REVIEW

How Our Practice of Histopathology, Especially Tumour Pathology has Changed in the Last Two Decades: Reflections from a Major Referral Center in Pakistan

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Abstract

Continued advances in the field of histo pathology (and cyto pathology) over the past two decades have resulted in dramatic changes in the manner in which these disciplines are now practiced. This is especially true in the setting of a large university hospital where the role of pathologists as clinicians (diagnosticians), undergraduate and postgraduate educators, and researchers has evolved considerably. The world around us has changed significantly during this period bringing about a considerable change in our lifestyles and the way we live. This is the world of the internet and the world-wide web, the world of Google and Wikipedia, of Youtube and Facebook where anyone can obtain any information one desires at the push of a button. The practice of histo (and cyto) pathology has also evolved in line with these changes. For those practicing this discipline in a poor, developing country these changes have been breathtaking. This is an attempt to document these changes as experienced by histo (and cyto) pathologists practicing in the biggest center for Histopathology in Pakistan, a developing country in South Asia with a large (180 million) and ever growing population. The Section of Histopathology, Department of Pathology and Microbiology at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan's largest city has since its inception in the mid-1980s transformed the way histopathology is practiced in Pakistan by incorporating modern methods and rescuing histopathology in Pakistan from the primitive and outdated groove in which it was stuck for decades. It set histopathology in Pakistan firmly on the path of modernity and change which are essential for better patient management and care through accurate and complete diagnosis and more recently prognostic and predictive information as well.

Keywords: Histopathology - cytopathology - molecular pathology - cancer

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Introduction

The continued advances in the field of Histo (and cyto) pathology over the past two decades have resulted in dramatic changes in the manner in which these disciplines are now practiced. This is especially true in the setting of a large university hospital where the role of histo (and cyto) pathologists as clinicians (diagnosticians), undergraduate and postgraduate educators, and researchers has evolved considerably. The world around us has changed significantly during this period bringing about a considerable change in our lifestyles and the way we live. This is the world of the internet and the world-wide web, the world of Google and Wikipedia, of Youtube and Facebook where anyone can obtain any information one desires at the push of a button. The practice of Histo (and cyto) pathology has also evolved in line with these changes. And for those practicing this discipline in a poor, developing country, these changes have been breathtaking. This is an attempt to document these changes as experienced by histo (and cyto) pathologists practicing in the biggest center for Histopathology in Pakistan, a developing country in South Asia with a large (180 million) and ever growing population. The Section of Histopathology, Department of Pathology and Microbiology at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan's largest city has since its inception in the mid-1980s transformed the way histopathology is practiced in Pakistan by incorporating modern methods and rescuing histopathology in Pakistan from the primitive and outdated groove in which it was stuck for decades. It set histopathology in Pakistan firmly on the path of modernity and change which are essential

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for better patient management and care through accurate and complete diagnosis and more recently prognostic and predictive information as well. We receive cases from the whole country through our collection points located all over Pakistan. In fact, the bulk of our specimens come from outside the hospital, and from outside Karachi and we now receive specimens even from Afghanistan, our neighboring country. Many of the authors of this article are graduates of the Department's own residency program (almost certainly the best Histo and Cytopathology residency program in the country). The principal author (ZA) joined the residency program in 1996 and after acquiring Fellowship in Histopathology from the College of Physicians and Surgeons Pakistan (CPSP), is now part of the Histopathology faculty at AKUH. The year 1996 appears to be an ideal starting point to document and highlight the exciting changes that have occurred in the practice of Histopathology in our institution over the last two decades. The ensuing discussion should be seen through our perspective: practicing histopathologists in a poor, volatile, violence ridden and heavily populated country racked by terrorism, rampant poverty and little access (for the majority of the population) to health, education and even clean drinking water. However, we had the advantage of being trained in and now practicing in the premier center for histopathology in the country which has consistently taken the lead role in ensuring that the histopathology services that are offered are not just the best in the country and the region but of truly international standards. The role and contribution of the senior Histopathologists in the Section in developing and establishing these services cannot be overemphasized and they remain, even today, a source of guidance and inspiration to all. This article discusses in detail the service component of the section which constitutes the bulk of our work. The role as educators and researchers may be discussed in a separate article in future. We had published an article in 2009 regarding the difficulties and challenges faced by practicing histopathologists in Pakistan (Ahmad et al., 2009). The current article focuses on the evolution of histopathology practice in Pakistan over the past two decades.

Synoptic Reporting of Cancer Specimens

We report over 50,000 surgicals (biopsies and resection specimen) and almost 20,000 cytology specimens (gynae and non-gynae) every year and the number is consistently growing. Although we see both neoplastic and non-neoplastic cases, the most important diagnosis that we make is obviously that of cancer. When ZA joined the residency program in 1996, all cancer biopsies and resections were reported in the descriptive format. No checklists were followed to ensure that all relevant and essential information was incorporated in the reports. By the beginning of the new millennium, a few cancer resection reports had been converted to synoptic format by following College of American Pathologists (CAP) checklists for reporting of cancer specimens. Currently, all our cancer reports, both biopsies and resections are reported strictly according to the CAP protocols and every relevant and essential information and parameter is included in the final report. The gross as well as microscopic information is now reported synoptically according to the CAP checklists (CAP, 2012). In those days, comprehensive staging was also not carried out. However, around 2001, we started using the TNM Staging System for all cancers and strictly incorporated TNM staging in all our cancer resection reports. Over the years, we have ensured that any modifications in the TNM staging of any cancer are immediately incorporated in our reports, and that at any given point in time, our reports incorporate the latest TNM staging of any cancer (Edge and Compton, 2010).

Urinary Bladder Pathology

When ZA joined the residency program in late 1996, we were still using the Ash grading system (classification) for epithelial bladder neoplasms (Ash, 1940), although sometimes Mostofi's classification (Mostofi, 1960) was also followed. During ZA's residency years there was a gradual shift towards the World Health Organization/ International Society of Urological Pathology (WHO/ ISUP) consensus classification of Urothelial neoplasms of the urinary bladder (Epstein et al., 1998). By 2001, we had fully adopted this classification and were using it regularly. Currently, we use the 2004 WHO Classification of urethelial neoplasms of the urinary bladder (WHO, 2004). Over the years, we became more sensitive about the importance of lamina propia and muscularis propria invasion in urothelial neoplasms. We submit more material until muscle invasion is detected. On the other hand, we submit the entire tissue for histopathological examination if muscle invasion is not detected even after extensive sampling. At the same time, we take great care not to misinterpret prominent fascicles of muscularis mucosae as muscularis propria (Engel et al., 1992). Various studies have demonstrated the great importance of muscularis propria invasion on therapy and prognosis of bladder cancers (Amin et al., 1997a; 1997b). A study performed in our section in 2002 demonstrated a direct relationship between the histologic grade of urothelial carcinoma and muscularis propria invasion (Ahmad et al., 2002). The number of radical cystectomies received in the section has slowly increased over the years.

Male Genital Tract Pathology

At the time ZA joined the residency, the section only received transurethral resection (TUR) or enucleation specimens of the prostate, both for benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma. There were hardly any needle biopsies. This trend was prevalent even in the early years of the new millennium. It was only sometime after 2005 that the trend began to change albeit gradually. Similarly, serum Prostate Specific Antigen (PSA) levels were hardly ever available. TUR and enucleation were performed with both diagnostic and therapeutic intent. No radical prostatectomies were performed as there was no surgical expertise available in the country. Even today our institution (together with

