Table 1 Phototherapy in France: quantitative data from the National Health Insurance Register

Year	2007	2008	2009	2010	2013	2014	2015	2016
Number of UV treatment (code QZRP 003)	421 426	435 462	448 065	473 269 +12.3%*	450 365	438 205	396 732	382 733 −15%† −9%‡
Number of patients	25 270	25 718	27 180	28 183 +11.5%*	26 056	25 394	23 182	21 997 −15.6%† −12.9%‡
Number of UV treatment per patient	16.7	16.9	16.5	16.8	17.3	17.2	17.1	17.4
Number of prescribers	NA	NA	NA	NA	1324	1271	1224	1162 −12.2%†

NA: not available.
*2010 vs. 2007.
†2016 vs. 2013.
‡2016 vs. 2007.

perspective, declining reimbursement rates in combination with the higher cost of new, more efficacious NB-UVB office units, the need for trained phototherapy staff may deter physicians from prescribing phototherapy.[2] Furthermore, increased awareness of skin cancer risk, lack of physician training and explosion in demand for aesthetic dermatology procedures may also contribute to this decline. Lastly, newer biologic therapies may drive to the dermatologists more patients seeking more efficient treatments for psoriasis.[6] However, we cannot exclude a decrease of all dermatological indications of phototherapy even if currently available biologics used in dermatology are mostly for the treatment of psoriasis.[1]

It should be noticed that the decline of phototherapy was observed more than 10 years after the introduction of biologics. We do not have any clear explanation for this delay, but the therapeutic inertia[7] leading to delay the use of biologics may be suggested.

In summary, although phototherapy remains an important cost-effective therapeutic modality for psoriasis[8] and other dermatoses, we confirm the decline of phototherapy in France that can be explained by the increased use of biologics for psoriasis.

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

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 sequencing[1] 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), 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

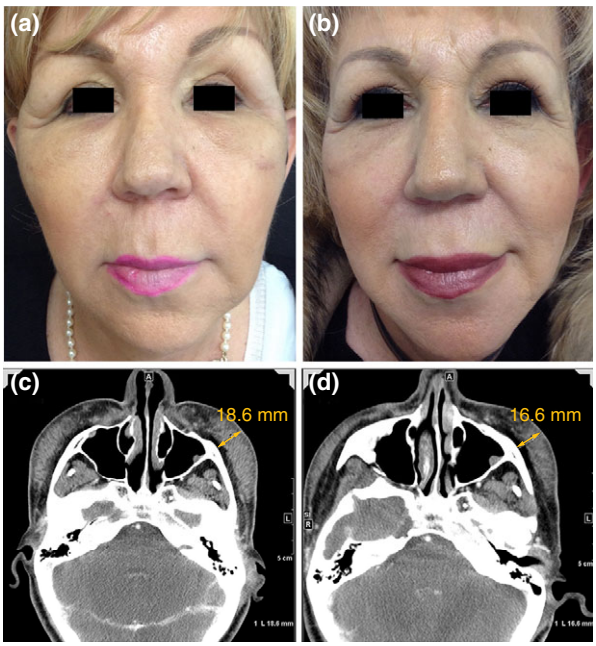

Figure 1 Clinical and Radiographical Findings. (a) Initial presentation of facial swelling and periorbital oedema with indurated nodules of the malar and zygomatic cheeks bilaterally. (b) Clinical improvement of bilateral facial swelling and periorbital oedema with notable reductions in subcutaneous 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.

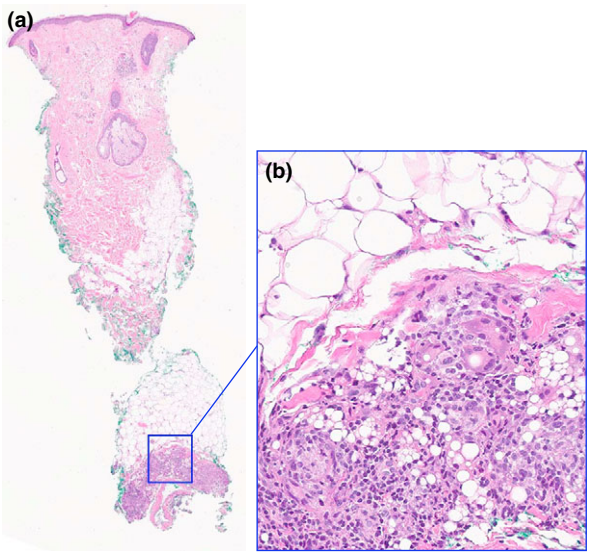

Figure 2 Histopathological Findings. The low-power image shows a non-necrotizing lymphogranulomatous infiltrate within the subcutaneous fat. The dermis is largely uninvolved. Higher power magnification reveals that the infiltrate is composed of lymphocytes, histiocytes and multinucleated giant cells associated with vacuolated/empty spaces, features consistent with a reaction to prior filler injection (a. 20×, b. 400×, haematoxylin and eosin preparation).

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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Ultrastructural aspects of hairs of Chediak-Higashi syndrome

Editor

Chediak-Higashi syndrome (CHS) belongs to a group of partial oculocutaneous albinism and immunodeficiency. Five autosomal recessive conditions are recognized in this group, characterized by hypopigmentation of hair, skin and eyes, associated with recurrent infections.[1]

Additionally, CHS can present coagulopathies, neurological dysfunction and large granules in many cell types.[2–4] A majority of patients will develop an accelerated phase consisting of a lymphoproliferative syndrome also known as haemophagocytic lymphohistiocytosis.[1]

Less than 500 cases have been reported worldwide in the past 20 years. Parental consanguinity is common.[2]

The underlying defect in CHS is abnormal organellar protein trafficking, leading to aberrant fusion of vesicles and failure to transport lysosomes to the appropriate site of action.[5] This defect is due to a mutation in the lysosomal trafficking regulator (*CHS1/LYST*).[5–7] Most mutations are nonsense or null mutations, resulting in an absent CHS1/LYST protein. Described milder forms with missense mutations encode probably a partially functioning protein.[8]

Giant azurophilic granules, evident in neutrophils, eosinophils and other granulocytes, are diagnostic of the disorder.[5] Definite diagnosis is based on the molecular genetic testing.[9,10]

Most of the affected individuals die at young age by haemophagocytic lymphohistiocytosis unless bone marrow allogeneic transplant is performed.[3,5]

A 3-and-a-half-year-old girl with no relevant neonatal history showed silvery hair at 4 months of age and a tanned skin at 7 months. At the age of 18 months, she was asymptomatic and was taken for consultation due to different hair coloration (greyish), which differed from the family (Fig. 1a). Neutropenia (1130 neutrophils) with intracytoplasmic granules was observed. Hair shafts examined with light microscopy showed uneven distribution of melanin, sometimes arranged linearly (Fig. 1b,c). Ophthalmologic and neuropsychomotor development evaluations were normal, and abdominal ultrasound showed hepatomegaly. At 3 years of age, the patient was hospitalized to