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Pemphigus vulgaris possibly associated with application of a tissue expander in a patient with Crohn's disease and primary sclerosing cholangitis

George Badavanis[1], Efstathia Pasmatzi[2] ✉, Nikiforos Kapranos[3], Alexandra Monastirli[1,2], Pavlos Constantinou[4], George Psaras[5], Panayiota Protopapa[6,7], Dionysios Tsambaos[1,2]

Abstract

Pemphigus vulgaris (PV) is an autoimmune disease of the skin and mucous membranes characterized by suprabasal acantholysis and formation of blisters and erosions due to generation of IgG autoantibodies directed against desmosomal proteins. Tissue expanders are devices that, through controlled mechanical overstretch, are capable of generating new skin that is used to cover wounds or extended surgical defects. We report the case of a 13-year-old girl suffering from Crohn's disease (CD) and primary sclerosing cholangitis (PSC) who developed PV after application of a tissue expander for surgical removal of a giant congenital melanocytic nevus (GCMN). To the best of our knowledge, the case presented here is the first report of PV possibly associated with the application of a tissue expander and also the first report of coexistence of PV with either PSC or with PSC and CD in the same patient. Triggering or acute exacerbation of PV may be considered a possible side-effect of tissue expander application, especially in patients with a genetic predisposition for pemphigus and/or other autoimmune diseases. In view of the increasing use of tissue expanders in clinical practice, physicians should be aware of this rare side-effect in order to promptly diagnose it.

Keywords: pemphigus vulgaris, tissue expander, Crohn's disease, primary sclerosing cholangitis, giant congenital melanocytic nevus

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Introduction

The term *pemphigus* is derived from the Greek word *pémphix* 'blister', which is used to describe a group of potentially life-threatening autoimmune mucocutaneous blistering disorders. The main pathogenetic feature of pemphigus is the generation of circulating mostly IgG autoantibodies directed against desmosomal adhesion protein molecules, which leads to acantholysis (loss of coherence between keratinocytes) and intraepithelial blister formation (1).

Pemphigus vulgaris (PV) is the most common type of pemphigus, and it accounts for over 80% of cases with the highest incidence in the 5th and 6th decades of life. It affects both sexes equally and is rarely observed in children, being classified as childhood PV when it occurs in patients < 12 years old and as juvenile PV in patients 12 to 18 years old (2). The primary lesion of PV is characterized by a flaccid blister or bulla containing clear fluid that mostly arises on apparently normal skin or mucosa lining the oral cavity, esophagus, nose, eyes, and anogenital region. Rupture of the intraepithelial blisters/bullae usually leads to the formation of painful erosions. PV is caused by circulating IgG autoantibodies primarily directed against desmoglein 3 (Dsg3) and/or desmoglein 1 (Dsg1), and against large numbers of other non-desmoglein proteins known to regulate the adhesion and survival of keratinocytes (3). Systemic corticosteroids (with or without concomitant administration of immunosuppressants) represent the first-line treatment of PV (4).

Giant congenital melanocytic nevus (GCMN) is a pigmented melanocytic lesion present at birth or developing soon thereafter (incidence < 1:20,000 newborns), which will reach a diameter of at least 20 to 40 cm in adult life. It is due to mutations in the BRAF or NRAS genes, which result in defects in the differentiation, mitotic activity, and migratory potential of melanoblasts, or melanocyte precursor cells (5). It may affect any region of the body, but it is usually observed on the trunk and the extremities, revealing variable shades of black and diverse clinical characteristics of its surface (hairy or not, smooth, coarse, raised, or flat). Apart from the tremendous negative psychosocial impact on patients and their families, GCMN has two serious complications: neurocutaneous melanosis and malignant transformation. However, the rate and incidence of the latter still remain controversial.

Excision-based plastic surgery is the mainstay of therapy for GCMN, although it provides no guarantee of protection against malignancy because about half of melanomas found in patients with GCMN occur elsewhere on the body (6, 7). The surgical removal of GCMN has always been a challenge for surgeons, with full-thickness replacement of the skin being the procedure of choice. The technique of tissue expansion, which was introduced more than 60 years ago (8), has revolutionized the management of GCMN, permitting the safe excision of sizeable lesions with favorable cosmetic results (9).

We report the case of a 13-year-old girl suffering from Crohn's disease (CD) and primary sclerosing cholangitis (PSC) who developed PV after application of a tissue expander for surgical removal of a GCMN. To the best of our knowledge, this case is the first report of PV possibly associated with the application of a tissue expander and also the first report of coexistence of PV with either PSC or with PSC and CD in the same patient.

