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## **ANATOMIC PATHOLOGY**

### **Recent Developments in Vulvovaginal Pathology**

**W G McCluggage**

This review discusses recent developments in vulvovaginal pathology. A variety of morphologically bland mesenchymal lesions occur at this site with considerable histological and immunohistochemical overlap. Aggressive angiomyxoma exhibits HMGA2 immunoreactivity in approximately 50% of cases, and this nuclear transcription factor is emerging as a useful and relatively specific marker for aggressive angiomyxoma, although occasional vulvovaginal smooth muscle neoplasms are positive. HMGA2 is useful in the diagnosis of aggressive angiomyxoma and its distinction from mimics, in the evaluation of resection margins and in the assessment of the presence or absence of residual disease in re-excisions. Aggressive angiomyxoma is almost invariably positive with oestrogen and progesterone receptors, and there have been several reports of a dramatic reduction in size following gonadotropin releasing hormone agonist therapy. Recent series of the relatively newly described entities cellular angiofibroma and superficial myofibroblastoma of the lower female genital tract have expanded upon the morphological spectrum of these neoplasms. Recently described mesenchymal lesions at this site include massive oedema and prepubertal vulval fibroma. Gastrointestinal stromal tumours have been described as primary neoplasms in the vagina, and rectovaginal septum and extragastrointestinal stromal tumour should be added to the differential diagnosis of a vulvovaginal mesenchymal lesion. Many mesenchymal lesions in the vulvovaginal region exhibit immunoreactivity with both CD34 and desmin, a somewhat unusual immunophenotype in mesenchymal lesions at other sites. It is now established that there are two distinct types of vulval intraepithelial neoplasia (VIN), most commonly termed classic and differentiated VIN, the former associated with human papillomavirus (HPV) infection. There are two corresponding types of vulval squamous carcinoma with HPV-associated and non-HPV-associated variants, the latter often arising in a vulval dystrophy and associated with p53 mutation. However, in some cases there is clinicopathological overlap between HPV-associated and non-HPV-associated squamous carcinomas, and immunohistochemistry with p16 is more reliable than morphology in predicting the presence of HPV. There have been new developments regarding Paget's disease of the vulva with the identification of markers that are useful in diagnosis and evidence that the neoplastic cells represent a proliferation of adnexal stem cells residing in

sebaceous units. The newly described entity vaginal tubulo-squamous polyp typically exhibits immunopositivity with prostatic markers, possibly indicating derivation from displaced periurethral Skene's glands.

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## **The Practice of Histopathology in a Developing Country: Difficulties and Challenges; Plus a Discussion on the Terrible Disease Burden we Carry**

**Ahmad, Z; Qureshi, A; Khurshid, A**

Histopathology as a science is still evolving in Pakistan. A majority of lesions which should be biopsied are actually never biopsied, and even many resection specimens are never sent for histopathological examination. For a population of 160 million people, there are only three to four centres of note where meaningful histopathology is practised. We work as consultant histopathologists at the Department of Pathology, Aga Khan University (AKU), in Karachi, Pakistan's largest city. The Section of Histopathology at the Department of Pathology, AKU is the largest centre for histopathology in Pakistan. Other major centres for histopathology in the country include the Shaukat Khanum Memorial Cancer Hospital (SKMCH) in Lahore, and the Armed Forces Institute of Pathology (AFIP) in Rawalpindi. In addition, there are a few smaller centres in various cities which can be counted on fingers. In the vast majority of clinical laboratories across the country, histopathology facilities are very primitive and on a very small scale. There is a great dearth of qualified histopathologists, and basic tools for accurate histopathological diagnosis (especially facilities for immunohistochemistry, which is the most valuable adjunct to H&E staining in diagnostic histopathology), are not available at more than half a dozen centres. Even in the larger centres, issues of costing and expenditure have led to slashing of budgets and rising costs of histopathology, with resultant losses to the centres, and increased cost to the patients. Hence, most laboratories and pathology centres in the country are reluctant and not too keen to provide optimum histopathology facilities, which as mentioned above, are rather primitive in nature. In addition, many clinicians (both physicians and surgeons), especially those practising in smaller cities and towns across the country, are unaware (or unwilling) to accept the importance of a histopathological evaluation in the diagnosis and management of disease. In many cases, tissues are not sent for histopathological examination, because patients are poor and cannot afford the costs. Government healthcare is generally poor, the majority of the population has no health cover, and government pathology centres often lack both the proper facilities for histopathology as well as qualified histopathologists. Hence, people have no alternative but to turn to private pathology centres, especially for reporting of histopathology specimens, which are obviously expensive.

