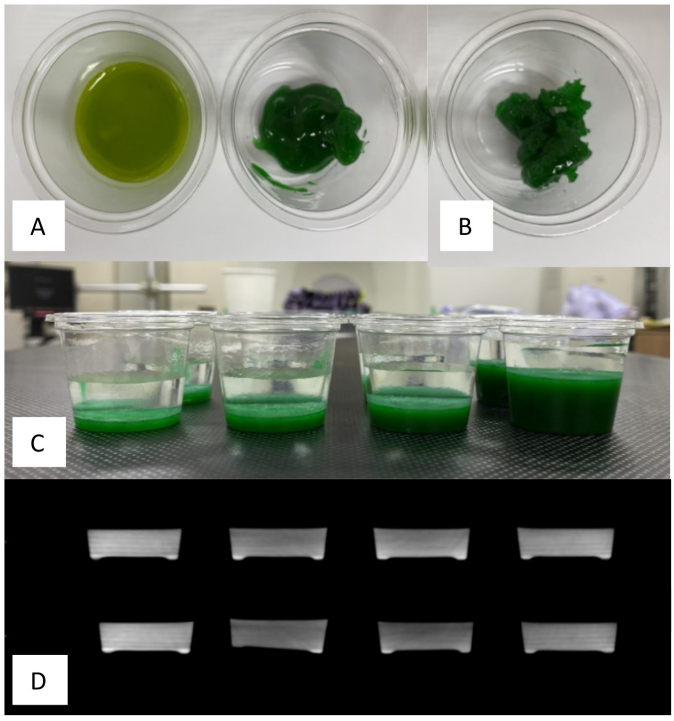

Fig. 1. Carboxymethyl cellulose (CMC) 1 g with a green dye and saturated zinc chloride water (2 ml) were added into a cup and mixed immediately. A: The liquid was light green (modified Mohs paste based on CMC [moM-CMC] liquid, the left image). One milliliter of purified water was then added to the liquid with stirring (moM-CMC sol, the right image). The moM-CMC liquid or sol was transferred to a new cup. B: After an hour, the moM-CMC sol transitioned to a gel. C: 10 ml of saline solution was poured into the moM-CMC sol of different thicknesses (front: 1.6, 4.1, 5.7, and 14.7 mm from left, behind: 3.7, 4.5, 7.3, 13.4 mm from left). D: The saline solution was removed, measured, and subjected to computed tomography (window level 200 Hounsfield unit [HU] and window width 200 HU).

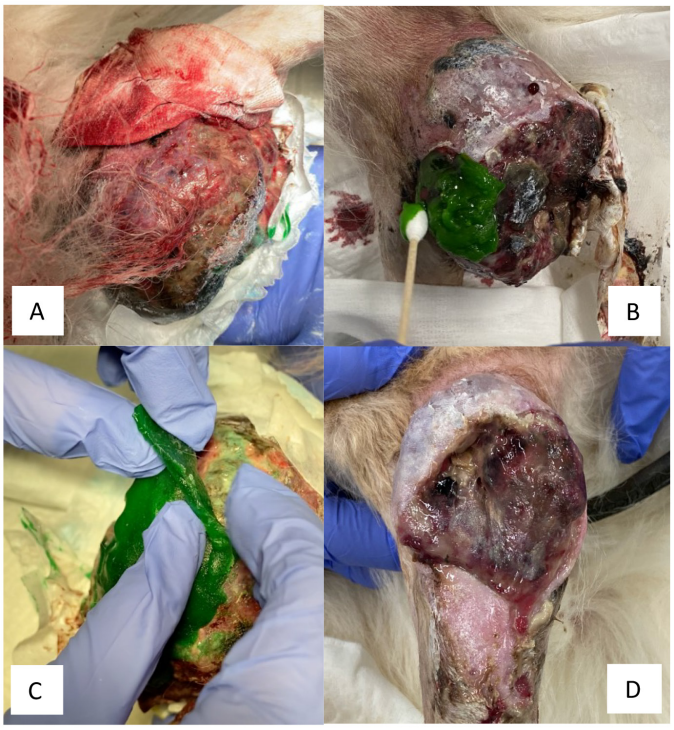

Fig. 2. Case 1. A: The tumor was bleeding for 3 days after the first modified Mohs paste treatment. B: The modified Mohs paste based on carboxymethyl cellulose (moM-CMC) sol was applied as a paste on the malignant wound using a cotton swab. The green sol shown in the image is the moM-CMC sol. C: The moM-CMC sol transitioned to moM-CMC gel, and it was removed using hands after the treatment. D: After 10 days of last treatment, the tumor size was found to be reduced, and the ulcerated skin lesion below the moM-CMC treatment site started to heal.

immobilization device [7]. A CT scan was taken for tumor staging, and the nasal tumor was classified as T3N0M0. The tumor was ligated using braided silk. The application of moM-CMC sol did not stop active bleeding; therefore, hemostatic cotton (Surgicel Absorbable Hemostat; Johnson & Johnson, Tokyo, Japan) was used. After achieving hemostasis, the moM-CMC sol was applied on the surface of the tumor for an hour. The moM-CMC gel was removed using an 18-G needle (Fig. 3B). The malignant wound was washed with a small amount of saline solution. A CT scan was taken immediately after removing the moM-CMC gel (Fig. 3C). High CT values of zinc atoms were observed at a depth of approximately 2 mm from the malignant wound surface. Firocoxib 5 mg/kg once a day was administered for a week.

