# A case series on resin allergy during clear aligner therapy

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Clear aligner therapy (CAT) has gained popularity due to its aesthetic benefits, especially among adults. However, with ongoing advancements in appliance materials, concerns about resin allergies have emerged because of the extended contact between aligner plastics and the oral tissues. This case series highlights important clinical features of this rare and increasingly recognised issue. Diagnosing the allergies proved challenging due to variability in the presentation and test results. All of the cases were females aged 23 to 28 years with no prior history of allergy to food nor dental materials. Clinical manifestations varied between the patients and ranged from redness and swelling of the lips and gums to numbness and ulceration. Allergy testing, including serum immunoglobulin E (IgE) and patch tests, yielded inconsistent results for two of the cases. Therefore, diagnosis was based primarily on clinical signs and symptoms. CAT was discontinued for two of the patients. In conclusion, it is crucial for dental practitioners to be aware of hypersensitivity reactions and thereby facilitate early detection of resin allergies in patients undergoing CAT.

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## Introduction

Clear aligner therapy (CAT) has become a popular alternative to conventional fixed orthodontic appliances for patients with high aesthetic demands. CAT has evolved due to its advantages, which include fewer clinical visits, reduced orthodontic emergencies, improved periodontal health, and lower pain levels.[1] Since Sheridan introduced the concept of vacuum-formed Essix polyurethane plastic appliances for minor tooth movements in 1995,[2] a number of aligner systems have been developed as a result of advancements in digital technology related to computer-aided design and computer-aided manufacturing (CAD-CAM). This progress has led to the creation of Invisalign by Align Technology in 1998, along with several other clear aligner (CA) systems. Recently, aligners have even been produced locally as in-house appliances.[3]

With the advancement of digital technology, the fabrication of the aligner has progressed from the conventional thermoforming method to direct printing.[4] The conventional process for manufacturing CAs consists of four main stages: firstly, by capturing the patient's teeth through either an impression using polyvinyl siloxane material or a digital scan; secondly, adjusting the placement of the teeth sequentially to predetermined positions; thirdly, the 3D printing of models; and fourthly, the thermoforming of the appliances on the acquired models. The latest technology allows clinicians to 3D

print aligners directly, thereby eliminating the need for thermoforming. This new technique has increased the accuracy and precision of the aligners while reducing resin waste.[5,6]

The plastic materials used in the fabrication of CAs can be categorised based on the manufacturing methods. Thermoplastic polymers and polymer blends are the dominant materials used in the conventional thermoforming process. Common materials in the thermoplastic polymer category include polyurethane, polypropylene, polycarbonate, polyvinyl chloride, ethylene vinyl acetate, and polyester. A proprietary polyurethane and copolyester (LD30) blend is currently used commercially by Invisalign (Align Technology, Santa Clara, CA, USA). In contrast, for the direct 3D printing method, Tera Harz TC-85 (Graphy, Seoul, South Korea) is the only directly printable material commercially available that has been approved by the Korean Food and Drug Administration (KFDA) and the U.S. Food and Drug Administration (FDA).[4]

Aligners have become increasingly popular, especially among adults, primarily due to their aesthetic appeal. The appliances also serve as an excellent alternative for patients with an allergy to the nickel content found in metal fixed appliances. The aligners fit snugly around the teeth, extending a few millimetres above the gingival margin. They must be worn for at least 20 hr daily for optimal effectiveness, with new aligners provided every 10 to 14 days. The prolonged contact within the oral environment makes bio-compatibility a crucial concern and in recent years, there has been an increase in dental patients presenting with resin allergies.[7] In-vitro studies have reported increased water absorption rates in thermoplastic materials. This can lead to significant leaching of unreacted components, which may then remain in contact with tissues if exposure is prolonged, as in CAT, in which treatment durations range from six months to two years, depending on the severity of the initial malocclusion.[8] An in-vitro study on gingival fibroblast cell lines demonstrated slight to moderate cytotoxicity levels from exposure to thermoplastic aligner materials of several systems.[9]

