Delayed Foreign Body Granulomas in the Orofacial Region after Hyaluronic Acid Injection

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Objective: *To evaluate and analyse granulomatous reaction caused by intradermal injections with hyaluronic acid (HA) fillers in the orofacial region.*
Methods: *A retrospective review of 11 cases of foreign body granulomas caused by HA fillers was performed. Demographic data, clinical symptoms, imaging features, treatments, pathology results, history of facial cosmetic procedures and prognosis were reviewed.*
Results: *Most of the cases appeared as painless palpable nodules with no significant growth, located in the cheeks, chin, lips or temples. The nodules were excised, and pathological examination revealed amorphous basophilic material surrounded by foreign body giant cells and macrophages. No patient's clinical and pathological diagnosis was linked to HA during the first appointment. During follow-up, all patients admitted that they had received dermal filler injections from 3 to 10 years previously. Most of the patients had a favourable prognosis; one patient complained of facial asymmetry and another reported mild pain in the upper lip after surgery.*
Conclusion: *The increase in the number of cases showing delayed complications caused by HA fillers merits closer clinical attention. A thorough understanding of the patient's medical history and biopsy specimen are necessary to make a definite diagnosis and offer appropriate treatment.*
Key words: *complications, delayed foreign body granulomas, hyaluronic acid, orofacial region*
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Intradermal injections with hyaluronic acid (HA) fillers in the orofacial region are extremely popular aesthetic procedures[1]. They are frequently used to smooth out wrinkles and skin folds for facial rejuvenation and to enhance the facial features[2]. HA is fast becoming the material of choice because of its biocompatibility and biodegradability[3].

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HA is one of the most prevalent glycosaminoglycans in the dermis, and HA fillers are stabilised by cross-linking of HA and binding of water molecules to it[2]. Over time they are slowly 'digested' in vivo by endogenous hyaluronidase through enzymatic degradation. Their effect usually lasts from around 6 months to 2 years[3]. Accordingly, patients are advised to have top-up treatments to maintain the results.

HA fillers typically have favourable safety profiles[4,5]. The most common side effects include treatment site reactions such as swelling, bruising, redness, pain and tenderness. These generally disappear within 1 week of the injection[6]. Delayed side effects are rare.

Over the last 10 years, we encountered several patients with nodules in the orofacial region. Their pathological manifestations indicated granulomatous foreign body reaction to blue-stained material related to HA fillers. No clinicians had considered that the reaction could be related to aesthetic procedures before surgery. During follow-up, it was surprising to note that

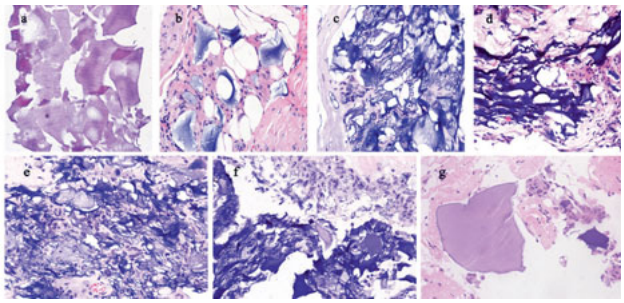

Fig 1 Amorphous basophilic material surrounded by a large number of foreign body giant cells and macrophages, which was the pathological characteristic of HA-induced foreign body granulomas (HE, 40×), in patients 1 to 7, respectively.

patients had received HA filler injections 3 to 10 years previously. The absorbable fillers did not get absorbed by the surrounding tissues and rather caused granulomatous reactions years after the filler was injected. Therefore, we sought to determine why compatible HA fillers cause delayed foreign body granulomas, and why residual absorbable filler was still present in tissues years after it was injected.

This article summarises cases of delayed granulomatous reactions in the orofacial region following HA filler injections and discusses the potential mechanisms to help clinicians to better understand the characteristics of delayed foreign body granulomas caused by HA fillers and offer suitable treatments accordingly.

Materials and methods

Pertinent studies published in English were reviewed and a summary was drawn up of reported cases of delayed granulomatous reactions after HA injection[7-18] (Table 1). According to the literature, HA-induced granulomatous reactions were characterised by amorphous basophilic material (positive with Alcian blue staining), surrounded by multinucleated giant cells and epithelioid histiocytes in the dermis and subcutaneous fat.

