

- CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. *Cancer* 2000; **89**:1835–44.
- 6 Paul T, Radny P, Kröber SM et al. Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144**:1239–43.
 - 7 Kütting B, Bonsmann G, Metze D et al. *Borrelia burgdorferi*-associated primary cutaneous B-cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon alpha-2a. *J Am Acad Dermatol* 1997; **36**:311–14.
 - 8 Lee LA, Fritz KA, Golitz TJ et al. Second cutaneous malignancies in patients with mycosis fungoides treated with topical nitrogen mustard. *J Am Acad Dermatol* 1982; **7**:590–8.
 - 9 Fragu P, Lemarchand-Venencie F, Benhamou S et al. Long-term effects in skin and thyroid after radiotherapy for skin angiomas: a French retrospective cohort study. *Eur J Cancer* 1991; **27**:1215–22.
 - 10 Davidson T, Westbury G, Harmer CL. Radiation-induced soft-tissue sarcoma. *Br J Surg* 1986; **73**:308–9.

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IgE antibodies to penicillin are indicative for but not conclusive proof of penicillin allergy

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SIR, Predictive testing for drug hypersensitivity, without an individual history of specific problems, is controversially discussed, as diagnostic procedures might lead to false-positive as well as false-negative results due to a lack of high sensitivity and absolute specificity. Thus the specificity of fluorescence enzyme-linked immunoassay (FEIA) tests for specific IgE for benzylpenicilloyl (BPO) is reported to range between 87% and 100%.^{1,2} However, arbitrary definitions of the term 'specificity' may give rise to controversial conclusions.

We report a healthy young man who, as a student, worked in the aminopenicillin production department of a drug company for 2 years. When he applied for a permanent position in that company he was tested for penicillin antibodies in vitro using the Pharmacia CAP-FEIA method (Sweden Diagnostics, Uppsala, Sweden): sIgE for penicillin G was 0.64 kU L⁻¹, penicillin V 0.82 kU L⁻¹, ampicillin 1.52 kU L⁻¹ and amoxicillin 0.43 kU L⁻¹, and his total IgE level was 573 kU L⁻¹. On account of this positive test result the job application was turned down. The individual consulted us for a second opinion as he had frequently taken oral antibiotics in the recent past and encountered no difficulties. The laboratory result thus seemed to be clinically irrelevant. We redetermined IgE levels, again using the CAP system: the results remained positive. However, skin prick and intradermal testing with penicillin and amoxicillin at the appropriate test concentrations³ were negative (readings at 20 min, 24 h and 72 h) except for mild erythema at the intradermal test site for amoxicillin (reading

at 20 min). Oral provocation with amoxicillin (in combination with clavulanic acid), starting with half the normal dose and progressing rapidly to a predefined daily dose, was well tolerated. No immediate or late reactions occurred. The patient's serum was then sent blinded to an independent laboratory, where the ADVIA Centaur® (Bayer Diagnostics, Tarrytown, NY, U.S.A.) immunoassay system was used. Here the results were negative (<0.35 kU L⁻¹) for both penicillin V and penicillin G. The patient's negative history, skin tests, provocation test and IgE detection using the ADVIA Centaur® system led us to conclude that he is not allergic to penicillin. Hence the positive IgE test results using the CAP-FEIA method were deemed to be false-positive.

IgE tests for penicillin have proved useful to identify individuals at risk for anaphylaxis or mild immediate hypersensitivity reactions to therapeutic doses.⁴ However, the sensitivity of the procedure is quite low, as proven by values of around 37% in patients with immediate reactions to β -lactams.^{2,5} In contrast to its low sensitivity, the specificity of the procedure was reported to be as high as 100%.¹

Specificity is defined as the percentage of correct negative results in a nondiseased control population. With respect to IgE detection for BPO, this value should be determined on the basis of penicillin-exposed patients who tolerate penicillin well, and not healthy nonexposed controls. Failure to employ this approach may have influenced some of the data published in the literature.⁶ Clinical experience has shown that patients with (excessively) high total IgE levels or individuals heavily exposed to penicillins may exhibit low, yet positive, IgE antibodies to penicillins. This is especially true for the CAP-FEIA method, a highly sensitive system that, however, appears to be susceptible to false-positive results due to irrelevant specific IgE antibodies with low affinity, and also to cross-reacting IgE.⁷ These types of reactions are minimized in other systems, e.g. the ADVIA Centaur®.⁷

The message conveyed by this case report is significant: IgE detection for penicillin should not be performed prospectively. One is likely to obtain false-positive test results in selected populations as the negative predictive value for penicillin antibody testing is controversially defined. The definition is either based on a clinical or a laboratory approach. If predictive IgE testing is performed at all, the clinician is advised to select a system in which low-affinity antibodies are irrelevant. It should be noted that test systems for penicillin are only standardized for the assessment of persons with a clinical history of immediate allergic reactions,³ and not for predictive testing. In this regard, skin testing is the better instrument to predict tolerance.⁸

The practice parameter on drug hypersensitivity⁹ indicates that testing should be reserved for those with a positive history (e.g. testing by the employer/drug manufacturer in the case report would not be appropriate). It also summarizes that there is a 50% chance of a reaction even with a positive history and positive tests for IgE. Lastly, it states that even with negative test a small percentage may react. Predictive testing for drug hypersensitivity should therefore be declined, at least

as long as criteria such as sensitivity and specificity are not better defined.