another in Islamabad) remains the only source of radical prostatectomies. The number of radical prostatectomies has increased very slowly. Even today, the majority of prostatic adenocarcinomas are diagnosed on TUR or enucleation (rather than needle biopsy specimens) and usually show large volume of tumor indicating the presence of extensive and advanced disease (Arshad and Ahmad, 2013). The reason is that the facility of serum PSA testing and needle biopsies is still not widely available especially in the smaller cities and towns. In the years of ZA's residency, there was little practice of recording even overall tumor volume on needle biopsies let alone on separate cores. The same was true for Gleason grading, (Gleason and Mellinger, 1974; Gleason, 1992) which has been shown by various studies to be the best grading system for prostatic adenocarcinoma with acceptable interobserver reproducibility among both urologic and general pathologists (Allsbrook et al., 2001a; 2001b). However, the findings of multiple studies have demonstrated that tumor volume (percent of tumor in each positive core), Gleason score on each core, and presence of perineural invasion in each core are important prognostic factors that correlate well with positive surgical margins, extraprostatic extension, seminal vesicle invasion, positive lymph nodes etc. on radical prostatectomy specimens (Sebo et al., 2000; Freedland et al., 2002; 2013; Kryvenko et al., 2012). During the past few years, we have become sensitive to the recording of tumor volume and exact Gleason score on both TUR (or enucleation) and needle biopsy specimens. We now record tumor volume, Gleason score and presence or absence of perineural invasion on each needle biopsy core (Ahmad and Arshad, 2013). Most of our needle biopsies used to be sextant but we now also receive 8 to 10 cores in some cases. We also now regularly record the presence or absence of perineural invasion and tertiary Gleason grade (when applicable) on all specimens containing adenocarcinoma. In the past two years or so, we have modified our Gleason grades 3 and 4, expanding the latter according to the 2005 WHO recommendations (Billis et al., 2008; Shah, 2009; Dong et al., 2012). The use of serum PSA levels and needle biopsies in the diagnosis of prostatic adenocarcinoma is now much more established in our practice. Serum PSA levels are provided more commonly now compared to ten years back. We now also routinely use immunohistochemical stains like Prostate Specific Antigen (PSA) (Nadji et al., 1981; Varma et al., 2002) in poorly differentiated carcinoma (when there is confusion with high grade bladder carcinoma), and Cytokeratin 5/6 (Abrahams et al., 2002), P63 (Shah et al., 2002) and 34βE12 (Kunju et al., 2006) to confirm the diagnosis of carcinoma in equivocal cases (absence of staining for these basal cell markers is highly significant). As mentioned above, radical prostatectomies are still only performed in only two institutions (including ours) in the entire country. After some hiccups in the initial years, we now process, submit, histologically examine and report radical prostatectomy specimens strictly according to international guidelines and protocols (Walsh, 1994; Catalona, 1995). We submit the entire specimen for histologic examination. We record tumor volume, Gleason score, extraprostatic extension, status of surgical margins, seminal vesicle invasion etc (Memon et al., 2009). In cases of benign prostatic hyperplasia (BPH), we have become sensitive towards recording the weight of TUR and enucleation specimens (Arshad and Ahmad, 2013).

In the initial years, we did not strictly record Johnson Score on testicular biopsies sent for infertility. All testicular biopsies at that time were sent in formalin. However, later the number of testicular biopsies sent in Bouin Solution increased. Since 2000, we record Johnson score in every biopsy and for the last five years our recording of Johnson scores has become more accurate and precise e.g. 8.9, 9.3 etc (Johnson et al., 1980). We also report the presence or absence of any intratubular or invasive germ cell neoplasia. When ZA joined the residency, we were following the Dixon and Moore (1952) classification of Testicular Neoplasms (Dixon and Moore, 1952). There were some advocates of the British Collins and Pugh classification (Collins and Pugh, 1964) but it was not favored due to its difficult terminology. Since 2005, we have been using the WHO histological classification of testicular tumors (WHO, 2004). In the years of ZA's residency, we relied on morphology and special stains like PAS (for glycogen) for diagnosis of germ cell tumors. Initially we only had immunohistochemical stain Placental alkaline phosphatase (PLAP) to help us in diagnosing seminomas (Jacobsen and Norgaard-Pederson, 1984). Later, we also acquired CD30 (for embryonal carcinoma) and few years back CD117 (for seminoma) (Emerson and Ulbright, 2005; Gopalan et al., 2009). In all testicular resections, extensive sampling is performed to rule out/identify mixed germ cell tumors (Gopalan et al., 2009). Majority of germ cell tumors in our practice are indeed malignant mixed germ cell tumors. Diffuse large B-cell non-Hodgkin lymphomas are common in older men. We also search for intratubular germ cell neoplasia (IGCN), which is often present in the residual non neoplastic testis (Gondos and Migliozzi, 1987). Some studies report its frequency in over 80% of testes with invasive germ cell tumors (Loy and Dieckmann, 1990). However, its frequency has been very low in our practice.

Neuropathology

The frequency and complexity of Central Nervous System (CNS) tumors that we see in our practice has slowly increased over the past fifteen years, and today it appears to us as if we are in the midst of a CNS tumor epidemic (Arshad er al, 2010; Ahmad et al., 2011). We have become the most important referral center for CNS tumors in the country. When ZA joined the section in 1996, we were following the Daumas-Duport/St. Anne Mayo grading system (Daumas-Duport et al., 1988) for gliomas. However, by 2001, we had switched to the World Health Organization (WHO) grading system for all CNS tumors (WHO, 2000) and now follow the latest version of the WHO classification (WHO, 2007).

We have an active neurosurgery service in our university hospital and we receive a number of in house CNS tumor cases for histopathology which include a number of cases which are initially sent for intraoperative consultation. We prepare both touch preps and frozen

sections in these cases. However, the majority of our CNS tumor cases come from outside the hospital and from other cities and towns. Until around 2008, we had never diagnosed gliosarcoma (Kleihues et al., 2007; WHO, 2007), central neurocytoma (Figarella-Branger et al., 2007; WHO, 2007), or atypical teratoid/rhabdoid tumor (AT/RT) (Judkins et al., 2007; WHO, 2007). We have now diagnosed a number of cases of these entities. We plan to publish a case series of central neurocytoma next year. Currently, we do not have the IHC stain INI1 for AT/RT. The cases of AT/RT that we have reported were diagnosed on the basis of age of patient, location, morphology and supporting IHC stains to rule out close differentials like meduloblastoma, primitive neuroectodermal tumor (PNET) etc. However, the diagnosis was later confirmed thanks to the generosity of friends in the United States (U.S.). Blocks were sent to a prestigious neuropathology center in the US and IHC stain INI1 was performed and turned out to be negative. However, we are now in the process of acquiring INI1, hopefully in 2014. In AT/RTs, there is loss of nuclear expression of INI1 in the tumor cells (Haberler et al., 2006). Similarly, we plan to start molecular detection of mutations in AT/RT. Mutation or loss of the INI1 (hSNF5/SMARCB) locus on chromosome 22q 11.2 is a hallmark of AT/RT (Biegel et al., 1999). We also hope to acquire the IHC stain Neuronal Nuclear antigen (NeuN) which will help us in cases of suspected central neurocytoma. A significant number of tumor cell nuclei are positive for NeuN in almost all cases of central neurocytoma (Soylemezoglu et al., 2003).

IHC stains like glial fibrillary acidic protein (GFAP) which we acquired in the late nineties, and others have been invaluable to us in our practice. Examples include synaptophysin (for medulloblastoma and central neurocytoma) and to distinguish these neoplasms from anaplastic ependymoma and oligodendroglioma respectively (Figarella-Branger et al., 1992); inhibin for hemangioblastoma (Jung and Kuo, 2005); epithelial membrane antigen (EMA) and CD34 for meningioma and to distinguish meningiomas from hemangiopericytomas, schwannomas, and solitary fibrous tumor or SFT – meningiomas being EMA positive, while hemangiopericytomas and SFTs are CD34 positive (Perry et al., 1997; Burger et al., 2002). We now use the new WHO grading i.e. hemangiopericytomas, WHO grade II and anaplastic hemangiopericytomas, WHO grade III for these tumors (Giami et al., 2007; WHO, 2007). Meningiomas are the single most common CNS tumors seen in our practice. We now regularly diagnose variants of meningioma such as clear cell, secretory, rhabdoid etc which we did not in the past. Among gliomas, oligodendrogliomas and anaplastic oligodendrogliomas, glioblastoma multiforme (GBM) and ependymomas are very common. In children, medulloblastomas are the commonest tumors that we see. We now apply strict microscopic criteria to all CNS neoplasms according to the latest WHO grading system (WHO, 2007). The proliferative marker Mib1 (Ki67) has helped us a lot in supplementing the histologic grading of gliomas and meningiomas (Perry et al., 2007; WHO, 2007). Since last three years, we have also reported several cases of anaplastic oligoastrocytoma, WHO grade III and glioblastoma with oligodendroglioma component (GBM-O), WHO grade IV (Brat et al., 2008).