[1]Center for Dermatologic Diseases, Limassol, Cyprus. [2]Department of Dermatology, School of Medicine, University of Patras, Patras, Greece. [3]Laboratory for Molecular Histopathology, Athens, Greece. [4]Histopathology & Cytology Laboratory, Nicosia, Cyprus. [5]Plastic Surgery Department, University of the Witwatersrand, Johannesburg, South Africa. [6]Paediatric Liver, GI, and Nutrition Centre, Archbishop Makarios III Hospital, Nicosia, Cyprus. [7]King's College Hospital, London, United Kingdom. ✉**Corresponding author: pasmatzi@med.upatras.gr, pasmatzi@otenet.gr**

Case report

A 13-year-old Caucasian girl presented in December 2018 to the Center for Dermatologic Diseases in Limassol, Cyprus with an 11-month history of multiple pruritic blisters on the trunk and the extremities. They had appeared 3 weeks after partial surgical removal of a GCMN on her right tibia subsequent to a 12-month application of a tissue expander made of silicone, which was removed a few minutes prior to surgery. Interestingly, these lesions had begun in the region of the expanded skin (Fig. 1a) and subsequently spread to involve the trunk and the extremities. The past medical history of the patient was significant for CD and PSC, which were diagnosed in 2007 and presently remain in remission. Systemic treatment for these disorders at the time of her presentation included azathioprine (50 mg/day), sulfasalazine (1.5 g/day), and ursodeoxycholic acid (1.0 g/day). She is being closely monitored by our colleagues at the Paediatric Liver, GI, and Nutrition Centre of Archbishop Makarios III Hospital in Nicosia, Cyprus and at King's College Hospital in London.

Clinical examination revealed multiple annular bullous lesions scattered all over the trunk and extremities (Figs. 1b & c), which revealed a positive Nikolsky's sign. The results of histopathological examination of biopsies obtained from the lesional skin (Fig. 2a) and of direct immunofluorescence of biopsies obtained from the perilesional skin (Fig. 2b) were consistent with PV. Enzyme-linked immunosorbent assay (ELISA) revealed no circulating autoantibodies against Dsg1 and/or Dsg-3. For technical reasons, circulating antibodies against other desmosomal adhesion protein molecules could not be determined. The results of routine hematological and biochemical investigations were within normal limits.

In view of the coexisting CD and PSC, the treatment of PV in our patient was undertaken by a multidisciplinary team (including dermatologists, pediatricians, gastroenterologists, and hepatologists) according to the guidelines of the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV) (4). Initial treatment for PV consisted of oral prednisolone 20 mg daily (0.5 mg/kg/day), and oral omeprazole (20 mg/day) was given for gastric ulcer prophylaxis. A complete clinical remission was achieved within 9 days. According to the above guidelines, prednisolone should be tapered by a 25% reduction in biweekly steps (at < 20 mg/day more slowly). During steroid tapering by a 25% reduction every 3 weeks, the patient experienced a massive relapse upon initiation of prednisolone 10 mg/day. Then, in view of the devastating psychological impact of this relapse on the patient and in an attempt to achieve a rapid resolution, it was decided to increase the prednisolone dosage to 25 mg/day, which led to a complete remission within 5 days. Nevertheless, 3 days after reduction of the dosage to 20 mg/day a new relapse occurred, which was initially unexplained to us until we were informed by the patient's parents that in the previous few days she had experienced excessive emotional stress and had been exposed to sunlight for many hours. Because both emotional stress and sunlight exposure are well-known major triggering/aggravating factors in patients with PV (10, 11), the relapse of the patient was attributed to these factors and it was decided to go back to the dosage of 25 mg/day and to increase the azathioprine dosage of 50 mg/day (which she has received in the last 6 years for treatment of her CD) to 100 mg/day in an attempt to take advantage of the steroid-sparing effect of this agent.

A complete remission was achieved after 12 days of combined treatment. The patient is currently receiving prednisolone 15 mg/day and azathioprine 100 mg/day, and she remains lesion-free. Further careful steroid tapering will follow.

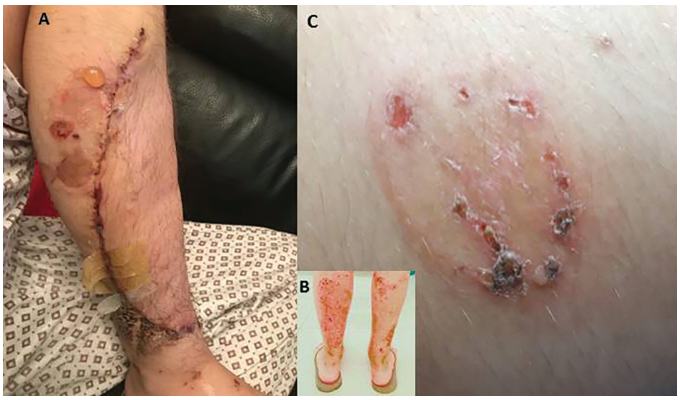

Figure 1 | a) Occurrence of bullae in the area of expanded skin, 3 weeks after partial surgical removal of a GCMN on the patient's right tibia subsequent to application of a tissue expander. b & c) On clinical examination, multiple polycyclic annular bullous lesions were seen on the trunk and extremities.