The Section of Histopathology at AKU receives approximately 45 000 surgical pathology specimens and approximately 25 000 cytology specimens per year. There is a dynamic faculty with diverse interests. Some of the consultant histopathologists are US or British trained, while others are the product of our own residency programme. The histopathology residency programme at AKU is recognised by the College of Physicians and Surgeons, Pakistan (CPSP), which regulates and controls residency programmes in various disciplines of medicine, and awards the FCPS diploma (Fellow of the College of Physicians and Surgeons) to candidates who successfully complete four to five year training programmes in their respective disciplines at centres recognised for such training by the college, and clear

the fellowship exam in their specific field. The College has played a major role, through the FCPS programme, in improvement of specialised health care in the country. The AKU residency program in histopathology is considered the best histopathology programme in the country. Other notable histopathology programs include those of AFIP in Rawalpindi, and SKMCH in Lahore. Graduates of our residency programme have done remarkably well. Some of us have gone on to become consultants in our own department, while others are serving other institutions in the UK and Pakistan with great distinction. Since 9/11, the world situation has hampered our efforts to attract qualified histopathologists, even of Pakistani origin from abroad, and therefore our great emphasis now is to retain and groom the graduates of our own programme for faculty positions, so that we can meet our ever expanding needs in the future. One of the principal authors (ZA) is also a graduate of our residency programme. We receive surgical and cytopathology specimens not only from our own hospital, but also from outside through our collection points, which are located not only in Karachi but in cities and towns throughout Pakistan. The same is true for the other major histopathology centres of the country. As awareness about the importance of histopathology is gradually increasing, the workload on the major histopathology centres is increasing tremendously. In effect, the number of histopathology specimens that any consultant histopathologist working in any of the major centres in the country reports every year is well above the numbers recommended by the Royal College of Pathologists or College of American Pathologists. This does create major safety and patient care issues, but in a country where there is such a great disproportion between demand (very high) and supply, ie, the availability of qualified histopathologists and centres (very low), there is little option. All the consultant histopathologists in our institution hold academic appointments, and in addition to the tremendous service and postgraduate teaching load, there is in addition a substantial undergraduate teaching load throughout the year, plus heavy administrative responsibilities. In addition, there is great pressure to do meaningful research, which in the presence of such heavy a workload is extremely difficult, to put it very mildly. In addition to a dearth of qualified histopathologists, the resources and the technological support for expansion are also inadequate. Histopathology technologists take years to become proficient in their work; however, due to meagre pay (at technologist level), we lose experienced technologists regularly as they seek greener pastures in areas like the Middle East. The loss of experienced technologists sets us back in our efforts for expansion and quality improvement. We even lose many qualified histopathologists who leave the country for a better future, as pay is not optimum, and the capacity of the few major centres for histopathology to hire more consultants is limited. We need major investment in this field, ie expansion of existing centres, opening of new centres, training facilities for technologists, effective retention policies for technologists (especially meaningful improvement in pay and other incentives, for example provision of formalities for further training), as well as better pay for histopathologists. For the last few years, the section of histopathology at AKU was so overwhelmed by the ever increasing number of cases, that in mid 2006, in an unprecedented step, we stopped accepting cases from most parts of the country (during this period, the situation was aggravated by two or three experienced consultants leaving for the USA or UK). As a result, we ourselves realised that in the absence of adequate resources, patient safety was being compromised, and the staff (consultants, residents and fellows, and technologists), were physically and mentally overworked, exhausted, stressed and demotivated. Since, this “capping” on cases was implemented, we have invested heavily by expanding our faculty (mostly by inducting our own trainees after they passed the FCPS exam), purchasing the latest equipment, etc. However, one area where we still lag is technological support. The technologists still do not have a desirable pay structure (to say the

least), experienced technologists are few, and they are under constant stress; to say that they are not too motivated is an understatement. We have lost and remain in peril of losing technologists (once they have gained sufficient experience) to greener pastures, somebody else's gain being our loss. The strengthening of our technological support base is crucial to our future needs.

