IgA pemphigus

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Introduction and AIMS

Short Definition in Layman Terms

IgA pemphigus is a distinct form of pemphigus characterized by tissue-bound and circulating IgA autoantibodies against desmosomal and non-desmosomal surface antigens.

IgA pemphigus is a rare disease mediated by IgA autoantibodies against desmosomal and non-desmosomal epithelial cell surface antigens

Learning Objectives

After reading this chapter you will be able to diagnose and differentiate pustular dermatoses and to recognize the classic clinics of IgA pemphigus. You will be able to perform and interpret the immunological tests and to make a treatment algorithm.

Case Study: Part 1

77-year old male patient presented with widespread annular erythematous plaques with tiny pustules at the periphery on the trunk and extremities (Fig. 11.1). There was erythema, edema and desquamation on the palms and footpads. The body folds like armpits, groin were not affected. Patients had malaise, but no fever was detected.

Previously there were no changes in medication. Medical history was negative for atopic disease and psoriasis. No drug allergy was previously documented.

Didactical Questions: Cross Section of Questions to Prime the Readers Interest

How can you diagnose a sterile pustular dermatosis? What would you see in the histopathological section? How can you make the difference between autoimmune and autoinflammatory diseases? In this section the focus is on the clinical differential diagnostics and work up of patients with extensive pustular dermatosis.

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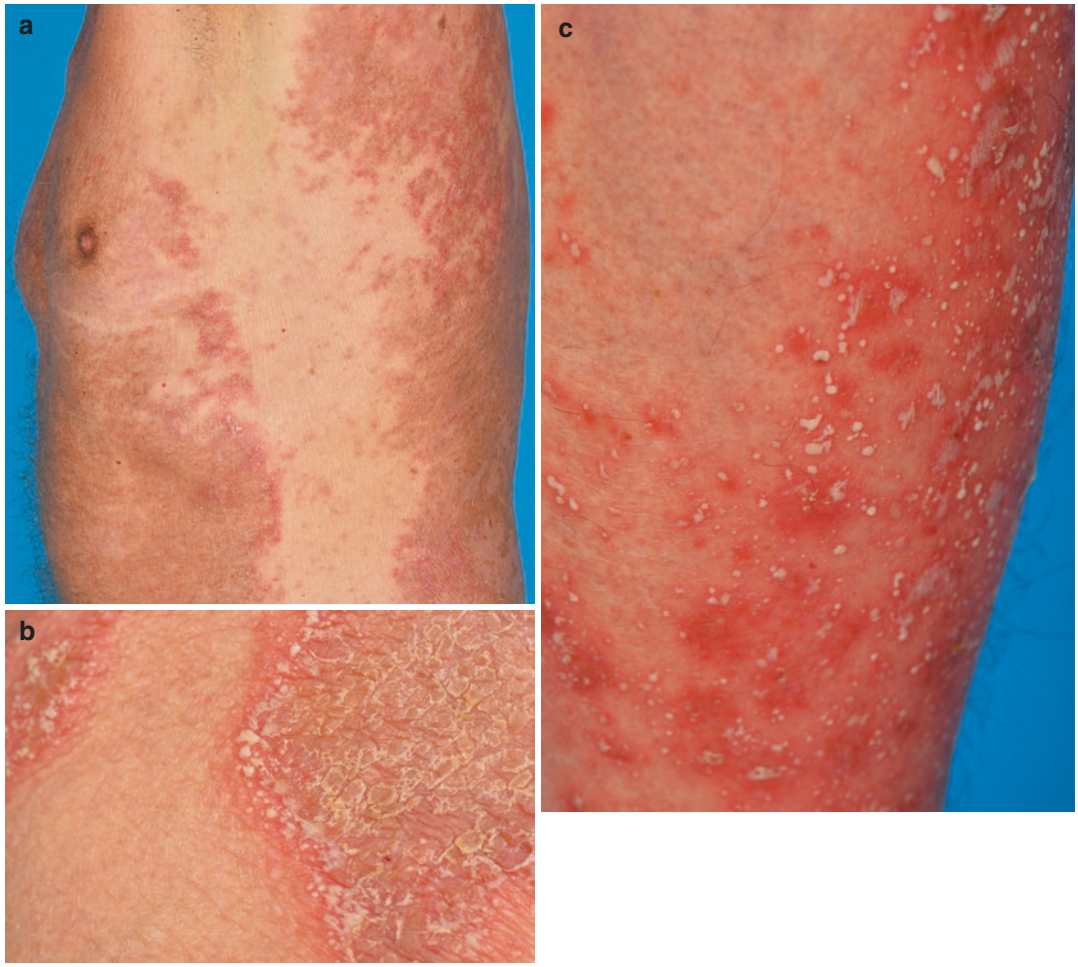