The malignant wound dried, and the malodor disappeared after a week (Fig. 3D). The second moM-CMC treatment session was performed after a month. The tumor response was stable disease. A skin ulcer around the tumor was observed as an adverse event. However, no treatment was necessary for the ulcer. The malignant wound did not require treatment by the owner for 1 week. The dog was still alive at the time of manuscript writing.

Case 3: A 12-year-old spayed female miniature Dachshund weighing 3.8 kg presented with oral melanoma. A radiotherapy regimen was completed; however, the tumor recurred after three months. Tumor removal (pedunculated tumor was ligated, and the remaining tumor was scrubbed until fresh surrounding tissues were visible) and moM-CMC sol treatment were performed once a month for 10 months. The owner complained of tumor growth and malodor (Fig. 4A). The tumor stage was T4N0M0, and it was located in the oral cavity. The dog was anesthetized after a month for moM-CMC sol application; however, hypotension and bradycardia were observed, and the treatment was postponed. Twelve months after treatment initiation, the last treatment session was performed (Fig. 4).

The β-1 adrenergic drug dobutamine (Dobutrex; Kyowa Pharmaceutical Industry Co., Ltd., Osaka, Japan) 1 µg/kg/min was continuously infused to maintain the blood pressure of the dog. General anesthesia was administered, and the tumor and necrotic mandibular bone were resected. Subsequently, the moM-CMC sol was applied to the scar using a syringe (Fig. 4B). Applying a thick layer of moM-CMC sol would grow down; therefore, a thin layer of the sol was applied and the scar was maintained

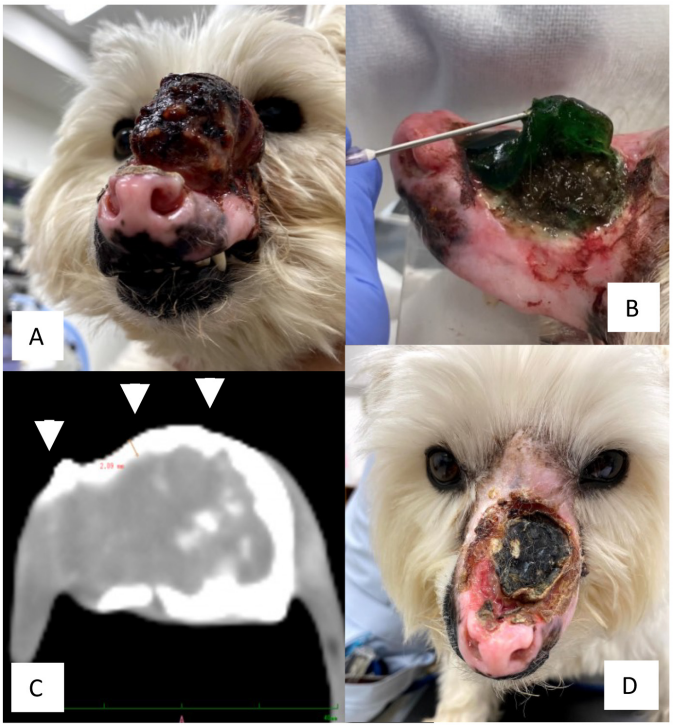

Fig. 3. Case 2. A: Appearance at initial treatment. B: modified Mohs paste based on carboxymethyl cellulose (moM-CMC) gel was removed using a needle. C: Computed tomography (CT) scan was taken immediately after removing the moM-CMC gel. The image is shown in the transverse plane. The window level and width were 0 and 300 Hounsfield unit (HU), respectively. High CT values of zinc atoms were observed at approximately 2-mm depth from the wound surface (arrow). D: After 1 week, the malignant wound was found to be dried, and the malodor disappeared. Skin ulcer caused by the moM-CMC sol around the tumor was observed as an adverse event.

