Pemphigoid gestationis in a female with progressive facial hemiatrophy: microchimerism as a speculative shared background is disputable

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The commonest source of naturally acquired microchimerism, i.e. small numbers of foreign cells within the organism, is two-way mother-fetus transplacental trafficking during pregnancy. Here, the first report on coexistence of pregnancy-associated pemphigoid gestationis (PG) and progressive facial hemiatrophy, a form of "*en coup de sabre*" morphea, is presented. HE histopathology (eosinophil-rich subepidermal infiltration, inverted teardrop sign), direct immunofluorescence (linear IgG1, but not IgG4, deposits along the dermal-epidermal junction) and ELISA (elevated levels of serum and blister fluid IgG autoantibodies to BP180) corroborated the PG diagnosis. Microchimerism as a speculative shared background of those two rare autoimmune diseases is disputable.

Key words: pemphigoid gestationis, Parry-Romberg syndrome, microchimerism.

Introduction

Pemphigoid gestationis (PG) is a subepidermal autoimmune bullous dermatosis associated eminently with pregnancy. Blister formation in this rare disease is caused by IgG autoantibodies binding hemidesmosomal protein BP180. The extracellular fragment of the longest, non-collagenous domain of this protein, BP180NC16A, consists of 4 epitopes (MCW0, MCW1, MCW2, MCW3). The inner heptapeptide of amino-terminal MCW-1 epitope seems to be the most immunogenic in PG. The PG autoantibodies, particularly of IgG1 subclass, have complement-activating capacities, thus triggering neutrophil and eosinophil infiltration [1].

Progressive facial hemiatrophy (Parry-Romberg syndrome – PRS), a rare neurocutaneous syndrome of unclear etiology, seems to be a form of "*en coup de sabre*" morphea. The onset of the disease frequently occurs in the first or second decade of life and it progresses for years until the condition stabilizes at the "burn-out" stage. There might be a higher incidence in females [2].

Microchimerism refers to the presence of small numbers of foreign cells within the organism. Microchimerism can persist for decades. Such foreign cells derive from many sources, yet the commonest source of naturally acquired microchimerism seems to be two-way transplacental traffic occurring routinely between a mother and a fetus during pregnancy [3]. While microchimerism may take part in immune tolerance in pregnancy, it may also contribute to immune disease. Anti-maternal graft-versus-host reaction by fetal cells seems to be involved in the pathogenesis of the PG [4], while anti-fetal graft-versus-host reaction may be involved in the pathogenesis of scleroderma [5, 6]. This is the first report of a female with coexistence of PG and PRS, two rare autoimmune diseases, with microchimerism as a possible shared background.

Case report

A 35-year-old pluriparous pregnant female presented with clinical features suggesting PG (Fig. 1 A) and PRS (Fig. 1 B). Histopathological examination

of the lesional skin (hematoxylin and eosin staining) revealed eosinophil-rich subepidermal infiltration with an inverted teardrop sign, caused by edematous widening of the upper part of dermal papilla with its narrowed lower part, that is regarded as suggestive of PG (Fig. 1 C). Direct immunofluorescence of perilesional skin showed linear IgG1(+) (Fig. 1 D) and C3(+++) deposits along dermal-epidermal junction. There were no IgA, IgM, IgG and IgG4 deposits. Indirect immunofluorescence (IIF) on monkey esophagus revealed neither IgG nor IgG4 serum autoantibodies suggestive of pemphigus and pemphigoid dermatoses. Anti-BP180-NC16-4X IgG ELISA (Euroimmun, Germany), one of two available enzyme-linked immunosorbent assays with confirmed sensitivity and specificity in diagnosing diseases of bullous pemphigoid circle, revealed elevated IgG anti-BP180 levels in both serum and blister fluid: 189.32 RU/ml and 144.74 RU/ml (cut off score 20 RU/ml), respectively, thus supporting the diagnosis of PG. Anti-BP230 IgG ELISA, both in serum and blister fluid, was negative. The IIF on HEp-2 cells/monkey esophagus mosaic revealed IgG antinuclear antibodies (ANA) at the titre of 1/640 in homogenous and speckled pattern. ANA Profile 3 (IgG) blot-type test revealed IgG antibody against proliferating cell nuclear antigen (PCNA) ("+" level) (Euroimmun, Germany).

