Case Report

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Facial Cosmetic Filler Injections as Possible Target for Systemic Sarcoidosis in Patients Treated with Interferon for Chronic Hepatitis C: Two Cases

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Key Words
Dermal filler · Sarcoidosis · α-Interferon

Abstract
Background: Cosmetic filler injections are now a very common procedure for aesthetic purposes. Today no contra-indication is given anymore to any patient for an intradermal filling. ***Objectives:*** We draw attention to a possible side effect of facial fillers in a population at risk. ***Results:*** We report 2 similar cases of systemic sarcoidosis in patients who both developed a sarcoidal granuloma at the location of a cosmetic filler injection during combined interferon and ribavirin treatment for chronic hepatitis C infection. Cosmetic fillers were hyaluronic acid for one patient and probably silicone for the other. ***Conclusion:*** Patients with chronic hepatitis C have a higher risk of interferon-induced sarcoidosis. Physicians must be aware of the risk that a granuloma can develop after a dermal filler injection especially in patients treated with interferon for chronic hepatitis C. These reactions may reveal a systemic sarcoidosis. We propose to perform a test for a hepatitis C virus infection before injecting a dermal filler and to inform the patient of this risk in case of a hepatitis C infection that could necessitate an interferon treatment.

Cosmetic filler injections are becoming common in aesthetic procedures. An increasing number of dermal fillers is now available. All injectable products may cause a foreign-body-type reaction [1], and some patients will develop granulomas. In a few of them, these granulomas may reveal a sarcoidosis. Today no contra-indication is given to any patient for intradermal filling as an aesthetic procedure. We report 2 similar cases of systemic sarcoidosis in patients who developed a sarcoidal granuloma at the location of a cosmetic filler injection during combined interferon and ribavirin treatment for a chronic hepatitis C infection. We discuss the risk of this procedure in general and especially in hepatitis-C-virus (HCV)-infected patients treated by α-interferon.

Case Report

Case 1

A 48-year-old woman had been treated for 7 months with combined pegylated interferon (150 μg injected subcutaneously once weekly, Viraferonpeg®) and ribavirin (400 mg orally twice daily, Rebetol®) for chronic hepatitis C. A good virological response was obtained. However, she developed skin lesions in both legs. Clinical examination showed firm nodules that were palpable in both legs. A skin biopsy yielded a sarcoidal granulomatous lesion (fig. 1). A few weeks later, she developed oedema in the face with infiltrated masses in the melolabial and nasolabial folds (fig. 2, 3). A permanent dermal filler had been injected in these areas 5 years before. It was impossible to uncover the composition of this filler. A new biopsy specimen demonstrated non-caseating granulomas with vacuolated macrophages that are characteristic of silicone granulomas (fig. 4). A chest CT scan at first considered as normal demonstrated slight abnormalities (micronodular opacities). Moreover, pulmonary function tests revealed an important decrease in the diffusion capacity of carbon monoxide (58% of the normal value), and tuberculin anergy was observed. Corticosteroid (1 mg/kg prednisone) was given for the treatment of the facial oedema with a good initial response.

Case 2

In March 2001, a 64-year-old woman got an injection of hyaluronic acid in the peribuccal and lion's wrinkles. In September 2002, chronic hepatitis C was diagnosed, and a treatment with pegylated interferon and ribavirin started in November 2002. In March 2003, she developed

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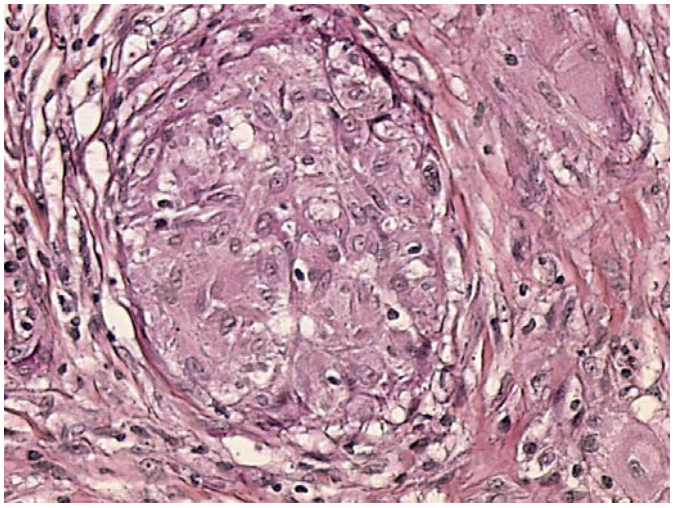

Fig. 1. Typical sarcoidal granuloma (case 1). ×20.