Recent studies have shown that GBM-O has distinct genetic and clinical characteristics with presence of oligodendroglioma component predictive of longer survival. Thus, GBM-O differ in clinical behavior and genetic alterations from conventional GBM. (Wang, et al., 2012; Appin et al., 2013) Since last year, we are performing the 1p/19q codeletion test for oligodendroglioma (and anaplastic oligodednroglioma) which provides important prognostic (associated with longer survival) and predictive (patient with codeletion of 1p/19q are very sensitive to procarbozine CCNU and vincristine (PCV) regimens with good response) information (Kros et al., 2007; Giannini et al., 2008) and even helps in diagnosis of difficult cases (astrocytomas and GBM do not show this codeletion). In 2014, we hope to start molecular tests for EGFR mutations (amplifications) which are common in high grade astrocytomas but mostly negative in anaplastic oligodendroglioma and mixed anaplastic oligoastrocytomas, thus helping in diagnosis in difficult cases (Schmitt et al., 2002); IDH1 and 2 mutations (which are seen in 50 to 80% of grade II and III astrocytomas and oligodendrogliomas, secondary GBM and GBM-O but seldom in primary GBM) and are associated with better prognosis (longer overall survival) (Yan et al., 2009; Gupta et al., 2011). IDH mutation screening is rapidly becoming part of the routine pathological workup of gliomas, providing both diagnostic and prognostic information (Ichimura, 2012); and MGMT (O6 Methylguanine-DNA-Methyltransferase) promoter methylation. Such methylation occurs, according to different studies, in 44 to74% patients with GBM and has been shown to be associated with better prognosis, better progression free survival and better overall survival in GBM patients regardless of therapeutic intervention, and is also predictive to a degree. GBM patients are treated with Temozolamide and MGMT methylation may result in increased benefit from Temozolamide therapy (Kim et al., 2012; Zhang et al., 2013). Similarly, we plan to start tests for determining c-myc and n-myc amplifications in medulloblastoms which are associated with worse prognosis (Lamont et al., 2004). Since medulloblastoma is the commonest pediatric CNS tumor in our practice, we are mindful of the exciting new advancements coming up in these tumors. We have already mentioned that we plan to start molecular studies to detect the c-myc and n-myc alterations in the near future. In addition, we plan to classify our cases according to histology (classic, desmoplastic/nodular, medulloblastoma with extensive nodularity or MBEN, large cell/anaplastic) as well as according to the consensus molecular classification (WNT or wingless, SHH or sonic hedgehog, group 3 and group 4) which will help in disease-risk stratification of medulloblastoma. The prognosis is worse in patients with partially resected tumors, metastatic disease, c-myc and n-myc amplification, large cell/anaplastic histology, non SHH/WNT subgroups 3 and 4. IHC antibodies β-catenin (which we already have) and GAB1 (which we plan to acquire shortly) will enable us to diagnose the WNT group (classic type) and SHH group (desmoplastic/nodular and

MBEN) respectively (Ellison et al., 2011; Northcott et al., 2011; Sadighi et al., 2012).

Gastrointestinal, Liver and Biliary Tract and Pancreatic Pathology

When ZA started his residency in 1996, we hardly ever received gastrointestinal polyps for histopathological examination. We rarely, if ever, reported adenomatous polyps. The simple reason was that polyps were rarely removed. However, thanks to a busy gastroenterology service at our institution and the presence of several qualified gastroenterologists with busy practices in the country, we now not only commonly report adenomatous polyps but lately have reported new and rare entities like sessile serrated polyp with dysplasia (Snover et al., 2010; WHO, 2010), inflammatory cap polyps (Esaki et al., 2001) etc. In the last few years, we have also reported several cases of inflammatory fibroid polyps (Miettinen et al., 2010; WHO, 2010) and eosinophilic gastroenteritis (Talley et al., 1990) etc that we had never reported before. We even reported and published a case of diffuse gangliomatosis of intestine (Ahmad et al., 2011). We now follow the WHO Classification of Tumors of the Digestive System for all tumors of the gastrointestinal tract including tumors of liver, gall bladder, bile ducts and pancreas (WHO, 2010).

At the time ZA entered the program, Gastrointestinal Stromal Tumor (GIST) was a hardly known entity, especially in Pakistan, and was not diagnosed. We diagnosed and reported our first cases in the late nineties, and by 2001, the entity had become well established was being regularly reported. Since 2003, we began to group GISTs into the low, intermediate and high risk categories (based on tumor size and mitotic activity) as proposed in the consensus approach by Fletcher et al. (2002). However, recently we have attempted to use the more detailed algorithm proposed by Miettinen and Lasota (2006) and hope to regularly use it in our routine practice. The IHC stains CD117 and CD34 have proved valuable in the accurate diagnosis of GISTs (Miettinen et al., 2000; Hornick amd Fletcher, 2004). We have also recently acquired the DOG1 antibody for the same purpose (Espinosa et al., 2008; Miettinen et al., 2009).

In the past, we were classifying and reporting gastrointestinal neuroendocrine tumors as carcinoid tumors or neuroendocrine carcinomas. However, the classification of gastrointestinal tract (GIT) neuroendocrine tumors (NETs) has, over the years, undergone several modifications. We initially used the WHO (2000) classification for NETs of GIT including pancreas (WHO, 2000) and are currently using the WHO (2010) classification (WHO, 2000). We had a few years back started using the consensus grading system for GIT NETs based on mitotic count and Ki67 index which was developed by Rindi et al. (2006) Recently, we have started using the 2010 modified WHO grading system for GIT NETs which represented a significant change from the 2004 WHO system in that NETs are now graded and staged separately and NETs represent G1 and G2 lesions regardless of stage (WHO, 2010).

When ZA started his residency in 1996, we were using the Astler and Coller (1954) staging system (Astler and Coller, 1954) for colorectal cancer. However, around 2001, we switched to the TNM staging system. We now use the latest TNM staging system for all gastrointestinal tract cancers including tumors of liver, gall bladder, biliary tract and pancreas (WHO, 2010).

In gastric carcinomas, most of our cases are poorly differentiated diffuse signet ring type. We now perform immunostaining for HER2/cerb-2, the amplification of which is a predictor of response to trastuzumab targeted therapy in a subset of gastric cancer patients (Grabsch et al., 2010; Jorgensen, 2010). Helicobacter infection is very common in our country and we report large numbers of gastric biopsies as chronic helicobacter gastritis. Since the last five years, we are seeing biopsies with proton-pump inhibitor changes and fundic gland polyps (Ally et al., 2009), which we hardly ever saw or reported in the past. Again, the main reason is the large number of endoscopic biopsies that are now performed by gastroenterologists around the country. Esophageal carcinoma is among the commonest cancers we report and consistently over the years, most of our cases have come from a single geographic area, the province of Baluchistan in South West Pakistan located next to Iran and China, a region where esophageal carcinoma has always been very common (Curado et al., 2007; IARC, 2007). Celiac disease (CD) was believed to be very rare in Pakistan. However, we are reporting more and more cases (many more then in the past) now and it appears that unlike the common perception, CD is quite common in our country,. We published a paper on small intestinal biopsies in 2012 (Arshad and Ahmad, 2012).

In the appendix, we were always rather confused in the past regarding the terminology and behavior of mucinous tumors. However, since the last two years, we are using the classification proposed by Pai et al. (2009) and the WHO Classification (Carr and Sobin, 2010; WHO, 2010) for reporting appendiceal epithelial mucinous tumors.

When ZA joined the residency program, we hardly ever reported pancreatic solid pseudopapillary neoplasm. We diagnosed the first cases of this entity around 2002 and to date we have reported over two dozen cases. ZA remembers that one of the first few cases that we reported metastasized and generated considerable debate at that time. It was subsequently published (Ahmad et al., 2005). The number of biopsies showing ampullary and periampullary carcinomas has also greatly increased and so has the number of whipple resection specimens that we receive for histopathological examination. We hope to publish our findings on whipple resections soon. Ulcerative colitis is very common and Crohn's disease very rare in our population and this trend has been consistent in our practice – from the time ZA joined and right upto the present time. In the past, no biopsies were sent to us with a question of microscopic (lymphocytic or collagenous) colitis (Warren et al., 2002) but over the last two to three years we have received many biopsies with this query. However, the number of cases which fulfilled the criteria and were reported as microscopic colitis remains to date very small, and all these cases were reported as collegenous colitis.

