combined with EBA was established and methylprednisolone (80 mg/d) combined with azathioprine (50 mg/d) was started, with a slow response. After 15 months with the maintenance therapy methylprednisolone 4 mg/d and azathioprine 50 mg q.o.d, the skin on her ankles was completely healed with some milia, however, from time to time she suffered unexpected flares of blisters. As the clinical picture resembled the rare DEB-like acral EBA, we searched her family history and found toenail dystrophy in her daughter (figure 1F); her two grown sons had no skin or nail problems but she recalled onychodystrophy in her father. COL7A1 mutational search in the genomic DNA of the patient and her daughter was performed by denaturing high performance liquid chromatography and bidirectional sequencing. Both were shown to be heterozygous for glycine substitution mutation p.Gly2046Asp (c.6137G>A) in the triple helix domain of COL7A1 and a correct diagnosis of dominant DEB pruriginosa was established.

This mutation has been reported to be associated with the generalized DDEB subtype [2]. Thus, the same genetic lesion can underlie a spectrum of phenotypes ranging from nail dystrophy to localized DDEB-Pr in the same family or to generalized DDEB. The presence of autoantibodies against collagen VII in DDEB-Pr can be explained by an autoimmune reaction against dysfunctional collagen VII. In recessive DEB, collagen VII is reduced or absent. In DEB-Pr, collagen VII was detected both in recessive and dominant forms [3]. The target epitope in EBA is the non-collagenous NC1 domain of collagen VII, while the part affected by the mutation p.Gly2046Asp (exon 73) is the collagenous domain close to the hinge region. The disease course of our patient, with flares of blistering and response to immunosuppressive therapy, suggests the pathogenicity of the autoantibodies. In DEB-Pr, intact blisters are rare and other reported cases showed low or no response to immunosuppressive therapy [4].

The coincidence of DEB-Pr with EBA has not been described yet, although recently, bullous pemphigoid with suspected non-Herlitz junctional epidermolysis bullosa was reported [5]. EBA is an autoantibody-mediated autoimmune disease. However, fragile skin, sparse inflammatory infiltrate and reduction of anchoring fibrils in some cases indicate an involvement of non-inflammatory mechanisms in the pathogenesis [6].

DEB-Pr represents a diagnostic challenge due to its rareness, late manifestation and variable clinical picture. This case broadens the spectrum of clinical variations of DEB-Pr with associated autoantibodies against collagen VII, and raises the question of the role of collagen VII structural changes in the pathogenesis of non-inflammatory EBA.


doi:10.1684/ejd.2012.1709

Superimposed lateralized exanthema of childhood: a proposed explanation for an enigmatic disorder

Lateralized forms of exanthema occurring in children represent a perplexing group of disorders that have been described under the names “asymmetric periungual exanthem of childhood” [1] or “unilateral laterothoracic exanthema” [2]. The asymmetric rash tends to resolve after some weeks. A viral etiology is rather likely [1, 2]. So far, the striking asymmetry as noted in such cases has remained unexplained. Here, arguments are presented in favor of the concept that this disorder represents a superimposed mosaic manifestation of a rash that affects, in principle, both sides of the body.

Evidence of a less severe contralateral involvement

Many authors have noted that, after unilateral onset of the disease, some minor contralateral lesions likewise appear [1-4]. A typical example is shown in figure 1. McCuaig et al. [2] even stated that, after the initial rash affecting one side, “the exanthem then extends centrifugally to become bilateral in almost all patients.”
Figure 1. Superimposed lateralized exanthema of childhood.
A) Pronounced lesions involving the left side in a 2 year-old boy. B) Less severe contralateral lesions that appeared one week later.

The concept of superimposed segmental manifestation of polygenic skin disorders

During the past, the concept of superimposed mosaic manifestation of acquired skin diseases with a polygenic background was proposed to explain the origin of linear or otherwise segmental lesions, as noted in various common disorders such as psoriasis, atopic dermatitis, lichen planus, or vitiligo [5]. Analogously, lateralized exanthema of childhood may be interpreted in the following way. The unilateral arrangement of the initial lesions may represent a particular form of segmental involvement, reflecting mosaicism. An early postzygotic point mutation would give rise, on one side of the body, to different cellular epitopes, which would change the responsiveness of the skin to infective agents [6]. This altered cutaneous reactivity would become manifest in a superimposed lateralized exanthema of childhood. Most likely, cases of isolated unilateral exanthema of childhood result from a similar mechanism. In such patients, the cutaneous reactivity of the unaffected side of the body would be so weak that no skin lesions developed.