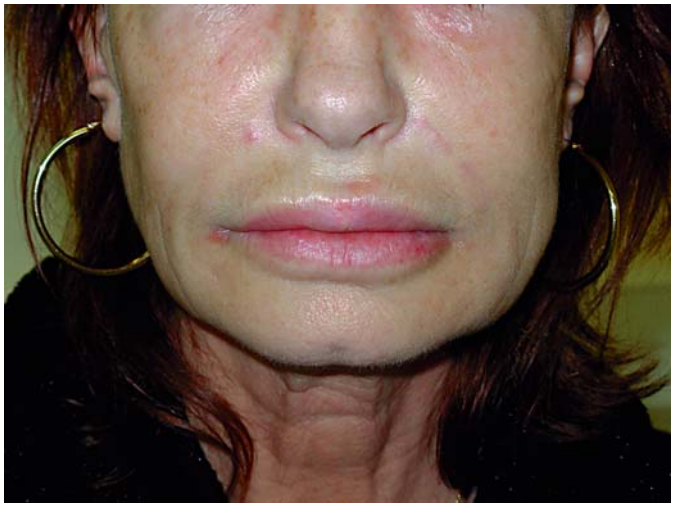

Fig. 2. Facial oedema in areas previously injected with a dermal filler (case 1).

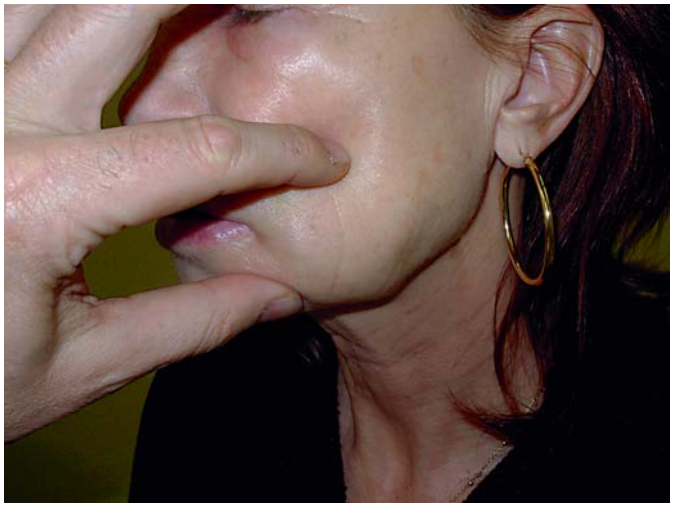

Fig. 3. Infiltrated masses were palpable (case 1).

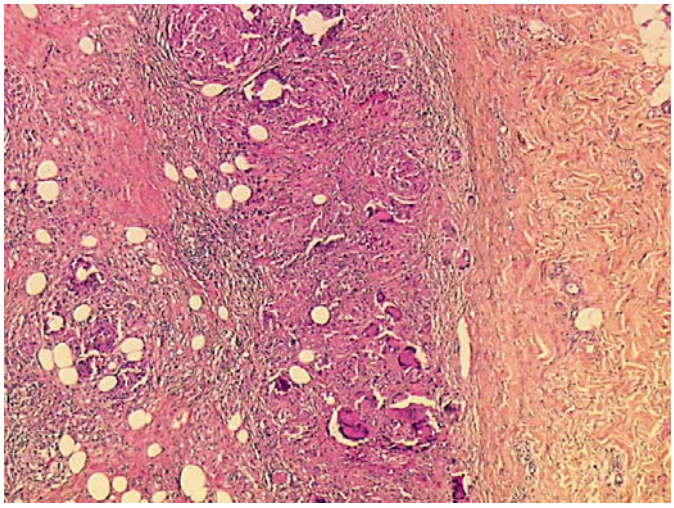

Fig. 4. Foreign-body granuloma in injected lip with vacuoles (case 1). ×2.5.