The number of hepatocellular carcinomas that we report has gradually increased over the years. Almost all the cases were reported on trucut biopsies and the authors recall only half a dozen surgical specimens in all these years. Surgical expertise for resection of liver carcinomas is not available in Pakistan. Most cases arise in a background of Hepatitis B or C infections. These viral infections are endemic in Pakistan and most liver biopsies are performed for grading and staging of chronic hepatitis. Since the mid-nineties, we have used the Scheuer system (Scheuer, 1991) for grading and staging of hepatitis in liver biopsies. During the last five to seven years, we have also begun to report such diverse entities like primary sclerosing cholangitis (LaRusso et al., 2006), extra hepatic biliary atresia (Sokol et al., 2007), congenital hepatic fibrosis (Desmet, 1992), neonatal hepatitis (Ballistreri and Bezerra, 2006), nonalcoholic steato hepatitis (NASH) (Ludwig et al., 1980) etc. Metastatic carcinomas are commonly seen in our trucut liver biopsies, and cytokeratins 7 and 20 and other more specific IHC markers supplement the histologic features and help us in determining the probable sites of origin. There has also been a gradual increase in the frequency of gall bladder carcinoma resection specimens in the last five to ten years. Most carcinomas have involved full thickness of gall bladder wall when resected. ZA remembers a case of primary signet ring carcinoma of the gall bladder which was later published (Ahmad and Qureshi, 2010). Gall bladders removed for cholecystitis and cholelithiasis are among the commonest specimens we receive and cholesterosis is a frequent finding. We have recently submitted an original article encompassing all aspects of our GI practice, it has already been accepted and hopefully will be published shortly.

Breast Pathology

When ZA started his residency in 1996, we were following the Bloom and Richardson histologic grading system for breast carcinoma (Bloom and Richardson, 1957) but soon adopted the Ellis and Elston (1991) modification of the above system and are using this modified system to date. Breast cancer is the commonest cancer in females in our country and we are seeing younger and younger women being affected by this cancer. The number of trucut biopsies in diagnosis of breast cancer (both as frozen sections and permanent sections) has greatly increased, while the number of lumpectomies, which were the commonest mode of diagnosis even around 2001 has greatly declined. Sentinel node biopsies are also quite common. The first sentinel node biopsies were sent around 2000. All apparently negative sentinel node H&E sections are stained with cytokeratins. Sentinel node biopsies have become the international standard of care for the evaluation and management of breast cancer and we submit three step sections stained with H&E plus one section stained for cytokeratin (Silverberg, 2002; Schwartz et al., 2002). We still rely on traditional prognostic factors such as lymph node status, tumor size, histologic type, histologic grade, lymphatic invasion etc. However, we routinely use assessment of Estrogen and Progesterone receptor status (ER and PR) and HER2/neu protein over expression by IHC on formalin fixed tissue and HER2/neu gene amplification by fluorescence in situ hybridization (FISH) as predictive factors in determining the likelihood of response to hormonal therapy (ER,PR) and to chemotherapeutic agent trastuzumab or Herceptin (Her2/neu) respectively (Hicks and Kulkarni, 2008; Barron et al., 2009). The routine use of these tests has allowed our clinicians to optionally select patients for hormonal or Herceptin (a monoclonal antibody that targets the HER2/neu protein) therapy. We use the American Society of Clinical Oncology (ASCO) and CAP guidelines for performance and evaluation of ER, PR and Her2/neu status in breast cancer (Harris et al., 2007; Wolff et al., 2007). As BRCA1 and BRCA2 mutations (Angliana Breast Cancer Study Group, 2000; Tan et al., 2008) are common in female breast carcinoma, we intend to start molecular testing for these mutations by the end of 2014, so that we can offer this valuable information to our clinicians and help in the better management of these cancers in women with family history of breast carcinoma, and to determine the choice between close follow-up and prophylactic mastectomy (Robson et al., 2005; Robson and Offitt, 2007). BRCA1 protein expression can be detected immunohistochemically and cytoplasmic expression may be associated with unfavorable prognosis (Rakha et al., 2008).

In the last three years, we have recognized the luminal A, luminal B, HER2 overexpressing, basal like and triple negative carcinomas (Rhodes et al., 2002; Bertucci et al., 2008; Reis-Filho and Tuff, 2008; Foulkes et al., 2010; Papoudiado et al., 2010). Triple negative carcinomas are usually high grade invasive ductal carcinoma, are highly aneuploid and have a tendency to metastasize to brain and lungs (Foulkes et al., 2010). We have also, to some extent, used the Nottingham Prognostic Index (Galea et al., 1992) in our breast carcinoma cases. IHC has helped us in breast carcinomas in several ways which include: antibodies to myoepithelial cells like smooth muscle actin (ASMA) in distinguishing between in situ and invasive carcinomas (Foschini et al., 2000), E-cadherin in distinguishing between ductal and lobular carcinomas in difficult cases (Acs et al., 2001), E-cadherin being absent in lobular carcinoma. We also plan to start using p120-catenin which shows a cytoplasmic staining for the same purpose soon (Dabbs et al., 1992). Since 2001, we began diagnosing metaplastic carcinoma, a type of breast carcinoma in which the neoplasm is predominantly composed of a cell type or types other than epithelial (Okada et al., 2010; Yamaguchi et al., 2010). We used to classify papillary lesions of the breast according to Azzopardi's criteria (Azzopardi, 1979). However, especially in the last five years, we have upgraded our classification of papillary neoplasms. We currently use the terms intraductal papilloma, Atypical Papilloma, Intracystic or in situ Papillary Carcinoma (ICP) and invasive papillary carcinoma based on strict criteria (Collins and Schnitt, 2008; Ueng et al., 2009; Koerner, 2010). IHC stain ASMA has greatly helped us in the adequate characterization of papillary lesions of the breast. Over the past five years, we have also reported entities such as columnar

cell change and flat epithelial atypia (Abdel-Fateh et al., 2007; Lerwill, 2008), pseudoangiomatous stromal hyperplasia (PASH) (Vuich et al., 1986), nipple adenoma etc. The latter can mimic intraductal papillary carcinoma and infiltrating ductal carcinoma which can arise in the nipple (Rosen and Caicco, 1986; Jones and Tavassoli, 1995). ZA remembers one case of nipple adenoma in 2006 which we misdiagnosed as invasive ductal carcinoma. Benign, borderline and malignant phyllodes tumors are quite commonly seen in our practice and we follow the WHO classification of these tumors. All breast tumors (carcinomas, phyllodes tumor etc.) are classified according to the latest WHO classification (WHO, 2012).

Female Genital Tract Pathology

Our practice of female reproductive (genital) tract pathology has also evolved over the years. Since the turn of the century, apart from hydatidiform mole and choriocarcinoma, we began to recognize and report entities like exaggerated placental site, placental site nodule (Huettner and Gersell, 1994) and placental site trophoblastic tumor (PSTT) (Young and Scully, 1984). ZA remembers a case of PSTT in 2006 which behaved very aggressively and metastasized to lungs and adrenals, it was subsequently published (Raza et al., 2006). Around 2001, we also began to receive uterus specimens with clinical suspicion of placenta accreta and began to report placenta increta and percreta (Morken and Henriksen, 2001). In the vulva and vagina, we began to report entities such as angiomyofibroblastoma (Alameda et al., 2006) and aggressive angiomyxoma (Ockner et al., 1997) with confidence (entities that confused us previously, especially in differentiating these lesions from the more common fibroepithleial polyp) by very careful observation of the histologic features. In the cervix, we initially used the CIN (Cervical Intraepithelial Neoplasia) classification of the 1970s for squamous intraepithelial lesions, but in the early 2000s, we switched to the SIL (Squamous Intraepithelial Lesion) system (Richart, 1973; National Cancer Institute Workshop, 1988; Crum, 2003). Squamous intraepithelial lesions and squamous cell carcinomas of cervix are not very common in Pakistan. Around 2001, we also began to report microinvasive carcinoma of cervix (Sevin et al., 1992) and have now reported a number of cases. We currently follow the criteria for microinvasion recommended by both the International Federation of Gynecology and Obstetrics (FIGO) and the Society of Gynaecologic Oncology (SGO) which are depth of 5 mm and 3 mm respectively. It must be mentioned here that the 3 mm criteria given by SGO is now incorporated in FIGO as FIGO stage Ia1 (Burghardt et al., 1991; Pecorelli and Odicino, 2003). Although uncommon, we do see many cases of squamous cell carcinoma including rare variants like lymphoepithelioma like carcinoma (Mills et al., 1985), but glandular neoplasms of cervix are very rare and the authors in all these years remember only two cases reported as Adenoma malignum (Gilks et al., 1989).

