BRIEF ARTICLES

A Case of Granulomatous Hypersensitivity Reactions to a Dermal Filler Precipitated by PD-1 Checkpoint Inhibitor Therapy

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ABSTRACT

Injection of filler material has become a routine procedure in dermatology practices in an attempt to improve the appearance of rhytides and prevent skin volume loss associated with aging. While the vast majority of injections are performed without complications, foreign body reactions may develop in 0.04-0.3% of individuals who receive fillers[1]. We recently encountered a 65-year-old woman with recurrent malignant melanoma who presented with a 2 month history of marked thickening of the skin along the sides of her face. She had been receiving nivolumab infusions for recurrent malignant melanoma and noted that these symptoms worsened after each infusion. She reported undergoing cosmetic procedures three years prior, one of which was an injection of a long-lasting dermal filler, polymethylmethacrylate microsphere enhanced bovine collagen (Bellafill). A biopsy of two areas revealed nodular infiltrates of histiocytes with small round lobules identified as polymethylmethacrylate microspheres. Based on clinical and histopathologic findings, a diagnosis of granulomatous dermatitis filler reaction was rendered. Nivolumab is a PD-1 checkpoint inhibitor that disrupts T-cell inhibitory pathways leading to increased immune activation. In this case, hyper-immune activation triggered a florid granulomatous reaction to the filler the patient had been injected with 3 years previously. This is a newly recognized side effect of PD-1 checkpoint immunotherapy and patients who are about to initiate such therapy should be warned about this potential complication.

INTRODUCTION

Dermal filler injections have grown rapidly in popularity over the last decade. They provide an effective way of improving the appearance of individuals with rhytides and tissue loss secondary to skin aging.[2,3] While the vast majority of these injections are accomplished without complication, foreign body reactions may develop in 0.04%-0.3% of bovine collagen injection cases. Factors influencing these reactions include filler material impurities, procedural techniques, and co-existing systemic infections and concurrent medications or immunotherapy.

Foreign body reactions are host responses that develop to remove foreign material and repair surrounding tissue. This reaction is a part of the inflammatory and wound healing process that may develop when patients have surgical implantation of prosthesis, placement of medical devices, or injection of biomaterials.[4] They are also seen in response to dermal fillers, of which hyaluronic acid and collagen are most common.[4] Foreign body granulomatous inflammation involves five phases:

recognition of inflammation, protein adsorption, macrophage adhesion, macrophage fusion, and “crosstalk” among inflammatory cells[4]. The granulomas are comprised of multinucleated giant cells, T-lymphocytes, histiocytes and fibroblasts.[4]
We recently encountered a patient who developed a florid delayed granulomatous reaction to polymethylmethacrylate microsphere enhanced bovine collagen injected 3 years prior to receiving therapy with a PD-1 checkpoint inhibitor for malignant melanoma.

CASE PRESENTATION

A 65-year old Caucasian woman with a 2 month history of malignant melanoma presented with hardening and thickening of the skin along the sides of her face. Two years prior to presentation she was diagnosed with a non-ulcerated Clark's level 4, 1.25 mm malignant melanoma of the left calf. She underwent wide excision and sentinel lymphadenectomy, which was negative for metastasis.

In March of 2019, two years after the malignant melanoma had been excised, she noticed discoloration proximal to the previous surgical site. A biopsy confirmed recurrence of melanoma and another wide local excision was performed. Sentinel node biopsy was performed and again negative for metastasis. Further work up included positron emission tomography (PET) scanning which was negative, and she was staged at T4aN0M0 representing IIB with recurrence. Her oncologist recommended immunotherapy treatment with nivolumab. Her first infusion was given in April 2019 and continued on a monthly basis. The patient noted "thickening" of the skin near the temples three weeks after the first nivolumab infusion. After each subsequent infusion, she developed additional nodules along her temples, nasolabial folds, lips, and chin which progressively became more painful and firm. Cutaneous examination demonstrated firm dermal nodules around the corners of her lips and peri-orbitally. (Figure 1)