Scientific clinical reports on allergic reactions to aligner materials are limited. The Invisalign system has only one documented case of adverse clinical events.[10] Between 2006 and 2016, a total of 173 medical device reports were recorded in the Manufacturer and User Facility Device Experience (MAUDE) database (U.S. FDA, Silver Spring, MD, USA), with 97.7% classified as adverse events. These included allergic reactions ranging from mucositis to systemic reactions most commonly respiratory difficulties.[10]

The cytotoxicity of aligner plastic materials can be influenced by several factors, including the chemical composition of the polymers, the types of additives as well as processing and environmental conditions related to their storage time in water, the polymerisation cycle, the polymerisation method, temperature, humidity, pressure, and thermal history.[11] Additionally, allergic reactions to CA materials may be triggered by reactions to pigments, dyes, or slurries used in manufacturing, the sensitivity to cleaning solutions, or the crystallisation detergents used for maintenance.

In the present study, an allergy to aligners is described and characterised by mildly painful redness and swelling of the lips following appliance exposure. The aligners prescribed for the patients were printed by the Research and Development Department of the Standards and Industrial Research Institute of Malaysia (SIRIM, Malaysia) in accordance with the manufacturer's instructions. The appliances were immediately sent to the Faculty of Dentistry, Universiti Kebangsaan Malaysia where the clinicians used only nitrile gloves during the clinical procedures. According to current knowledge, no previous studies have reported a resin allergy with symptoms related to clear aligners that are currently available.

### *Case report 1*

A 23-year-old female Malay patient, a dental student, attended a dental clinic in December 2023 for upper and lower arch aligners. She presented with a Class 1 skeletal relationship and mild crowding in both arches. The patient had no past history of orthodontic treatment nor allergies to known food nor dental materials, even among her family members. She also mentioned that she was not taking any medications and had not received any recent vaccinations. The treatment aimed to alleviate crowding and correct the overbite and overjet by utilising interproximal reduction (IPR). The plan for the aligners involved 15 trays over 7.5 months for the upper arch and 23 trays over 11.5 months for the lower arch, including a Class II elastic cutout for bonded buttons.

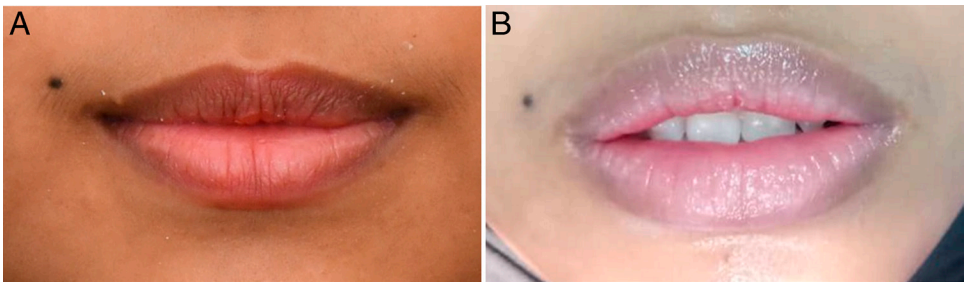


Figure 1. Upper and lower lips; (A) Pre-treatment; (B) Dryness and swelling.

On the day of delivery of the trial set, the patient received 12 attachments: six units for the upper teeth and six units for the lower teeth. The trial sets of the aligners (Mx0 and Md0) were delivered, but no IPR was performed at this time. The IPR was scheduled prior to starting set 1 (Mx1 and Md1). Oral and aligner care instructions were provided, along with a pain assessment questionnaire and feedback on aligner wear at four and 24 hr, and again at seven and 14 days.

After wearing the aligners for ten days, the patient noticed painful swelling and redness of the upper lip. The following day, the swelling spread to the lower lip and was accompanied by redness of the labial and buccal mucosa. Suspecting a dermatitic allergy, the patient was immediately administered an oral antihistamine (4mg chlorpheniramine, three times daily) to alleviate the itchiness and swelling. The antihistamine was taken for only one day. The aligners were temporarily discontinued, and the symptoms improved within 24 hr. The patient then continued to wear the aligners, but within 12 hours, the pain and discomfort returned. A localised reddish lesion was noted on the soft palate and gingival area around the edge of the aligners. Dryness and swelling of the upper and lower lips was experienced, along with numbness, pin head ulceration of the labial mucosa and thickening of the buccal mucosa (Figures 1 and 2).

The patient was referred to the Oral Pathology and Medicine (OPM) Specialist Clinic the next day and, following an examination, was provisionally diagnosed with orofacial granulomatosis and a possible case of Crohn's Disease. She was, therefore, referred to the Gastroenterology Clinic of Kuala Lumpur Hospital. On the same day, the patient was prescribed Dexaltin oral paste (Dexamethasone 1.0mg/g) to be applied to the affected area three times a day for two weeks. Additionally, she was instructed to take a 0.5 mg tablet of Dexamethasone three times a day. The tablet was to be crushed, diluted in 15ml of water, and used as a gargle. The patient was also prescribed Oradex mouthwash (Chlorhexidine gluconate 0.12%) to rinse three times daily for two


Figure 2. (A) Redness and thickening of the buccal mucosa; (B) Pin head ulceration on the labial mucosa; (C) Localized reddish lesion on the soft palate.

weeks. However, the mouthwash was only used twice because of a burning sensation and, as a result, the patient was advised to discontinue its use.

Two weeks later, the patient reported that the swelling had subsided, and she resumed wearing the Mx1 and Md1 aligners. The patient was reminded to report any recurring signs or symptoms, and within 24 hr, she experienced mild but bearable discomfort and continued wearing the aligners. Therefore, she wore the aligners irregularly, removing them when experiencing discomfort and replacing them once the symptoms improved.

Meanwhile, an allergy specialist at the Institute of Medical Research (IMR) of the Ministry of Health Malaysia enquired about the patient's condition in relation to the aligner's material and arranged a referral to the Dermatology Clinic at Kuala Lumpur Hospital (DCKLH). An allergen history was gathered, and a blood sample was collected. Two weeks later, the patient underwent an allergy patch test against 71 allergens, including 34 common inhalant and food allergens, 34 dental materials, and three supplied materials (Table I). The test was completed in a week.

Blood tests using Fluoroenzyme Immunoassay (FIA) methods indicated an elevated total immunoglobulin E (IgE) level of 197 ku/L (normal range for adults = <100 ku/L). However, specific allergen testing showed an undetectable IgE level of < 0.1 ku/L. Clinically, the patch test indicated a highly positive reaction to the aligner resin, while negative reactions were observed for the other allergens. The patient was confirmed to be allergic to the aligner resin, and so treatment was immediately discontinued.

### *Case report 2*

A 28-year-old female Malay patient who worked in a human relations office attended a dental clinic in mid-January 2024 to receive aligner treatment. She presented with mild crowding of the upper and lower arches on a Class I skeletal pattern. The patient had not received any previous orthodontic treatment. No allergy history either from food nor dental materials was reported. The patient also indicated that she was not taking any medications nor had recent vaccinations. A treatment plan aimed to upright the canines and relieve the crowding following IPR. The plan involved 22 trays over eleven months for the upper arch and 10 trays over five months for the lower arch.

On the day of delivery of the trial set, 12 tooth attachments were placed. The passive trial set (Mx0 and Md0) of aligners was inserted, and instructions on appliance care and wear time were provided. On the eleventh day, the patient complained of swelling of her upper lip. Immediately, the patient was advised to stop wearing the aligners and attend the clinic for an oral examination. Since the patient was unavailable because of her working hours, she could not attend the clinic and therefore, she went to a nearby General Dental clinic where she was differentially diagnosed as having a lip allergic reaction. She was administered Piriton and Bufencon 1ml intramuscularly and prescribed Cetrizine and Prednisolone to ease her discomfort.