Next, we performed an electronic search of pathological reports dated between 2009 and 2019 from the Department of Oral Pathology at the Peking University School and Hospital of Stomatology, Beijing, China, using the keyword 'basophilic' matched with 'foreign body', and 17 cases were selected. After preliminary screening, we carefully reviewed the pathological sections of the possible cases and identified cases of foreign body granulomas caused by HA fillers based on their pathological characteristics. Two cases were excluded because their pathological manifestations were not in accordance with HA fillers. We then obtained the complete medical records and contacted the patients for their detailed cosmetic histories and prognosis. Four cases were excluded because it was not possible to contact the patients or they refused to provide their medical histories.

Finally, a total of 11 patients who had developed delayed granulomatous reactions after receiving HA injections and underwent surgical resection in our hospital were included in the study. A retrospective chart review of the patients was conducted that included their age and sex, history of facial cosmetic procedures, symptoms, interval between the time of injection and the first visit, imaging features, treatments, pathological results and outcomes. All patients provided written informed consent for this review to be carried out.

Results

The clinical characteristics of the 11 patients are summarised in Table 2. All were women, with a mean age of 38.5 years. In most cases, the granulomas appeared as palpable nodules with slow or no growth, no pain, moderate hardness, a smooth boundary and normal mobility. The nodules had developed 3 months to 6 years before the surgery. The nodules were located in the cheeks, chin, lips or temples. Patients numbered 1, 6 and 9 underwent ultrasound examinations in other hospitals before the surgery. The lesions showed a lower echo with a definite boundary. The nodule in patient 6 was located in the mandible and was suspected by the sonographer to be a lymph node abscess.

The patients' medical histories seemed unremarkable during the first visits and the clinicians were not aware of their past cosmetic procedures. The clinicians only provided a descriptive diagnosis such as 'soft tissue nodule' before the surgery.

All patients underwent surgical removal of the nodules and histopathological examination. During surgery, the nodules had capsule walls and were filled with a yellow paste- or cheese-like substance. The pathological manifestations were characteristic. All haematoxylin and eosin-stained sections revealed amorphous basophilic material under the microscope, surrounded by a large number of foreign body giant cells and macrophages (Fig 1). However, the microscopic appearances of the basophilic materials showed minor differences. The pathological features of patients 1, 6, and 7 showed pools of amorphous basophilic material. Cells seldom traversed the pool. The pathological features of patients 4 and 5 showed blueish material with a honeycomb-like, filamentous appearance. Giant cells were numerous and scanty material was also seen in the

Table 1 Summary of reported cases of delayed granulomatous reactions after HA injections.

