*Journal of Islamabad Medical & Dental College (JIMDC); 2013;2(2):56-57*

- Editorial

# Immunohistochemistry
# A Useful Diagnostic Tool in Histopathology

**Usman Hassan**

Consultant Histopathologist
Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore

Like many other disciplines in medicine, pathology is revolutionizing at an incredible pace and sometimes one feels as a bystander in one's own 'pathology world'. It is becoming increasingly important for pathologists to keep updated with the ever-increasing dimensions in their respective specialties. In the past pathologists had to work without any support of ancillary techniques. Haematologists and histopathologists had to rely mostly on morphology alone. Scenario has changed now. In advanced pathology centres, pathologists can take help of highly advanced technologies, be it flow cytometry, immunohistochemistry (IHC), immunofluorescence, molecular studies like polymerase chain reaction, tissue microarrays or FISH etc. One can say that it is very easy for modern pathologist to work with all this support. But I think these technologies can only be used by very learned and up-to-date pathologists. Otherwise these can play havoc in unsafe hands.

Immunohistochemistry is one example. The principle of IHC has been known since the 1930s, but it was not until 1942 that the first IHC study was reported. Coons *et al.* (1942) used antibodies to identify pneumococcal antigens in infected tissue. Since then, improvements have been made in protein conjugation, tissue fixation methods, detection labels and microscopy, making immunohistochemistry a routine and essential tool in diagnostic and research laboratories. For a non pathologist doctor, it is very easy to believe that IHC is a magic and it is very easy to diagnose surgical biopsies by simply applying IHC antibodies. For instance when Vimentin was introduced it was thought that when differential diagnosis lies between sarcoma and carcinoma, vimentin can decide between them. Unfortunately this is not that simple. Studies now prove that vimentin is one of the most nonspecific markers which can stain not only sarcoma but even carcinomas. Likewise Cytokeratin (CK) which is still considered as a very specific carcinoma marker cannot be used in isolation. Again research has proved that although CK is a very specific marker for carcinoma, it can stain many sarcomas like synovial sarcoma, epithelioid sarcoma, leiomyosarcoma, epithelioid malignant peripheral nerve sheath tumors, epithelioid angiosarcomas and Ewing's sarcoma. It can even stain epithelioid hemangioendothelioma. Story does not end here. Unfortunately whenever a new antibody is launched in market, they are declared very much specific and sensitive for diagnosing a particular disease entity. I think a lot of commerical bias is attached with these antibodies. For instance when CD117 stain was launched it was considered a very specific marker for gastrointestinal stromal tumor (GIST). It still is very specific for GIST and oncologists put their patients on Glivec once histopathologists diagnose GIST after the application of CD117. Again research has proved that CD117 shows expression in seminoma, dysgerminoma, angiomyolipoma, angiosarcoma (50%), clear cell sarcoma, chronic myeloid sarcoma, epithelioid sarcoma, Ewing sarcoma, adenoid cystic carcinomas. Same uncertainties are shared by other immunostains. CD99, once considered to be a very useful stain for diagnosing Ewing's sarcoma has also lost its credibility as being sensitive or specific. It can show expression in acute lymphoblastic lymphoma, small cell variant of osteosarcoma, rhabdomyosarcoma, desmoplastic round blue cell tumors and many others. Only a histopathologist can understand that when differential diagnosis involves these aforementioned round blue cell tumors, only CD99 cannot help. A panel of immunostains must be used. There are now hundreds of IHC antibodies available. A histopathologist must have knowledge about every antibody regarding its uses and pitfalls. Otherwise IHC is going to do more harm than good. LCA is another immunostain which shows expression in lymphocytes and lymphomas. However one should know that there are also few lymphoproliferative disorders which can be LCA negative like anaplastic large cell lymphoma and plasma cell neoplasms. In my opinion whenever an antibody is launched, the company immediately gives

funds for research regarding that antibody. Because these researches target specific lesions, results are always good. As more and more researchers jump in, they at last manage to prove that a particular antibody is not that specific.

In short no antibody can be used in isolation. A histopathologist should know how a panel of immunostains can be used in order to reach a final diagnosis. I personally feel that at least a panel of five to six antibodies should be used. For example a basic panel of CD20, CD3, BCL2, Ki67, CD10, BCL6, and Cyclin D1 should be used in diagnosing lymphomas. Of course there is a lot of variation which one can use depending upon the morphology. Similarly a panel of LCA, tdt, Desmin, Myogein, CD99, FLI1 is applied in diagnosing round blue cell tumors. For sarcomas, CK, S100, SMA, MDM2, Desmin and CD34 can be used. These are very basic panels and there is a lot of variation which one has to adopt. Despite of development of immunohistochemistry and genetics, histology is still the gold standard. It is only the histology which directs a pathologist in right way. Otherwise applying immunostains blindly on a case is just like finding your way in the dark.

Lastly a very important matter to be addressed is that it is only the histopathologist who can decide which panel of immunostain is to be applied for a particular lesion. I have seen in my practice that sometimes treating oncologists order stains of their choice based on their clinical impression. They get very much annoyed when we do not apply those stains. They do not understand limitation of their own knowledge regarding immunostains. They cannot compete with a pathologist in deciding appropriate immunostains. Therefore they should leave this decision on pathologists.

Many targeted therapies are nowadays being used depending upon the results of immunostains. Rituximab is used in diffuse large B-cell lymphomas (DLBCL) based on CD20 positivity in DLBCL. Glivec is used in GISTs based on CD117 expression. Anti EGFR therapy is used in Non small cell lung carcinomas and Herceptin is used in HER-2/ neu positive breast tumors. Lot of studies and research are in progress in the field of targeted therapies. However nothing is absolute in this world.

To conclude IHC is a very useful technique when used in skillful hands.