oedema and infiltrated nodules with purpura in the lips and the injected areas (fig. 5). She complained that she had trouble opening her mouth (fig. 6). The biopsy of a skin lesion confirmed a foreign-body granuloma. Interferon and ribavirin were discontinued, and her skin symptoms spontaneously improved. But in September 2004, a cirrhosis was diagnosed following a liver biopsy, and pegylated interferon (at high dose, 360 μg/week, Pegasys®) and ribavirin were given again (Copegus®). She developed sicca symptoms (involvement of lacrimal and salivary glands), and her previous skin symptoms (oedema and purpuric infiltrated lesions) flared up again around and in her mouth. She noted infiltration of her cutaneous biopsy scar and at the site of a venous infusion. Biopsy was typical of sarcoidosis. A chest CT scan demonstrated pulmonary sarcoidosis with lymphadenopathy, and micronodules were confirmed by gallium scintigraphy. Corticosteroids (prednisone 1 mg/kg) were given starting in January 2005 after 3 months of combined interferon and ribavirin therapy for the treatment of skin lesions. Her skin problems quickly improved and disappeared completely 1 year after phasing out the corticosteroid therapy.

Discussion

The association of sarcoidosis and other granulomatous dermatoses with α-interferon is now well known [2–5]. It is not limited to patients treated for chronic hep-

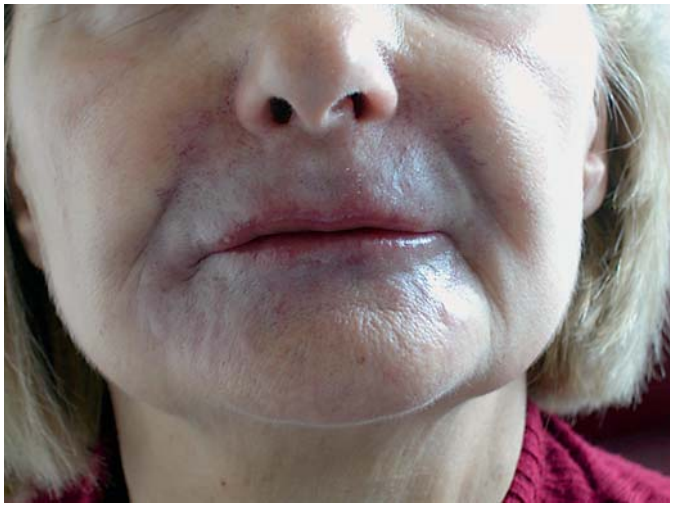

Fig. 5. Facial oedema with nodules in areas previously injected with a dermal filler (case 2).

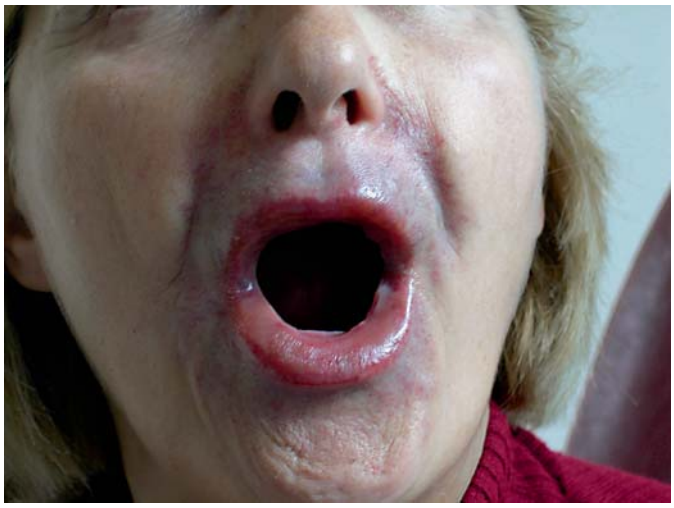

Fig. 6. Reduction in mouth opening (case 2).

atitis C. For instance, interferon-induced sarcoidosis has been reported in patients treated for chronic myelogenous leukaemia and melanoma [6, 7]. These interferon-induced sarcoidoses often have a good prognosis [2–4]. A complete healing of sarcoidosis may be expected after stopping the interferon treatment. When systemic symptoms occur or when cutaneous manifestations are severe, corticosteroids are usually administered. But corticosteroids may increase the HCV viral load and a monitoring of an HCV infection is necessary.