Fig. 11.1 IgA pemphigus in a patient with erythematous plaques with miliary to lenticular pustules over (**a**) the trunk, and (**c**) extremities. (**b**) In detail, the pustules are distributed on the advancing edge (circinate) of the erythematous plaques

Facts and Figures

Definitions and Classification

IgA pemphigus (IGAP) is an autoimmune blistering disease characterized by tissue-bound and circulating autoantibodies exclusively from de IgA class against desmosomal and non-desmosomal surface proteins of the epidermis [1, 2]. Based on the clinics, histology and the autoantibody pattern it is divided into two major forms; the *subcorneal pustulosis dermatosis* type (SPD-type) and the *intraepidermal neutrophilic IgA dermatosis* type (IEN-type). However, there are still cases of atypical overlapping phenotype of IGAP which can't be classified into these two

forms [3]. Moreover, in classic subcorneal pustular dermatosis or Sneddon-Wilkinson's disease no autoantibodies are detected in skin or serum.

Sneddon-Wilkinson's disease is similar to IgA pemphigus SPD type but without the IgA depositions in the skin

Epidemiology

IGAP has several synonyms such as intraepidermal neutrophilic IgA dermatosis, intercellular IgA dermatosis, IgA pemphigus foliaceus, intraepidermal IgA pustulosis, and IgA herpetiform pemphigus. A recent systemic review identified around 100 cases of IGAP [3]. IGAP has a slight female predominance with an age distribution of 1-month to 92-years, with an average of 51.5 years [3, 4]. It seems widely distributed all over the word as several cases are reported from all over the world.

Pathogenesis

In the SDP-type the IgA autoantibodies target the desmosomal cadherins. In most cases the major autoantigen is desmocollin 1 (Dsc1) which is expressed in the upper part of the epidermis [4, 5], but also other desmocollins can be targeted like desmocollin 2 (Dsc2) and desmocollin 3 (Dsc3). The autoantigen profile of the IEN-type more heterogeneous, no major autoantigen is identified yet. Some studies report reactivity against desmogleins 1 and 3, desmocollins 1–3, as well as other, still unknown, non-desmosomal proteins on the epithelial cell surface [6].

Using immunoelectron microscopy gold particles are mostly seen in the extracellular spaces between keratinocytes at desmosomes in SPD-type IGAP. In contrast, in IEN type, the gold particles are mainly in the intercellular spaces in non-desmosomal areas [6].

Once IgA is bound to the keratinocyte surface neutrophils accumulate in the epidermis leading to intraepidermal blister, later pustule formation. However the exact pathomechanism is still unknown.

In the SDP-type IGAP the IgA autoantibodies target mostly desmocollin 1, whereas the autoantigen profile of the IEN-type are heterogeneous; the major autoantigen is still not revealed.

Diagnosis Paths

History and Physical Examination

Onset of IgA pemphigus is subacute [1], first small fragile vesicles appear but soon they transform to pustules. The lesions spread centrifugal and form annular plaques with collarette-like scaling. The **SPD-type** is undistinguishable from the classic SPD; there are erythematous skin lesions with **tiny superficial** circinate pustules**,** and later desquamation from the edges surfacing the entire body, particularly in the intertriginous areas. In contrast the **IEN-type** is characterized by annular erythematous plaques with circinate pustules and crusts that spread outwards and heal inwards , giving the lesions a so-called **sunflower-like appearance**. Mucous membranes are almost always spared [1].

General Diagnostics

Routine histopathology in the SPD-type IGAP shows infiltration of neutrophils in the epidermis and upper dermis with subcorneal pustules, acantholysis can be seen, but not always. The IEN-type is characterized by blisters filled with neutrophils in the middle layers of the epidermis, acantholysis is sparse or absent. Sometimes eosinophils are seen in the intraepidermal pustules [7].

A recent systematic review revealed that 18% of the IGAP patient has a coexistent malignancy (mostly IgA gammopathy), but also concomitant appearance of solid tumors, autoimmune diseases, like ulcerative colitis, Crohn's disease, Sjogren syndrome and also HIV infections were reported. As none of the patient had a known IgA

gammopathy before the diagnosis of IGAP, despite the low evidence, screening for IgA gammopathy is advisable [3].

In IGAP screening for IgA gammopathy is advisable.

Specific Diagnostics

By direct immunofluorescence, the SPD-type IGAP shows IgA depositions on cell surfaces in the uppermost layers of the epidermis. Conversely, in the IEN-type the IgA depositions are distributed over the whole thickness of the epidermis [8]. As mentioned before in 10% of the cases a combined IgA/IgG and C3 deposition is detectable.

The circulating IgA antibodies are detectable only about 66.7% of the cases on indirect immunofluorescence [3]. Using normal human skin sections, autoantibodies react with the upper part of the epidermis in the SPD-type, whereas with the whole epidermis in the IEN-type [2].

