Basophil activation test in interstitial nephritis. Some comments

Test de activación de basófilos en la interstitial nephritis. Algunos comentarios

Dear Editor:

The recent paper by Lara Belmar Vega and coworkers introduced the role of a $CD123^{pos}/HLADR^{neg}$ basophil activation test (BAT) in a case report of interstitial nephritis, suggesting the occurrence of an interstitial nephropathy secondary to the use of omeprazole.[1] Omeprazole is well known from past reports to cause interstitial nephritis.[2] The renal oedematosus interstitium having a massive infiltration of leukocytes and eosinophils, suggested the author to assess an immune response, due to the omeprazole therapy. This case report should assess the optimal use of BAT in omeprazole hypersensitivity.[3] Despite the fact that the authors were not endowed with further allergic tests, such as skin prick test (SPT) or serum IgEs to assess their evidence, they moved on the clinical suspicion of an allergy-driven nephropathy caused by an hypersensitivity response to omeprazole and found a CD63 stimulation index (SI) $\geq$4.1 and $\geq$10% respect the basal, non activated level.[1] The analytical performance of a BAT based on the $CD123^{pos}/HLADR^{neg}$ gating protocol allowed the authors to easily capture basophils in a flow cytometry (FC) approach and to assess cell activation by evaluating the CD63 membrane upregulation upon the activation from omeprazole-caused drug hypersensitivity. Yet, the activation is only slightly higher (i.e. 10.25%) than the indicated cut off, which is $\leq$5% and did not reach the much more encouraging level of an fMLP-mediated activation (34.9%).[1] Causes underlying this moderate, poor activation may be further elucidated by introducing in the test a polyclonal anti-IgE agonist, to probe the level of releasability and activation of basophils in the IgE-mediated mechanism.[4] Furthermore, a CD203c marker to assess also a possible involvement of non IgE-mediated reactions might be useful to better comprehend the observed reaction to omeprazole.[1] Noteworthy, omeprazole targets H2-receptors, so hampering the counter-regulation of basophil activation by histamine, their costitutive activation and the subsequent down-regulation of the FcεRI/IgEs complexes, causing therefore a desensitized cell and/or a CD63 exhausted pool.[5–8] The apparently low level of activation can be also explained by the same gating strategy used by the authors. As already reported in our labs, capturing basophils as $SSC^{low}/CD123^{pos}$ cells, results in the inclusion of further non basophilic $CD123^{pos}$ cells.[9] These cells can be differentiated as $CD45^{pos}$ cells and/or $CD203c^{neg}$ leukocytes, while basophils are notoriously $CD45^{dim}/CD123^{bright}$ cells.[9] The inclusion of more $CD123^{pos}$ events in the gate, while basophils are only $Cd123^{bright}$ cells, underestimates the CD63%, because a possible apparet "cellular loss", as previously reported, actually caused by a biased gating protocol.[10,11]

Therefore, the enthusiastic conclusion about the use of BAT in drug hypersensitivity, should be softened by introducing some bias-preventing warnings:

a) basophils should be optimally captured in FC as CD45dim/CD123bright/HLA-DRneg cells, without starting in the FSC/SSC dot plot;
b) the introduction of a CD203c activation marker may be particulaly useful to discern non IgE from IgE-mediated responses.

In the case report described by the authors one cannot exclude the hypothesis that the effect of omeprazole on basophils may be of immune, pharmacological origin, rather than allergic. The interaction with H2 and H4-receptors may block the histamine-mediated loop to deactivate basophils, causing the ongoing release of IL-4 from these leukocytes and the activation of a Th-mediated response, an effect that can increase the production of IgGs, with consequent nephritis onset.[12,13]

This paper is interesting because permits to focus onto the major effect exerted by a BAT in the clinics.

Conflict of interest

The authors state they have no conflict of interest.

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Glomerulonefritis necrosante en un paciente con VIH, VHC y leishmaniasis visceral

Necrotizing glomerulonephritis in patients with HIV, HCV and visceral leishmaniasis

Sr. Director:

La coinfección VIH/leishmaniasis visceral es frecuente y cursa de forma tórpida y recurrente. La afectación renal incluye glomerulonefritis y afectación tubular. Presentamos un caso poco frecuente.

Se trata de un varón de 46 años adicto a alcohol y drogas parenterales diagnosticado en 2006 de infección VIH estadio C y VHC genotipo 4. Inicia TARGA en 2011, tras su primera descompensación ascítica por cirrosis hepática Child C, con hipertensión portal, esplenomegalia y pancitopenia. Lo suspende voluntariamente en mayo de 2015 y lo reinicia en noviembre del 2016 (raltegravir, abacavir y lamivudina). Un mes después, con carga viral no detectable y sin restauración inmune (CD4 74/mm^3), desarrolla fracaso renal agudo no oligúrico (creatinina máxima 5,7 mg/dL), proteinuria mixta de 2 g/día, microhematuria y tumoración en el dorso de la lengua (fig. 1) con biopsia de displasia epitelial severa y candidiasis mucosa. En las pruebas complementarias destacaba descenso de C'3, gammapatía policlonal, aumento de inmunoglobulinas y de cadenas kappa y lambda y ANA positivos (1/640). Las crioglobulinas, el Mantoux y las serologías (VHB, sífilis, *Toxoplasma*) fueron negativas. Se determinaron IgG de CMV y *Leishmania* y antígeno rK39 en sangre, que resultaron positivos. La PCR para *Leishmania* en la lengua y la médula ósea fueron negativas. Se realizó biopsia renal, en la que se identificaron 6 glomérulos, uno con focos de necrosis segmentaria con fibrina y 2 con semilunas celulares sin trombos (fig. 2). En el intersticio aparecía inflamación crónica moderada y fibrosis, sin alteraciones tubulares. No había signos de vasculitis. La IFD era positiva de predominio mesangial para C'3 (++), IgG (+), C1q e IgM (+), y negativa para IgA y cadenas ligeras. No se identificó amiloide con la técnica del Rojo Congo. ME no estaba disponible. El paciente inició tratamiento con anfotericina B liposomal, normalizando 3 semanas más tarde la función renal y mejorando las alteraciones urinarias. Dos meses después inició tratamiento