Immunohistochemistry in Clinical Practice

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Immunohistochemistry in clinical practice has become the cornerstone of diagnostic pathology. The use of immunohistochemistry continues to grow with increased number of available tests. Immunohistochemistry can confirm the diagnosis and exclude or rule out other entities in the differential diagnosis. It is particularly helpful when used in conjunction with routine morphology and other ancillary techniques. A wide variety of immunohistochemical tests are available to detect CD markers (for hematopoietic proliferations), markers for endothelial and epithelial cells, mesenchymal tissue markers, neural markers, and neuroendocrine markers. Numerous viruses can also be detected with immunohistochemical stains such as herpes simplex viruses, cytomegalovirus, adenovirus, hepatitis B virus, human papilloma virus, Epstein-Barr virus and papovaviruses. In fact any protein can be localized to the cytoplasm, cytoplasmic membrane or the nucleus through immunohistochemistry.

The division of immunohistochemistry has recently acquired new tests that are becoming important in diagnostic pathology and has hence increased the antibody inventory to >60 tests. These new tests include:

1) C4d. C4d is a stable complement split product of C4 factor of the classic complement pathway that is deposited in the endothelium of capillaries. Detection of C4d deposition is proven a valuable tool for detecting humeral mechanisms of acute rejection in various solid organ transplantations. In the kidney, capillary C4d deposition is recognized as a specific and independent diagnostic and prognostic marker of antibody-mediated rejection (AMR) in renal allograft biopsies, and recently it was included in the Banff classification as a criterion for the diagnosis of acute and chronic AMR. In heart transplants, C4d staining of the capillaries also has been found to correlate well with anti-donor serum alloantibodies, and is sometimes used as one of the criteria for antibody-mediated cardiac rejections. In liver transplantation, where humeral mechanisms by far play a smaller role in mediating acute rejection, the use of C4d detection methods have also been recognized in detecting this type of rejection and in the differential diagnosis between acute rejection and hepatitis C infection in HCV-positive patients. Interacinar deposition of capillary C4d has also been postulated to play a potential role in antibody mediation rejection of pancreatic allografts. Immunohistochemical methods for C4d detections are useful in the absence of frozen sections and whenever preserved tissue morphology is desirable. These methods provide a useful tool for detecting AMR in solid organ allografts where frozen tissues are not routinely kept.

2) SV-40. This immunohistochemical test is used to demonstrate infections caused by ds-DNA circular viruses including BK virus and human polyomavirus JC virus. BK virus infection is common but remains latent throughout life. The virus gets reactivated in immunocompromised individuals and produce infection in kidney allografts (Fig 1). The human polyoma JC virus causes progressive multifocal leukoencephalopathy which is a fatal demyelinating disease with characteristic cytopathic changes in oligodendrocytes and astrocytes.
3) Calretinin: This immunostain detects a 29kD intracellular calcium-binding protein that is present in a variety of cells including mesothelial cells. In clinical practice it is most valuable in the distinction between pulmonary adenocarcinoma and pleural mesothelioma in tissue sections and fluid cytospins. Calretinin is also present in schwannoma, granular cell tumor and adrenal cortical tumors. In sex cord stromal tumors of the ovary it displays greater sensitivity than inhibin. Recently calretinin has attracted attention in its ability to label ganglion cells and nerves in rectal biopsies performed for Hirschsprung’s disease (Fig 2). Absence of calretinin immunoreactivity indicates aganglionosis in Hirschsprung’s disease.

4) Beta-catenin: Beta-catenin binds to the cytoplasmic domain of E-cadherin, forming a component of cell-cell adhesion. Normal cells therefore show membrane staining for \( \beta \)-catenin, while cytoplasmic and/or nuclear staining is abnormal. Beta-catenin expression is regulated by the adenomatous polyposis coli (APC) gene. Dysregulation of \( \beta \)-catenin occurs in Gardner’s syndrome, where it leads to both familial adenomatous polyposis and fibromatosis. Expression of beta-catenin with demonstrable nuclear immunoreactivity is increased in desmoid fibromatosis, solitary fibrous tumor, synovial sarcoma, endometrial stromal sarcoma and carcinosarcomas. Although low level nuclear positivity is seen in a wide variety of tumors, the main diagnostic utility of beta-catenin is in confirming the diagnosis of desmoid fibromatosis.

References: