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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Necrotising glomerulonephritis in a patient with HIV, HCV and visceral leishmaniasis☆

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

Dear Editor,

Concomitant human immunodeficiency virus (HIV) infection and visceral leishmaniasis is frequent and follows a torpid and recurrent course. Kidney involvement includes glomerulonephritis and tubular impairment. We report an uncommon case.

A 46-year-old man addicted to alcohol and parenteral drugs was diagnosed in 2006 with stage C HIV infection and hepatitis C virus (HCV) genotype 4. He started highly active antiretroviral therapy (HAART) in 2011, following his first episode of decompensated ascites due to cirrhosis with a Child-Pugh score of C, with portal hypertension, splenomegaly and pancytopenia. He voluntarily suspended HAART in May 2015 and restarted it in November 2016 (raltegravir, abacavir and lamivudine). A month later, with an undetectable viral load and no immune restoration (CD4 + T cells 74/mm^3), he developed non-oliguric acute kidney failure (peak creatinine 5.7 mg/dl), mixed proteinuria of 2 g/day, microhaematuria and swelling on the back of the tongue (Fig. 1). A biopsy demonstrated severe epithelial dysplasia and mucosal candidiasis. Complementary tests revealed decreased C3, polyclonal gammopathy, increased immunoglobulins and kappa and lambda chains, and positive antinuclear antibodies (ANAs) (1/640). Cryoglobulins, a Mantoux test and serology (hepatitis B virus [HBV], syphilis, *Toxoplasma*) were negative. Cytomegalovirus (CMV) and *Leishmania* IgG and rK39 antigen in blood were tested and found to be positive. PCR for *Leishmania* in the tongue and bone marrow were negative. A kidney biopsy was performed in which six glomeruli were identified, one with

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