Study	Sex/age	Location	Trade name and type of filler	Time since injection	Clinical characteristics	Histopathological characteristics	Treatment	Prognosis
Kaczorowski et al[7]	F/52	Right buccal area	Unknown HA filler	2 y	Nodule	Foreign body granulomas, amorphous basophilic material (AB+), dense fibrosis	Excision	Not given
Parulan et al[8]	F/49	Right medial lower eyelid area	Juvina and Aliaxin (two different types of HA)	2 y and 10 mo (two injections)	Swelling	Foreign body granulomas, amorphous basophilic material (AB+)	Punch biopsy, hyaluronidase, triamcinolone	Good response
Tamiolakis et al[9]	F/48	Upper lip	Unknown HA filler	6 mo	Nodule	Foreign body granulomas, amorphous basophilic material	Excision	No recurrence
Alcântara et al[10]	F/54	Upper and lower lips	Perlane	1 y	Multiple nodules	Foreign body granulomas, amorphous basophilic sometimes eosinophilic material, fibrous capsule	Excision	No symptoms
Rongioletti et al[11]	F/59	Glabella, cheeks, nasolabial and perioral areas	Juvederm and other unknown fillers	2 mo and 2 y (multiple injections)	Multiple nodules	Foreign body granulomas, amorphous basophilic material (AB+), vacuoles	Punch biopsy, minocycline	Slight improvement
Rongioletti et al[11]	F/72	Upper lip	Two different types of HA and other unknown fillers	5 y	Nodule	Foreign body granulomas, two different shapes of amorphous basophilic material, vacuoles	Excision	Good esthetical results
Kim et al[12]	F/21	Nose dorsum	Restylane	2 y	Nodule	Foreign body granulomas, amorphous basophilic material (AB+)	Punch biopsy	Remission
Curi et al[13]	F/65	Upper lip	Restylane	12 y	Multiple painful nodules	Foreign body granulomas, amorphous basophilic material	Incisional biopsy, hyaluronidase, anti-inflammatory therapy	Remission
Tseng et al[14]	F/73	Left mouth angle	Juvederm Voluma Xc	3 mo and 18 mo (two injections)	Nodule	Foreign body granulomas, amorphous basophilic material (AB+), mucicarmine positive	Biopsy	Not given
Cecchi et al[15]	F/50	Infraorbital zone	Restylane	5 mo	Several skin ulcers	Foreign body granulomas, amorphous basophilic material (AB+), colloidal iron positive	Repeated debridement, anti-inflammatory therapy	Uncontrollable
Cozzani et al[16]	F/72	Glabella and periorbital area	Restylane and collagen	6 mo	Erythematous nodules	Foreign body granulomas, amorphous basophilic material (AB+)	Betamethasone	Not given
Yang et al[17]	F/58	Periorbital area	Matridex (HA and dextranomer)	6 mo	Four nodules	Foreign body granulomas, amorphous basophilic material, cyst-like particles	Punch biopsy, triamcinolone	Mild improvement
Alsaad et al[18]	F/61	Periocular area	Juvederm Ultra	2 mo	Painful erythematous nodules	Foreign body granulomas, amorphous basophilic material	Punch biopsy, hyaluronidase, triamcinolone	Resolution
Alsaad et al[18]	F/49	Horizontal lateral canthal lines	Unknown HA filler	3 mo	Red nodules	Foreign body granulomas, amorphous basophilic material	Punch biopsy, hyaluronidase	Resolution, no recurrence

(AB+): Positive with Alcian blue staining

Table 2 Demographics and clinical characteristics of patients with delayed foreign body granulomas in the orofacial region.

Patient	Sex/ age	Site(s) of lesion	Symptoms	Duration	Physical examination	Treatment	Intraoperative findings	Follow-up	History of facial cosmetic procedures
1	F/36	Right cheek	Palpable nodule with no growth or pain	6 y	Nodule measuring 1.5 cm in diameter, moderate hardness, smooth boundary, normal mobility	Excision	Light yellow cystic nodule with integrated membrane containing yellow keratin	No recurrence but facial asymmetry	Injection of unknown fillers into cheeks 10 years previously
2	F/48	Upper lip	Palpable nodule with no growth or pain	6 mo	Nodule measuring 1.5 cm in diameter, tough quality, normal mobility	Excision	Nodule with intact envelope and yellow cheese-like contents	No recurrence but pain in upper lip	Injection of HA into upper lip 3 years previously
3	F/47	Chin and temples	Palpable nodules with no growth or pain	2 y	Nodule measuring 1 cm in diameter, moderate hardness	Excision of nodule in chin	Oval nodules with thin wall and pasty yellow contents	No recurrence in chin but nodules retained in temples	Injection of HA into chin and temples 10 years previously
4	F/26	Both cheeks	Palpable nodules with slow growth and no pain	1 y	Nodules measuring 1.5 cm in diameter, smooth boundary, normal mobility, tough quality	Excision of nodules in both cheeks	Solid nodule in right cheek with yellowish-white cross section; cystic nodule in left cheek with pasty yellow contents	No recurrence or symptoms	Injections of botulinum toxin in both cheeks twice, 2 and 3 years previously
5	F/35	Right cheek	Palpable nodules with slow growth and no pain	3 mo	Nodules with moderate hardness, smooth boundary, irregular shape	Excision	Multiple nodules in right cheek with pseudocapsules	No recurrence or symptoms	Injection of HA and botulinum toxin into chin 10 years previously
6	F/33	Right mandible	Palpable nodule with slow growth and no pain	4 y	Nodule measuring 2 cm in diameter; soft, smooth boundary, good mobility	Excision	Irregular and soft nodule with capsule and yellow cheese-like contents	No recurrence or symptoms	Injection of HA into chin 5 years previously
7	F/37	Left upper lip	Palpable nodule with slow growth and pressing pain	1 y	Nodule measuring 1 cm in diameter, tough quality, good mobility	Excision	Cystic nodule and labial gland	No recurrence or symptoms	Injection of HA into lips 6 years previously
8	F/22	Chin	Palpable nodule with no growth or pain	3 y	Soft nodule	Excision	Transparent jelly material without boundary	No recurrence or symptoms	Injection of HA into chin 4 years previously
9	F/50	Left cheek	Palpable nodule with no growth or pain	3 y	Nodule measuring 1.5 cm in diameter, smooth boundary, moderate hardness	Excision	Irregular soft tissue	No recurrence or symptoms	Injection of HA into cheeks 5 years previously
10	F/50	Chin	Palpable nodule with slow growth and no pain	5 y	Nodule measuring 2 cm in diameter, smooth boundary, soft, good mobility	Excision	Irregular brown soft tissue with capsule	No recurrence or symptoms	Injection of unknown fillers into chin and nasal dorsum 8 years previously
11	F/45	Right cheek	Palpable nodule with slow growth and no pain	3 mo	Nodule measuring 5 cm in diameter, smooth boundary, tough quality	Excision	Cystic nodule with pasty contents	No recurrence or symptoms	Injection of HA into cheeks 10 years previously

