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Facial swelling and foreign body granulomatous reaction to hyaluronic acid filler in the setting of tyrosine kinase inhibitor therapy

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Dear Editor,

Cosmetic injection of dermal fillers is common, with late complications increasingly recognized. Herein, we report a granulomatous reaction to hyaluronic acid filler occurring during the use of neratinib.

A woman in her fifties, with metastatic adenocarcinoma of unknown primary involving the skin and bones, was referred for new-onset facial swelling. Notable past medical history included progression of disease on carboplatin/paclitaxel and a hemithyroidectomy for papillary thyroid cancer. Targeted tumour sequencing¹ had identified a somatic ERBB2 mutation, and neratinib (240 mg by mouth daily) had been initiated 6 weeks prior. Her medications included zoledronate 4 mg monthly, ramipril 10 mg daily and levothyroxine 125 mg daily. She denied recent illnesses, oral/tongue swelling, chest tightness, dysphagia or additional skin lesions.

Examination revealed well-defined, indurated subcutaneous nodules of the malar and zygomatic cheeks bilaterally (Fig. 1a). Computed tomography (CT) revealed subcutaneous facial soft tissue infiltration consistent with sequelae of cosmetic procedures (Fig. 1c). Upon questioning, she reported receiving hyaluronic acid (HA) filler injections and onabotulinumtoxinA injections in the face over a year prior without any reported allergic reactions or adverse effects. Further details regarding the exact frequency and timing of her prior injections could not be obtained. Histopathological examination of a skin biopsy revealed a non-necrotizing lymphogranulomatous panniculitis with features of filler reaction (Fig. 2). Special stains (periodic acid–Schiff–diastase and acid-fast bacillus) were negative for fungal and mycobacterial organisms. No polarizable foreign material was identified. Laboratory testing included C1 esterase inhibitor (31 mg/dL, normal range 21–39 mg/dL),

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C3 (132 mg/dL, normal range 81–1577 mg/dL), C4 (32 mg/dL, normal range 13–39 mg/dL), T3 (94 ng/dL, normal range 60–180 ng/dL), free T4 (1.29 ng/dL, normal range 0.90–1.80 ng/dL) and TSH (0.53 mcU/mL, normal range 0.55–4.78 mcU/mL).

Neratinib and ramipril were held, and she received prednisone (40 mg/day by mouth for 5 days, 10 mg taper every 3 days) with improvement reported by the patient. Upon restarting neratinib, her facial oedema subjectively worsened. Oral prednisone (10 mg/day) was reinitiated, and 75 units of hyaluronidase (Vitrase, Bausch & Lomb Inc., Tampa, FL, USA) was injected to each side, which led to a reduction in swelling. CT performed 1 month later showed a reduction in facial panniculitis (Fig. 1d). She received two more injections of hyaluronidase, 100 units to each side, with patient- and clinician-reported clinical improvement at 6-month follow-up (Fig. 1b).

Herein, we report a delayed granulomatous reaction to HA dermal filler after starting neratinib, a tyrosine kinase inhibitor. The incidence of foreign body granuloma formation after dermal fillers is estimated to be 0.02–0.4%². Macrophages that have phagocytized filler particles are postulated to be activated by infection, drugs, autoimmune diseases or immunomodulators^{3,4} fuse into multinucleated giant cells and interact with T lymphocytes.

Neratinib targets HER2 (neu/ERBB2) positive cancer through epidermal growth factor receptor (EGFR), HER2 receptor and HER4 receptor blockade.⁵ In this patient, recurrence of swelling upon re-exposure to neratinib suggests a neratinib-associated reaction to the HA fillers; an alternative explanation of this temporal observation includes reaction to HA filler from an unidentified trigger, rebound effect of corticosteroid withdrawal or chance alone. However, EGFR blockade can modulate chemokine production, upregulate major histocompatibility class I and II molecules expression and increase T-cell recruitment to the skin, which suggests biological plausibility to a foreign body reaction associated with neratinib.⁶ Treatment of granulomatous filler reactions includes corticosteroids, surgical excision and/or hyaluronidase injection.²

Our case demonstrates that systemic medications, and specifically neratinib, may rarely be associated with a delayed foreign body reaction to dermal fillers. These reactions can be potentially ameliorated without interrupting systemic treatments. Moreover, physicians assessing patients with facial nodules/swelling and a history of aesthetic procedures should be aware that delayed reactions to fillers are possible.

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Figure 1.

Clinical and Radiographical Findings. (a) Initial presentation of facial swelling and periorbital oedema with indurated nodules of the malar and zygomatic cheeks bilaterally. (b) Clinical improvement of bilateral facial swelling and periorbital oedema with notable reductions in subcutaneous nodules at 6 months after treatment with oral corticosteroids and injections of hyaluronidase. (c). Computed tomography scan demonstrating soft tissue inflammation secondary to granulomatous reaction to dermal fillers. (d) Computed tomography scan with improvement of bilateral facial panniculitis 1 month after first injection with hyaluronidase.

Figure 2.

Histopathological Findings. The low-power image shows a non-necrotizing lymphogranulomatous infiltrate within the subcutaneous fat. The dermis is largely uninvolved. Higher power magnification reveals that the infiltrate is composed of lymphocytes, histiocytes and multinucleated giant cells associated with vacuolated/empty spaces, features consistent with a reaction to prior filler injection (a. 20 $\times$, b. 400 $\times$, haematoxylin and eosin preparation).