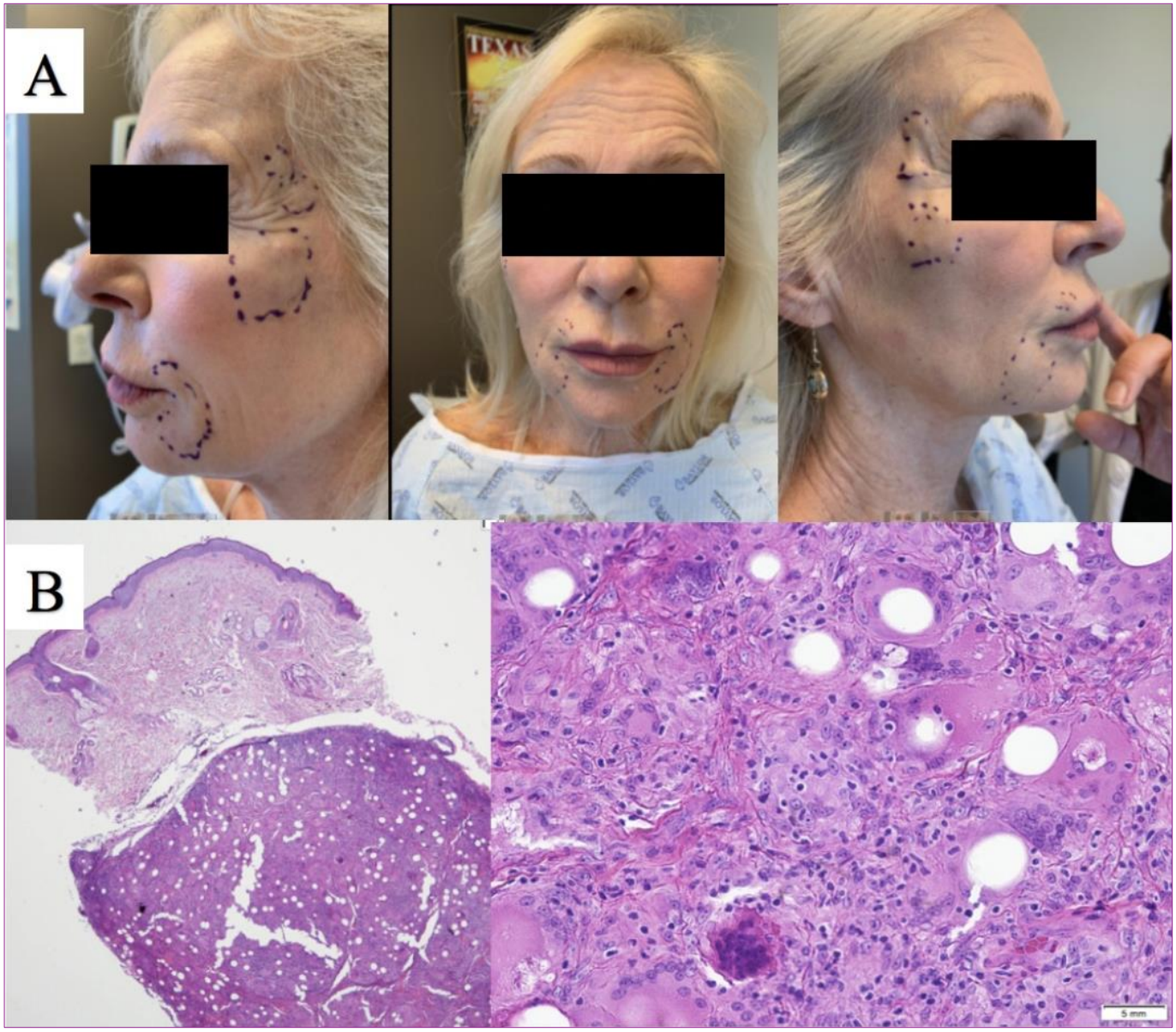
Upon further questioning, she reported undergoing cosmetic procedures one year prior, one of which was a dermal filler injection, Bellafill, comprised of bovine collagen with non-resorbable polymethylmethacrylate microspheres. She did not have any skin testing prior to these procedures and experienced no adverse reactions at the time. She denied any other cosmetic procedures since then. Two of the affected areas of her face were biopsied and demonstrated a diffuse granulomatous dermatitis with exogenous filler recognizable as polymethylmethacrylate spheres within histiocytes. (Figure 1) The patient was seen at follow-up by her oncologist and plastic surgeon, who both recommended continuing infusion therapy unless the foreign body reaction worsened to the point of necrosis.

