

Allergic Reaction to Botulinum Toxin: Positive Intradermal Test

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The authors have indicated no significant interest with commercial supporters.

Botox (Allergan, Irvine, CA) was introduced in Brazil in 1992 for the treatment of hyperhidrosis and neurologic disorders, and in 2000 it was approved for cosmetic use. Each Botox vial contains 100 U of botulinum toxin (BTX), 0.9 mg of sodium chloride, and 0.5 mg of human albumin, and its protein load is –5 ng. Prosigne (Lanzhou Institute of Biological Products/Cristália, Lanzhou, China), each vial containing 50 or 100 U of BTX, was approved for the treatment of hyperhidrosis, neurologic disorders, and hyperfunctional lines in 2005. The excipients in Prosigne are 5 mg porcine gelatin (Haemacell), 25 mg of dextran, and 25 mg of sucrose, and the protein load is 4.0 to 5.0 ng/100 U of BTX.

Case Report

A 46-year-old female patient was treated with Prosigne (Lanzhou Institute of Biological Products/Cristália). The injection was performed to improve the hyperkinetic lines on the frontal and glabellar regions and the crow's feet. According to her clinical history, after being injected with the product 7 months earlier, she developed edema and erythema all over the treated region, which spread to the entire treated functional unit and worsened. She also reported that the worst period occurred between 24 and 48 hours postinjection. She was really worried with the physicians' disbelief in the adverse effect and decided to visit the dermatology service again, where we suggested the performance of an intradermal test.

Botox (Allergan) was used as a counterproof and Prosigne (Lanzhou Institute of Biological Products/Cristália) was used to verify the allergic reaction. Both vials were simultaneously diluted with 1 mL of saline solution (0.9% pure NaCl) immediately before the test. The forearm region was marked on its flexion portion 5 cm away from the cubital fold, and the spot was marked with surgical ink for further identification. Two units (0.02 mL) of Prosigne (Lanzhou Institute of Biological Products/Cristália) was intradermally injected into the left forearm, and the same procedure was performed on the right forearm using an identical dosage of Botox (Allergan). The patient was observed for 30 minutes in the office before being discharged and instructed to return within 24 hours for a clinical evaluation and again within 72 hours for the biopsy of the injections sites.

Twenty-four hours later, a 0.6-cm papule with an erythematous area of 2.0 to 1.3 cm diameter was observed on the left forearm (injected with Prosigne, Lanzhou Institute of Biological Products/Cristália). There were no reactions on the right forearm (Botox, Allergan). Figure 1 shows the allergic reaction on the left forearm and Figure 2 shows the right side with no changes. Seventy-four hours later, the skin improved and there were no signs on the forearms. On this occasion, a biopsy was performed. The histologic sections of the left forearm biopsy revealed a skin fragment with the epidermis within normal limits and the superior dermis showing an edema. The superior and reticular dermis showed intense

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Figure 1. Allergic reaction after Prosigne intradermal injection.

mononuclear inflammatory infiltrate around a number of skin vessels and adnexal structures leading to a diagnosis of dermal vascularitis (Figure 3). The histologic sections of the specimen collected from the right forearm showed epidermis within normal limits. At the superior and reticular dermis, a few mononuclear inflammatory cells around some small vessels were observed, and the pathologist concluded that the epidermis and the dermis were within normal limits (Figure 4).

Discussion and Conclusion

Some patients became resistant to BTX following its therapeutic use. In such cases, the circulating anti-



Figure 2. No reaction after Botox intradermal injection.