An example in this context is our frozen section services. Unlike other surgical pathology specimens which are received from all over the country, specimens for frozen section are received from within AKU and from the rest of Karachi. The results of our frozen sections are excellent and comparable to international results.<sup>1</sup> However, our frozen section turnaround times (times in which frozen section is reported) are too long (average 23 minutes versus average 15 minutes in international studies). The cause is mainly lack of sufficient skilled frozen section technologists available, especially if multiple frozen sections arrive simultaneously. Usually only one technologist is assigned to the frozen section bench (and that too only partially as he/she is also assigned simultaneously to some other bench). Often no other technologist with sufficient skill and experience in cutting of frozen sections can be diverted in such situations to the frozen bench, with the result that frozen sections can only be cut serially and not simultaneously (even if more than one frozen section machine is available as in our case), leading to prolonged frozen section turnaround times. This again emphasises our earlier argument that we need to invest in technologists as much as we are investing in buying hardware.

The amount and the absolute diversity of cases that we get to see is literally breathtaking. We see "everything", there being no concept of being "subspecialists" only. There are obvious shortcomings in this, as we are forced to be "jacks of all trades and masters of none". However, the fact of the matter is that there are so few of us, and there is so much work that we cannot afford to confine ourselves to specific systems only. This "luxury" is not available to us. However, all of us have developed our own interests and through our own efforts and self-learning, we manage to acquire some level of expertise in particular fields. The hospital provides FDA (Faculty Development Awards) to each faculty, for which we can apply once every three years. In addition, funds are available to each faculty annually to attend meetings, conferences, workshops, etc. We utilise these facilities, as well as our contacts with colleagues in the West to obtain attachments for one to three months. In this way, we hone our skills in particular subspecialties, and although none of us claims to be a subspecialist, many of us have become to an extent, local experts in particular subspecialties. Also, all of us get to see so much of everything that we do acquire a reasonable level of proficiency in most subspecialties. For example, we see more lymphomas every day than many lymphoma experts in the West. The same is true for any other subspecialty. What I am suggesting is that through sheer exposure, hard work and self-learning, we try our best to solve the most different and complex cases reasonably accurately. We accept this as a challenge as a large chunk of the huge population of our country depends on us. In the past, we had regular avenues open, in particular the Armed Forces Institute of Pathology (AFIP), Washington, DC, USA for referring difficult and challenging cases, but that option is now closed. However, many patients, especially the well to do, take blocks from us abroad for a second opinion, and by the grace of God, the feedback is positive, with western pathologists mostly corroborating our diagnoses.

The cutting edge that our section has over the major histopathology centres in the country is due not only to the wealth of material (truly a national treasure), and the presence of a large

(and diverse) faculty, but also to a large (and comprehensive) immunohistochemistry panel which is constantly expanded and updated to include the latest markers. We perform immunohistochemistry wherever required quite liberally, and we do not charge extra money from the patients for performing this, whereas the few other centres in the country with immunohistochemistry facilities charge the patients for each antibody test that they perform. We perform whole panels in difficult cases and do not charge anything extra to the patient. We conducted studies to see the impact of immunohistochemistry on our practice. Immunohistochemistry was performed in over 29% of all malignant tumours. The results showed the enormous impact that immunohistochemistry had in accurate characterisation of poorly differentiated or undifferentiated malignant tumours, as well as in the typing of non-Hodgkin and Hodgkin lymphomas. We receive complex and challenging cases from all over the country, as well as a large number of cases for a second opinion. Another study conducted by us to see the importance of seeking a second opinion in a developing country like Pakistan, where as emphasised above, most centres have very primitive histopathology facilities, showed some startling results. There were major differences in the original diagnosis (given outside AKU), and the subsequent diagnosis (given at AKU) on blocks received in almost 36% of such cases (with major prognostic and therapeutic implications); immunohistochemistry played a major role in reaching a correct diagnosis with major implications for the patients. This study clearly showed that in a developing country, like Pakistan, where few laboratories are equipped to function as modern histopathology centres, it is important to get a second opinion on difficult cases, for optimum patient management.

