Cutaneous zosteriform squamous cell carcinoma metastasis arising in an immunocompetent patient

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Abstract of: Clinical dermatology.

Cutaneous metastases from internal malignancies or primary skin cancers are uncommon, and a zosteriform pattern is very rare. Histologically, these cutaneous metastases usually appear as malignant epithelial cells located throughout the dermis or subcutaneous fat and without connection to the overlying epidermis. The presence of melanocytes in such lesions is atypical. Moreover, although zosteriform cutaneous metastases of cutaneous squamous cell carcinoma have previously been described in immunosuppressed patients, they have not been reported in immunocompetent patients. We report an unusual case of a woman with cutaneous hyperchromic zosteriform metastases, clinically mimicking a metastatic melanoma but appearing histologically as epidermotropic and pigmented melastases of a cutaneous squamous cell carcinoma.

Upregulation of natural killer cells functions underlies the efficacy of intratumorally injected dendritic cells engineered to produce interleukin-12

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Abstract of: Exp Hematol 2002 Mar;30(3):195-204.

Objective: Injection of dendritic cells (DC) engineered with recombinant adenoviral vectors to produce interleukin- 12 (IL-12) inside experimental murine tumors frequently achieves complete regressions. In such a system the function of CD8(+) T cells has been shown to be an absolute requirement, in contrast to observations made upon depletion of CD4(+) T cells, which minimally affected the outcome. The aim of this work was to study the possible involvement of natural killer (NK) cells in this setting.

Materials, methods, and results: Depletions with anti-AsialoGM1 antiserum showed only a small decrease in the proportion of complete regressions obtained that correlated with induction of NTC activities in lymphatic tissues into which DC migrate, whereas combined depletions of CD4(+) and NK cells completely eliminated the antitumor effects. Likewise in vivo neutralization of interferon-gamma (IFN-gamma) also eliminated those therapeutic effects. Trying to define the cellular role played by NK cells in vivo, it was observed that injection of cultured DC inside the spleen of T- and B-cell-deficient (Rag 1 (-/-)) mice induced upregulation of NK activity only if DC had been adenovirally engineered to produce IL-12. In addition, identically transfected fibroblasts also activated NK cells, indicating that IL-12 transfection was the unique requirement. Equivalent human DC only activated in vitro the cytolytic and cytokine-secreting functions of autologous NK cells if transfected to express human IL-12.

Conclusions: Overall, these results point out an important role played by NK cell activation in the potent immunotherapeutic effects elicited by intratumoral injection of IL-12--secreting DC and that NK activation under these conditions is mainly, if not only, dependent on IL-12.

Undersurface ablation of the flap for laser in situ keratomileusis retreatment

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Abstract of: Ophthalmology 2002;109:1453-64.

Objective: To develop a novel technique, undersurface ablation of the flap (UAF), for laser in situ keratomileusis (LASIK) retreatment in eyes with insufficient posterior stroma.

Design: Noncomparative, interventional case series.

Participants: From 30 eyes examined, 25 eyes with a spherical equivalent residual refraction between -0.75 and -3.25 diopters (D) and astigmatism between 0.0 and -1.5 D were prospectively included in the study. In these eyes, calculated postenhancement flap thickness was >150 µm using micropachymetric optical coherence tomography (OCT), whereas with further ablation of the bed, posterior stromal thickness would have been <250 µm. Primary LASIK procedures had been performed with the Hansatome microkeratome.

Intervention: The flap was lifted and the eye deviated downward, so that the corneal visual axis mark aligned with the laser beam. Mirror pattern ablations with an optical zone of 5 mm were performed on the flap stroma using either the Summit Apex Plus excimer laser or the Technolas Keracor 217 spot-scanning excimer laser. New axis orientation for toric ablations was calculated with the formula: ß = 180° -α.

Main outcome measures: Refraction, visual acuity, OCT pachymetry, tangential videokeratography, and patient satisfaction.