cytoplasm. Eosinophils were seen beside the giant cells. More vacuoles were found in the basophilic material of patients 2 and 3. Although all pathological reports included basophilic material as well as foreign body reactions, HA filler was not mentioned because the pathologists were unfamiliar with the histological pattern of HA fillers and did not know the detailed medical history of the cases during the first appointment.

During the postsurgical follow-up, we collected information about patients' detailed cosmetic histories and prognosis. All patients admitted having received injections of dermal fillers from 3 to 10 years ago. Eight of them reported that they had received HA fillers, two could not remember the nature of the filler material, and the other reported a filler substance that was inconsistent with her histological findings.

Nine of the 11 patients had a favourable prognosis with no symptoms or recurrence. One patient complained of facial asymmetry after surgery and another patient reported mild pain in their upper lip.

Discussion

A foreign body granuloma is a chronic inflammatory reaction mainly involving multinucleated giant cells and is one of the most serious complications of soft filler procedures[19]. The granuloma presents as firm, often mobile, subdermal or submucosal focal, bosselated or multifocal nodules that are sometimes coupled with infection and understandably have a negative effect on facial aesthetics[20]. Their incidence ranges from 0.01% to 14% according to the different chemical nature of the injected fillers[21]. Compared with permanent materials, absorbable materials have a much lower risk of foreign body reactions[10].

As a biological substance that naturally presents in the dermis without species specificity, HA should, in principle, be tolerated by all living organisms. However, HA products injected as cosmetic fillers are not the natural glycosaminoglycan found in the dermis. To avoid enzymatic degradation by endogenous hyaluronidase, cross-linking is essential to prolong the product's half-life. Regardless of whether HA is produced by engineering techniques of microbiological or avian origin, impurities are inevitable. Therefore, HA fillers can trigger an immune reaction in the human body tissue. Reports of foreign body granulomas in the orofacial region caused by HA fillers are few, especially those of delayed granulomas appearing years after the injection. According to the literature, the time between injection and the appearance of the first foreign body granuloma is usually 6 to 24 months[22]. In our patients, however, the time between injection and the onset of foreign body granuloma was up to 10 years.

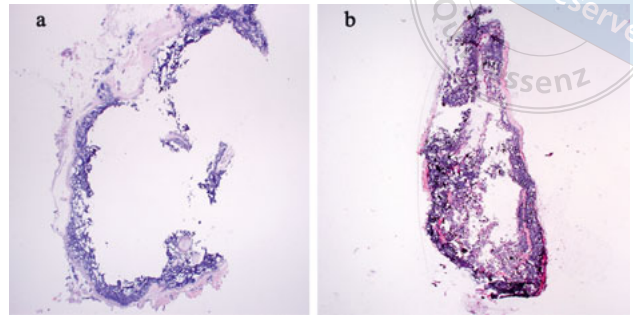

Fig 2 The fibrous capsule around HA fillers that prevents the absorption of HA fillers into the surrounding tissues (HE, 1.25×). **(a)** Pathological manifestation of patient 3; **(b)** Pathological manifestation of patient 4.