Endometrial curretings and hysterectomies (often with bilateral salpingo-oophorectomy) are among the commonest specimens that we receive. The former, we receive mainly for dating and identification of abnormal patterns. In the past, we were not very confident in reporting abnormal endometrial patterns but now we regularly report mixed secretory pattern, luteal phase defect, secretory change superimposed on abnormal nonsecretory pattern etc. We have also learned to recognize exaggerated placental site reaction in hysterectomy specimens. In biopsies, we commonly see exogenous hormonal patterns. In cases, where changes fall short of endometrial hyperplasia, we use the terms 'excessive estrogen effect' in younger patients and 'disordered proliferative endometrium' in relatively older patients (McCluggage, 2011). For endometrial hyperplasia we use the classification (simple, complex and atypical hyperplasia) proposed by Kurman et al. (1986) (WHO, 2002). Endometrial polyps, adenomyosis and leiomyomas are the commonest lesions we find in uteri removed for 'dysfunctional uterine bleeding' or DUB (McCluggage, 2011). Endometrial adenocarcinoma is much more common than cervical cancer and we are now seeing and reporting more cases than in the past. Also many cases occur in relatively younger women. We used the FIGO staging and grading system for these cancers, and currently use the modified FIGO surgical staging and grading system (Mikta, 1993; Ayhan et al., 2003; Zaino, 2009). In the nineties we did not report uterine papillary serous carcinoma (Gitsch et al., 1995) but we now have reported several cases during the last ten years. We have also in recent years reported a number of cases of endometrial intraepithelial carcinoma (EIC) which is believed to be associated with and probably is a precursor of serous carcinoma (Darvishian et al., 2004; McCluggage, 2011). Although we have always reported Malignant Mixed Mullerian tumor, we only started reporting adenosarcoma in the late nineties (Clement and Scully, 1990; Kaku et al., 1992). In the past, we followed Norris and Taylor's classification of endometrial stromal neoplasms (Norris and Taylor, 1966). However, we now use Evan's terminology for these neoplasms dividing them into endometrial stromal nodule, low grade endometrial stromal sarcoma and high grade undifferentiated uterine sarcoma (Evans, 1982). The IHC stain CD10 has proved valuable to us in distinguishing stromal neoplasms from smooth muscle neoplasms (McCluggage et al., 2001). Leiomyomas are extremely common and leiomyosarcomas extremely rare in our practice. Apart from the usual leiomyomas, we report variants like atypical (symplastic) and mitotically active leiomyoma. We have also reported an occasional case of benign metastasizing leiomyoma, one of which we published (Fatima and Ahmad, 2010).

Ovarian tumors are very common in our population. We report both benign and malignant epithelial, germ cell and stromal tumors very frequently. Among surface epithelial tumors, endometrial carcinomas are the most common. In the past, we reported all mucinous neoplasms in the ovary as primary ovarian tumors. However, in the last decade we have realized that many, perhaps the majority of borderline and malignant mucinous neoplasms in the ovaries are actually metastatic tumors especially from the gut (appendix). This is what the literature also supports (Seidman et al., 1993; Ronnett

et al., 1995). Also, in the initial years, we were not very sensitive about extensive sampling of ovarian tumors. However, we now submit at least one section per cm of tumor. Endometrioid carcinomas are very common and many arise in a background of endometriosis. Endometriotic cysts of the ovary are very commonly seen in our practice. Apart from metastatic mucinous tumors from the appendix, bilateral krukenberg tumors from the stomach are also quite common in our practice. Among the sex-cord stromal tumors of the ovary, we starting reporting juvenile granulosa cell tumor (which has a worse prognosis compared to adult granulosa cell tumor) (Young et al., 1984) around the turn of the century. All germ cell tumors are very common especially mature cystic teratoma. Recently, we saw a number of cases with oligodendroglioma arising in the glial component and published this series (Ud Din et al., 2012). The use of IHC markers like inhibin, CD117 etc has helped us in the diagnosis of stromal and germ cell tumors like granulosa cell tumor, dysgerminoma etc (McCluggage et al., 1997; Sever et al., 2005). For ovarian carcinoma also, we follow the WHO Grading and AJCC and FIGO Staging Systems (Heintznet al., 2001; WHO, 2003; Edge and Compton, 2010). Recently, we have also become aware of the new model for the pathogenesis of surface epithelial tumors of the ovary, according to which ovarian carcinomas are divided into type-I and type-II carcinomas (Cho and Shih, 2009; Kurman and Shih, 2010).

Lymph Node Pathology

When ZA started his residency in late 1996, we were following the International Working Formulation for the classification of lymphomas (National Cancer Institute Non Hodgkin Lymphoma Classification Project, 1982). Around 1998, we switched to the Revised European American Lymphoma (REAL) classification (Harris et al., 1994; Chan et al., 1995). Around 2002, we finally switched to the WHO classification (WHO, 2001). We have taken care to always follow the modifications in the WHO classification and currently we use the 2008 WHO classification for lymphoid and hematopoietic neoplasms (WHO, 2008). With the switch from the International Working formulation came the phenotyping of Non Hodgkin Lymphoma (NHL) into B and T types. With the use of IHC, we began to report NHLs according to their phenotype. By the early years of the new century, our practice in terms of both Non Hodgkin and Hodgkin Lymphomas (HL) was well established. Based on the WHO terminologies, and with newer IHC markers to supplement the morphology, we began to diagnose not just the older entities with greater confidence but started to recognize and report newer entities like Anaplastic Large Cell Lymphoma (ALCL) (Kinney et al., 1991), blastoid variant of Mantle Cell Lymphoma (Zucca et al., 1994), anaplastic and ALK positive variants of Diffuse Large B Cell Lymphoma (DLBCL) (Haralambieva et al., 2000; Delsol et al., 2008; WHO, 2008; Chan and Chan, 2010), Extranodal Natural Killer (NK)/T cell lymphoma (Chan et al., 2008; WHO, 2008) Post-Transplant lymphoproliferative disorder (PTLD) (Swerdlow et al., 2008; WHO, 2008) etc. We also published a case of Post-transplant peripheral T cell lymphoma (Ahmad et al., 2007). We have become a national referral center for diagnosis of lymphoproliferative disorders. We probably see more lymphomas than many 'lymphoma centers' in the West. IHC markers have played a major role in this regard. The use of CD30 (Ki1) and Epithelial Membrane Antigen (EMA) (Delsol et al., 1988) and Alk-protein has helped us tremendously in diagnosing ALCLs, both Alk-positive and Alk-negative (Delsol et al., WHO, 2001). We intend to start performing the classic t(2;5)/NPM-ALK translocation for ALCL from 2014. Cyclin D1 has helped us in the diagnosis of Mantle cell lymphoma, (De Boer et al., 1995; Swerdlow et al., 1995) and TdT in the diagnosis of precursor Lymphoblastic Leukemia/Lymphoma (Brunning et al., 2001a; 2001b), whereas in the nineties, we only relied only on morphology and CD99 (Mic2) to diagnose lymphoblastic lymphomas. Similarly, BCL2 has helped us a lot in follicular lymphomas (Lai et al., 1998). We intend to start performing the +(14;18) translocation seen in 70-95% cases of follicular lymphoma (Chorsman et al., 1995) from 2014. PAX-5 has helped us in difficult cases of diffuse large B cell lymphoma and Hodgkin lymphoma (Foss et al., 1999). In HL, we started diagnosing Nodular Lymphocyte predominant Hodgkin Lymphoma(Poppema et al., WHO, 2008) around 2000 and to date have diagnosed several cases of this entity. The proliferation marker Mib1 (Ki67) has been very valuable as an adjunct to mitotic activity in differentiating between low and high grade NHLs. Its greatest use has been in Burkitt lymphoma where it shows positivity in 100% tumor cells (Spina et al., 1997). Burkitt lymphoma is common in our practice, and we have also diagnosed a few cases of atypical Burkitt/Burkitt like lymphoma recently (Leoncini et al., 2008; WHO, 2008). We routinely perform Mib (Ki67) in all our cases of NHL. In plasma cell neoplasms, the IHC stains CD138, MUM1 and CD56 have proved invaluable (Lin et al., 2004; McKenna, 2008; WHO, 2008). In Angio Immunoblastic T Cell Lymphoma (AITL), IHC stain CD21 has proved helpful in highlighting the follicular dendritic cell meshworks around venules (Jones et al., 1998). At the molecular level, we started performing the translocation t(8;14) for Burkitt lymphoma (Leoncini et al., 2008; WHO, 2008) a couple of years back. We hope to start performing T cell receptor gene rearrangements (Tan et al., 2006; Attygalle et al., 2007) which are seen in 75-90% cases of Angioimmuoblastic T-cell lymphoma and translocations for follicular lymphoma (14;18) (Horsman et al., 1995), mantle cell lymphoma (11;14) (Li et al., 1999) and ALCL (2;5) (Delsol et al., 2001) in 2014. It must be mentioned here that we report only the solid lymphoid tumors (on paraffin blocks). Leukemias (on peripheral blood film) and bone marrow are reported in the separate Section of Hematology. We also started Flow Cytometry services in 1996 and currently perform acute leukemia and lymphoma panels, ZAP 70 for chronic lymphocytic leukemia (CLL)(Crespo et al., 2003; Rassenti et al., 2004), CD4/CD8 counts(Jaffe et al., WHO, 2001), tests for minimal residual disease (MRD) and multiple myeloma etc.

