Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.02.020.

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Recurrent anaphylaxis to a gelatin-based colloid plasma substitute and to cetuximab following sensitisation to galactose-alpha-1,3-galactose

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Editor—Galactose-alpha-1-3-galactose (α-Gal) is a ubiquitous epitope, part of many mammalian glycoproteins and glycolipids found in food and in some animal-derived drugs (e.g. gelatin-based colloids) or in α-Gal glycosylated chimeric monoclonal antibodies, such as cetuximab, used for treatment of metastatic colorectal cancer or head and neck squamous cell carcinoma.[1] Pre-existing immunoglobulin E (IgE) directed against the α-Gal epitope has been linked to severe immediate hypersensitivity reactions to cetuximab,[1,2] and severe allergic reactions to red meat (α-Gal syndrome)[3] and to gelatin, including gelatin-based colloid plasma substitute.[4] We report a case of a patient who developed three severe reactions to gelatin-based colloid plasma substitute and cetuximab (with the patient's consent). A 43-yr-old man, with no history of allergy, underwent pharyngolaryngectomy in July 2014 for laryngeal squamous cell carcinoma. The anaesthesia protocol included i.v. remifentanil, propofol, ketamine, succinylcholine, lidocaine, cefotaxime, hydrocortisone, atracurium, phenylephrine, norepinephrine, cefuroxime, and trimethoprim–sulphamethoxazol. Gelatin-based colloid plasma substitute (Gelofusine®, Braun Melsungen AG) was infused to correct hypovolaemia, followed 10 min later by major arterial hypotension (57/27 mm Hg), tachycardia, circulatory shock, and oxygen desaturation with cyanosis. He

Table 1 Hypersensitivity reaction characteristics. IgE, immunoglobulin E; ND, not done; QAM, quaternary ammonium morphine; α-Gal, galactose-alpha-1-3-galactose. *Severity grade according to the Ring and Messmer[6] scale. †According to the consensus (Valent and colleagues[5]). ‡Histamine threshold >10 nmol L^{-1} (defined by the manufacturer). ¶ImmunoCAP threshold >0.1 kUA L^{-1} (defined by the manufacturer). §Retrospectively tested.

	First reaction				Second reaction				Third reaction			
Clinical signs												
Cutaneous	None				Diffuse red rash				Erythema Itching			
Cardiovascular	Hypotension Tachycardia Circulatory shock				Hypotension Bradycardia				Hypotension Tachycardia			
Respiratory	Desaturation Cyanosis				None				None			
Other	None				Loss of consciousness Seizures				None			
Severity grade*	3				2				2			
Culprit drug	Gelofusine				Cetuximab				Gelofusine			
Biology testing				**Interpretation**				**Interpretation**				Interpretation
Time from onset (h)	0.5	2.25	>24		1	3	>24		0.25	1.25	23	
Tryptase (μg L^{-1})	13.5	16.1	1.8	Positive†	32.7	28.9	2.8	Positive†	7.5	11.5	2.0	Positive†
Histamine (nmol L^{-1})	553	5.2	ND	Positive‡	710	0.3	ND	Positive‡	165	7.2	ND	Positive‡
IgE ImmunoCAP (kUA L^{-1})¶												
QAM	0.1			Negative	ND				ND			
Suxamethonium	<0.1			Negative	ND				ND			
α-Gal	33.8§			Positive	>100			Positive	19.4			Positive
Skin testing												
Skin prick (neat)	Positive (3 × 3 mm) for Gelofusine				ND				ND			
Intradermal (1:1000)	Positive (6 × 10 mm) for Gelofusine											

was treated with epinephrine and i.v. fluid therapy with a favourable outcome. High plasma concentrations of tryptase (ThermoFisher, Phadia AB, Uppsala Sweden; increased value $\geq 1.2 \times$ basal value+2 μg L^{-1})[5] were measured: 16.1 μg L^{-1}; basal value: 1.8 μg L^{-1}. Histamine concentration also increased at 553 nmol L^{-1} (Beckman Coulter Immunotech, Marseille, France; threshold >10 nmol L^{-1}). Specific IgE to succinylcholine and quaternary ammonium morphine (ImmunoCAP®; ThermoFisher, Phadia SAS; normal value <0.1 kilo units of allergen [kUA] L^{-1}) were negative. Skin tests performed 3 months later with all the administered drugs and latex were negative except for Gelofusine with a positive prick test and intradermal tests (1:1000 to 1:10 diluted solutions). The allergist concluded anaphylaxis to Gelofusine (Table 1).