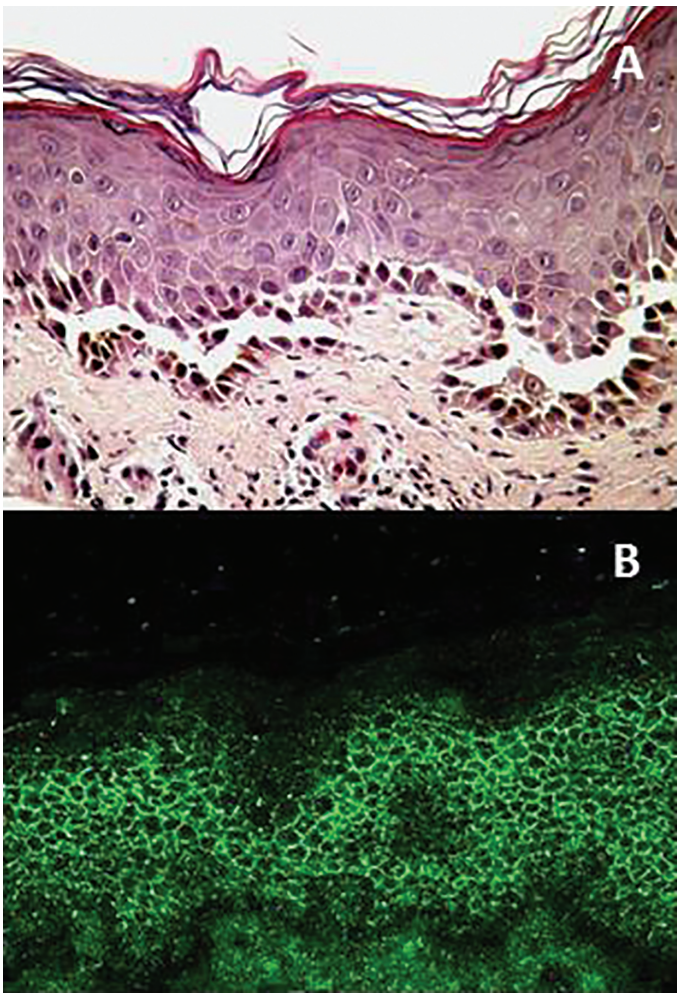

Figure 2 | a) On light microscopy of the lesional skin, suprabasal acantholysis with clefting, blister formation, and a single row of keratinocytes attached to the basement membrane were observed. There was a minimal perivascular inflammatory lymphohistiocytic infiltrate with several eosinophils (H&E ×40). b) On direct immunofluorescence of the perilesional skin, intraepidermal intercellular IgG deposits were seen along the epithelial cell surfaces (×20).

Discussion

CD is a relapsing inflammatory bowel disease with increasing incidence and prevalence worldwide. Although it mainly affects the gastrointestinal tract, extraintestinal systemic manifestations and

associated immune disorders are quite common. Its typical clinical picture is characterized by abdominal pain, fever, diarrhea (occasionally containing blood and/or mucus), and clinical signs of bowel obstruction (12). It is thought that environmental factors trigger susceptibility loci, resulting in a disturbed innate and adaptive immune response toward a diminished diversity of commensal microbiota (12).

PSC is an idiopathic, slowly progressive cholestatic liver disease characterized by inflammation and fibrosis of the intra- and extrahepatic ducts, which may progress to cholangiocarcinoma, cirrhosis, and end-stage liver disease (13, 14). The association between PSC and inflammatory bowel disease is well established because about 60 to 80% of PSC patients are expected to suffer from concurrent ulcerative colitis or CD (13, 14).

Although the coexistence of CD and PV has previously been reported in many patients, a possible association between the two conditions still remains obscure (15). In an uncontrolled cross-sectional study in a sizeable cohort of hospitalized patients, Hsu et al. (16) found no significant association between the two entities. Kridin et al. (17), using a database of 4.5 million patients, performed a cross-sectional study of the prevalence of CD comparing PV patients with age-, sex-, and ethnicity-matched controls. They found no association between PV and CD in the general population because the prevalence of CD in patients with PV was comparable to that found in controls; however, a significant association was observed between PV and CD in patients younger than 40 years. To the best of our knowledge, there are no published reports of the coexistence of PV and PSC or of PV with concomitant PSC and CD in the same patient.

