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CASE REPORT

Anaphylactic Shock after Traditional Russian Beauty-Treatment-Unpleasant Surprise in a Strongly Penicillin-Sensitized Patient

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SUMMARY **Beta-lactam drugs can induce allergic immune responses due to their antigenic determinants, promoting IgE-binding and anaphylactic reactions to penicillin. We report a case of a 44-year-old woman who experienced several severe systemic reactions after being exposed directly or indirectly to penicillin. An anaphylactic shock occurred after anal installation of her daughter's urine, who had been treated with penicillin. Skin testing revealed immediate type reactions to major and minor determinants of penicillin indicating an IgE-mediated sensitization. *In vitro* tests showed elevated levels of penicillin specific IgE. Clinical features, difficulties in taking history and test options for patients with IgE-mediated sensitizations are briefly reviewed in the context of the presented case of unexpected reactions to penicillin due to an immediate type hypersensitivity.**

After its isolation and characterization, penicillin G (benzylpenicillin) was first introduced as an anti-microbial drug in 1940.[1] It was frequently used during World War II, and with this novel therapy a new cause of anaphylaxis appeared. Only five years later drug-induced reactions to penicillin have been published;[2] O`Donnovan and Klorfajn[3] reported on anaphylaxis and desensitization to penicillin.

Over the past decades many antigenic structures of penicillin and clinically relevant IgE binding sites of β-lactam drugs have been identified.[4] Due to its poor stability, the β-lactam ring opens and covalently binds to proteins forming the pencilloyl or "major" penicillin determinant.[5] Many other conjugates of heterogeneous structure, classified as "minor" determinants, can also trigger immediate type hypersensitivity with symptoms like urticaria and angioedema, sometimes with full blown anaphylaxis. We report on a case of a strong IgE-mediated sensitization to penicillin and different episodes of acute allergic reactions in a Russian woman after injections, oral administration, inhalation, cutaneous or mucosal exposure and after scratch testing of penicillin.

CASE HISTORY

A 44-year-old woman reported several anaphylactic reactions after cutaneous applications of antibiotics. Eight years ago she repeatedly received penicillin injections due to a chronic ear infection which were well tolerated without any side effects. Nine months later after oral administration of penicillin the patient developed an urticarial and erythematous eruption of the abdominal region and on her face accompanied by dyspnea. Twelve hours later symptoms had disappeared, and she was back to normal again. After this event she started another oral penicillin treatment purchased over the counter in Russia. A quarter of an hour later she developed hypotension, became unconscious and collapsed. A quite similar episode occurred after a gluteal injection of erythromycin: three to five minutes later she developed acute dyspnea, red palms, a generalized flash and collapsed. Twenty-four hours later she showed an urticarial rash. Five

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years later the patient instilled half a liter of her daughter's urine intraanally daily for one week based on a Russian concept of traditional beauty treatment. Simultaneously her daughter was undergoing an oral penicillin treatment. Immediately (within one minute) after being rectally exposed to the penicillin-contaminated urine, sudden symptoms appeared: she developed angioedema, vomiting, diarrhea, generalized urticaria, collapsed and remained unconscious for approximately 20 minutes. The life-threatening character of this immediate reaction caused her husband to start mouth to mouth resuscitation and external cardiac massage. Twelve hours after the instillation she experienced dyspnea and her blood pressure dropped again. Successful emergency intervention included a prednisone injection and clearing of the rectal tube with water.

Besides these severe episodes the patient experienced several other less dramatic incidences. Erythema and difficulty in breathing occurred when she was near cattle that was treated with penicillin. The symptoms promptly improved outdoors. Even when she smelt or coincidentally inhaled penicillin in a hospital or in a private house, immediate symptoms with erythema of the face and hands appeared. Once she had to clean the floor after a vial of penicillin had broken. A few minutes later she showed a periorbital edema and contact urticaria of her hands and on those areas of the face being touched with her contaminated palms. Peculiarly, the patient remembered an oral itch after a kiss of her husband who had taken penicillin tablets.