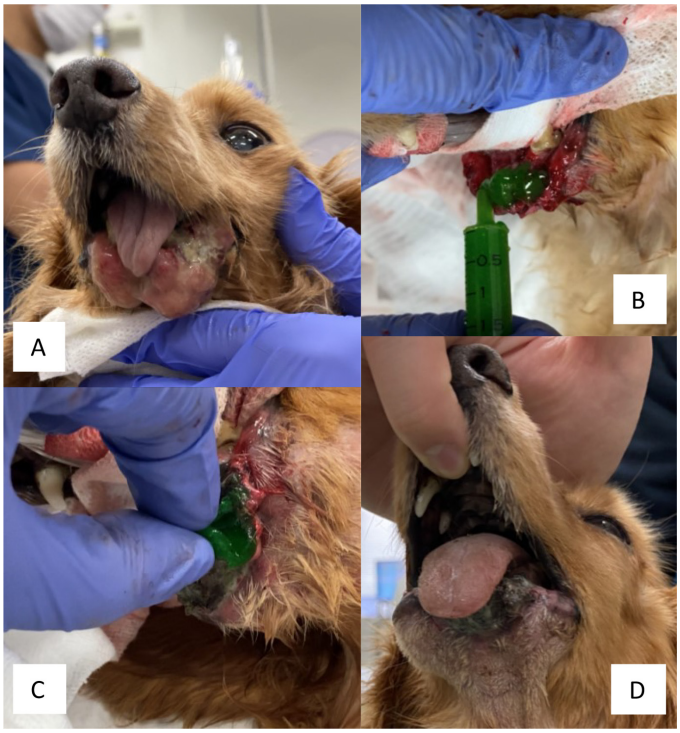

Fig. 4. Case 3. A: Appearance before modified Mohs paste based on carboxymethyl cellulose (moM-CMC) treatment. B: The moM-CMC sol was applied using an injection syringe. C: moM-CMC gel was removed using hands after 20 min. D: Appearance after the treatment. The tumor was removed, and the treated part changed from brown to black.

horizontally. The moM-CMC gel was removed 20 min later with gloved hands (Fig. 4C). After the session, exudate was not observed, and the malodor disappeared (Fig. 4D). Most of the macroscopic tumors were resected, and adverse events were noted a day after the treatment. The mucous membrane on the ventral side of the tongue was eroded, suggesting a chemical burn due to the tongue coming in contact with the zinc chloride scab. Firocoxib 5 mg/kg once a day was administered for 1 week, and the malodor disappeared after a week. However, this dog was died one month later.

Our case series showed that the moM-CMC sol transitioned to moM-CMC gel when applied to malignant wounds. Zinc chloride has a dehydrating effect on the surrounding tissues [8] and causes exudate generation. The exudate from the malignant wound was absorbed by CMC [5]. Therefore, moM-CMC sol absorbs exudates from malignant wounds and becomes a gel, similar to the transition of moM-CMC solution from sol to gel with time when purified water is added (Fig. 1). To remove the modified Mohs paste, the malignant wound had to be scrubbed with tap water in case 1. The moM-CMC gel was easily removed from the malignant wound with gloved hands or a needle. Only the pet litter sheet containing the rinsed saline solution was discarded as medical waste after moM-CMC gel removal. Therefore, the moM-CMC sol was found to be superior to the modified Mohs paste in term of removal.

The benefits of the modified Mohs paste included the reduction of hemostasis and malodor [1, 3, 15]. The moM-CMC sol also controlled the clinical signs in the present cases. The modified Mohs paste adhered to 1.3 mm of tissue at 6 hr and 2.8 mm of tissue at 24 hr of application in an experimental study, as determined by CT images [14], and moM-CMC adhered to 2 mm of tumor tissue after an hour in case 2 of the present study. The penetration depth of moM-CMC might have been more than that of the modified Mohs paste. The results of this case series showed that the moM-CMC sol is beneficial for managing malignant wounds in dogs, similar to the modified Mohs paste.

Skin ulcers were observed in two cases and mucous membrane erosion was observed in one case. Previously, in seven cases involving the application of the modified Mohs paste, only nasal mucosa erosion was observed; this was because the modified Mohs paste dripped onto the tumor during application [1]. The release rate of zinc varies with the base material [14]. Here, the application of the moM-CMC sol on the tumor was frequently checked to ensure that it did not extend to the surrounding skin, but

a skin ulcer was detected in case 2. The moM-CMC gel may also release zinc chloride, as evidenced by the unintentional skin ulcer that occurred in the sixth treatment session in case 1. This suggested that zinc may be easily released from the moM-CMC sol and gel. Therefore, efforts should be taken to reduce adverse effects by applying petroleum jelly on the surrounding healthy tissues or shorten the contact time with zinc chloride.

There were some limitations to this case series. First, the number of cases was less. Second, the moM-CMC sol was not compared with the conventional modified Mohs paste. Third, the preserved moM-CMC gel did not adhere on the tumor because the moM-CMC gel could not attach to the surface of the tumor. The transition from sol to gel was unilateral. Therefore, moM-CMC must be prepared just before each treatment. Fourth, localized pain could not be assessed in this case series because most dogs were administered general anesthesia. Further research is needed to investigate their application to different types of tumors and the adverse effect profile.

In conclusion, our case series showed that moM-CMC sol requires less time and effort for i) preparation, ii) use, and iii) cleaning. i) moM-CMC sol was prepared in the treatment room within a few minutes in all cases. ii) The moM-CMC sol can be handled easily; the paste could be applied using a syringe in case 3. iii) Metal-containing liquid waste was not generated because moM-CMC gel removed without scrubbing the malignant wound, and the equipment used could be conveniently discarded as medical waste. Moreover, the efficacy of moM-CMC sol might be similar to that of modified Mohs paste. Therefore, moM-CMC sol can be considered an alternative for the management of malignant wounds.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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