The next day, the twelfth day, she re-presented and said that she had taken the medication as prescribed and felt the swelling had improved. Extraorally, the clinical examination revealed a swollen upper lip without pain (Figure 3), while an intraoral examination revealed slight redness of the gingivae near the lower left second molar, and associated sharp edges of the aligners were then removed. The edges were carefully trimmed and polished to eliminate any potential irritation. The patient was advised to continue the medication and wear the aligners. However, the patient was advised to discontinue using the aligners and inform the clinician if the swelling worsened.

Five of the attachments dislodged over a week, and so she presented at the Orthodontic clinic for replacements. She was also prescribed her first set of aligners, which included Mx1 and Md1. After two days of wear, the patient complained of oral itchiness which involved the lips, tongue, and buccal mucosa and an appointment was arranged with an OPM specialist for further investigation. The patient was advised to wear the aligners for appointment purposes.

The following day, subsequent to the OPM clinical examination, she had a differential diagnosis of material allergy, and was referred for an allergy test. The patient was then prescribed chlorhexidine mouthwash to relieve her symptoms. The aligners were discontinued.

Table I. Type of allergen tested

| Type | Allergen |
|---|---|
| Standard series | Potassium dichromate |
| | p-PHENYLENEDIAMINE (PPD) |
| | Thiuram mix |
| | Neomycin sulfate |
| | Cobalt(II)chloride hexahydrate |
| | Caine mix III |
| | Nickel(II)sulfate hexahydrate |
| | 2-Hydroxyethyl methacrylate |
| | COLOPHONIUM |
| | Paraben mix |
| | N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) |
| | LANOLIN ALCOHOL |
| | Mercapto mix |
| | Epoxy resin, Bisphenol A |
| | Peru balsam |
| | 4-tert-Butylphenolformaldehyde resin (PTBP) |
| | 2-Mercaptobenzathiazole (MBT) |
| | FORMALDEHYDE |
| | Fragrance mix I |
| | Sesquiterpene lactone mix |
| | SODIUM METABISULFITE |
| | Propolis |
| | METHYLISOTHIAZOLINONE + METHYLCHLOROISOTHIAZOLINONE |
| | Budesonide |
| | Tixocortol-21-pivalate |
| | METHYLDIBROMO GLUTARONITRILE |
| | Fragrance mix II |
| | HYDROXVISOHEXYL |
| | 3-CYCLOHEXENE CARBOXALDEHYDE |
| | METHYLISOTHIAZOLINONE |
| | BENZISOTHIAZOLINONE |
| | Textile dye mix |
| | DECYL GLUCOSIDE |
| | FLAVIN |
| | CHLORAMPHENICOL ME |
| | 1(Antibiotic) -no2 |
| Dental series | Methyl methacrylate |
| | Triethylene glycol dimethacrylate |
| | Urethane dimethacrylate |
| | Ethylene glycol dimethacrylate |
| | Bisphenol Aglycerolate dimethacrylate (BIS-GMA) |
| | N, N-Dimethyl-4-toluidine |
| | BENZOPHENONE-3 |
| | 1,4-Butanediol dimethacrylate |
| | Bisphenol A dimethaerylate (BIS-MA) |
| | Potassium dichromate |
| | Mercury |
| | Cobalt(II)chloride hexahydrate |
| | 2-Hydroxyethyl methacrylate |
| | Gold(I)sodium thiosulfate dihydrate |
| | Nickel(II)sulfate hexahydrate |
| | EUGENOL |
| | COLOPHONIUM |
| | N-Ethyl-p-toluenesulfonamide |
| | FORMALDEHYDE |
| | 4-Tolyldiethanolamine |
| | Copper(II)sulfate pentahydrate |
| | Methylhydroquinone |
| | Palladium(II)chloride |
| | Aluminium(II)chloride hexahydrate |
| | BORNANEDIONE |
| | DIMETHYLAMINCETHYL METHACRYLATE |
| | 1,6-Hexanediol diacrylate |
| | DROMETRIZOLE |
| | Tetrabydrofurfuryl methacrylate |
| | Tin |
| | Sodium tetrachloropalladate(II) hydrate |
| | CARVONE |
| | 2,2-bis(4-(2-Methacryl-oxyethoxy) phenyl)propane (BIS-EMA) |
| | GLUTARAL |
| Supplied | Mouthwash oradex |
| | Latex Glove |
| | Resin TC-85DAC |