The mechanism and trigger factors for the sudden onset of granulomatous reactions after an uncertain delay period are not fully understood. Three possibilities have been proposed. First, biofilms on the surface of HA fillers enable persistent minimal infection with little host response. Bacteria can lie dormant for long periods and can cause granulomatous inflammation when they emerge from their planktonic state[5,12]. Second, HA molecules or impurities could trigger immune-mediated delayed hypersensitivity reactions[23]. Moreover, it has been reported that the incidence of hypersensitivity declined significantly after the purity of HA increased[24]. Third, the disintegration of the cross-linked product may provoke an inflammatory response. Small fragments are proinflammatory whereas long chains inhibit inflammation[6,25]. The glycosaminoglycans may act as superantigens to activate the immune reactive cells[26].

Granuloma formation involves several phases: protein adsorption, macrophage adhesion, macrophage fusion and crosstalk[19,27]. The physical properties of fillers, such as particle size, surface shape, surface charge and particle concentration, can influence phagocytosis[5]. In cases where the particle volume is greater than the macrophage volume, macrophage aggregation is required and foreign body giant cells are formed. Macrophages secrete factors that recruit and activate fibroblasts, and a fibrous capsule develops around the material that prevents the absorption of injected material into the surrounding tissues (Fig 2). Hence, HA fillers were still found several years after injection in our cases.

The clinical presentations of foreign body granulomas including single or multiple nodules or swelling lack specificity and resemble other conditions such as

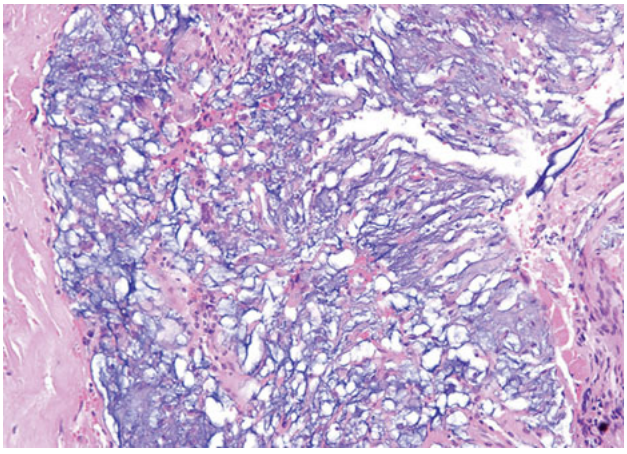

Fig 3 Pathological manifestation of foreign body granulomas induced by polyacrylamide gel (HE, 10×), which needed to be distinguished from HA-induced foreign body granulomas. Polyacrylamide gel is admixed and intermingles with vacuoles and cystic spaces of variable sizes.

cysts, tumours and other chronic diseases. They usually appear as small anechoic pseudocystic structures on ultrasound and fluid attenuation that may infiltrate subcutaneous fat on computed tomography (CT) scans. It is difficult to distinguish foreign body granulomas from other cystic lesions even with the help of imaging examination[8]. Diagnosis of foreign body granulomas is challenging without establishing a history of cosmetic procedures. When a granuloma occurs weeks or months after a dermal filler injection, the patient will probably recognise the lesion as a complication of the treatment and consult with their cosmetologist for help. In delayed cases, however, patients are usually unaware of the possibility of adverse effects and omit to mention their cosmetic history. We recommend that clinicians should inquire about cosmetic history in detail when they encounter an inexplicable granuloma in the orofacial region, especially in young or middle-aged women.

