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Case report

Pemphigus foliaceus exacerbated by radiation, in association with myasthenia gravis

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Abstract

Pemphigus foliaceus (PF) is a sporadic autoimmune blistering disease of unknown etiology. The production of immunoglobulin G4 antibodies against desmoglein-1 is responsible for the clinical manifestation of PF. We present a case of a woman with a recent diagnosis of myasthenia gravis (MG), who was also recently treated with radiation therapy for breast cancer. The clinical exam, supported by biopsy and direct immunofluorescence, were consistent with PF. We present this case to increase the awareness of the potential exacerbation or induction of PF with radiation, and of the association of PF and myasthenia gravis. Only five prior cases of radiation-exacerbated or radiation-induced PF have been reported in the literature to date. Furthermore, the co-existence of the autoimmune entities of myasthenia gravis and PF has been reported in the literature in only 9 cases and was also noted in this patient.

Keywords: myasthenia gravis, pemphigus foliaceus, pemphigus vulgaris, paraneoplastic pemphigus

Abbreviations:

DIF	**Direct immunofluorescence testing**
IIF	**Indirect immunofluorescence**
MG	**Myasthenia gravis**
PF	**Pemphigus foliaceus**
PV	**Pemphigus vulgaris**
PNP	**Paraneoplastic pemphigus**

Introduction

Pemphigus foliaceus (PF) is a sporadic autoimmune blistering disease that occurs secondary to the production of immunoglobulin G4 antibodies against desmoglein-1. In this case we present a 44-year-old woman with a recent diagnosis of myasthenia gravis (MG) and breast cancer treated with lumpectomy and radiation, who presented with a presumed radiation burn. Biopsy and direct immunofluorescence were consistent with PF. The patient's skin findings significantly improved after initiation of oral prednisone,

topical steroids, and oral dapsone. Only five prior cases of radiation-exacerbated or radiation-induced pemphigus foliaceus have thus far been reported in the literature. In addition, only 9 published cases have reported the co-existence of the autoimmune entities of myasthenia gravis and pemphigus foliaceus, as was also noted in our patient. We present this case to increase the awareness of the potential exacerbation or induction of PF with radiation and of the association of PF and MG.

Case synopsis

A 44-year-old woman with a recent diagnosis of myasthenia gravis and breast cancer, treated with lumpectomy and radiation, was admitted to the university hospital with a presumed radiation burn. Within a few weeks of radiation to the left breast, performed as part of her breast cancer treatment, the patient developed confluent erosions in the location of the radiation on the left breast. In addition, the patient developed innumerable flaccid bullae and erosions on the chest, abdomen, back, neck, bilateral axillae, periocular, and perioral regions, with rare scattered crusted erosions on the upper and lower extremities (Figure 1,2,3). There was no involvement of the intra-oral, ocular, or genital mucosal areas.

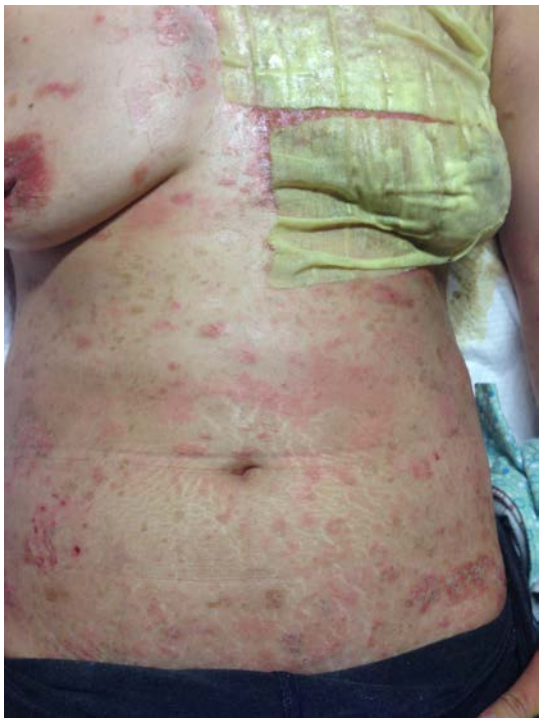

Figure 1. Numerous flaccid bullae and erosions distributed over the chest and abdomen. Confluent erosions cover the entirety of the left breast, which was the site of radiation. **Figure 2.** Flaccid bullae and erosions with several scattered crusted erosions on the back.