For diagnostic purposes, a scratch skin test with penicillin G was performed in a private practice. After ten minutes, the blood pressure dropped with a weak peripheral pulse, in addition cold sweat and general erythema occurred. Emergency treatment included 1,000 mg of prednisolone and antihistamine dimenhydrinate injected intravenously. After one day a wheal was reported at the scratch test site.

Laboratory testing revealed a total serum IgE level of 256.5 kU/l, antigen specific IgE antibodies to penicilloyl V of 2.0 kU/l (CAP class 2) and no detectable IgE antibodies to penicilloyl G (< 0.35 kU/l), indicating a moderate sensitization to phenoxymethypenicilloate, but not to benzylpenicilloate. However, skin prick tests showed positive reactions for benzylpenicillin (Fig. 1, right panel: 10 IU/ml, ++; 100 IU/ml, +++; 1,000 IU/ml, ++++) and ampicillin (100 IU/ml, +), imipinem after 90 minutes, +; negative reactions for ciprofloxacin and cefuroxim 10 mg/ml, histamine-hydrochloride giving a reaction of +++. Prick testing with penicilloyl-polylysine PPL (titrated up to 7 nmol/ml PPL, representing 10 molecules of benzylpenicillin attached to one polylysin carrier, Allergopharma, Reinbeck, Germany) was negative. Intradermal test with the highest concentration was positive (Fig. 1, 6) and the mixture of minor determinants (titrated up to 1:100 MDM, representing a minor determinant mixture of 17 nmol/ml Na-benzylpenicilloate and 13 nmol/ml Di-Na-benzylpenicilloate) was prick-tested ++ (Fig. 1, left panel). There were also immediate type reactions to house dust mite, *Dermatophagoides pteronyssinus* and dog dander (skin reactions not shown).

DISCUSSION

This case report highlights the broad variety of immediate type allergic reactions to penicillin. Since 10% of all hypersensitivity reactions are caused by penicillin (prevalence from 2 to 3%),[6] penicillin is the most important allergen. Cutaneous applications have the highest risk of sensitization (10-15% of penicillin-allergic patients), especially in inflamed areas, whereas oral treatment is the safest (0.1-0.5%). Even small doses (1/100 IU penicillin) can provoke severe systemic reactions. Sensitization to penicillin can occur early in life due to its use in dairy products and meat.[7] In our case the contamination of the daughter's urine with penicillin was sufficient to provoke a severe systemic reaction.

Penicillin is eliminated via the kidneys (90%) quite quickly ($t_{1/2}$ = 40 minutes).[8] The penicillin concentration in the urine has no therapeutic role in the treatment of urinary tract infections and is usually no risk factor for unexpected allergic reactions. Urine levels of penicillin have been monitored to check the compliance with antibiotic therapy.[9] Bioassays as well as high performance liquid chromatographic methods are used to detect antibiotic activity in urine. The detection limits of these method are 2.5 to 25 ng penicillin per ml urine.[10] Concentrations of 5 to 500 µg penicillin per ml urine have been measured in patients undergoing on penicillin therapy.[11] These small amounts were sufficient to cause a near fatal reaction in our patient, indicating a strong sensitization to penicillin.

Indeed, skin prick testing revealed a strong IgE-sensitization to penicillin G and to its minor determinants, often related to unexpected and severe systemic reactions to penicillin. Considering approximately 3 µl of allergen solution penetrating the skin during a successful prick puncture test, 0.0003 IU penicillin G were sufficient to provoke a histamine-equivalent cutaneous response in our patient. In addition, intradermal