Heterogeneity of superimposed lateralized exanthema of childhood

According to present knowledge it is very likely that different viruses cause this asymmetric disorder. On the other hand, we can distinguish different patterns of distribution of the lesions. In most patients, involvement is non-linear [1, 2], whereas in other cases the superimposed lateralized lesions are arranged along Blaschko’s lines [3, 4]. Both non-linear and linear superimposed unilateral lesions would reflect postzygotic mutations, but the molecular mechanisms underlying these dichotomous patterns are so far unknown.

Conclusion

The proposed concept offers an explanation for the striking asymmetry of some exanthemas occurring in children [1-4] or, by way of exception, in adults [6]. The fact that the unilateral lesions are sometimes arranged along Blaschko’s lines [3, 4] strongly suggests that they reflect a particular form of mosaicism resulting from an early postzygotic mutation. Future molecular research may show whether this assumption holds true.


Etanercept-induced lichen planus-like eruptions following the lines of Blaschko

A 56-year-old female suffered from rheumatoid arthritis and Sjögren syndrome, which had been treated with prednisolone 6 mg daily. When she experienced an exacerbation of the arthritis, she began taking etanercept 25 mg twice a week and the prednisolone dosage could be reduced to 3 mg. Ten months after the initiation of etanercept, she noticed pruritic skin eruptions. Monotonous erythematous papules formed several bands following the lines of Blaschko on the left side of her body (figures 1A-D). Serologies for hepatitis B and C were negative. A biopsy specimen showed interface dermatitis (figure 1E). Epidermal spongiosis and perivascular infiltration were not observed. Immunohistochemistry with a monoclonal antibody against human mixoma virus protein A (MxA, clone KM-1124, dilution 1:200; from Prof. K Nagata, Tsukuba University, Japan) [3] revealed a strong expression of MxA in keratinocytes and in the infiltrating mononuclear cells (figure 1F). A diagnosis of lichen planus-like eruption (LPLE) due to etanercept was established. Within one month after the cessation of etanercept, the eruptions disappeared.

Tumor necrosis factor (TNF-α) blockade can cause paradoxical reactions such as psoriasis and lichenoid dermatitis [1]. Although paradoxical psoriasis appears to be the more common, reports of LPLEs are increasing. It is even suggested that paradoxical psoriasis is different from true psoriasis and constitutes a new model of adverse drug reaction [2]. LPLE is characterized histopathologically by its lichenoid dermatitis but the clinical appearance is diverse. It is divided into three groups: those with the clinical appearance of typical lichen planus, those with non-specific maculopapular morphology and those with the clinical appearance of psoriasis [1]. Clinical features of LPLE such as the timing of the onset, the disease course and the reactivity to a rechallenge test are similar to those of paradoxical psoriasis [1, 4]. Interestingly, the patient in this study showed the eruptions distributed unilaterally along the lines of Blaschko. To our knowledge, this is the first case of TNF-α blocker-induced LPLE following the lines of Blaschko. Only a case of LPLE in a zosteriform distribution has been reported [5] but it was not stated whether the eruptions followed the lines of Blaschko.

Why do TNF-α blockers cause LPLE? One hypothesis is that it results from a cytokine imbalance between TNF-α and interferon (IFN)-α [1, 2]. Type I IFNs play a central role in lichenoid reactions [6]. IFN-α is mainly produced by plasmacytoid dendritic cells (pDC) and induces Th1-biased immune responses. In a normal state, TNF-α suppresses IFN-α by inhibiting the maturation of pDCs and the production of IFN-α. Artificial TNF-α blockade by biologics may disturb this cytokine balance and result in inappropriate up-regulation of IFN-α. In the current case, strong expression of MxA in keratinocytes and inflammatory cells suggests an up-regulation of IFN-α.

Since LPLE does not occur in all patients undergoing TNF-α blocking therapy, the up-regulation of IFN-α seems to be insufficient to induce LPLE. A long latent period after the initiation of biologics also indicates that TNF-α blockade is not solely responsible. IFN-α plays an important role in antiviral defense and tumor immunity. The ‘second hit’