Results: The average follow-up was 6.36 ± 2.64 months (range, 3-12 months). Mean preenhancement spherical equivalent (-2.05 ± 0.75 D) was reduced to -0.19 + 0.38 D at the last visit (P=0.00 1). Mean cylinder decreased from -0.48 ±

0.53 D before retreatment to -0.23 ± 0.28 D at the last follow-up (P 0.003). Best-corrected visual acuity worsened by 1 line in two eyes (8%), and no eye lost 2 or more lines. Satisfactory globe stabilization and stromal smoothness during ablation were more difficult to achieve than with conventional LASIK enhancements. The average central flap thickness before UAF, 187 ± 13 μm, decreased to 164 ± 12 μm after 1 month (*P* = 0.00 1). No keratectasia developed. Finally, 92% of cases were satisfied with surgery compared with 48% before UAF retreatment (*P* = 0.001).

Conclusions: UAF retreatment for low residual refractive errors after LASIK in eyes with sufficient flap stroma seems to be effective and may prevent future keratectasia.

Immunocytochemical Detection of Orexin A in Endocrine Cells of the Developing Mouse Gut

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Abstract of: The Journal of Histochemistry & Cytochemistry 2002;50:63-69.

Orexins are novel neuropeptides that were originally localized in neurons of the hypothalamus and neuronal fibers of the brain. Recently orexin A and its receptor have also been reported in neurons and endocrine cells of the gastrointestinal tract. Because no studies have been done at the embryonic period, we studied the appearance and distribution of orexin A during the development of mouse gastrointestinal tract using immunocytochemical methods. Immunoreactivity to orexin A was detected in neuroendocrine cells of the pyloric region of the stomach at gestational Day 14 and 1 day after in the small intestine. The numbers of immunoreactive cells progressively increased through development until the adult pattern was reached. Staining of reverse-face sections demonstrated that orexin A and serotonin co-localized in some endocrine cells of the mouse stomach and small intestine. These findings suggest that orexin A may be relevant in the growth and maturation of the gastrointestinal tract during intrauterine life.

Flow Cytometric Cellular Allergen Stimulation Test (FAST/FLOW-CAST) Technical and Clinical Evaluation of a New Diagnostic Test in Allergy and Pseudo-Allergy

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Abstract of: ACI International 2002;14:204-15.

The flow-cytometric basophil allergen stimulation test (FAST) is a new *in vitro* diagnostic technique that has proven quite helpful in the hands of various groups for the diagnosis of IgE-mediated and non-IgE-mediated allergies and pseudo-allergies.

Although relatively simple, various technical details such as the use of isolated leukocytes instead of whole blood, proper storage following blood sampling, suitable negative and positive controls, as well as allergens calibrated for the test have proven important for optimal sensitivity and specificity. In a number of instances, the FAST test, particularly when combined with sulfidoleukotriene determination (CAST) has proven superior to other *in vitro* tests, including the widespread allergen-specific IgE determinations.

Among the clinical indications, allergies to inhalant allergens, food allergies, latex allergy, *Hymenoptera* venom allergies, immediate-type allergies, and pseudo-allergies to drugs as well as detection of autoantibodies in chronic urticaria have been documented and validated.

Clinical Evaluation of *In Vitro* Tests in Diagnosis of Immediate Allergic Reactions to b-Lactam Antibiotics

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Abstract of: ACI International 2002;14:185-93.

Background: The aim of this study was to compare the diagnostic efficiency in immediate type allergy to β-lactam (BL) antibiotics of three *in vitro* tests individually or in combination: specific IgE determination (CAP), sulfidoleukotriene production by allergen-stimulated blood basophils (CAST) and allergen-induced basophil activation (FAST).

Methods/data base: Seventy-nine patients who presented with urticaria and/or anaphylaxis following administration of benzylpenicillin (BP), amoxicillin (AX), or cephalosporins (CE) and had positive skin tests to BP-derived reagents and/or AX or CE were investigated by CAP, FAST, and CAST. Group 1 included 23 patients treated with AX or BP showing positive skin tests to BP and AX or BP only, and 6 patients treated with CE and presenting positive skin tests to CE. Group 2 included 34 patients treated with AX showing positive skin tests to AX only. An additional 16 patients (group 3) were treated with AX but showed negative skin test. Their sensitivity to β-lactams was confirmed by positive in vitro tests and/or positive provocation with the culprit drug. Finally, 30 patients with negative skin tests who tolerated β-lactams were considered as controls (group 4).