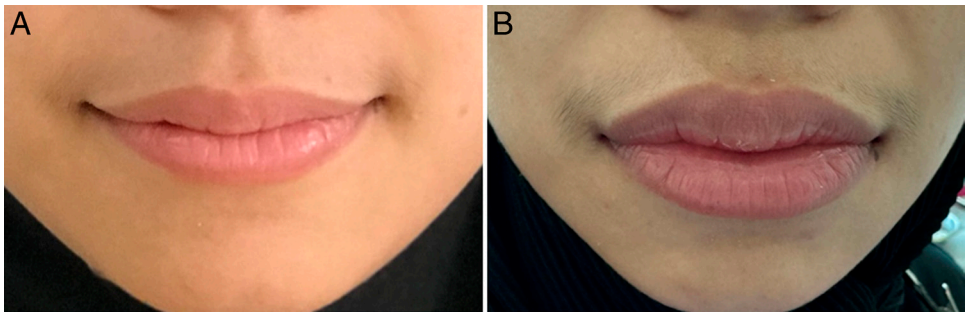


Figure 3. Upper and lower lips; (A). Pre-treatment; (B) Swollen lips on day twelfth.

A month later, the patient had her initial appointment at the DCKLH to determine her eligibility for a patch test. Due to her prior commitments, her next appointment was scheduled four months later. During the first appointment, the patient had a blood sample taken and underwent the patch test (Table I), which was completed within a week. The aligner material in liquid form and latex gloves were provided to the DCKLH.

The blood tests following FIA methods showed a total IgE level of 2.99 kuL, which indicated a negative result. Even specific allergens produced a negative result. Clinically, the patch test showed a mild positive result for the aligner resin and latex, which confirmed an allergic reaction.

### *Case report 3*

In February 2024, a 23-year-old Malay female patient attended the Orthodontic clinic for upper and lower arch aligners. Clinically, she presented with a Class 1 incisor relationship in a Class 1 skeletal pattern, with mild upper and lower arch crowding. She reported no history of allergies to food nor dental appliances for herself nor her family members. The treatment addressed the crowding in the upper and lower arches using IPR. The plan involved eight trays over four months for the upper arch and ten trays over five months for the lower arch.

On the day of delivery, the patient received six attachments: four units on the upper teeth and two units on the lower teeth. The trial sets of the aligners (Mx0 and Md0) were provided, but no IPR was performed at this stage. The IPR was scheduled before the first aligner set (Mx1 and Md1). The appliance care instructions and details were explained. The same questionnaire regarding pain and the experience of wearing the appliances was distributed for completion at four and 24 hr and after seven and 14 days.

The patient received the first set (Mx1 and Md1) of aligners, and by the tenth day of wearing, redness and pinhead-sized ulcers were noted on the buccal mucosa at the attachment sites (Figure 4). The condition worsened by the twelfth day when discomfort began and the lesions spread to the entire lip and buccal mucosa areas. It was painful for the patient when brushing her teeth and using Listerine