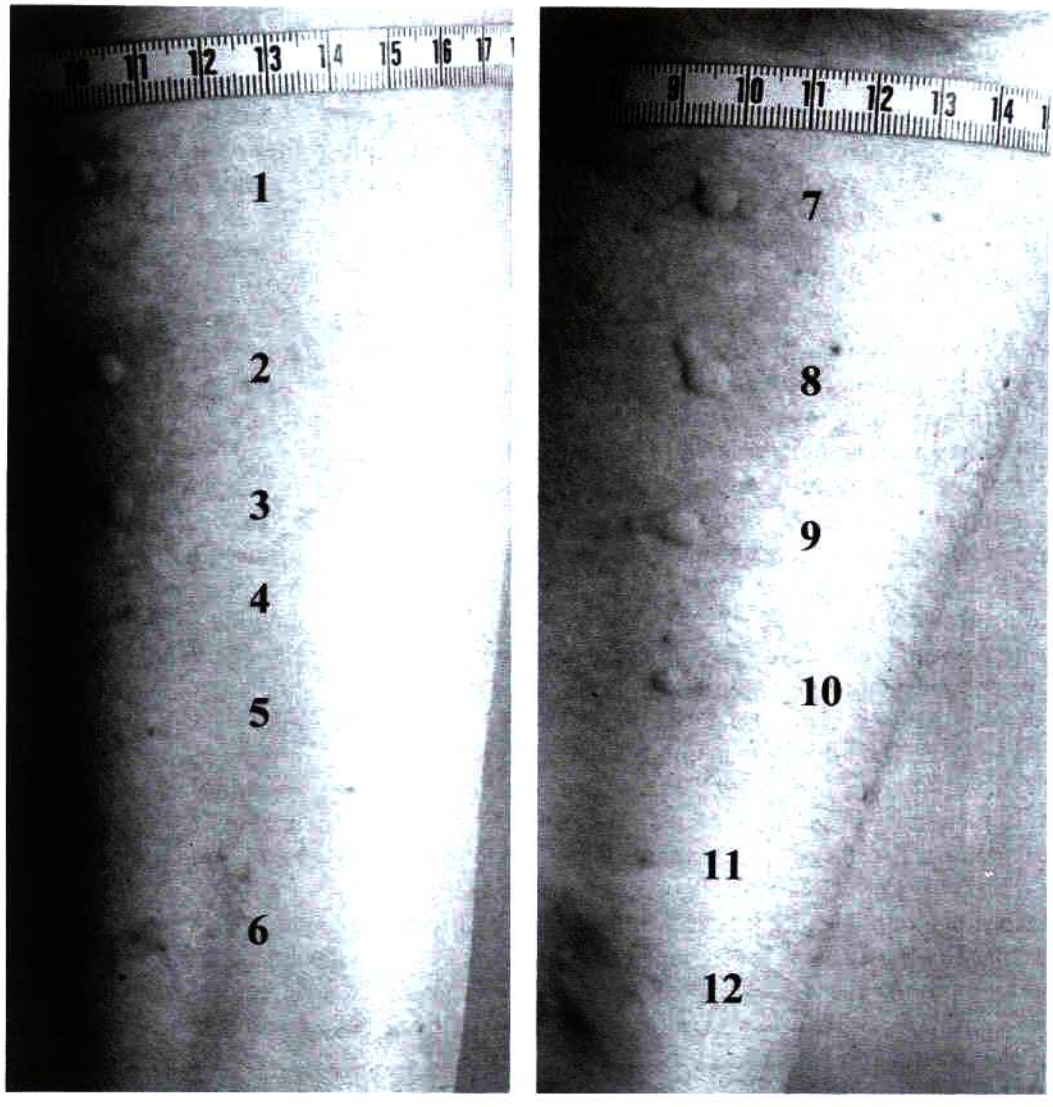

Fig. 1 Immediate type skin test results to penicillin determinants in a patient with severe allergic reactions to penicillin after direct and indirect exposure.
Left panel: right forearm, 1-5, skin prick test reactions: 1, positive control with histamine-hydrochloride (10 mg/ml); 2, minor determinant mixture (MDM) 1:100 (17 nmol/ml Na-benzyl-penicilloate and 13 nmol/ml Di-Na-benzyl-penicilloate); 3, MDM 1:1,000; 4, MDM 1:10,000; 5, normal saline; 6, intradermal test reaction to penicillin major determinant diluted 1:1 (35 µg/ml or 7 nmol/ml benzylpenicillin-polylysine PPL, representing 10 molecules of benzyl-penicillin attached to one polylysine carrier).
Right panel: left forearm, 7-12, skin prick test reactions: 7, histamine-hydrochloride (10 mg/ml); 8, penicillin G 1,000 IU/ml; 9, 100 IU/ml; 10, 10 IU/ml; 11, 1 IU/ml; 12, negative control with normal saline.

testing showed a moderate IgE-mediated sensitization to the major determinant, which was not able to elicit a positive result by skin prick testing. *In vitro* testing revealed an isolated IgE-mediated sensitization to phenoxymethylpenicilloate, but not for benzylpenicilloate. This example, demonstrating discording results after *in vivo* and *in vitro* testing, highlights the necessity applying various diagnostic methods to evaluate drug related allergic reactions.