Unfortunately, the exact history of filler injections was not available in most cases, particularly when the granulomas were delayed or developed in an area distant from the initial injection. Sometimes patients reported the wrong filler substances, making the diagnosis more challenging. When the exact history of filler injections is not available, histopathological study remains the gold standard for exact diagnosis and identification of the responsible filler material. Thus, oral pathologists should be familiar with the histological pattern of each filler type. With haematoxylin and eosin (HE) staining, HA fillers are microscopically characterised by amorphous basophilic material, and Alcian blue staining is positive[6]. In our patients, the microscopic appearance of the basophilic materials showed small differences because they were from different brands of HA filler. There are now almost 200 HA products on the market[6]. Each product differs widely from the others in its manufacturing process and physical properties[3]. For example, biphasic HA fillers such as Restylane (Galderma, Lausanne, Switzerland) and Hylaform (Genzyme, Cambridge, MA, USA) contain a range of microsphere sizes and display a granular, filamentous or wispy morphology because of the sizing technology in the processing[28], whereas monophasic fillers such as Juvéderm (Allergan, Dublin, Ireland) elicit a homogenous appearance because of the Hylacross technology[3,28].

Among the commonly used dermal fillers including collagen, poly-L-lactic acid (PLLA), calcium hydroxylapatite (CaHA), silicon and polymethylmethacrylate (PMMA), only HA and polyacrylamide gel (PAAG) present as basophilic material under HE staining. A difficulty in the diagnosis of HA-induced foreign body granulomas is the histological differentiation between HA and PAAG. In some cosmetic advertisements, PAAG was described as a kind of permanent HA. However, they have quite different properties and must be distinguished to offer appropriate treatments. It has been said that staining with Alcian blue is strongly positive with HA and faintly positive with PAAG[11]. Eosinophils are frequent around basophilic HA, while intense necrosis is frequent with PAAG[29]. HA exhibits a wavy structure, while PAAG is admixed and intermingled with vacuoles and cystic spaces of variable size[6,11]. Based on the distinguishing features of histological manifestations, we successfully identified a case of PAAG-induced foreign body granuloma in our study (Fig 3). We found that the patient with PAAG-induced foreign body granulomas had received an injection of Amazingel 12 years ago. Amazingel filler is a nonabsorbent material and is forbidden from use in China due to its high risk of adverse reactions.

After the diagnosis of HA-induced foreign body granulomas, conservative treatment should be the first choice. According to previous reports, intralesional hyaluronidase, systemic and local steroids and antibiotic therapy have been used and led to obvious improvements in patients' conditions[8,13,18]. Among these, local steroid injection with a high dose of triamcinolone is the most common treatment. Systemic therapy can be used to treat widespread inflammatory granulomas[19]. When the granulomas were caused by multiple cosmetic injections and different fillers, conservative treatment may be less effective[11]. Surgical procedures are the most suitable choice after multiple unsuccessful conservative therapies.

Most of our patients were satisfied with the outcomes of resection surgery. However, one patient complained of asymmetry of the cheeks following removal of excessive dermal and subcutaneous tissue and another complained of pain in the lip, which may have resulted from a nerve injury during surgery. These sequelae should be considered, and surgery should be avoided when possible.

The patients received dermal filler injections to enhance their facial aesthetics without surgery. However, those with foreign body granulomas did not achieve a satisfying appearance and rather suffered as a result of facial nodules and resection surgery. To avoid granuloma formation, physicians should pay attention to several aspects. First, different dermal fillers should not be injected into the same anatomical location[5] as the interaction between the materials is unpredictable[11]. Second, injecting fillers into the subcutaneous fat layer is considered safer than injecting them into the dermal layer[30], as the skin has a strong immune function and actively mounts foreign body reactions[22]. Third, well-known brands with good safety profiles should be preferred as their complication rates are much lower than non-standard brands. Untested cheap products should never be used.

Conclusion

Foreign body granulomas can develop years after HA injection. The diagnosis of HA-induced foreign body granulomas was clinically challenging without the exact history of filler injections. Clinicians should inquire about patients' cosmetic history in detail when they encounter inexplicable nodules in the orofacial region, especially in young or middle-aged women. In this case, biopsy specimens are helpful. The pathologist should be familiar with the histological characteristics of different dermal fillers to offer proper diagnosis and avoid unnecessary surgery. As the popularity of cosmetic procedures grows, the occurrence of complications associated with injectable fillers is also expected to increase. This article may increase clinicians' awareness of these complications and help them select the appropriate therapy.

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Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Fang Fei ZHANG collected the data and drafted the manuscript; Dr Zhi Xiu XU performed the pathological examinations; Dr Yan CHEN designed the study and revised the manuscript. All authors approved the final manuscript.

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