Another major problem is that most clinicians do not provide any history or clinical details (even with very complex cases) and expect the histopathologists to act as “magicians”. In fact, many clinicians are very sceptical if we ask them for a history. As a result, we often look at cases “blindly”. This problem is mostly seen with cases which come from smaller cities and towns, but is also present to a smaller degree even in the cases coming from the big cities and large institutions, where most consultants are foreign trained and qualified. Even more critical is the absence of any follow-up. Except for cases from our own hospital (and cases from some other clinicians practising in Karachi), we do not and cannot hope to have any meaningful follow-up of the cases reported by us. On the one hand, this does not allow us to audit ourselves (regarding our diagnoses) since we never get to know the patient outcomes; and on the other hand, it hampers us in our efforts to do meaningful research and write original research papers. We feel as pathologists that there is a great need to educate clinicians regarding the importance of providing the pathologist with a detailed and relevant clinical history with the biopsy or resection specimens. We also strongly feel the need for a close liaison between clinicians and histopathologists, so that adequate follow-up of the patients can be maintained. This obviously is not only of great benefit to the patient but will also ultimately benefit the clinician and the pathologist. However, establishment of such a close relationship, especially in a country like ours is extremely difficult, because as mentioned above, we receive specimens from the whole country, from clinicians and hospitals scattered in a population of 160 million people. But we do believe that the struggle, in this respect, must go on.

A major strength of our Section of Histopathology is the Departmental Consultation Conference (DCC). In addition to personal consultations between two or more pathologists in the section, an intradepartmental consultation session is held daily on a multiheaded microscope. It is based on quality assurance and quality improvement manuals published internationally. It is a prospective system by which all difficult, controversial and problematic cases are presented for review and discussion, and a consensus diagnosis is reached. These

cases are then signed out under the primary consultant, but a comment identifying the presentation of these cases in the DCC is incorporated in the final report, immediately following the diagnosis. The daily session is run by the most senior consultants in the Section of Histopathology, and is attended by all histopathology consultants, instructors (equivalent to fellows) and residents. This conference has been held regularly, more or less on a daily basis, for the last seven years with great success, so much so that it has become an integral part of the routine working of the Section of Histopathology, AKU.

The Section of Histopathology regularly receives cases from College of American Pathologists (CAP) surveys, and these are also discussed formally. Different CAP surveys are assigned to individual consultants who are responsible for sending the answers within the determined time limits. They are also required to discuss the cases in formal teaching sessions in which all consultants, instructors and residents participate. Hence, these CAP surveys also play an important role in our postgraduate training. However, most histopathology centres in Pakistan, with few exceptions, lack these quality assurance and quality control mechanisms.

A major weakness in our centre is the absence or lack of regular audits or random reviews of surgical pathology, frozen section or cytopathology. The main reason is the overwhelming workload. However, we are seriously discussing this issue at present, and hopefully, in the near future, we will start regular audit/review processes.

Another major deficiency in our section (and in our residency programme) is the lack of autopsy cases. In Pakistan, autopsies for religious, social and cultural reasons are very uncommon, and are limited to armed forces institutes and government hospitals. We perform fetal autopsies regularly but no adult autopsies are performed. There have been half-hearted attempts in the past to send our residents for a particular duration to army hospitals where autopsies are performed. However, no regular and permanent system is in place. In addition, only those consultants who are US or UK trained have autopsy training and experience, while the rest of us who are products of our own residency programme are deficient in this respect. Other weaknesses in our department include the absence of an electron microscope (even renal biopsies are reported on the basis of light microscopy and immunofluorescence alone); limited flow cytometry and FISH (fluorescence in situ hybridisation); and very little cytogenetics and molecular pathology. So far, we have used the technique of flow cytometry only in leukaemias—however, we are planning to shortly use flow in solid tumours as well. As most studies on flow suggest, the main role of flow cytometry is as a prognostic indicator. Karyotypic analysis of tumours (cytogenetics), which was until now used only for research and experimental purposes, is also now being developed for routine diagnostic purposes, and as a pilot, it is to be used in suspected Ewing sarcomas (and primitive neuroectodermal tumours (PNETs)), and synovial sarcomas. These will no doubt help us in reaching more accurate diagnoses in histopathologically homogeneous tumour types, and as suggested by Sandberg et al, in determining the site of the primary tumour when a specific cytogenetic change is found in a metastasis. Molecular methods are beginning to have a major impact on surgical pathology practice, so rapidly is this field advancing. We are using PCR to detect immunoglobulin or T cell gene rearrangements in lymphomas/leukaemias to determine the clonality of B and T cell proliferations. But we are under pressure to discontinue this service due to cost constraints. We have used interphase cytogenetics (analysis of chromosomes in non-dividing cells) utilising the FISH technique, in haematological malignancies; but as technical advances now allow the procedure to be carried out in frozen sections and paraffin