Results: In group 1, CAP was positive to BP in 38% of patients and to AX in 17%. FAST was positive to BP in 35% and to AX or CE in 42%, while CAST was positive to BP in 35%

and to AX in 21%. However, since positivity to CAP, FAST, and CAST are not always associated, the combined diagnostic sensitivity of FAST and CAST reached 76%. Similarly, in group 2, consisting of putatively selectively AX-sensitive patients, the combined diagnostic sensitivity of FAST and CAST, which was individually 29% and 32% for AX, reached 61%. Of these patients, 62% were found on *in vitro* tests to have some immunological sensitivity towards BP-derived determinants. In group 3, the combined FAST and CAST tests enabled to confirm diagnosis in 47% of the cases.

Results in group 4 confirmed specificities of 90%-93% for CAP, 93% for FAST, and 83% for CAST.

Conclusions: The newly developed FAST test, as well as CAST, and particularly their combination (FLOW-CAST™) are of great interest in confirming *in vitro* the diagnosis of immediate-type allergy to β-lactams in patients with a clinical history and positive or negative skin tests. Particularly when used in combination, together with CAP, these tests achieve good sensitivity and probably allow to avoid cumbersome and potentially risky provocation tests.

Secretion of Cytokines, Histamine and Leukotrienes in Chronic Urticaria

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Abstract of: Int Arch Allergy Immunol 2002;129:254-60.

Background: Approximately 35-40% of patients with chronic urticaria have an IgG autoantibody to the IgE receptor which can activate basophils and mast cells so that they release histamine. In this study we assessed the cytokine profile present in chronic urticaria sera, and then measured cytokine and leukotriene release from basophils and mast cells upon incubation with chronic urticaria sera. Finally we assessed cytokine expression at the single-cell level and characterized the T cell subpopulations involved in their production. We chose IL-4 as representative of Th2 lymphocytes and IFN-γ for Th1 lymphocytes.

Methods: We analyzed IL-4, IL-5 and IFN-γ in 60 chronic urticaria sera versus 51 controls. Sera were incubated with purified human basophils and cutaneous mast cells and the release of histamine, IL-4 and leukotrienes (C_4, D_4, E_4) was quantitated. Immunoblotting was performed to identify IgG antibody to FcεRIα, a subunit. We measured intracellular cytokine production in peripheral blood mononuclear cells of 17 chronic urticaria patients compared to 50 healthy controls. Results: We found higher IL-4 levels ($p=0.028$) in the sera of chronic urticaria patients (1.03 pg/ml) versus healthy donors (0.20 pg/ml) but no difference between urticaria sera and atopic control sera (0.52 pg/ml). We did not detect IFN-γ or IL-5 in any serum. However, sera that activated basophils so that they released histamine also produced leukotriene and IL-4, and leukotriene production by cutaneous mast cells and basophils was closely correlated. However, there was no correlation between immunoblotting and the functional ability to induce either histamine or IL-4. After stimulating with PMA-ionomycin we found significant differences in CD4+ lymphocyte production of IL-4 and IFN-γ with no differences in CD8+ lymphocyte production of either cytokine.

Conclusion: Our data support the presence of basophil and mast cell activators in the sera of patients with chronic urticaria which can lead to the production of leukotrienes and IL-4 in addition to the histamine. IL-4 levels are similar to those seen in atopic subjects. We found that CD4+ T cells from patients with chronic urticaria are activated and tend to produce higher cytokine levels than CD4+ T cells from healthy controls. There were no differences when cytokine production by CD8+ lymphocytes was similarly assessed. These results are conšistent with the histology found in biopsies of chronic urticaria lesions, where a CD4+-predominant infiltrate is found with cytokine production suggesting either a Th0 response or a mixture of Th1 and Th2 lymphocytes.

Use of CD63 expression as a marker of *in vitro* basophil of activation and leukotriene determination in metamizol allergic patients

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Abstract of: Allergy 2003;58:312-7.