At her follow up visit, the dermal nodules showed spontaneous regression despite continued immunotherapy. Her melanoma remained in remission. After clearance from her oncologist, she underwent 2 botulinum toxin injections for her rhytides (at her request), which resulted in no adverse reactions.

DISCUSSION

Nivolumab is a human immunoglobulin G4 (IgG4) that is approved by the Food and Drug Administration (FDA) for treatment of various cancers including advanced melanoma.[4] Nivolumab blocks the interaction of PD-1 receptors with program cell death ligands PD-L1 and PD-L2, and

Figure 1. (A) Inflammation and lichenification at previous sites of *Bellafil* dermal injections. (B) Nodular infiltrates of histiocytes with small round lobules recognizable as polymethylmethacrylate microscpheres (H&E, 10x and 20x)



restores cytotoxic T-cells' ability to destroy tumor cells.[5] In this case, immune activation triggered a florid granulomatous reaction to the filler the patient received 3 years prior. Nivolumab's ability to activate T cells indirectly led to stimulation of macrophages to phagocytose filler particles that were previously non-immunogenic, leading to the formation of granulomas with multinucleated histiocytes. These cells likely reacted with T-lymphocytes creating a delayed hypersensitivity immune response.[6] To our knowledge, there is one similar case report of a granulomatous inflammatory reaction triggered by an immune checkpoint inhibitor in which ipilimumab therapy for malignant melanoma caused significant hilar granulomatous inflammation that simulated

sarcoidosis.[9] However, that case was not related to filler injections.

PD-1 inhibitors vary significantly from one another in terms of adverse reactions, and the likelihood of checkpoint inhibitors causing reactions remains unclear. Common side effects impact the skin and thyroid, while CTLA-4 inhibitors have been linked to GI symptoms. In one case report, nivolumab treatment was linked with facial flushing and dyspnea, while pembrolizumab caused no reactions in the same patient[6]. Ipilimumab, a CTLA-4 inhibitor, can cause similar adverse reactions as nivolumab. Therefore, it can be difficult to predict what type of adverse reaction a patient will have.

In a cross-sectional study, hyaluronic acid (HA) fillers were associated with infection and swelling, making up approximately 84.2% of the total 0.01% complication rate for all HA filler injections[8]. HA based fillers have a disproportionately higher rate of infection than was predicted. However, studies suggest that patients were diagnosed with infection prematurely and complications were largely a result of breaking sterile protocol and procedural techniques. Alternately, Bellafill fillers were often accompanied by nodule formation, comprising 40% of the 0.01% complication rate. HA has been considered the preferable option due to its lower viscosity, greater withdrawal with injection, and capability for reversal with hyaluronidase. Bellafill, consists of bovine collagen and PMMA microspheres, which have lower withdrawal with injection and serve as a signal to the body to produce more collagen, rather than a natural replacement for collagen[7]. In our patient, the lesions spontaneously resolved over time even though the infusions continued. While intralesional injections with corticosteroid might have been effective, it was not necessary. The reason the inflammation abated spontaneously is however unknown.

Some of the known adverse reactions to PD-1 inhibitors include morbilliform eruptions, erythematous plaques, bullous dermatoses, psoriasiform dermatitis and now, granulomatous inflammation at sites of prior dermal filler injections. A prior history of melanoma and rapid development of nodules in our patient raised concern for dermal metastases, which fortunately was excluded by biopsy.

Clinicians should be wary of this phenomenon and counsel patients about the possibility of its development before initiating an immune checkpoint inhibitor. A thorough history, including previous cosmetic procedures, can help to avoid potential complications during immune checkpoint therapy. While our patient's reaction spontaneously resolved, this may not always be the case.

CONCLUSION

Hyper-immune activation is a recognized complication of PD-1 checkpoint immunotherapy. Given the prevalence of cosmetic injections, dermatologists must consider a dermal filler related granulomatous reaction in patients that develop nodules while being treated with checkpoint inhibitors.

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