

Recurrent Urticarial Vasculitis Related to Nonanimal Hyaluronic Acid Skin Filler Injection

JAUME ALIJOTAS-REIG, MD, PhD*

The author has indicated no significant interest with commercial supporters.

Nonpermanent biodegradable dermal fillers injections including nonanimal stabilized hyaluronic acid (NASHA) compounds have been considered to be nontoxic and nonimmunogenic implant fillers, although recent evidence shows that these statements can no longer be corroborated. Studies about localized and generalized hypersensitivity reactions, immune-mediated granulomas formation, and sarcoidosis-like disease have been published.^{1–4} We report on a case of a 45-year-old woman who sought medical attention because acute urticaria and purpura appeared, possibly after Restylane (Q-Med, Uppsala, Sweden) filler was administered to correct facial wrinkles. Vasculitis was histologically confirmed afterward. A second bout of vasculitis appeared, supposedly related to a new exposure to hyaluronic acid (HA). This article analyzes the possible relationship between hyaluronic acid and NASHA (Restylane) compounds with vasculitis. The role played by contaminant proteins and cross-linking compounds related to NASHA is discussed as well.

Case Report

A 45-year-old woman sought medical attention because acute urticaria and angioedema appeared after NASHA filler was administered to correct facial wrinkles. One mL of NASHA (Restylane) was placed in each nasolabial fold. Three weeks later, she noticed pruritus, urticarial lesions, and fever. She had not taken any drugs in the previous few months.

Facial angioedema appeared promptly, and urticarial lesions spread through her body. A few days later, urticarial lesions became less apparent, and rash with palpable purpura in the trunk, arms, and legs appeared. Temperature was 37.6°C. Mild lymphadenopathy and mild peripheral arthritis were also present. Laboratory tests disclosed a high erythrocyte sedimentation rate (50 mm); C-reactive protein, 10 mg/L (normal value <1 mg/L); alpha-2-globulin, 15%; antinuclear antibody test, 1:160 (normal value <1:40, speckled pattern); C4, 13 mg/dL (normal value >15 mg/dL). C1, C1q, C3, anti-DNA antibodies, anti-neutrophil cytoplasmic antibodies test, cryoglobulins, and anti-extractable nuclear antigen antibodies were normal or negative. Hepatitis B and C, cytomegalovirus, and Epstein-Barr virus were not found. Streptococcal antibody test (anti-streptolysin O) was negative. Anti-DNAse B was not performed. Renal function, urine sediment, and proteinuria were normal or negative. Chest X-ray and electrocardiogram recorder were also normal. Histology of a leg skin biopsy showed a typical pattern of leucocytoclastic vasculitis, with small-vessel involvement, lymphomonocytic infiltrates, and fibrin deposition. Small foci of C3 deposits in capillaries were also present. Antihistamines and prednisone (1 mg/kg per day) were begun. This treatment was successful, and angioedema, constitutional symptoms, and arthritis disappeared in a few days. Purpura cleared in less than 6 weeks. Steroids were tapered in 8 weeks. Two months later, a new bout of similar clinical charac-

*Ageing and Systemic Autoimmune Diseases Unit, Department of Internal Medicine I, Vall d'Hebron University Hospital, Universitat Autònoma, Barcelona, Spain; and Department of Medicine, Universitat Autònoma, Barcelona, Spain

teristics appeared again. The patient had used a topical application of facial cosmetic cream containing HA 2 to 3 days before the beginning of the second bout, as a unique possible valuable antecedent. It was resolved with a short oral prednisone treatment course. Anti-HA antibodies were not performed. The patient refused a HA skin challenge test. Twenty-six months later, new bouts had not appeared, and the patient remained asymptomatic.