Standard immunoblotting technique can be disappointing, as no consequent reactivity can be seen, maybe due to the conformation sensitive epitopes in IGAP. Only some cases with anti-Dsg3 showed reactivity in immunoblot [2]. ELISA testing for IgA to desmoglein 1 and 3 is not standard [2]. The most useful assay to detect IgA antibodies targeting conformation dependent epitopes on desmocollin 1 is using cDNA transfected COS-7 [4]. However this technique is available only in specific laboratories.

Case Study: Part 2

Routine laboratory examination showed leukocytosis (WBC: 16.9 10^9/ml) with neutrophilia (15.46 10^9/ml), elevated ESR (71 mm per hour) and CRP (177 IU/ml).

Common bacterial swab of the pustule and blood showed no microorganism. On histopathological examination were intra-en subcorneal neutrophil accumulations (pustules) seen in the epidermis without the presence of eosinophil granulocytes.

Direct immunofluorescence microscopy showed fine granular ECS depositions of IgA (2+) in the upper epidermal layers (Fig. 11.2). On indirect immunofluorescence no circulating autoantibodies either of IgA or IgG class were detected on monkey esophagus. Further serological examinations on salt-split skin, Western blot, and desmogleins 1 and 3 ELISA were all negative for both IgA and IgG.

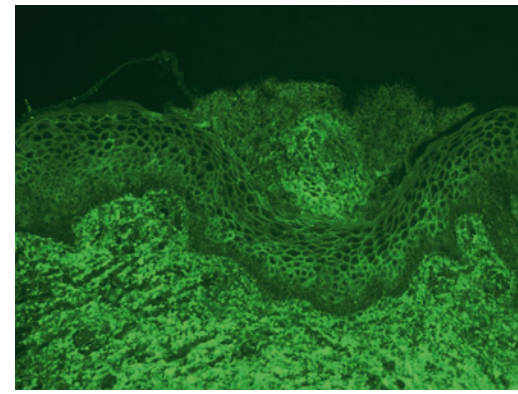

Fig. 11.2 Direct immunofluorescence of skin biopsy reveals epithelial cell surface (ECM) depositions of IgA in the epidermis. Note the pustule in the center due to subcorneal accumulation of neutrophils

Treatment Tricks

Initial Treatment and Therapeutic Ladder

Due to its rarity treatment protocols are missing. Treatment algorithm is adapted and from pemphigus and from the neutrophil dermatoses.

The first line therapy is dapsone (25–125 mg/day) because it suppresses several functions of neutrophils (see box Dapsone Chap. 20) [9]. If dapsone is contraindicated or not effective reti-

noids are the drugs of choice. Previously etretinate was given with success, nowadays several success is reported by acitretin [10] or isotretinoin.

Topical or systemic corticosteroid are also used. There are single case reports describe positive effect of adalimumab and mycophenolate mofetil, colchicine, tetracycline, sulfamethoxazole/trimethoprim, methotrexate, cyclosporine. Surprisingly positive effect of UVA photochemotherapy (PUVA) is observed [11].

The first line therapy is dapsone because it suppresses several functions of neutrophils

Case Study: Part 3

After excluding glucose-6-phosphat dehydrogenase (G6PD) deficiency patient received dapsone orally. The initial dose was 50 mg per day, which was increased up to 75 mg daily after 1 week under blood controls. Unfortunately soon after patient developed dyspnoe and acral cyanosis. Blood examination showed a slightly elevated methemoglobin within the normal range and elevated sulfahemoglobin, patient still had good hemoglobins levels, but the reticulocytes were low (not compensating hemolysis). After tapering and stopping dapsone the cyanosis improved, but patient was not able to restart dapsone because of the return of acrocyanosis and dyspnoe. In the next step patients received topical clobetasol ointment daily with acceptable result.

Follow-Up and Tapering

IGAP seems to be recalcitrant disease, so frequently combined therapy is needed [11].

Review Questions

1. What is not a subtype of IGAP?
   (a) Subcorneale pustulosus dermatosis type
   (b) Intraepidermal neutrophilic IgA dermatosis type
   (c) Sneddon-Wilkinson disease
2. Which form of IGAP is characterized by erythematous skin lesions with tiny superficial pustules, particularly in the intertriginous areas?
   (a) SPD-type
   (b) IEN-type
   (c) Both types
3. Which form of IGAP is characterized by the so called sunflower-like appearance?
   (a) SPD-type
   (b) IEN-type
   (c) Both types
4. First line treatment of IGAP is
   (a) dapsone
   (b) systemic corticosteroids
   (c) azathioprine
5. Which medication is the 2nd choice?
   (a) Super potent topical corticosteroids
   (b) retinoids
   (c) azathioprine

Answers

1. c.
2. a.
3. b.
4. b.
5. a.

On the Web

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