

Anaphylaxis to bovine serum albumin tissue adhesive in a patient without meat allergy

Running title: Anaphylaxis to BioGlue

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BioGlue® (Cryolife, Kennesaw, Ga) is a surgical adhesive, used since 1998 as an adjunct to standard methods of achieving hemostasis in adult patients in open surgical repair of large vessels. The adhesive is therefore commonly used as surgical sealant in thoracic surgery [1]. It is composed of purified bovine serum albumin (BSA) and glutaraldehyde which are dispensed by a controlled delivery system. Upon mixing, the components polymerize into a flexible mechanical seal. Contraindications are quite limited (sensitivity to materials of bovine origin, intravascular use, cerebrovascular repair). Since then, BioGlue use has been expanded notably to repair of traumatic liver laceration [2].

A 67-year-old atopic man, was admitted to the hospital for an aortic aneurysm. A Bentall operation was performed using a BioGlue. He experienced an anaphylactic shock with bronchospasm and hypotension shortly after this application, requiring crystalloids, norepinephrine, epinephrin and salbutamol. A blood sample taken during this even showed an elevated serum tryptase level (18.5µg/L). The patient was referred to our allergology department for evaluation. He had a history of allergic rhinitis to cat, but no food allergies. Skin prick test with cat, dog, hamster, guinea-pig and rabbit were positive. Specific IgE (sIgE) were positive for Fel d 1 (21.6 kU/L); Fel d 2 (3.7 kU/L) and Fel d 4 (10.7 kU/L)

(ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden), but negative for Bos d 6. Skin prick tests were performed using both components of BioGlue, native bovine serum albumin (BSA) and glutaraldehyde. The test was positive for BSA (5 mm), negative for glutaraldehyde and the mix of both.

In order to further elucidate the target of the patient's IgE antibodies, we performed immunoblot inhibition assays on the BSA component of BioGlue and commercial BSA (Sigma-Aldrich, Diegem, Belgium). Proteins were separated by Coomassie stained SDS-PAGE or immunoblotted as reported (Fig 1A) [3]. IgE-reactivity was directed mostly to high (>100 kDa) and low (35-40 kDa) molecular weight components in BioGlue and BSA samples. Reactivity could be completely abolished by inhibition with BSA (100 µg/ml), confirming that all reactivity was directed to the BSA component of BioGlue. In order to further understand the discrepancy between a positive immunoblot to BSA and a negative IgE test by ImmunoCAP, we assayed IgE-binding to BSA in a native and denatured form (Fig. 1B). BSA was denatured using 1% SDS and 0.35 M β-mercaptoethanol and spotted onto a nitrocellulose membrane. IgE-reactivity to denatured cat serum albumin (CSA), the BSA component of BioGlue and BSA is much stronger than that to native albumin, suggesting that IgE-binding is predominantly directed against non-conformational epitopes. This would explain a negative ImmunoCAP test with Bos d 6. A similar case of anaphylactic shock to BioGlue was reported in a patient who presented with pork-cat syndrome, but negative for Bos d 6 [4]. Our patient did not report any symptoms upon ingestion of meat but he owns a cat since several years and has a history of allergic rhinitis in the presence of cats. We hypothesize that Fel d 2 cross-reactive epitopes on BSA would be exposed briefly to IgE-antibodies during denaturation when mixing the two components, BSA and glutaraldehyde. Solidification of the mix and strong protein cross-linking would then preclude any further

IgE-binding and lead to asymptomatic further outcome. The severity of the reaction is probably due to the high concentration of BSA used in the product. A recent report on human serum albumin (HSA) induced anaphylaxis due to intravenous administration supports the idea that treated albumin could present structural changes capable of inducing sensitization and subsequent allergic responses upon administration. The patient was tolerant to human blood and plasma derivatives and did not present sIgE to animal serum albumins [5]