Unexpected symptoms of hypersensitivity to penicillin without former reactions are not un-

usual, because intermittent application can booster an allergic immune response.[6] A history of drug allergy is associated with an increased rate of allergic reactions to penicillin.[12] All peculiar events of our patient have likely resulted from type I hypersensitivity described by Coombs and Gell, though penicillin can induce all four types of allergic reactions. There is still a lack of understanding in the pathogenesis of clinically distinct drug eruptions like the development of exanthema, erythema multiforme, fixed eruptions, bullous and vesicular exanthema, for examples. Urticaria, angioedema, rhinitis, extrinsic asthma and anaphylactic shock (3-5% of all reactions) are symptoms of an immediate type I reaction, whereas hemo-lytic anemia, neutropenia and thrombocytopenia are considered type II reactions. Serum-sickness (2-4%), vasculitis and purpura (type III) can also occur as well as contact dermatitis (type IV).[6] The allergic reactions to penicillin can also be classified by the time of onset: immediate, accelerated and delayed reactions. According to 151 fatal reactions reported[6] and confirmed by our nearly fatal case, the earlier the onset, the more serious the event.

Another important aspect is that life threatening events can occur during skin testing, as reported in our case. The structure of penicillin seems to play a certain role. Strong sensitizers are penicillin G, V and O.

Diagnostic tools are most advanced in detecting IgE-mediated sensitizations to penicillin with the following procedure being proposed:[13] *In vivo* testing should include penicilloyl-polylysine (PPL) as the major determinant and a mix of penicillin minor determinants (available as commercial test kits, i.e. Allergopen®, Penkit®). Only after a negative skin prick test, titrated using several log-dilutions, the intradermal test should be performed (consecutive titration of 50 and 250 nmol/ml). This procedure appears to be safe, an important prerequisite, since the intradermal and even the open patch test with penicillin can lead to severe anaphylactic symptoms.[14,15] A negative skin test to penicillin excludes an IgE-mediated mechanism; a future application of penicillin is not likely to prompt an immediate type reaction and rarely shows any side effects. A study with 5,063 patients emphasizes this diagnostic procedure: 95% of the patients with a positive history of penicillin-induced reaction and negative skin test received a full therapy of penicillin without any side effects, whereas 5% presented minor side effects.[16]

Few cases show a sensitization to another epitope of a penicillin derivative than the ones detected with the available commercial test kits. Therefore, some other penicillin derivatives should be considered for skin prick and scratch tests after a negative skin prick test with major and minor derterminants has been done (Table 1).

Serologic tests for the detection of antigen specific IgE antibodies to penicillin leave a level of uncertainty, because they are not very sensitive and depend on the interval between drug reaction and the blood sampling in contrast to the skin tests. On the other hand Weiss and Adkinson[16] recommended the serologic *in vitro* tests in case of anaphylactic reactions because they are often IgE-mediated in contrast to serum sickness and exanthema. Novel reagents for the detection of allergen specific IgE to a variety of side determinants would be very useful and might close the gap in serological tests.

Some clinical laboratories provide quantitative measurement of circulating IgG antibodies by radioallergosorbent test (RAST) or enzyme-linked immunosorbent assay (ELISA). They have been postulated to play a role in penicillin allergy, but the pathogenetic significance remains unclear. Therefore, this test should not be applied in routine diagnostic procedures for penicillin hypersensitivity.[17]

Anaphylactoid reactions during skin testing are rare but an effective emergency treatment protocol is necessary. General measures

Table 1 Recommended tests in penicillin allergy[13]