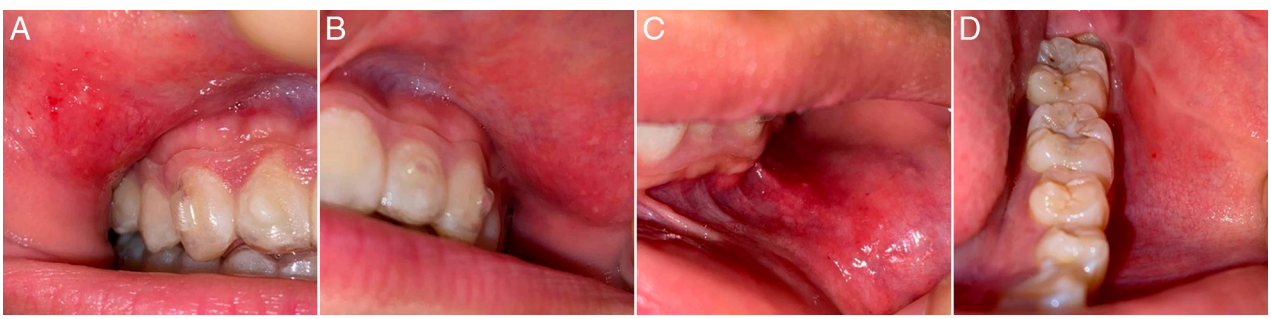


Figure 4. Redness and a pinhead-sized ulcer at the buccal mucosa of the attachment site (A) upper right; (B) upper left; (C) lower left canine area; (D) lower posterior left.

Zero mouthwash. The patient was instructed to stop wearing the aligners and advised to use Oradex (chlorhexidine gluconate 0.12%) rinse twice daily for three days. Gengigel (gel form) was recommended and applied to the affected areas whenever necessary. The symptoms subsided within a week, and so the aligners were continued.

Concurrently, the patient was also referred to the DCKLH, and a week after persevering with aligner wear, she presented for an initial appointment, during which a blood sample was taken. She underwent an assessment and a patch test was scheduled within one week. A patch test involving 71 allergens was performed (Table I), and the patient continued to wear the aligners.

Blood tests using FIA methods showed an elevated total IgE level of 160 ku/L (normal range for adults = < 100 kuL). However, a specific IgE level is undetectable when multiple allergens are tested (< 0.1 kU/l). Clinically, the patch test showed negative results for the tested allergen. The elevated total IgE may have indicated that the patient was allergic to other allergens that were not tested.

## Discussion

It is commonly known that nickel and chromium are allergens found in fixed metallic orthodontic appliances. Due to the resin polymeric materials used, such as polymethyl methacrylate (PMMA), polyurethane and other polymers, removable appliances and CAs, though less frequently implicated, may still trigger allergic reactions after prolonged contact with the oral tissues.[12–14]

The polymerisation reaction involved in the manufacture of CAs is primarily a free radical additional polymerisation process, in which incomplete polymerisation can leave residual monomers that may leach into the oral cavity, potentially leading to adverse biological reactions.[9] The presence of residual monomer in polymeric biomaterials can cause harmful effects at both the tissue and cellular levels, and involve gingival inflammation, an immune response, apoptosis, and disruptions to the cell cycle. The concentration of residual monomer varies depending upon the polymerisation method, and factors related to the polymerisation technique, the powder-to-liquid ratio, and storage duration, all of which influence the cytotoxicity of the materials.[11]

Polyurethane is the primary polymer used in most commercially available CA systems, such as Invisalign (Align Technology, Santa Clara, CA, USA) and the newly developed Graphy shape memory aligner manufactured using Tera Harz TC-85 (Graphy, South Korea). Isocyanates, key components in polyurethane, are known to trigger allergic reactions. When isocyanates contact tissues, they quickly bind with proteins and other bio-macromolecules, initiating immunogenic reactions that can lead to sensitisation in humans. Short-term exposure to isocyanates can irritate the mucous membranes, and prolonged exposure may result in asthma or hypersensitivity reactions.[15]

Pre-treatment testing is crucial for patients with known allergies to ensure safe and effective orthodontic treatment. It helps to identify potential allergens, particularly for individuals with sensitivities to orthodontic materials. This enables clinicians to choose hypoallergenic materials and offer alternative treatments. There are various diagnostic tests for allergies, which include patch tests, prick tests, blood tests, and histopathological examinations.[16] Each method has unique applications, advantages, and limitations. The choice of test depends on patient-specific factors and clinical circumstances.