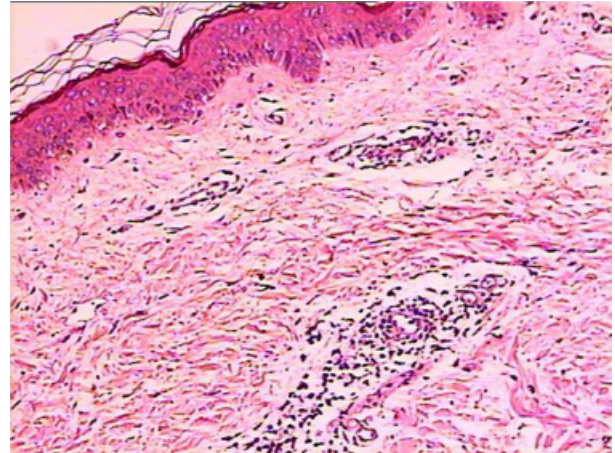


Figure 3. Superficial and reticular vascular lymphocytes dermatitis. HE $\times 160$.

body found was immunoglobulin G, and that effect was expressed by the absence of patient response to treatment.^{1,2} Goschel and colleagues³ reported that the formation of antibodies (BTX produced by Allergan) was proportional to the quantity of

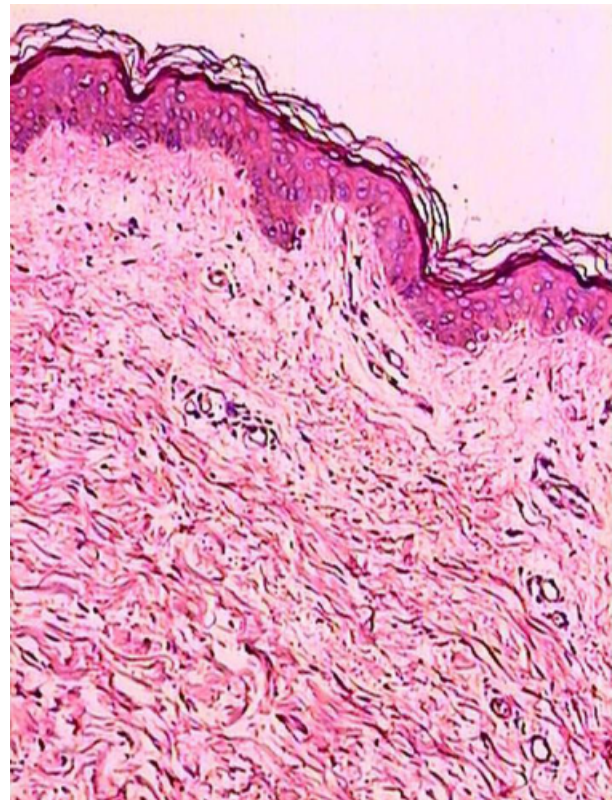


Figure 4. Discrete perivascular lymphocytes in superficial dermis. HE $\times 160$.

toxin used, and this was estimated to have occurred in less than 1% to 5% of patients receiving higher doses than 300 U.⁴⁻⁷ Tests for antibodies in human serum in cases of secondary nonresponsiveness such as monoclonal antibodies (with a high rate of false-negative results) may be used, as well as mouse protection bioassay (Speywood Pharmaceuticals, London, UK) and endopeptidase-based tests.^{8,9} Tamura¹⁰ showed that no changes were observed in the skin before and after BTX injection for the treatment of hyperhidrosis when the markers anti-CD4 + , anti-CD8 + , anti-HLA-DR, anti-ICAM-1, anti-TNF- α , anti-CD25, anti-LihL-4, anti-IFN- γ , and anti-CD1a were evaluated in the epidermis and dermis.

BTX-specific antibodies and the reaction to the ingredients in commercially available products need to be discussed. Reviewing the literature for adverse reactions to BTX-associated components, there is a case report describing a fixed pigmented erythema related to lactose, which is one of the ingredients of Dysport/Neurotox/Reloxin (Ipsen/Galderma, Watford, UK). A higher percentage of skin rash in Chinese patients injected with the Chinese BTX (Lanzhou Institute of Biological Products/Cristália) than in those injected with Botox (Allergan) was reported by Wan and Tang.¹¹ Several authors describe major allergic reactions such as anaphylactic to anaphylactoid reactions, and there are even further studies on HLA (human leukocyte antigen), mainly in the Japanese population, as well as on individual Th1 and Th2 response to immediate and nonimmediate reactions to gelatin. The Chinese toxin has gelatin in its formulation, which is known to be an allergenic substance. Our case is likely to have shown the same Type I allergic reaction as described by Kamin and coworkers¹² in the cases seen during the mass inoculation.

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