Soft Tissue and Bone Pathology

When ZA joined the residency program in 1996, we were using the system proposed by Trojani et al. (1984) for grading soft tissue sarcomas. In 2007, we switched to the French Federation of Cancer Centers Sarcoma Group System (FFCCS) (Coindre, 2006). Currently, we are following the WHO system for classification of soft tissue tumors (Fletcher et al., 2013; WHO, 2013). Until recently we were using the AJCC staging system for staging of soft tissue sarcoma (Green et al., 2002), but now we use TNM classification of soft tissue sarcomas for staging (Sobin et al., 2010). IHC markers have proved invaluable to us in the diagnosis of soft tissue sarcomas and have served as powerful adjuncts to histological features. Apart from vimentin (which in poorly differentiated cases often helped to determine that a neoplasm was mesenchymal in origin or not), the IHC markers which proved very useful to us in the early years, included desmin, actin, CD68, S100 protein, CD99 (MIC2) etc. This panel was greatly strengthened after 2000 by the additional of several useful markers including CD 34 in vascular neoplasms (Miettinen et al., 1994) and solitary fibrous tumor (SFT) (Nielsen et al., 1997); cytokeratin 19 in epithelioid sarcoma (Miettinen et al., 1999); CD34 in dermatofibrosarcoma protuberans (DFSP) (Mentzel et al., 1998); EMA and cytokeratin 19 in synovial sarcoma (Miettinen et al., 2000; Olsen et al., 2006); CD31 in vascular neoplasms (DeYoung et al., 1995); Myo D1 in rhabdomyosarcoma (Cessna et al., 2001; Morotti et al., 2006) etc. In the last five years, we have begun to recognize and diagnose newer entities like myxofibrosarcoma (Mentzel et al., 2013; WHO, 2013) and low grade fibromyxoid sarcoma (Folpe et al., 2013; WHO, 2013). Also a few years back, we stopped making the diagnosis of Malignant Fibrous Histiocytoma (MFH) and now diagnose these tumors as undifferentiated pleomorphic sarcoma (Fletcher et al., 2013; WHO, 2013). During the past three years, we also started to perform molecular tests to detect chromosomal abnormalities in synovial sarcoma i.e. t(x;18) (Ladanyi et al., 2002) and Ewing sarcoma/Primitive Neuroectodermal tumor (PNET) i.e. t(11;22) (Turc-Carel, 1998). We hope to start performing molecular tests on certain other soft tissue sarcomas by 2014. One IHC marker which we have very recently, albeit belatedly added, is Beta catenin to help us in the diagnosis of Fibromatosis in difficult cases (Bhattacharya et al., 2005). In the past few years, we have also laid emphasis on recognizing and diagnosing lesions such as proliferative myositis and fasciitis, lipoblastoma, myxoma, myositis ossificans and inflammatory myofibroblastic tumor, to name a few. Among vascular neoplasms, Kaposi sarcoma is very rare in our country. Recently, we have diagnosed rare variants of synovial sarcoma (calcified variant which has a better long term prognosis) (Varela-Duran and Enzinger, 1982) and schwannoma (pigmented or melanotic which is potentially metastasizing thus requiring long term followup) (Vallat-Decouvelare et al., 1999).

In bones, we see large number of cases of chronic pyogenic and tuberculous osteomyelitis. In the past, we hardly ever got radiological films for correlation, but now with increasing awareness, we receive x-rays with most cases of bony lesions or get them on contacting the patient or the clinician. Previously, we used the system proposed by Enneking (Wolf and Enneking, 1996) to stage bone sarcomas. Currently, we use the WHO classification for bone tumors (Fletcher et al., 2013; WHO, 2013) and the TNM staging system (Fletcher et al., 2013; WHO, 2013). For grading of bone tumors, neoplasms are divided into benign, locally aggressive or rarely metastasizing and malignant according to the system proposed in the WHO classification of tumors of soft tissue and bone (Fletcher et al., 2013; WHO, 2013). In chondrosarcoma, we use the grading system proposed by Evans et al. (1977). In the past, we did not grade chondrosarcomas. Among bone tumors, the histologic diagnosis of myeloma has been complemented by IHC stains CD138, Mum1 and CD56 (Falini et al., 2000; O'Connel et al., 2004; Cao et al., 2008). As mentioned above, we perform cytogenetics test i.e. translocation t(11;22) for Ewing sarcoma (Ture-Carel, 1998). Osteochondroma is the most common benign chondroid neoplasm in our practice. Since the last ten years we began to recognize and diagnose variants of osteosarcoma such as telangiectatic, small cell, parosteal and periosteal. Giant cell tumor (osteoclastoma), aneurysmal bone cyst, fibrous dysplasia and metaphyseal fibrous defect are extremely common in our practice. Recently, we have started to incorporate the effects of chemotherapy on surgical resection specimens of malignant bone tumors such as osteosarcoma and Ewing Sarcoma as per CAP guidelines (Edge and Compton, 2010). We published our data for common bone sarcomas in 2010 (Qureshi et al., 2010).

Respiratory Tract Pathology

In the nose and nasopharynx, nasopharyngeal carcinoma is quite common while sinonasal carcinoma is distinctly uncommon in our country. Many of our cases of nasopharyngeal carcinoma are positive for Ebstein Barr Virus (EBV) (Leibowitz, 1994), highlighted by the IHC stain which we started performing after 2001. In the nineties, we hardly ever diagnosed olfactory neuroblastoma. However, since after 2000, we have diagnosed this tumor regularly with the morphology being supplemented by IHC stains like synaptophysin, neurofilamant, chromogranin, neuron specific enolase (NSE) and keratins (Choi abd Anderson, 1985). We have reported a few cases of nasal extranodal NK/T-cell lymphoma over the last ten years and in the past few years we have diagnosed a number of cases of teratocarcinoma and also published a case series recently (Fatima et al., 2013). Inflammatory (allergic) nasal polyps (many with fungal infection), benign laryngeal nodule and carcinoma of the larynx and vocal cords are extremely common. In the pleura, malignant mesothelioma is relatively rare in our population. However, we do report cases fairly regularly and the acquisition of IHC stains like calretinin, CK 5/6, WT1 etc (Oates and Edwards, 2000; Ordones, 2005) have helped us greatly in difficult cases and in distinguishing mesothelioma from pulmonary adenocarcinoma. The diagnosis of SFT of the pleura has

also been greatly facilitated due to availability of IHC stains CD34 and BCL2 (Nielsen et al., 1997). In the lung, we now regularly get biopsies for non-neoplastic conditions such as usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP) etc. We hardly ever received such biopsies even five years ago. Most lung biopsies, even today, are performed for tuberculosis or carcinoma. We currently follow the WHO Classification for lung carcinoma (Travis et al., 2004; WHO, 2004). Lung resection specimens are still very uncommon. IHC stains like TTF1 (Lau et al., 2002; Yatabe et al., 2002), CK5/6, p63, 34βE12, CK7 and 20, CD56, BerEP4 etc (Johansson, 2004) have been of great help to us in diagnosis of various types of lung carcinoma, in distinguishing between small cell carcinoma and non-small cell (squamous cell and adenocarcinoma) carcinoma, and in differentiating between primary lung carcinoma and metastatic tumors. We plan to start performing tests for k-ras mutations (Silini et al., 1994) in 2014, and even more importantly for EGFR (epidermal growth factor receptor) mutations (Bell et al., 2008) which are important for selecting patients for tyrosine kinase inhibitor (gefitinib) therapy. Asian ethnicity, adenocarcinoma on histology, never smoking and female gender are linked to higher incidence of EGFR mutation and increased response to gefitinib therapy. As we currently do not perform this test, and because the current international recommendation is to document EGFR mutation in non-small cell lung cancer before offering gefitinib (Mok et al., 2009; Pirker et al., 2010), we send our cases (paraffin blocks) to Singapore for this purpose. Very recently, we have acquired the IHC stain Napsin A which will be helpful in diagnosis of lung cancer (Bishop et al., 2010).