The present case shows that patients with sIgE to Fel d 2, even at low levels, may have a high risk of perioperative anaphylaxis upon using BioGlue as tissue adhesive. Cat-allergic patients should be screened for sIgE to Fel d 2 before undergoing thoracic surgery. Up to 14-23% of cat-allergic patients have been reported to be sensitized to Fel d 2 and about 1-3% are likely to present a pork-cat syndrome [6]. Despite the fact that surgical sealants composed of purified bovine serum albumin are widely used, this is only the second case reported in the literature. In addition to sIgE against Fel d 2, other yet unidentified co-factors might lead to the severe reactions described in our case and by Dewachter et al[4]. The risk-benefit balance should be carefully assessed for each patient and alternative sealants considered.

In conclusion, we report another case of perioperative anaphylaxis to BioGlue. We confirm the importance of IgE-screening for sensitization to Fel d 2 in cat-allergic patients, but we also want to caution clinicians against the fact that a negative IgE-test to Bos d 6 and tolerance of bovine or porcine meat does not exclude a potential risk of reactivity to BSA tissue adhesives.

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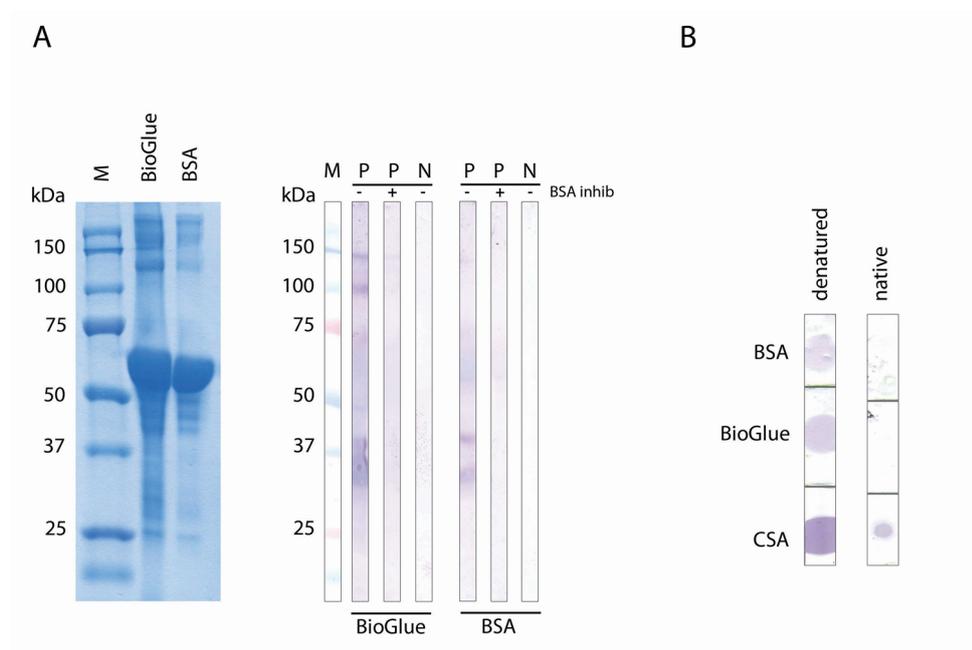
Conflict of interest

The authors have no conflicts of interest to declare.

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Figure 1: Patient IgE-reactivity to bovine serum albumin (BSA)



A, The BSA component of BioGlue (BioGlue) and a commercial BSA preparation were separated by SDS-PAGE, stained with Coomassie Blue (left) and immunoblotted with the patient's serum (right). Cold water fish gelatin (2%) (Sigma) was used as blocking buffer. IgE-reactivity to BioGlue and BSA could be completely inhibited by addition of BSA. P, patient serum; N, negative control.

B, Cat serum albumin (CSA), BioGlue and BSA were spotted onto nitrocellulose under denaturing or native conditions (10 μ g/spot) and immunoblotted. IgE reactivity was markedly enhanced under denaturing conditions.