Various factors are capable of triggering or exacerbating pemphigus in susceptible individuals, including drugs, vaccines, infections, malignant neoplasms, other autoimmune diseases, dietary factors, radiotherapy, pregnancy, emotional stress, UV-radiation, burning, and pesticides (11). Case reports on the occurrence of PV over surgical scars due to Koebner phenomenon (i.e., the appearance, after a lag time, of typical lesions of a disease following trauma) are sparse, and trauma is not considered a major triggering factor for PV (18–20).

Tissue expanders are devices that use controlled mechanical overstretch to generate new skin, which is used to cover wounds or extended surgical defects. In its typical form, the method consists of the surgical insertion of a biomimetic inflatable balloon beneath the skin that exerts progressively increased stretch, achieved by the periodic injection of saline solution into it. Infections and tumor or scar formation are the most significant side effects of the method (21, 22). Prolonged skin stretching by expander gives rise to multiple and complex morphological and functional changes at the molecular and cellular level and leads to the production and release of growth factors such as epidermal growth factor (EGF), transforming growth factor β (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and interleukins (IL), which play a pivotal role in the regulation of stress-induced cell growth. Moreover, mechanical stretching of the skin is capable of activating various signaling pathways that can promote cell proliferation or induce apoptosis (22, 23).

The pathogenetic mechanisms underlying the occurrence of PV subsequent to overstretching of apparently normal skin through tissue expanders are unknown. It seems possible, however, that skin injury through overstretching may lead to overexpression and enhanced presentation of epithelial pemphigus antigens, particularly in genetically predisposed individuals (24–26), and to an early nonspecific release of proinflammatory cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]), which results in blister formation through non-antigen-specific mechanisms (by modulating C3, plasminogen activator, and plasminogen activator inhibitor expression), whereas later development of blisters/bullae may be induced by recruitment of antigen-specific B and T cells (27, 28). In view of this, it seems reasonable to suggest that application of the tissue expander in our patient, together with the significant pathophysiological alterations caused by tissue stretching, possibly contributed to triggering PV in an individual with a strong genetic predisposition to autoimmune disorders.

The question of whether silicone, which the tissue expander was made of, might have been involved in the pathogenetic mechanisms of PV remains to be elucidated. This polymeric compound is widely used in medicine for multiple purposes and is not a biologically inert material, as previously thought, but exerts distinct immunological effects, and according to recent studies it seems to be associated with a higher likelihood of autoimmune/rheumatic disorder diagnosis (29–31).

Interestingly, in the case presented here, no circulating autoantibodies against Dsg3 and/or Dsg1 could be detected. Proteomic studies have revealed that numerous non-Dsg autoantibodies are present in the sera of patients with PV, which are directed against autoantigens involved in the physiology and cell adhesion of keratinocytes, such as autoantibodies against desmocollins, cholinergic receptors, mitochondrial proteins, thyroid peroxidase, plakophilin 3, E-cadherin, plakoglobin, and numerous other protein antigens (3, 32). In view of the negative results of ELISA for Dsg autoantibodies in the case presented, it would be interesting to know whether this young patient had developed autoantibodies against these proteins. However, detection and quantification of these autoantibodies are not among the routinely performed tests and cannot be carried out in our laboratory because they require techniques that are available only in specialized research units. These non-Dsg autoantibodies might be of importance in the pathogenesis of PV. Indeed, Chernyavsky et al. (33) found that non-Dsg autoantibodies in the sera of patients with Dsg1/3-negative acute PV are pathogenic because IgGs from these individuals induced skin blistering in neonatal mice subsequent to suprabasal acantholysis. Moreover, serum levels of autoantibodies to desmocollin 3 (Dsc3), M3 muscarinic acetylcholine receptor (M3AR), and secretory pathway Ca2+/Mn2+-ATPase isoform 1 (SPCA1) correlated with the disease stage of PV, whereas absorption of these autoantibodies on recombinant Dsc3, M3AR, or SPCA1 prevented skin blistering after passive transfer to BALB/c mice.

To the best of our knowledge, the case presented here is the first report of PV possibly associated with the application of a tissue expander. The possibility that the occurrence of PV in our patient was unrelated to the placement of the expander cannot be definitely ruled out; however, it seems extremely unlikely in view of the close temporal relationship of the development of the lesions and the application of the device as well as the occurrence of the lesions initially on the expanded skin of the ipsilateral limb before spreading to other areas.

In conclusion, triggering or worsening of PV may be regarded as a possible side-effect of tissue expander application, with patients having a history of pemphigus and/or other autoimmune disorders being at higher risk. In view of the increasing use of tissue expanders in clinical practice, physicians should be aware of this rare side-effect and able to promptly diagnose it.

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