Five months later, the same patient was treated with cisplatinum, 5-fluorouracil, and cetuximab. Immediately after the first cetuximab infusion, he experienced a diffuse red rash, bradycardia, hypotension, loss of consciousness, and seizures. Methylprednisolone, dexchlorpheniramine, and clonazepam were administered i.v., and he recovered within 20 min. High concentrations of tryptase and histamine were measured: 32.7 μg $L^{-}1$; basal value: 2.8 μg L^{-1} and 710 nmol L^{-1}, respectively. Anti-α-Gal IgE was also elevated (>100 kUA L^{-1}) (Table 1).

Three months later during replacement of his phonatory implant, he received a Gelofusine infusion and experienced hypotension, tachycardia, erythema, and itching. He was treated with methylprednisolone. Tryptase concentration was 11.5 μg L^{-1} (basal value: 2.0 μg L^{-1}) and histamine was 165 nmol L^{-1}. The anti-α-Gal IgE concentration was 19.4 kUA L^{-1}. Based on these results, serum obtained after the first Gelofusine reaction was retrospectively analysed and appeared positive (33.8 kUA L^{-1}) (Table 1) for α-Gal IgE.

Subsequently, we reviewed all hypersensitivity reaction cases in our hospital from 2013 to 2020, where gelatin-based colloid plasma substitute was used during anaesthesia and associated with positive mediator release (n=32). Of 10 of the 32 patients who had seen an allergist, seven were positive for intradermal gelatin-based colloid plasma substitute skin test and six had positive α-Gal specific IgE. Amongst the 22 patients without allergy assessment, two had positive specific IgE.

Galactose-alpha-1-3-galactose is a recently described allergen first identified as responsible for allergic reactions after cetuximab infusion.[1] It is found in red meat (beef, lamb, or pork), organs (pork kidneys, liver, heart, and intestines), and gelatin (marshmallows, jelly, and sweets). After ingestion, delayed-onset (3–6 h) anaphylaxis can be observed and is known as 'the α-Gal syndrome'.[3] Immediate anaphylactic reactions can be observed after i.v. administration of drugs derived from animal sources, such as gelatin-based colloid plasma substitutes,[4,7] which have a higher incidence rate of hypersensitivity reactions than other fluids. In one study, compared with albumin, the hypersensitivity reaction incidence rate ratio was 2.3 after dextran, 4.5 after hydroxyethyl starch, and 12.4 after gelatin-based colloid plasma substitute.[8]

Of the three severe hypersensitivity reactions observed in a single patient within 1 yr, two could have been avoided. Lack of knowledge about the common epitope (α-Gal) between cetuximab and gelatin-based colloid plasma substitutes explains the second reaction, and unawareness of the patient's allergy history led to the recurrent administration of Gelofusine and the third reaction. This case highlights the importance of the pre-anaesthetic interview for identifying allergy history and subsequent risk factors.[9]

Patients with anaphylaxis caused by cetuximab, gelatin-based colloid plasma substitute, or α-Gal syndrome should be explored in a complete allergy workup, including anti-α-Gal IgE. Positive results could contraindicate further cetuximab and gelatin-based colloid plasma substitute infusions. Therapy for shock should follow the 2019 consensus recommendations of Garvey and colleagues[10] to avoid colloid solutions in favour of crystalloids.

Declarations of interest

The authors declare that they have no conflicts of interest.

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