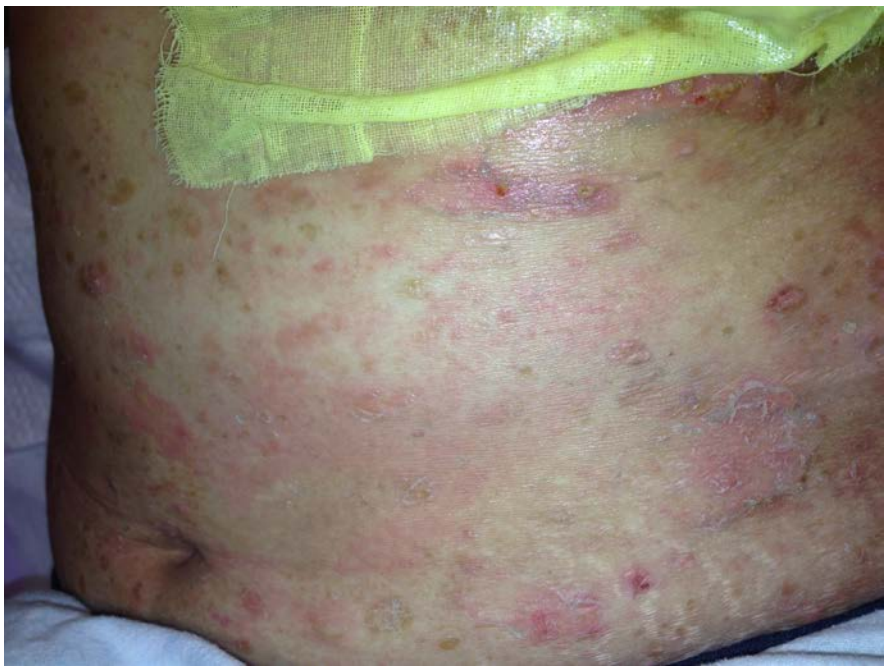

Figure 3. Close up of the abdomen showing superficial erosions and cornflake-like scale

The patient was initially treated for a presumed radiation burn with supportive care only. However, given the lack of improvement over several days, a dermatology consultation was requested for evaluation of the skin lesions. Upon further investigation, the patient reported rare flaccid bullae of the upper back for approximately one year prior to her current skin eruption. The patient had no known personal or family history of blistering diseases or autoimmune conditions, other than a pre-existing diagnosis of myasthenia gravis. Her home medications included tamoxifen, pyridostigmine, aspirin, calcium, and percocet. Basic metabolic panel, liver function tests, and complete blood count were unremarkable.

Biopsy of the affected skin and direct immunofluorescence testing (DIF) were previously performed in an outside hospital and the results were obtained. Histopathologic findings from the punch biopsy taken from the left flank revealed a subcorneal split with acantholysis of the superficial layers of the epidermis, consistent with pemphigus foliaceus (Figure 4). DIF demonstrated staining for intercellular IgG and C3, in addition to focal staining for c3d and c4d, further supporting the diagnosis of pemphigus foliaceus.