Our 2 cases are of interest as the patients developed sarcoidal granulomas in an area where previously a dermal filler had been injected. These cases are comparable to sarcoidosis developing in previously traumatic scars or tattoos quiescent for years that reactivate and become infiltrated [8–11]. In the same way, these modifications may either be the first manifestation of systemic sarcoidosis (case 2) or one of its manifestations (cases 1 and 2). It is important for dermatologists to recognize these manifestations as they may provide a clue for the diagnosis of sarcoidosis.

The pathogenesis of infiltrative scar sarcoidosis remains unknown. Recently the responsibility of CD4+CD25FoxP3+ lymphocytes (that have an antiproliferative action) has been demonstrated in anergic areas [12]. This paradoxical inflammatory response in old quiescent lesions until the development of sarcoidosis and inversely the development of an anergic reaction to tuberculin may be modulated by regulatory T cell lymphocytes. But the genetic background that confers susceptibility to sarcoidosis has not yet been identified.

α-Interferon may favour the development of sarcoidosis [2–4]. Interferon is known to stimulate natural killer cell activity. It regulates T-cell-mediated immunity and promotes cytokine synthesis (γ-interferon, interleukins 4, 5…) in activating macrophages. α-Interferon promotes the development and enhancement of Th1-mediated responses and has been associated with immune regulation disorders. It may exacerbate pre-existing auto-immunity or induce de novo auto-immune diseases.

It is not yet entirely clear whether HCV-infected patients treated by interferon can be considered to be at risk due to dermal filler operations/injections. Interferon-induced sarcoidosis seems more frequent in HCV-infected patients [2–4]. Some auto-immune disorders are associated with chronic HCV infection, such as mixed cryoglobulinaemia, and perhaps thyroiditis, Sjögren's syndrome and lichen planus [13]. Persistence of viruses in infected cells may trigger an auto-immune response. In the same way, the development of granulomas in an area where a dermal filler had been injected has been associated some months before the development of the granulomas with a special event: viral or bacterial infection, vaccination or local trauma [1].

Physicians and patients need to be aware of an adverse reaction to dermal fillers. Physicians should be careful in selecting patients, before injecting a dermal filler. The risk of developing foreign-body granulomas is evaluated at a rate of 0.01–1.0% in the general population [1, 14, 15]. This risk may only strike in the long term. Granulomas may appear anytime from 6 months to many years after the injection. The magnitude of the risk depends on the composition and the structure of the product. Recently 2 cases have been reported with Artecoll® (polymethylmethacrylate) injections in two 48-year-old women. The first had pulmonary sarcoidosis without any previous treatment with interferon [16]. As our patients, the second developed granulomas after starting a pegylated interferon alfa-2a and ribavirin therapy for chronic hepatitis C (after 10 weeks) [17]. Polymethylmethacrylate may favour the development of the cutaneous sarcoidal granulomas. They are less frequent with resorbable implants (hyaluronic acid, collagen). But the risk exists for all dermal implants and is probably underestimated. Screening for sarcoidosis has probably not been done in every case. A chest X-ray should be done to screen patients for latent sarcoidosis.

In a recent report, Lemperle et al. [1] evoked the risk of a sarcoidal reaction in

patients with sarcoidosis but they concluded that the relationship between foreign-body granuloma and sarcoidosis cannot be firmly established. We think that patients with sarcoidosis and patients infected with HCV who may receive α-interferon should be aware of this risk and be excluded from any filler injection. A blood test for HCV should be undertaken before injecting a dermal filler. In our first case, we do not know when this patient was infected by HCV. As proposed by Fischer et al. [17], physicians should know whether their patient had previously been injected with dermal fillers before administering α-interferon.

Whereas the chances of recovering from an interferon-induced sarcoidosis are good after discontinuing the interferon, it may be difficult to treat a local reaction to a dermal filler. Surgery was recently proposed without addressing the problem [18]. Insufficient data are available on the long-term effect of these granulomas. In our 2 cases, the response was favourable under corticosteroid treatment, but we do not have yet a long-term follow-up to see what happens after discontinuing the corticosteroid treatment.

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