Discussion

An ever-increasing number of persons are seeking solutions for their aging skin or for cosmetic reasons. In theory, dermal implant fillers, especially nonpermanent biodegradable compounds, do not provoke severe adverse effects. Recent evidence shows that these statements can no longer be corroborated, including for NASHA compounds.^{1,2} Evidence of not only nonimmunological side effects, but also localized and generalized hypersensitivity reactions, granuloma formation, and sarcoidosis-like disease has been published.¹⁻⁴ To the best of my knowledge, this is the first time that vasculitis probably related to NASHA has been communicated. NASHA is a specific biphasic HA launched in recent years under different brand names, one of them, Restylane. Its concentration is approximately 20 mg/mL, with 100,000 molecules of HA/mL. The capability of HA compounds to develop immune-mediated reactions is a matter of discussion. Theoretically, HA obtained biosynthetically by bacterial fermentation (NASHA) has the advantage of being free from the risk of transmitting diseases between species or eliciting allergic reactions in patients who are sensitive to foods such as beef, chicken, and eggs.⁵ Although more than 99% of NASHA is protein-free, it may contain small amounts of hyaluronin-associated proteins, and therefore a theoretic risk for adverse reactions exists and have been described.^{2,4} According to some reports, the protein load of Restylane is approximately 12 to 17 ng/mL.^{6,7} On the other hand, NASHA uses cross-linking compounds, mainly butanediol diglycidylether, which is not NASHA specific. Could this cross-linker play a role in the adverse effects related

to NASHA compounds? Although it may be possible, we do not know of any well-documented cases of cross-linking molecule-related toxicity. Because we do not have a biopsy of skin nodules or granulomas, we were not able to demonstrate the presence of HA in the granulomas using a specific stain with Alcian blue at pH 2.7.²

Urticarial vasculitis (UV) is a subset of vasculitis characterized clinically by urticarial and purpuric skin lesions and histologically by necrotizing vasculitis. Angioedema, arthritis, and purpuric skin lesions are the most usual clinical manifestations.⁸ Some different triggers—sun exposure, drugs, toxics, infections, and foreign proteins—have been related to UV. Small-vessel UV may be considered a form of hypersensitivity vasculitis.^{9,10} This patient fulfilled the 1990 American College of Rheumatology Criteria for the Classification of Hypersensitivity Vasculitis.¹¹ The true prevalence and incidence of this subgroup of vasculitis is unknown.⁸⁻¹¹ In this case, HA could be the cause of vasculitis because it may be considered to be a foreign protein. Because it has been discussed before, HA contaminants, especially bacteria-related proteins, cannot be excluded. In our cases, the lack of valuable titers of anti-streptolysin-O argues against streptococcus as the sensitizing protein, although negativity of anti-streptolysin-O and anti-DNAse B do not permit streptococcal infection to be excluded absolutely.¹² Although HA is a universal polysaccharide in living organisms and is considered inert, the immunogenic capacity of glycosaminoglycans has been described recently and may provoke humoral and cellular responses.¹³ Through the CD44 receptor, HA has proinflammatory effects, activating peripheral blood monocytes and promoting T and B cell activation and, subsequently, increasing Th1 phenotype cytokines.^{14,15} Thus, HA may play a role in the pathogenesis of local and systemic immune-mediated diseases. According to systemic manifestations, the patient was treated with oral steroids. Local treatments, hyaluronidase included, was not possible because of a lack of skin nodules. Although in recent years, it has been approved in many European

countries, and on November 2003, the U.S. FDA approved HA as a dermal filler, this case report and the literature review demonstrate that a more careful approach is warranted. The prevalence of delayed adverse effects related to HA is not truly known because of the tendency of doctors not to communicate negative events. According to published data in Europe, the prevalence ranges from 8.2% (Duranti et al.⁵) to 0.85% (Loewe et al.⁴) to 0.41% (André et al.,¹⁶) to 0.06% (Friedman et al.⁶). Because of that, some authorities⁴ have claimed that skin testing would be performed before HA injection for cosmetic reasons. So, although potentially severe adverse effects related to HA are probably not frequent, they may appear.