Background: We assessed the reliability of basophil activation test (FAST) and sulphidoleukotriene production (CAST) in the *in vitro* diagnosis of allergy to metamizol, evaluating its sensitivity and specificity.

Methods: Twenty-six patients allergic to metamizol and 30 control individuals were studied. Skin tests with metamizol, FAST, and CAST were performed.

Results: FAST sensitivity was 42.3% and specificity 100%. The PPV of FAST is 100% and the NPV 99.4%. The likelihood ratio for a positive value cannot be calculated because the specificity is 100% and the likelihood ratio for a negative value

is 0.58. CAST sensitivity was 52%, and specificity 90%. The PPV of the test is 5% and the NPV 99.5%. The likelihood ratio for a positive result was 5.2 and that for a negative result 0.53. FAST detects a larger number of cases when patients are studied within the first 6 months after the clinical reaction ($\chi = 4.2$, $P = 0.04$) than later. Together with skin tests, FAST allowed detection of 69.2% patients allergic to metamizol, the same as CAST 76%. The joint use of the three techniques allowed identification of 76.9% of cases.

Conclusions: FAST and CAST are useful for the diagnosis of allergy to pyrazolones. Its usefulness clearly increases when recent reactions are studied.

Flow-Cytometric Cellular Allergen Stimulation Test in Latex Allergy

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Abstract of: Int Arch Allergy Immunol 2003;130:33-9.

Background: The use of flow-cytometric basophil activation to different allergens has been recommended in recent years. In this study, we analyzed the diagnostic reliability of the flow-cytometric allergen stimulation test (FAST) after latex-specific stimulation *in vitro*. The diagnostic reliability of the technique was assessed as well as its correlation with other *in vitro* diagnostic parameters.

Methods: 43 patients allergic to latex with a positive history and skin test participated in the study. Thirty subjects (20 of them exposed to latex) with a negative history, skin tests and serum-specific IgE determination to latex were used as controls. In FAST the percentage of basophils that express CD63 as an activation marker after *in vitro* stimulation with allergen (latex) is determined by flow cytometry, following double labelling with the monoclonal antibodies anti-CD63-PE and anti-IgE FITC.

Results: Intraclass correlation coefficient in FAST with latex was 0.995 ($p < 0.0001$), which demonstrates the excellent reproducibility of this technique. Taking a cutoff point of 10% by means of ROC curves, FAST yields a sensitivity of 93% and a specificity of 100%. The FAST positive predictive value in latex allergy was 100% and the negative predictive value was 99.9%. We found a positive and significant correlation between FAST and specific IgE (CAP) with the histamine release test and specific sulphidoleukotriene production [cellular allergen stimulation test (CAST);$p < 0.005$].

Conclusions: FAST is a highly reliable technique (93% sensitivity and 100% specificity) in the *in vitro* diagnosis of IgE-mediated latex allergy.

Crítica de libros

Consejos médicos para la tercera edad

EUNSA, Pamplona, 2003, 317 págs.
Varios autores.

Es un libro redactado por profesores y antiguos alumnos de nuestra Facultad destinado a los mayores y sus familias. En efecto, proporciona consejos que facilitan evitar, en lo posible, las enfermedades más frecuentes en la tercera edad y, sobre todo, da una orientación sobre la gravedad de los achaques imprevistos. Ser conscientes de la gravedad de unos y actuar en consecuencia alertando al Servicio de Urgencias, puede salvar una vida. Por el contrario, asustarse ante un proceso banal es sembrar la inquietud en el afectado y su familia y sobrecargar el Servicio de Urgencias. Los capítulos del libro son los siguientes:

1. Atención a urgencias en los pacientes mayores.
2. Enfermedades cardiovasculares en el anciano.
3. Enfermedades infecciosas en el anciano.
4. Los cuidados en la demencia.
5. Cuidados psicológicos y psiquiátricos del anciano en casa.
6. Dermatología geriátrica.
7. Alimentación en la vejez.
8. Ejercicio y tercera edad.
9. El sueño y sus trastornos.