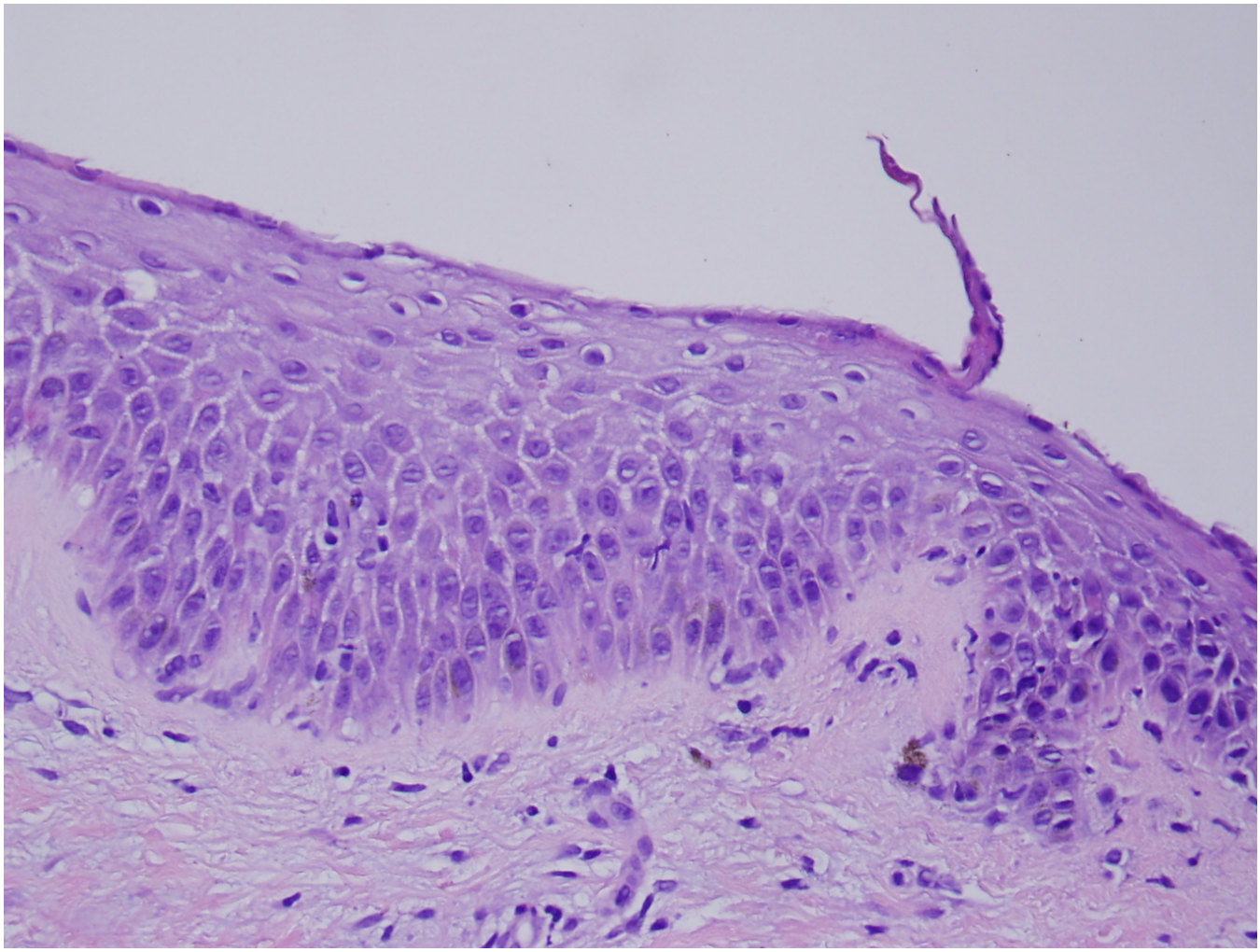

Figure 4. Punch biopsy, H&E, 40x. Subcorneal split with acantholysis of the superficial layers of the epidermis, consistent with pemphigus foliaceus.

During hospitalization, the patient was started on oral prednisone 1 mg/kg/day in addition to topical hydrocortisone 2.5% ointment twice daily to the face and clobetasol 0.05% ointment twice daily to the body, with some noticeable improvement. Upon discharge from the hospital, prednisone was tapered over several weeks and the patient was transitioned to oral dapsone, with subsequent clearing of the lesions.

Discussion

Pemphigus foliaceus (PF) is a sporadic autoimmune blistering disease, primarily affecting middle-aged and elderly adults. The bullae in PF are superficial and fragile; intact bullae are not often noted on examination. Thus, PF clinically presents as multiple shallow erosions, together with erythema, scaling, and crusting. The lesions are most commonly found in a seborrheic distribution, on the face, neck, chest, and upper back. Eyelid skin lesions can also occur, without conjunctival changes, which were noted in our patient [1]. Unlike pemphigus vulgaris (PV) and paraneoplastic pemphigus (PNP), mucosal involvement is extremely rare in PF. The disease can have a slow and localized onset, after which it can progress to a more generalized distribution, with a

recurrent course. In contrast to PV, PF patients are not severely ill. However, skin lesions may cause burning and pain, along with cosmetic disfigurement [2].

The production of immunoglobulin G4 (IgG4) antibodies against desmoglein-1, an adhesive cadherin protein found at the desmosomal cell junction, is responsible for the clinical manifestations of PF [3]. Histologic findings include acantholysis of the upper epidermis, resulting in a subcorneal cleft [4]. DIF, in conjunction with indirect immunofluorescence (IIF), is the most reliable test to diagnose PF; DIF typically shows intercellular IgG and C3 deposits mainly in the upper epidermis [5].