In the end, in patients with delayed adverse effects related to HA injections, the value of anti-HA antibodies has yet to be demonstrated definitively.^{17,18}

References

1. De Boulle K. Management of complications after implantation of fillers. *J Cosmet Dermatol* 2004;3:2–15.
2. Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, long term follow-up and review of the literature. *J Eur Acad Dermatol Venereol* 2008;22:150–61.
3. Dal Sacco D, Cozzani E, Parodi A, Rebora A. Scar sarcoidosis after hyaluronic acid injection. *Int J Dermatol* 2005;44:411–2.
4. Loewe NJ, Maxwell CA, Lowe P, et al. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 2001;45:930–3.
5. Duranti F, Salti G, Bovani B, et al. Injectable hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 1998;24:1317–25.
6. Friedman PM, Mafong EA, Kauvar ANB. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 2002;28:491–4.
7. Leonhardt JM, Lawrence N, Narins RS. Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. *Dermatol Surg* 2005;31:577–9.
8. Wisniewski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. *Medicine (Baltimore)* 1995;74:24–41.
9. Gibson LE, Su WP. Cutaneous vasculitis. *Rheum Dis Clin N Am* 1990;16:309–24.
10. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337:1512–22.
11. Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria form the classification of hypersensitivity vasculitis. *Arthr Rheum* 1990;33:1108–13.
12. Kaplan EL. Rheumatic fever. In: Kasper DL, Fauci AS, Longo DL, et al., editors. *Harrison's Principles of Internal Medicine*. 16th Edition. New York: McGraw-Hill; 2005. p. 1977–9.
13. Wang JY, Roehrl MH. Glycosaminoglycans are a potential cause of rheumatoid arthritis. *Proc Natl Acad Sci USA* 2002;99:14362–7.
14. Levesque MC, Haynes BF. Activated T lymphocytes regulates hyaluronan binding to monocyte CD44 via production of IL-2 and IFN- γ . *J Immunol* 2001;166:188–96.
15. Kelly L, Maiti A, Johnson P. Role of sulfation in CD44-mediated hyaluronan binding induced by inflammatory mediators in human CD14 + peripheral blood monocytes. *J Immunol* 2001;167:5367–74.
16. André P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA) in European countries: a retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venerol* 2004;18:422–8.
17. Micheels P. Human anti-hyaluronic acid antibodies. Is it possible? *Dermatol Surg* 2001;185–91.
18. Hamilton RG, Strobos J, Adkinson NF Jr. Immunogenicity studies of cosmetically administered nonanimal-stabilized hyaluronic acid particles. *Dermatol Surg* 2007;33(Suppl 2):S176–85.

Address correspondence and reprint requests to:
Jaume Alijotas-Reig, MD, PhD, Josep M^a de Segarra 2-F,
08190-Sant Cugat del Valles, Barcelona, Spain, or
e-mail: jalijotas@vhebron.net, 16297jar@comb.es

COMMENTARY

When I first read this article, I thought it was a classic example of the “Null hypothesis” (true-true but unrelated), which raises the question: If something appears to be coincidental, should it be published? I think we do have a responsibility to collect data on adverse events, and perhaps in as well-read a journal as this one, it will elicit others to come forward with a similar side effect (previously thought to be merely coincidental). My bias for feeling that this is not an example of true delayed hypersensitivity is threefold.

First, in the Perlane immunogenicity studies done as an adjunct to the FDA clinical trial, there was no histological evidence of NASHA-induced cell-mediated lymphocytic inflammatory reactions (type IV) or superficial dermal edema (type I). Also, in the 7.8% of patients that showed anti NASHA IgG at the start of the trial, there was no spike in IgG levels or clinical adverse events after Perlane administration. Second, a “re-challenge” with a topical HA would be a far-fetched association defying laws of pharmacokinetics. Last, in the face of normal complement levels, a cause for urticarial vasculitis is hardly ever found and all-to-easily associated with a “temporal” event.

Hamilton RG, Strobos J, Adkinson NF Jr. Immunogenicity studies of cosmetically administered nonanimal-stabilized hyaluronic acid particles. *Dermatol Surg*. 2007 Dec;33 Suppl 2:S176–85.

LISA M. DONOFRIO, MD
New York, NY