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Computer-Assisted Inflammation Analysis Of Kidney-Graft Biopsy To Improve Risk Stratification In Allograft Rejection

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Introduction/ Background

Kidney graft biopsy plays a key role in diagnosis of antibody-mediated rejection (AMR), the major cause of renal graft failure. The diagnosis of AMR requires the presence of i) donor specific antibodies (DSA), and ii) microvascular inflammatory lesions on kidney graft biopsy.

Aims

Histological assessment relies on Banff classification [1] that has quantitative and qualitative limitations and faces in terms of diagnostic accuracy and risk prediction:

1) this grading is categorical with risks of threshold effect;

2) the nature of inflammatory cells is not considered. Hence we propose a new method of computerized image analysis in order to finely characterize the quality and intensity of graft inflammation.

Methods

Data

57 kidney recipients fulfilled the Banff criteria for AMR between 2004 and 2012 at the Lyon Hospitals. Double immunohistological stainings were performed with CD31 (capillaries) and respectively CD68 (macrophages), CD3 (T lymphocytes), CD66b (granulocytes), CD20 (B lymphocytes). 288 glass slides were scanned (MiraxScan, 20x, NA=0.8).

Algorithms

The goal is to quantify the number of immune cells in the different parts of the kidney cortex. Due to the biopsy preparation such as biopsy slicing and image quality staining many variations within the observed object could happen and result to incorrect image segmentation. Hence we combine color component images to extract Regions of Interest (ROI) based on the use of their contextual data information in order to correctly extract the capillaries and immune cells. The algorithms are implemented in the Icy software (http://icy.bioimageanalysis.org) [2]. In the workflow: 1) color deconvolution [3], 2) pre-processing step to segment the pixel staining, 3) extraction of stained objects by combined information. The color deconvolution separates the initial image into 3 component-staining images: blue component for nuclei, brown component for capillaries and the purple one for immune cells. These component images are first preprocessed, by gaussian filtering and then by the k-means classification to segment the images. We combine the segmented ROI and their spatial relation to extract the objects of interest.

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Results

34 patients had C3d+ DSA and 23 had C3d- DSA. Al- though allograft survival was lower in the C3d+ group (p<0,001 by log-rank), Banff scores for AMR were similar in the 2 groups (3.4±1.1 vs 3.5±1.2, p=0.65). In contrast, our approach revealed notable differences in graft inflammation between the two groups. The number of CD68 cells in the capillaries and in the interstitium allows identifying patients with a risk of graft loss (HR=3.18, p<0.01 et HR=2.62, p=0.01 respectively). The combining C3d test and quantification of monocytes in interstitium allow clustering patients into 3 groups of renal prognosis: C3d-, C3d+/CD68 low and C3d+/CD68 high (p<0.0001 by log rank; C3d+/CD68 high vs C3d+/ CD68 low: HR=2.43, p=0.04; C3d+/CD68 low vs C3d-: HR=4.99, p=0.006).

The isolated C3d test has an excellent value negative prediction (89,5% for the 1 year graft loss) but perfectible positive prediction (52,9%) [4] . The monocyte quantification allows to accurate the prognosis of patients in the C3d+ group. Using this novel reproducible approach for topological quantification of inflammation, we observed that histopathological features of complement-binding DSA are different from that of non-complement. The computer-assisted analysis of graft inflammation improves the risk stratification of graft loss.

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