Patch testing is particularly valuable in diagnosing delayed-type hypersensitivity reactions, which are mediated by T-cells and typically manifest 48 to 72 hr after exposure to the allergen. This method helps identify specific allergens responsible for contact dermatitis.[17] Commonly, hypersensitivity reactions are not identified until after the onset of symptoms noted as erythema, swelling, or ulceration. Patch testing involves applying small amounts of potential allergens to the skin, usually on the back, and covering them with adhesive patches. The patches remain in place for 48 hours, after which the skin is examined for reactions and re-examined at 72 to 96 hr. An erythema, oedema, or vesiculation reaction at the test site indicates a positive test.

Additionally, patch testing can be customised using dental materials, including orthodontic brackets, wires, and elastics, to directly assess the patient's sensitivity to the specific substance.[18] Accordingly, this test is the gold standard for diagnosing contact hypersensitivity reactions to orthodontic materials.[19] The timing of the tests performed during treatment can vary but is crucial for managing and mitigating adverse reactions.[20]

Blood tests, including specific IgE antibody tests, are used to detect type I hypersensitivity reactions.[21] These tests measure the levels of IgE antibodies specific to various allergens in the blood. Precisely, the Radioallergosorbent Test (RAST) or ImmunoCAP can quantify specific IgE antibodies, providing valuable information about the patient's allergic status, and is particularly useful for patients with extensive dermatitis, in which skin testing might exacerbate the condition.[17,22]

While patch and blood tests are considered the gold standard for identifying hypersensitivity, it is important not to rely on them solely, as their results can sometimes be inconsistent, as demonstrated in the presented cases. Clinical signs and symptoms are also crucial for diagnosing hypersensitivity reactions. In the three cases, patients exhibited allergic reactions following the placement of the appliances, with symptoms resolving after aligner removal. Clinicians should be vigilant for signs of hypersensitivity, identified as swelling and redness of the oral mucosa, oral ulcers, or burning sensations after starting CAT. Additionally, clinicians should exercise caution if a patient has a history of metal or resin allergies, asthma, hay fever, dermatitis or childhood eczema. In Case 3, the intermittent nature of the patient's symptoms was thought to be related to fluctuations in resin leachability due to daily changes in the intra-oral environment related to exposure to fluoride or variations in food composition. Despite initially reporting hypersensitivity, the patient completed treatment, possibly due to the development of tolerance to the allergen.

A genetic predisposition, poor oral hygiene, previous sensitisation and the duration of treatment are factors that put patients at a higher risk of hypersensitivity. Therefore, understanding the clinical presentation along with effective diagnostic and treatment strategies is crucial for orthodontic practitioners to ensure appropriate management and the prevention of further reactions. Di Spirito et al. (2024) clearly described a clinical recommendation for managing an oral manifestation of hypersensitivity reactions in orthodontic patients with removable appliances and CAs.[16]

## Conclusions

Although rare, allergic reactions to CAs can occur and case reports provide an insight into the mechanisms whereby allergies can present in patients without a noted prior history. No specific risk factors were identified in the presented cases, and the results from allergy testing may be inconsistent. Therefore, increased awareness of delayed hypersensitivity reactions by orthodontists and dental practitioners is essential for the early detection of clinical signs and symptoms. Prompt referral for allergy testing is necessary to confirm the diagnosis and effectively manage the allergy.

## Conflict of interest

The authors declare that there is no conflict of interest.

### Ethical statement

Informed consent was acquired from the patients, who also consented to the publication of all images and clinical data in the manuscript.

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