Images in Allergy

Granulomas Induced by Botulinum Toxin

Pedro Giavina-Bianchi, MD, PhD, and Mara Giavina-Bianchi, MD, PhD *São Paulo, Brazil*

Investigation of the immunogenic profile of botulinum toxin A (BoNTA) is needed considering its worldwide utilization. We report the case of a 34-year-old woman who complained of frontal, glabellar, and periorbital nodules arising 11 days after she had received injections of onabotulinum toxin A (Botox) for aesthetic purposes (Figure 1, *A* and *B*). She had undergone 4 previous procedures with BoNTA and did not report any adverse reaction. Our patient also noticed that her Bacillus Calmette-Guérin (BCG) vaccination scar became erythematous (Figure 1, *C*). Her personal medical history included allergic rhinitis, alopecia areata on the scalp, which was in remission, and 2 silicone breast implant replacements due to foreign body–type reaction. Reviewing the histopathology of these reactions, we observed dense fibrosis forming a capsule around the implants, but without granuloma formation.

Biopsy of one of her frontal nodules was performed. Dermatopathology showed granulomatous inflammation, with numerous epithelioid macrophages and multinucleated giant Langhans cells without evidence of necrosis, infectious agents, or demonstrable foreign body material on polaroscopic examination. There are about 4 cases similar to the present one described in the literature.[1,2]

We formulated 3 hypotheses, which are not exclusive. (1) BoNTA or any substance present in the toxin compound acting as a foreign body and triggering the formation of granulomas. Against this hypothesis, we did not observe evidence of foreign bodies such as birefringent crystalline materials in the histopathology. Furthermore, this hypothesis does not explain why the BCG scar became inflamed. (2) Cutaneous sarcoidosis, which can be induced in scarring areas or by foreign bodies, even years before systemic sarcoidosis diagnosis. Again, foreign bodies were not observed. Systemic sarcoidosis was investigated and ruled out. (3) In addition to the injection trauma, BoNTA could act as a T_H1 immunogenic stimulus, activating old granulomas (BCG scar) and inducing new ones. However, what would be the target of the granulomatous immune response in the face, an autoantigen? Ahbib et al[2] showed in a similar case that the granuloma could be reproduced experimentally by an intradermal injection of BoNTA, but not saline, suggesting that the lesion was induced by the BoNTA and not by trauma.

Our patient's lesions improved with 1 mg/kg prednisolone, but they relapsed later during steroid tapering. After treatment with 10 mg/wk methotrexate and decreasing doses of prednisolone, the lesions resolved. Five months after the initial reaction, the patient is taking only 10 mg/wk methotrexate, with plans for tapering.

We speculate that BoNTA is a T_H1 stimulus that may induce the development of granulomas and reactivate old ones (BCG scar) as shown in the case reported here and illustrated in Figure 1. However, millions of doses of botulinum toxin are administered each year and granuloma induction is an extremely rare adverse reaction. What predisposition do these patients have? Sarcoidosis may be a predisposing factor, and the patients should be followed, paying special attention to this diagnosis. Future studies may further our understanding of possible mechanisms involving granuloma induction by BoNTA.

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Clinical Immunology and Allergy Division, School of Medicine, Universidade de São Paulo, São Paulo, Brazil

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Corresponding author: Pedro Giavina-Bianchi, MD, PhD, Clinical Immunology and Allergy Division, School of Medicine, University of São Paulo, Av. Brigadeiro Faria Lima, 2894, cj 23, São Paulo, SP 01454-010, Brazil. (E-mail: pbianchi@usp.br or marahgbianchi@gmail.com.)

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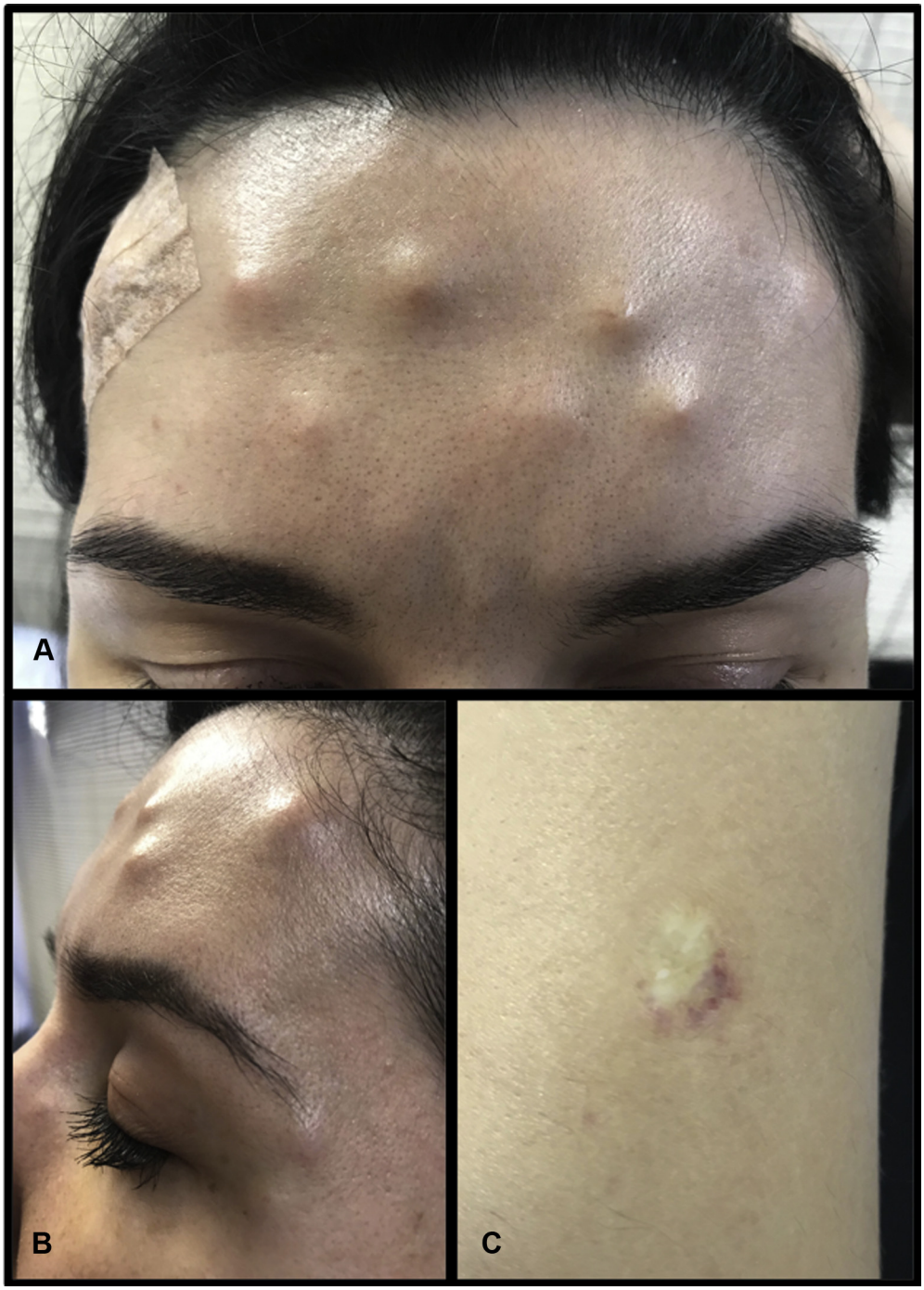

FIGURE 1. (**A**) Front photograph of facial nodules. (**B**) Profile photograph of facial nodules. (**C**) BCG vaccination scar with inflammation.