Anaphylaxis during intrauterine insemination secondary to bovine serum albumin*

Kathy R. Sonenthal, M.D.† Leslie C. Grammer, M.D.†
Tacoma McKnight, M.D.‡ Rajasingam S. Jeyendran, D.V.M., Ph.D.‡§
Martha A. Shaughnessy, B.S.†

Northwestern University Medical School, Chicago, Illinois

Anaphylaxis is an immediate, generalized, life-threatening reaction resulting from the release of bioactive mediators from mast cells and basophils. It usually occurs by clearly defined mechanisms, such as cross-linking of specific cell-bound immunoglobulin (Ig)E antibodies by exogenous antigens, which results in mediator release. An anaphylactic reaction to bovine serum albumin (BSA) has been observed in a patient undergoing autologous bone marrow transplantation in which BSA was used in the cryopreservation of the patient’s bone marrow cells.1 Additionally, BSA used in in vitro fertilization (IVF) has been implicated in serum sickness reactions.2 In the latter case, the reaction occurred 6 to 9 days after the IVF procedure; in vitro tests on the patient’s serum were positive for IgG1 but negative for IgG2, IgG3, IgG4, and IgE. To date, there are no reports available linking an immediate anaphylactic reaction to BSA used in intrauterine insemination (IUI) or IVF. We describe the clinical and immunological findings in a patient who experienced anaphylaxis after undergoing IUI in which BSA was used to supplement the sperm-processing medium.

CASE PRESENTATION

The patient was a 42-year old white female who presented with infertility. She was evaluated and referred for IUI as a part of her infertility therapy. The patient underwent her first IUI in October, 1990, and her husband’s semen sample was processed for IUI as follows. The semen was mixed with an equal volume of Tyrode’s solution with 0.1 g% of BSA fraction V (Sigma Chemical Co., St. Louis, MO), centrifuged at 500× g for 5 minutes, and the supernatant was discarded. After resuspending the sperm pellet in 0.4 mL of the Tyrode-BSA solution, the sperm suspension was filtered through a glass wool column previously rinsed with Tyrode’s solution containing 10 g% BSA and then 0.1 g% BSA to remove loose fibers. The filtered sperm was then used for IUI. Within 5 minutes after insemination, the patient developed severe uterine contractions, shortness of breath, and chest tightness. She experienced generalized pruritus and developed urticaria, initially on her abdomen. She was given diphenhydramine, 50 mg intravenously (IV), whereupon her symptoms resolved, and she was sent home. Subsequently, she presented to the emergency room at Northwestern Memorial Hospital complaining of diffuse urticaria and shortness of breath. She required four injections of epinephrine 0.3 mL 1:1000 subcutaneously approximately 1 hour apart, one injection of methylprednisolone 125 mg IV and three injections of diphenhydramine 50 mg intramuscularly approximately 1 hour apart to control her symptoms so that she could be discharged. She continued on diphenhydramine 25 mg orally four times a day and prednisone 40 mg orally every...
morning for 3 more days with the eventual resolution of her symptoms.

The patient returned for repeat IUI in November 1990. This time, however, her own heat-inactivated blood serum instead of BSA was used to process the sperm. The patient tolerated this procedure well and subsequently presented to the allergy service in January 1991 for evaluation of her presumed allergy to BSA.

The patient's past medical history was significant for a 17-year history of asthma and the removal of a spindle cell tumor from her left leg 7 years before presentation. She also had a history of drug allergies with anaphylactic reactions reported secondary to penicillin and phenytoin. She denied having previously received xenogeneic sera, nor had she ever been treated with beef products. She denied any known allergic or adverse reactions to foods and has often eaten beef and dairy products without incident. Physical examination was unremarkable.

IMMUNOLOGICAL EVALUATION

Skin testing using a prick test was performed on the patient's right forearm to evaluate immediate hypersensitivity to allergens. Prick testing was performed using commercial allergenic extracts (Allergy Laboratories of Ohio, Columbus, OH) to test beef, cow's milk, histamine 1:10,000 (Allermed, San Diego, CA), and normal saline control. Additionally, solutions used in sperm processing for IUI, including Tyrode's solution without BSA, human serum albumin (HSA, 25% Albumin; Armour Pharmaceutical Company, Kankakee, IL), 1 mg/mL, and BSA fraction V 1 mg/mL (Miles Scientific, Kankakee, IL) were tested. The patient reacted to histamine and BSA with erythema and wheal formation. She had no response to all other allergens tested.