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References

- 1 Blanca M, Mayorga C, Torres MJ et al. Clinical evaluation of Pharmacia CAP SystemTM RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy* 2001; **56**:862–70.
- 2 Sanz ML, Gamboa PM, Antepara I et al. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to beta-lactam antibiotics. *Clin Exp Allergy* 2002; **32**:277–86.
- 3 Torres MJ, Blanca M, Fernandez J et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; **58**:961–72.
- 4 Sheperd GM. Allergy to β -lactam antibiotics. *Immunol Allergy Clin North Am* 1991; **11**:611–34.
- 5 Romano A, Di Fonso M, Papa G et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 1995; **50**:113–18.
- 6 Aberer W, Kranke B, Hager A, Wick G. In vitro allergy testing needs better standardization—test results from different laboratories lack comparability mostly due to missing effective standards. *Int Arch Allergy Immunol* 1995; **108**:82–8.
- 7 Petersen AB, Gudmann P, Milvang-Grønager P et al. Performance evaluation of a specific IgE assay developed for the ADVIA Centaur[®] immunoassay system. *Clin Biochem* 2004; **37**:882–92.
- 8 Stember RH. Prevalence of skin test reactivity in patients with convincing, vague, and unacceptable histories of penicillin allergy. *Allergy Asthma Proc* 2005; **26**:59–64.
- 9 Executive summary of disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999; **83** (6 pt 3): 665–700.

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Successful treatment of Darier disease with topical 5-fluorouracil

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SIR, Darier disease (DD) is an autosomal dominant cutaneous disorder, characterized by persistent eruption of waxy, hyperkeratotic papules usually occurring over seborrhoeic areas. Although various pharmacological agents have been employed in an attempt to treat DD, effective therapeutic options have

remained elusive.¹ We describe a Korean woman with DD whose skin lesions and symptoms were successfully treated with topical 5-fluorouracil (5-FU).

A 20-year-old Korean woman presented with a 10-year history of pruritic, recurrent, multiple hyperkeratotic erythematous papules and coalesced plaques on the face, neck, trunk, flexures and extremities (Fig. 1a–c). Biopsy of lesional facial skin revealed hyperkeratosis, papillomatosis, suprabasal clefting with acantholysis, dyskeratosis (corps ronds and grains) and a dermal inflammatory cell infiltrate (Fig. 2). These histopathological findings were consistent with a diagnosis of DD. The patient was initially treated with topical steroids and antihistamines, but the eruptions did not improve. Considering her childbearing age, we switched treatment to 1% topical 5-FU in a cream base in order to avoid the risk of birth defects associated with retinoid treatment. The patient was instructed to apply the cream to her trunk and limbs once daily, and to her face and flexures every other day, so as to reduce local irritation. After 1 week of treatment with topical 5-FU, the skin lesions and pruritus showed significant regression, almost completely resolving at 1 month follow-up (Fig. 1d–f). Haematological parameters were unchanged during and after treatment, and local side-effects such as burning, itching and painful erosions were not observed. We recommended that strong sunlight be avoided and broad-spectrum sunscreen be applied during outdoor activities. New lesions that appeared from time to time were easily controlled by topical 5-FU cream without any additional treatment. On average, her monthly usage of 5-FU cream has been 15 g in the summer season and 5 g in the other seasons.

DD is an autosomal dominantly inherited disorder caused by mutation in the adenosine triphosphate (ATP) 2A2 gene, mapped to 12q23–24. ATP2A2 encodes the sarco/endoplasmic reticulum Ca^{2+} -ATPase isoform 2 (SERCA2), a calcium pump transporting Ca^{2+} from the cytosol to the lumen of the endoplasmic reticulum.² This SERCA2 dysfunction may lead to interruption of desmosomal assembly and cytokeratin anchorage and cause acantholytic dyskeratosis, the key histological feature of DD.³

DD is an uncommon inherited cutaneous disease, and is difficult to manage. To date, there has been no proven effective therapy for DD. Numerous treatments such as emollients, steroids, retinoids, dermabrasion, CO₂ laser and surgery have reportedly been used for the treatment of DD, with limited success. Of these, systemic retinoids are often relatively effective, but are frequently associated with deleterious side-effects such as mucosal dryness, nose bleeds, skin fragility and elevation of triglycerides and cholesterol. In addition, retinoids are teratogenic and should not be prescribed in women without adequate contraception.

5-FU is a chemotherapeutic agent that can be used both topically and intravenously. 5-FU inhibits thymidylate synthetase, leading to inhibition of DNA synthesis and cell death,⁴ which results in the inhibition of hyperproliferation and abnormal cytokeratin production associated with DD.⁵