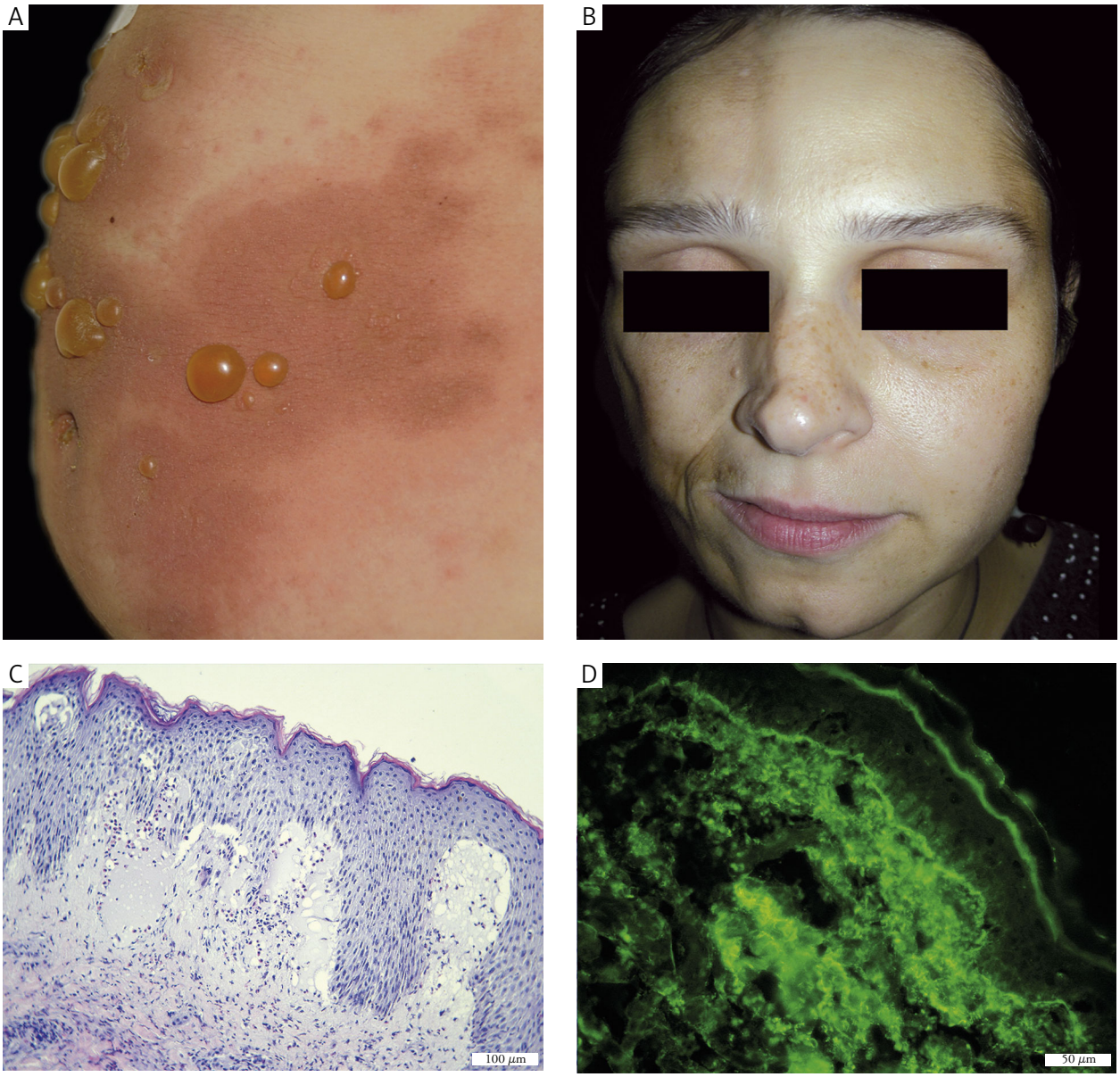

Fig. 1. Numerous tense bullae on erythematous abdominal skin. Courtesy of Leszek Bartoszak MD (A). Facial hemiatrophy with marked deformity of the right forehead, nose, nasolabial furrow and chin (B). Eosinophil-rich subepidermal infiltrate with inverted teardrop sign (HE staining, original magnification 200×) (C). Linear IgG1(+) deposits along dermal-epidermal junction (DIF of perilesional skin, original magnification 400×) (D)

Discussion

Microchimerism seems to be a constitutive component of physiology. The foreign cells may be pregnancy-associated or derived from blood transfusion or tissue transplantation. The cell transfer may be increased in case of a fetal defect, iatrogenic obstetric intervention, elective or spontaneous abortion and termination of pregnancy.

Gestation seems to be the main cause of naturally acquired microchimerism as it provides bidirectional feto-maternal cell transfer resulting in fetal graft in the mother and maternal graft in the fetus. Both benevolent and malevolent consequences of maternal microchimerism (MMc) and fetal microchimerism (FMc) are subject to investigation. The mechanism of FMc allowance in the mother and MMc allowance in the child may differ due to a different stage of immune system development. Dysfunctional immunity was speculated to cause loss of fetal foreign tissue tolerance, thus evoking autoimmune diseases. The fetal cell transfer into maternal circulation, that takes place routinely during pregnancy, increases with the gestational age and recedes postpartum, interestingly concurring with the PG occurrence during the second/third trimester [3, 7-9].

Autoreactive anti-BP180 IgG is directed against BP180, and is reported to be expressed in placental cells and amniotic membrane as well as in the hemidesmosome adhesion complex of the skin, what can be explained by common ectodermal origin of these tissues. While in most pregnancies, the maternal immune system adapts to pregnancy, in PG mothers, antigen-autoantibody reaction causes keratinocyte adhesion loss and subepidermal blister