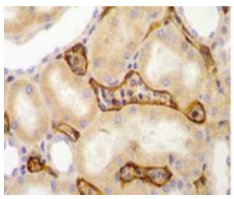
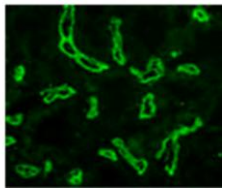
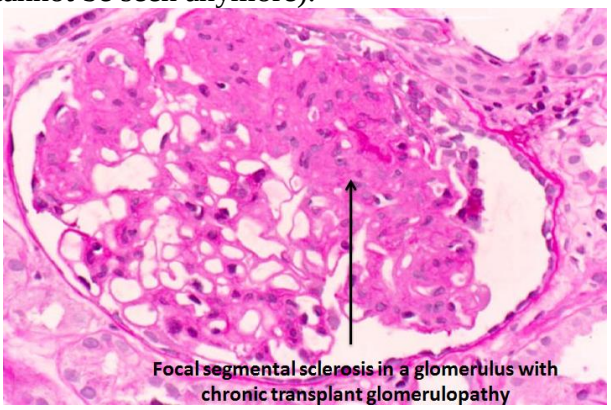
- **There are other causes which can cause dysfunction of the renal graft other than rejection. Some of these causes include the following:**
  - **Drug toxicity** (due to strong adverse effects of drugs given to the patient such as cyclosporine).
  - **Infection** (due to immunosuppressive drugs received by the patient and leaving him susceptible to get infectious diseases).
  - **Recurrent glomerular disease.**
- **Graft rejection:**
  - **Definition**: the body refuses the foreign transplanted organ.
  - **Types of rejection:**
    - ✓ Hyperacute rejection:
      - ❖ It occurs very close to the time of transplantation (immediately or within minutes of transplanting the kidney).
      - ❖ *Cause*: due to pre-formed antibodies. Nowadays, this type of rejection doesn't occur because the presence of these antibodies is detected by laboratory test which are done to the recipient before the procedure.
      - ❖ *Histopathology (see the image):* there will be infarction and tubular necrosis due to thrombosis which blocks blood vessels. Notice that the infarction is accompanied by neutrophils in blood vessels of the glomeruli.

    - ✓ Acute rejection:
      - ❖ It occurs between first few months to one year from the time of the procedure.
      - ❖ *If the transplant rejection is mediated by B-cells, this is called: acute antibody-mediated rejection:*
        - ➢ Main target will be the vessels which will show swelling of the endothelium, and with more advanced severe stages, ulceration with chronic inflammation.
        - ➢ C4d immunostain will help you to know if this acute rejection is antibody-mediated or not. C4d can be detected by two methods:
          - Immunohistochemistry (which will show C4d brown in color).
          - Immunofluorescence (which will show C4d green in color. Notice that this method requires the use of fresh tissues).

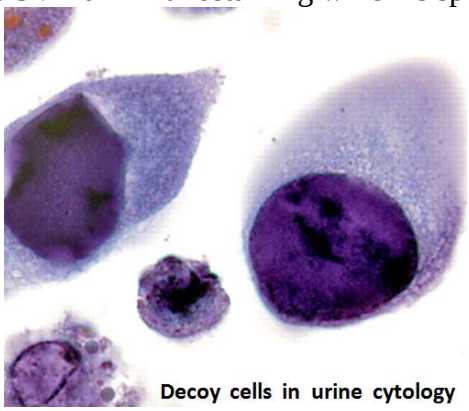
      - ❖ *If the transplant rejection is mediated by T-cells, this is called: acute cellular-mediated rejection:*
        - ➢ Main target will be renal tubules (resulting in tubulitis) which will contain lymphocytic infiltrate.
        - ➢ This condition can be subclassified to: mild, moderate and severe depending on the degree of inflammation in the tubules.

- ✓ Chronic rejection:
  - ❖ It occurs beyond one year of transplantation.
  - ❖ *Cause*: multiple recurrent acute rejections (no matter if these attacks show clinically or not).
  - ❖ *Histopathology (see the image):*
    - ➢ Chronic rejection results mainly in fibrosis (fibrointimal proliferation of vessels).
    - ➢ Atrophy of tubules.
    - ➢ Fibrotic interstitium.
    - ➢ Glomeruli will have segmental sclerosis (this is known as transplant glomerulopathy: which means that the capillary lumen cannot be seen anymore).


Focal segmental sclerosis in a glomerulus with chronic transplant glomerulopathy

- **Banff classification is the one which is used to evaluate the histologic appearance of renal allograft biopsies.**

- **Drug toxicity:**
  - **Cyclosporine toxicity: which is classified to:**
    - ✓ Functional toxicity: in which no abnormality will be seen in biopsies but the function of the kidney is reversibly deteriorated due to vasoconstriction caused by the drug.
    - ✓ Acute toxicity: changes will start to be seen under the microscope. The characteristic feature of this type of toxicity is the presence of isometric vacuoles.
    - ✓ Chronic toxicity: this occurs with prolonged use of the drug resulting in diffused interstitial fibrosis (known as striped fibrosis) and tubular atrophy.
    - ✓ Thrombotic microangiopathy: either happens within blood vessels of capillaries of glomeruli. This is the most dangerous type of toxicity which might lead to renal failure.
  - **Tacrolimus toxicity**: changes are similar to cyclosporine toxicity.
- **BK nephropathy:**
  - BK virus affects renal transplant patients.
  - **Screened by**: urine cytology to detect decoy cells.
  - Another method is to use SV-40 immunostaining which is specific for BK virus.


Decoy cells in urine cytology