Endocrine Pathology

When ZA joined the residency program in late 1996, we only had the IHC marker thyroglobulin which did not allow any help in differentiating a case of thyroid papillary carcinoma from benign thyroid tissue in difficult cases. We acquired the IHC Ab Thyroid Transcription Factor 1 (TTF1) (Bejarano et al., 2000) around 2001 but this antibody also does not discriminate between benign thyroid tissue and papillary thyroid carcinoma. However, during the past five years we have used antibodies like CK19 (Erkilic and Kocer, 2005) and 34βE12 (Cheung et al., 2001) which are believed to be negative in benign thyroid tissue and positive in carcinoma. However, the results have been variable. Very recently, we have acquired the IHC marker HBME-1 (Nasr et al., 2006) and now in difficult cases, we use all three Abs (HBME1, 34βE12 and CK19). Papillary and other thyroid carcinomas are quite common in our population. In follicular carcinomas, the vascular IHC markers like CD31 and CD34 are often helpful in documenting vascular invasion in difficult cases. Around 2005, we also adopted the terminologies proposed by the Chernobyl pathology group (Williams, 2000) for difficult cases of thyroid carcinoma: Well differentiated tumor of uncertain malignant potential (WDT-UMP) for papillary carcinoma (follicular variant); Follicular tumor of uncertain malignant potential (FT-UMP) for follicular carcinomas with questionable capsular invasion; and well differentiated tumor of uncertain malignant potential (WDT-UMP) for follicular carcinomas with questionable nuclear changes. In the nineties, we did not report tall cell and columnar cell variants of papillary carcinoma, which are more aggressive than conventional papillary carcinoma (Livolsi, 2010). We report these now although very rarely. Similarly, we started diagnosing the highly aggressive anaplastic (undifferentiated) carcinoma of the thyroid(Carcingin et al., 1985) only around the turn of the century. For medullary carcinoma, we relied in the past only on morphology and neuroendocrine markers (Katoh et al., 2000) apart from thyroglobulin, but now we also use the IHC markers TTF1 and calcitonin (Schmid et al., 1992). We hope to start molecular testing for BRAF mutations in papillary carcinoma in 2014 since tumors with these mutations have been shown to behave more aggressively (Xing et al., 2005 ; Elisei et al., 2008). In the adrenal cortex, we use the Weiss microscopic criteria (Weiss, 1984; 1989) (in addition to size and weight) to differentiate between adenoma and carcinoma. IHC stains like inhibin and melan-A (Busan, et al., 1998; Cho and Ahn, 2001; Loy et al., 2002) which we acquired around 2001 have helped us in determining the adrenal cortical origin of tumor (older stains like vimentin and synaptophysin have also been useful in this context) and in differentiating adrenal cortical carcinoma from renal cell carcinoma (former being vimentin, synaptophysin, Melan-A and inhibin positive and the latter being cytokeratin and CD10 positive) (Wick et al., 1986; Rosai, 2008). In differentiating between adrenal cortical and adrenal medullary neoplasms in difficult cases, we often rely on IHC stain chromogranin-A which is negative in adrenal cortical and positive in adrenal medullary neoplasms (Schmid et al., 1993). So an adrenal neoplasm which is inhibin and melan-A positive but chromogranin-A negative is likely to be adrenocortical rather than medullary in origin. For neuroblastomas we followed the Shimada classification of 1984 in the nineties (Shimada et al., 1984). But since 2002, we have used the International Neuroblastoma Pathology Classification (Shimada system) of 1999 (Shimada et al., 1999a; 1999b) with its neuroblastoma-ganglioneuroblastoma-ganglioneuroma spectrum. We use several IHC markers along with histologic appearance to diagnose neuroblastoma and to differentiate it from other small round blue cell neoplasms of childhood. These IHC markers include NSE, Neurofilamant (NF), and synaptophysin (Osborn et al., 1986; Oppedal et al., 1987; Wirnsberger et al., 1992). In 2012, we also started molecular testing for amplification of MYCN oncogene which is an adverse prognostic factor in neuroblastoma associated with rapid clinical progression (Bordow et al., 1998; Maris et al., 1999).

Renal Pathology

In non-neoplastic renal disease, we have always relied on light microscopy and immuno-fluorescence. Electron Microscopy (EM) could never be acquired because it was not financially feasible. This means that we are not able to diagnose hereditary glomerular diseases like

Alport Syndrome, thin basement membrane nephropathy and Fabry disease which require E.M. examination for their diagnosis (Gubler, 2008). Another limitation in renal disease is that we seldom receive relevant clinical history which makes it very difficult for us in some cases to give a definite diagnosis. We perform indirect immuniofluoresence using antibodies against IgG, IgA, IgM, C1q, C3, C4, kappa and lambda light chains, fibrinogen and fibrin. Some of our faculty are trained from Pakistan's premier center for renal disease (Sindh Institute of Urology and Transplantation or SIUT) and abroad and we are able to reach an accurate diagnosis on most renal biopsies. For light microscopy, in addition to the usual Hematoxylin and Eosin (H&E) stain, we use special stains including periodic acid-Schiff (PAS), reticulin and Gomorrhi silver stain (GMS). We follow the WHO classification of glomerular diseases (Churg et al., 1995). In Lupus nephritis, since 2006 we follow the International Society of Nephrology classification (Weening et al., 2004). Earlier, we used to follow the revised WHO classification (Churg et al., 1995).

Recently, the institution (AKUH) has decided to start renal transplantation services and we have moved forward on this front (together with the clinicians) and the services will start from 2014. We are in the process of training our consultants and technologists and recently sent one of our consultants to United States for this purpose. We will start tests like C4d, which is very useful for the diagnosis of antibody mediated acute allograft rejection (marker of poor graft survival) (Mauiyyedi et al., 2002; Colvin, 2007) and immune staining for BK virus which is an important pathogen causing BK-associated nephropathy in renal transplant patients (Hirsch et al., 2002; Hirsch, 2005). A number of recent studies have demonstrated that the deposition of C4d (a stable inactive degradation product of complement factor C4 formed when classic complement cascade is activated by the binding of antidonor antibodies to the graft endothelium) in graft peritublar capillaries is a reliable marker which correlates well with antibody mediated rejection and poor graft survival (Mauiyyedi et al., 2002; Colvin, 2007).

Among pediatric renal neoplasms, Wilms tumor is the commonest - most cases in our practice over the years have shown favorable histology. Among IHC stains in difficult cases, especially if biopsy tissue is very scanty, we use vimentin, keratins, WT1 (in the last five years or so, WT1 immunohistochemical stain has helped us a lot in difficult cases), CD56 etc (Vasel et al., 2008). Although in the early years, we did not diagnose clear cell sarcoma, we have reported a number of cases during the last fifteen years.

For renal neoplasms, we use the WHO classification (Eble et al., 2004; WHO, 2004). We rely on morphology, special stains like PAS, Hale Colloidal Iron (for chromophobe renal cell carcinoma) and immunohistopathology. Among IHC stains, we use keratin 7 (Gatalica et al., 1995) routinely for papillary renal cell carcinoma. We have observed in our practice that sarcomatoid renal cell carcinoma is quite common. Since the last five years, we have found positivity for CD10 (together with positivity for keratin and vimentin) to be valuable when we suspect metastatic renal cell carcinoma in extra-renal sites (Wick et al., 1986). We use these stains together with inhibin (Cho and Ahn, 2001) in the differential diagnosis with adrenal cortical carcinoma in challenging cases (RCC is negative for inhibin, while adrenal cortical carcinoma is positive). For clear cell RCC, we have traditionally used the Fuhrman's grading system (Fuhrman et al., 1982) and we have found the papers by Ficarra et al. (2005) and Lang et al. (2005) very useful in this regard. In angiomyolipoma, HMB 45 (Hoon et al., 1994; Roma et al., 2007) has proved to be a good adjunct to morphology. For oncocytoma, we lay emphasis on gross appearance (mahogany brown with central stellate scar) (Choi et al., 1983).