To estimate the antibody, an enzyme-linked immunosorbant assay (ELISA) was performed. Briefly, Immulon micro-ELISA plates of polystyrene (Greiner and Sons, Nurtingen, Germany) were coated with BSA fraction V or HSA at a concentration of 100 μg/mL in carbonate buffer and were subsequently reacted with patient serum and sera from six different volunteers. The patient's serum had significantly higher binding to BSA when compared with other sera. In contrast to BSA binding, there was negligible or no binding to HSA by either the patient's serum or other sera (Fig. 1). The results were recorded as the optical density of each well at 405 nm.

To evaluate the specificity of antibody binding, ELISA-inhibition studies were performed by preincubating the patient's serum for 30 minutes at 37°C with various concentrations of different proteins. The proteins tested for inhibition were HSA, BSA, bovine blood plasma, and bovine insulin (Lilly Co., Kalamazoo, MI). After incubation, the solutions were tested for response to BSA, previously coated on the ELISA plates. Inhibition was considered complete if the response of the patient's serum was less than two times the response of the negative control sera. The assays were performed in duplicate and on 2 different days. Results showed that incubation of the patient's serum with BSA resulted in complete inhibition and that this inhibition was dependent on BSA concentration (Fig. 2). Similarly, bovine blood plasma also resulted in complete
Figure 2 Inhibition of IgE binding to BSA by proteins that are related to BSA: Bovine insulin (△—△), HSA (●—●), BSA (♦—♦), and bovine blood plasma (○—○). The patient's serum was preincubated with these inhibitors to assess whether the IgE in the serum was bound before being placed in the ELISA wells previously coated with BSA. The negative control serum (○—○), two times the noninhibited negative control (□—□) and the patient's serum with no inhibitor added (□—□) are also shown. The SEM is also represented.

inhibition. In contrast, there was no inhibition when the serum was preincubated with beef insulin or HSA.

DISCUSSION

This is a report of a case of anaphylaxis in a woman undergoing IUI with sperm processed in a medium supplemented with BSA. Although anaphylaxis to human seminal fluid has been described, the antigen in question in our patient did not appear to be in the seminal fluid because she had never reacted to her partner's seminal fluid during prior sexual intercourse. Therefore, the anaphylaxis after IUI was most likely secondary to a substance used to process the sperm before IUI. The BSA used to supplement the sperm-processing medium was the most likely agent to have caused the anaphylaxis because repeat IUI with the patient's own serum rather than BSA in the sperm-processing medium caused no adverse reaction.

The presence of IgE antibody against BSA was demonstrated by the positive skin test and the positive ELISA assay. Her antibody did react with bovine blood plasma also but did not cross-react with HSA or beef insulin. Therefore, it appears that the native BSA was the antigen.

Bovine serum albumin used in IVF has previously been documented to cause serum sickness-like reactions. Bovine serum albumin has also been documented to cause an IgE-mediated immediate hypersensitivity reaction in an autologous bone marrow transplant recipient. The case study presented here is the first immunological evaluation of an immediate hypersensitivity reaction to BSA after IUI. The etiology of the sensitization in our patient is unclear, as were the etiologies in the previous reports.

Recently, a case of occupational asthma and rhinoconjunctivitis from inhalation of crystalline BSA powder was reported. This patient worked in a pharmaceutical research company where she occasionally worked with powdered BSA. She then developed symptoms of asthma and rhinitis within 5 to 10 minutes after BSA exposure. She had a positive cutaneous test to BSA and a positive bronchial challenge to BSA.

For several years, IUI was rarely practiced largely because occasionally strong uterine contractions were reported, which were probably because of the prostaglandins in the seminal plasma in the unwashed sperm specimen. It was also believed that IUI occasionally led to uterine infections because of bacterial contamination of the sperm specimen. Processing the sperm with media (in our case with Tyrode's solution supplemented with BSA) has been shown to reduce the above adverse effects and increase the conception rate. However, the use of BSA for IUI sperm processing does have risks in itself as we have outlined in this report. It is important for clinicians to be aware of this adverse effect of using xenogeneic proteins during IUI and other assisted reproductive techniques.

SUMMARY

A case of anaphylaxis is reported after IUI with sperm processed in Tyrode's solution supplemented with BSA. The patient had a positive prick cuta-
neous test to BSA and also had specific IgE antibody against it. Repeat IUI using the patient’s own blood serum instead of BSA for processing the sperm proceeded without incident. Clinicians should be aware of this rare, but not inconsequential, adverse effect of using xenogeneic proteins during IUI and other assisted reproductive techniques.

REFERENCES