The presentation of PF in our patient is particularly unique. To the best of our knowledge, only five cases of radiation-exacerbated or radiation-induced pemphigus foliaceus have previously been reported in the literature, making this the sixth reported case to date **(Table 1).** In our case, as well as all previously reported cases, lesions were initially localized to the irradiated skin and subsequently generalized to the classic distribution of pemphigus foliaceus. Our patient first noted a very mild blistering disorder on the upper back during the year preceding her radiation treatment. Thus we believe that she may have had a mild localized case of pemphigus foliaceus, which later flared and became disseminated after the initiation of breast radiation. Among the five previously reported cases, only one other patient had a history of pre-existing blistering disease prior to receiving radiation [6].

Table 1. Cases of pemphigus foliaceus induced or exacerbated by radiation

Authors and journal	**Age**	**Year**	**Type of cancer**	**Additional autoimmune disease**	**Time from radiation to start of eruption**	**Pre-existing blistering disease**	**Systemic therapy**
Tagami et al *Dermatologica*	37 yo M	1976	Thymic tumor	Myasthenia gravis	<1 month	no	Methylprednisolone, azathioprine, dapsone
Low et al *Arch Dermatol*	70 yo F	1990	Laryngeal SCC	Graves' disease	1 month	no	Prednisone (1mg/kg/day), azathioprine (50mg/day)
Ambay et al *JAAD*	92 yo F	2006	Breast cancer	Hypothyroidism (etiology not noted)	3 months	no	-
Cianchini et al *J Dermatolog Treat*	70 yo F	2006	Breast cancer	-	12 months	no	Dapsone (100mg/day→50mg/day)
Kikuchi et al *Acta Derm Venereol*	59 yo F	2014	Extramammary pagets	-	1 month	Yes (for >1 year)	Prednisolone (0.5mg/kg/day)
Liebman et al (Current case) *Dermatol Online J*	44 yo F	2016	Breast cancer	Myasthenia gravis	<1 month	Yes (for approximately 1 year)	Prednisone (1mg/kg/day), dapsone

Owing to its rarity, the pathogenesis of this phenomenon has not yet been fully elucidated, though several hypotheses with regards to dysregulation of the immune environment have been proposed [6, 7, 8, 9]. It is unknown if radiation induces an entirely *de novo* pemphigus foliaceus or if it unmasks the patient's tendency to develop the disease. In our patient, given the history of her prior lesions, it appears that the radiation exacerbated her pre-existing tendency toward development of pemphigus foliaceus. This phenomenon is likely a manifestation of the isoradiotopic response, in which the disease appears in an irradiated area. However, in our patient, the disease also generalized elsewhere on the body [9].

Another rarity specific to our case is our patient's recent diagnosis of myasthenia gravis in conjunction with her diagnosis of PF. To the best of our knowledge, only 9 cases of pemphigus foliaceus coexisting with myasthenia gravis have been reported in the literature [7, 8, 10, 11, 12, 13, 14, 15, 16]. Although pemphigus foliaceus and myasthenia gravis are both relatively common antibody-mediated autoimmune disorders, they have only rarely been noted to occur together. In some reported cases, patients have had pemphigus foliaceus in addition to both myasthenia gravis and a thymoma [10, 11, 12, 13, 14]. However, like several other cases reported, our patient did not have a thymoma [15, 16, 17, 18]. PF has also been associated with other neoplasms including B-cell lymphoma, T-cell lymphoma, prostate cancer, and squamous cell carcinoma; however, PF has not been noted to have any association with breast cancer [17, 18].

Conclusion

We present this case to make others aware of the potential exacerbation of PF associated with radiation treatments, as well as to report the rare association of myasthenia gravis and PF. Treatment of PF involves suppressing the immune system to decrease the production of pathogenic antibodies. In mild or localized PF, topical corticosteroids may suffice. In more active and disseminated disease, PF can be treated with an initial dose of prednisone 1 mg/kg/day, followed by an individualized and tapered dose. In severe and recalcitrant cases, steroid-sparing agents such as mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate, and cyclosporine can be used. Alternative therapies such as intravenous immunoglobulins and plasmapheresis have also been successfully in refractory cases. Additionally, dapsone has been used successfully both as monotherapy and as adjuvant therapy, though its exact mechanism of action has yet to be confirmed [2].

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