1. **Commercial tests (e.g. Allergopen®, Penkit®)**
   with PPL (penicilloyl-polylysine, "major determinant")
   and penicillin minor determinant mix
   - Prick test (50 and 250 nmol/ml)
   - Intradermal (after a negative prick test)
2. **In special cases with a suspected side chain allergy:**
   skin tests with other penicillin derivatives
   - Prick test
   - Scratch-test (after a negative prick test)
3. **Specific IgE antibodies**
   - Not generally recommended
     (many reactions are not IgE-mediated)
   - Useful to detect anaphylactic IgE-mediated reactions
4. **Specific IgG antibodies**
   - Not for routine diagnostic
     (Interpretation of results is uncertain)

include the immediate termination of the allergen application and containment, if necessary by tourniquet. Local cutaneous reactions do not demand systemic therapy, local corticosteroids are sufficient. Measures to control Stadium I (flush, generalized urticaria and pruritus) includes the opening of an intravenous line, EKG monitoring, control of vital signs, Trendelenburg's position and injection of an H_1-receptor antagonist (clemastinhydrogenfumarate 4 mg, i.v. or dimetindenmaleate 8 mg, i.v.) as well as injection of an H_2-receptor antagonist (cimetidine 200 mg slowly injected over 1 minute or ranitidine 50 mg, i.v.). Methylprednisolone (50-125 mg) is administered, pulmonary reactions require O_2 application. Stadium II (circular dysregulation, dyspnea, bronchospasm) requires additional volume substitution (500 ml Ringer's solution). Pulmonary reactions are treated with O_2 and inhalation of noradrenaline. Stadium III (menacing general reactions and shock) should be managed with additional administration of epinephrine (1 mg/-minute, i.v.). In case of Stadium IV (cardiovascular collapse) cardiopulmonary resuscitation is warranted.

Table 2 Cross reactivities of penicillin/β-lactam antibiotics[18]

1. **Semisynthetic penicillins**
   a) Penicillin V-derivatives
      - Pheneticillin
      - Propicillin
   b) Isoxazolyl-penicillins
      - Oxacillin
      - Cloxacillin
   c) α-substituted bencoyl-penicillins
      - Carbenicillin
      - Ticarcillin
      - Ampicillin
      - Amoxicillin
      - Azlocillin
      - Methicillin
2. **Cephalosporins**
   a) First generation (5.4-16.5%)
      - Cefalexin
      - Cephalotin
      - Cephaloridin
      - Cefazolin
   b) Second generation (1-4%)
      - Cefamandol
      - Cefaclor
      - Cefuroxim
   c) Third generation
      - Cefotaxim
      - Ceftriaxon
      - Cefixime
      - Cefpodoxime
      - Cefetamet
      - Ceftazidime (1.7%)
   d) Fourth generation (?)
      - Cefepime

The positive skin test results depicture also the difficulties to select alternative antibiotics, since drugs with similar structures might display cross reactivity to penicillin (β-lactam antibiotics). The members of this antibiotic class (semisynthetic penicillins, cephalosporins, carbapenems, monobactams) share the β-lactam ring structure, subsequently binding to lysine residues in proteins and forming the penicilloyl or cephalosporyl determinant. Cephalosporins which express the same side chain are often crossreactive (first generation 5.4-16.5%, second generation 1-4%, Ceftacidime 2.7%, Table 2)[18]

The choice of alternative antibiotics is dependent on the indication of the drug. Erysipelas should be treated with erythromycin (4 x 500 mg p.o. or 2 x 1 g, i.v.). For infections with a variety of bacterial species clindamycin is advised (3 x 0.6 g/d, i.v.), because of its broad spectrum and the good penetration in tissues. Severe infections can be treated with a combination of clindamycin (3 x 0.6 g/d, i.v.) and Cefuroxim (3 x 1.5 g/d, i.v.). In cases of syphilis tetracyclin (4 x 500 mg) or doxycyclin (2 x 100 mg, orally) can be given in non-pregnant patients as well as ceftriaxon (250 mg, i.m./10d).[19]

Our reported case highlights the possibility of unexpected reactions to penicillin. Both, frequency and severity of the allergic reactions demonstrate the importance of a detailed patient's history, profound diagnostic work-up and appropriate advice to the patient.

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