Cytopathology

The ratio of our surgical pathology to cytopathology workload has consistently been around 3:1. About half of our cytopathology workload is gynecologic cytopathology. In non-gynecologic cytopathology, our main specimens have always been fine needle aspirates (FNAs) mainly from lumps in breast, neck (lymph nodes, salivary glands, thyroid etc.) and fluids (pleural, peritoneal and sometimes pericardial). Cerebrospinal fluid (CSF) specimens in patients with leukemias are also relatively common specimens. Until the turn of the century, we only used smears in non-gynecologic cytopathology, but for the last ten years or so, we regularly complement smears with cell blocks. This has enabled us to perform IHC in difficult cases and allowed more accurate and specific diagnosis. For example, the use of IHC antibodies CK7, CK20, BerEP4, calretinin, TTF1, LCA, CD56 etc. help us in determining the site of origin of metastatic carcinomas in fluids, and in differentiating between carcinoma and mesothelioma or differentiating between small cell carcinoma and lymphoma in pleural fluids etc. Similarly, in neck lymph nodes, cell blocks and IHC have helped us in diagnosis of B and T cell lymphomas, Hodgkin lymphoma, salivary gland neoplasms etc.

Cervical cancer and precancerous lesions are much less common in Pakistan than in the West. In mid-nineties, we adopted the 1988 Bethesda System for reporting cervical cytology and have used this system consistently since that time, incorporating the revisions made in 1992 and 2001 (Kurman and Solomon, 1994; Solomon et al., 2002; Solomon and Nayar, 2004). In the next three to five years, we will be exploring the possibility of adding HPV testing (ALTS group, 2003) and reporting it concurrently with cytology results. In addition, we will be exploring the possibility of starting computer-assisted interpretation of cervical cytology (Prey, 2004). HPV testing is considered as sensitive as colposcopy in detecting cervical intraepithelial neoplasia (CIN) 2 or 3 and is very cost effective (Kim et al., 2002).

In Thyroid cytopathology, we recently switched to the Bethesda system for reporting of thyroid cytopathology (Ali and Cibas, 2010). In the breast, we to date mainly use descriptive diagnoses or specific diagnoses based on the WHO histological classification of breast tumors, which we also use in histology (Lakhani et al., 2012; WHO,

2012).

So far, we still use conventional cytology and have not switched to liquid based cytology preparation (LBC/LDP) because it was not considered financially feasible (owing to relatively small volume of gynecologic cytopathology). However, we are now in the process of switching to LBC. We hope to acquire SurePath (Tripath Imaging, Inc, Burlington, NC) in 2014 and start LBC regularly from 2014. Currently, we are also preparing our cytoscreeners and cytopathologists for LBC implementation by sending them abroad for training.

Frozen Section

The most common frozen section specimens that we receive include trucut breast biopsies for diagnosis of carcinoma (in the past we received lumpectomies but now these have become very uncommon), surgical margins from ENT (ear, nose and throat) specimens, brain tumor biopsies for diagnosis of tumors etc. In addition, we now receive sentinel lymph nodes (in breast cancers), pelvic lymph nodes (in prostatic cancer patients undergoing radical prostatectomies etc.) which we did not get before 2000. Other specimens that we get for frozen section include surgical margins (doughnuts) in cancers of stomach, colon etc.; thyroid specimens, parathyroids and adrenals (hyperplasia v/s adenoma v/s carcinoma), ovarian cysts (neoplastic and non-neoplastic such as endometriotic cysts) etc. In 2012, we performed 1868 frozen sections, whereas we reported 1607 frozen sections in the first nine months of 2013. Our concordance rates have consistently been above 97%, which corresponds to international data (Howanitz et al., 1990; Gephardt and Zarbo, 1997). Also, our turnaround times are within 20 minutes for around 90% of frozen sections, which is, once again comparable to international standards (Novis and Zarbo, 1997). Turnaround time is measured from the time the pathologist received the specimen to the time he/she conveyed the frozen section diagnosis to the surgeon. We have published two separate studies on the accuracy (and turnaround time) of our frozen sections in international journals (Ahmad et al., 2008; Ud Din et al., 2011).

Dermatopathology

Our dermatopathology practice is and has always been quite busy. In the earlier years, we did not often get the relevant clinical history, but things have changed for the better over the past five years and there is greater contact between dermatologists and histopathologist. The common non-neoplastic skin lesions that we see and report include viral warts, molluscum contagiosum, hidradenitis suppurativa (mainly in the axilla), cutaneous tuberculosis (lupus vulgaris), fungal diseases (especially tinea), psoriasis, lichen planus (especially in the oral mucosa), vasculitis, chronic discoid lupus erythematosus, scleroderma, pyoderma gangrenosum, vesiculobullous disease (especially dermatitis herpetiformis, bullous pemphigoid, erythema multiforme and epidermolysis bullosa), lichen sclerosus et atrophicus (mainly in the vulva) etc. Rarely, we also report leprosy, Darier disease, mastocytosis, granuloma annulare etc. Among neoplastic and tumor like conditions, we very commonly see seborrheic keratosis, fibroepithelial polyp (skin tag), benign adnexal tumors, squamous cell carcinoma, basal cell carcinoma, epidermal inclusion (epidermoid) cyst, trichilemmal (pilar) and dermoid cysts, pilomatrixoma, pyogenic granuloma and melanocytic nevi. IHC stains Ber-EP4 and CD10 have proved useful to us in differentiating between squamous and basal cell carcinoma in difficult cases, being negative in the former and positive in the latter (Beer et al., 2000; Wagoner et al., 2007). Benign fibrous histiocytoma (BFH), dermatofibrosarcoma protuberans or DFSP (many with progression to fibrosarcoma) are also very common. CD34 has proved very helpful to us in the diagnosis of DFSP (Dominguez-Malagon et al., 1995) and in differentiating for it from BFH, being negative in the latter (Abenoza and Lillemoe, 1993). Most of the melanocytic nevi we see are intradermal. Compound and junctional nevi are less common. Hemangiomas are extremely common, cutaneous lymphangiomas less so. We rarely see actinic keratosis, extramammary paget disease, blue and spitz nevi, atypical fibroxanthoma, masson hemangioma, Kaposi sarcoma, mycosis fungiodes etc. Malignant melanoma (MM) is also relatively less common. However we see and report cases regularly. Immunohistchemical stains like vimentin, S100 protein, HMB45 and Melan A help us a lot in diagnosis of MM (Mangini et al., 2002; Yaziji and Gown, 2003; de Wit et al., 2004). We use the Clark's system to divide melanomas into levels of invasion (Clark et al., 1969; 1979). Studies have shown a direct relationship between level of invasion, incidence of lymph node metastases and prognosis (Buttner et al., 1995). Similarly, we determine tumor thickness using the Breslow system (Breslow et al., 1975). which groups melanomas into low, intermediate and high risk categories. Again, there is direct relationship between tumor thickness and regional nodal metastasis (Balch et al., 1978). However, the performance of sentinel node biopsies in malignant melanomas is still very uncommon and we get such biopsies for reporting very rarely. This is in spite of the fact that studies have shown that sentinel node biopsy is very accurate as a staging procedure and a powerful predictor of prognosis (Balch et al., 2009; Kanzler, 2010). We use the American Joint Committee on Cancer (AJCC) staging system for malignant melanomas (Balch et al., 2001).

The above account is an attempt to provide a detailed picture of how the practice of Histopathology has evolved during the last two decades in a developing country like Pakistan, as experienced by histopathologists working at the largest center for Histo (and cyto) pathology in the country. We have attempted to cover most, if not all, of our work and hope that this detailed account will allow the readers (especially in the West) to appreciate that inspite of all obstacles, we have consistently endeavored to keep ourselves as up to date as possible and abreast of new advances in the field of histopathology with the aim of providing the best services to our patients, the citizens of our unfortunate but beloved country.

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