formation [10]. Pemphigoid gestationis is characterized by the complement-binding IgG1 and IgG3 subclasses. It seems that pathological autoimmunization is evoked not only by cross-reacting anti-BP180 IgG antibodies but also temporal malfunction of the immune system that regulates anti-BP180 IgG production. Some literature data suggest the role of abnormal expression of HLA class II molecules of the paternal haplotype in triggering immunization in females with PG, assuming the possible contribution of microchimerism phenomenon [7, 11, 12], yet other put the hypothesis in doubt [13]. Association of PG with pregnancy raises a question of implications of coexistence of 2 or more cell populations, as the prospective mother may harbor both her female ancestor cells and progeny cells.

The so-called "bad microchimerism" theory, assuming the malevolent role of FMc, outlines the role of such allograft in pathogenesis of autoimmune diseases [14]. Fetal hemopoietic and nonhemopoietic stem cells transferred to maternal circulation may participate in generating graft-versus-host-like response in the woman and subsequent maternal response to foreign fetal cells leading to pathological autoimmunization [15].

Parry-Romberg syndrome, a form of morphea/localized scleroderma manifesting in childhood, has some similar symptoms to graft-versus-host disease (GVHD). Foreign CD68+ or S100+ cells of the dendritic cell phenotype along with foreign T and B cells were detected in skin lesions in patients with localized scleroderma [16]. In that case, probable sources of acquired foreign cells comprise mother's cells, genetic material from vanished twin, twin or older sibling. Such persistent foreign cells in fetal circulation might be dormant until an unknown agent, such as infection [17] (in our case, chickenpox in childhood), drug, abnormal protein, serving as an antigen, changes the immunity balance and allows the disease to manifest. There are two possibilities concerning the pathogenic role of maternal cells. The MMc may be effector cells against host or a victim to the autoimmune reaction [3].

It is worth noticing that there is the other side of the coin. The "good microchimerism" theory puts forward the conjectural beneficial role of fetal microchimerism in maternal tissue reparation and immunity. Infiltrating the diseased organ, FMc and MMc cells may assist in tissue reparation. The MMc may participate in fetal and neonatal immune system development. On the other hand, microchimeric T-cells of fetal origin may express T cell receptors that do not occur on mother's T cells, thus enabling the host to expand the range of recognized antigens.

There are many variables including source of foreign cells, the time since acquisition, genetic factors or numerous still unknown agents that may influence the impact of microchimerism on the patient. The role of fetal-maternal exchange of genetic material in autoimmunity and health should be further explored.

We present the first report of a female with coexisting PG and PRS, two diseases speculatively associated with microchimerism. Numerous studies point out to both possible benevolence and malevolence of microchimerism. This phenomenon, although crucial to reproduction, by altering immunological mechanisms might take part in pathogenesis of autoimmune diseases.

References

1. Dmochowski M. Krąg pemfigoidu pęcherzowego. In: Autoimmunizacyjne dermatozy pęcherzowe. Dmochowski M (ed.). Wydawnictwo Naukowe Akademii Medycznej im. Karola Marcinkowskiego, Poznań 2006; 116-199.
2. Stone J. Parry-Romberg syndrome. Pract Neurol 2006; 6: 185-188.
3. Gammill HS, Nelson JL. Naturally acquired microchimerism. Int J Dev Biol 2010; 54: 531-543.
4. Nuara AA, Obadiah JM, Hurley MY. Pemphigoid gestationis: cutaneous manifestation of impaired fetal allograft tolerance. Skinmed 2010; 8: 121-123.
5. Chen K, See A, Shumack S. Epidemiology and pathogenesis of scleroderma. Australas J Dermatol 2003; 44: 1-7.
6. Nelson JL. Microchimerism: incidental byproduct of pregnancy or active participant in human health? Trends Mol Med 2002; 8: 109-113.

7. Nelson JL. Microchimerism and autoimmune disease. N Engl J Med 1998; 338: 1224-1225.
8. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. Immunol Invest 2008; 37: 631-644.
9. O'Donoghue K, Chan J, de la Fuente J, et al. Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy. Lancet 2004; 364: 179-182.
10. Kelly SE, Black MM, Fleming S. Pemphigoid gestationis: a unique mechanism of initiation of an autoimmune response by MHC class II molecules? J Pathol 1989; 158: 81-82.
11. Huilaja L, Hurskainen T, Autio-Harmainen H, et al. Pemphigoid gestationis autoantigen, transmembrane collagen XVII, promotes the migration of cytotrophoblastic cells of placenta and is a structural component of fetal membranes. Matrix Biol 2008; 27: 190-200.
12. Gilliam AC. Microchimerism and skin disease: true-true unrelated? J Invest Dermatol 2006; 126: 239-241.
13. D'Alessio MC, Mazzanti C, Di Simone N, et al. No evidence for fetal microchimerism in the skin of patients with pemphigoid gestationis. Eur J Dermatol 2010; 20: 122-123.
14. Nelson JL. Maternal-fetal immunology and autoimmune disease: is some autoimmune disease auto-alloimmune or allo-autoimmune? Arthritis Rheum 1996; 39: 191-194.
15. O'Donoghue K, Chan J. Human fetal mesenchymal stem cells. Curr Stem Cell Res Ther 2006; 1: 371-386.
16. McNallan KT, Aponte C, el-Azhary R, et al. Immunophenotyping of chimeric cells in localized scleroderma. Rheumatology 2007; 46: 398-402.
17. Rajendran R, Sivapathasundharam B. Disturbances of development and growth. In: Shafer's textbook of oral pathology. Sivapathasundharam B, Rajendran R (eds.). 6th ed. Elsevier, New Delhi 2009; 14-15.

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