sections, leading to their increasing use in solid tumours, we are also in the process of starting the use of the FISH technique in solid tumours.

We would like to emphasise here that except for haematopoietic malignancies (leukaemias), we report solid malignant tumours, and that cancers comprise the most significant burden of our cases. Indeed, we feel that there is a cancer “epidemic” in Pakistan, so prevalent is its occurrence. There is, however, no countrywide cancer registry to enable us to determine the incidence of various cancers and the exact burden of cancer in Pakistan; we only know that it is very great. However, recently regional cancer registries are being developed, and some people are doing excellent and valuable work in this regard, so that in the near future, Pakistan may have an official cancer registry. Not only is cancer very prevalent, it is also very advanced. We always see not just a lot of cancer, but in the large majority of cases, very advanced cancer. Cancers of various types are only topped by tuberculosis as far as the frequency of cases seen by us is concerned. We will try to give an idea of this terrible cancer burden by citing our own studies.

We diagnose all solid malignant and benign neoplasms in the Section of Histopathology, including lymphomas. However, leukaemias primarily are diagnosed in the separate Section of Haematology. A study of 20 000 consecutive cases carried out in our section showed that malignant neoplasms comprised 23.08% of all cases. According to this study, squamous cell carcinoma of the oral cavity, diffuse large B cell non-Hodgkin lymphoma, and prostatic adenocarcinoma were the three commonest malignant neoplasms in men, comprising 9.94%, 9.32% and 6.89% of all malignant neoplasms. These were joined in the five commonest malignancies in males by colorectal adenocarcinoma (6.56%) and urothelial carcinoma of the urinary bladder (5.77%). In the same study, infiltrating ductal carcinoma of the breast dwarfed all other malignant neoplasms in women, comprising 33.56% of all female malignancies. The other four malignant neoplasms comprising the top five in females were squamous cell carcinoma of oral cavity (7.06%), squamous cell carcinoma of oesophagus (5.35%), colorectal adenocarcinoma (4.27%) and diffuse large B cell non-Hodgkin lymphoma (3.96%).

Another study conducted in our section looked at the frequency of primary solid malignant neoplasms in different age groups. This study showed that malignant neoplasms in both sexes were most common in the fifth and sixth decades of life. In men, the commonest malignant neoplasms in the first, second and third decades, respectively, were Hodgkin lymphoma, osteosarcoma and colorectal adenocarcinoma, comprising 25.92%, 15.55% and 14.09% of all malignant neoplasms in these decades. In each of the fourth, fifth and sixth decades, squamous cell carcinoma of the oral cavity was the commonest malignant neoplasm, comprising 15.15%, 12.53% and 11.98% of all malignant neoplasms in these decades. Prostatic adenocarcinoma was the commonest neoplasm in the seventh decade, as well as above the age of 70, comprising 15.09% and 25.55% of all malignant neoplasms in this age group, respectively. Nephroblastoma and Ewing sarcoma/PNET were the commonest malignant neoplasms in women in the first and second decade, comprising 14.75% and 17% of all malignant neoplasms, respectively; from the third decade and onwards, infiltrating ductal carcinoma of breast was overwhelmingly the commonest neoplasm in each decade, comprising 23.17%, 47.23%, 41.46%, 30.75%, 27.94%, and 24.7% of all malignant neoplasms in the third, fourth, fifth, sixth, seventh and eighth decades respectively. Infiltrating ductal carcinoma of breast was the single commonest malignant neoplasm in both sexes combined, comprising literally a breast carcinoma epidemic in our country; by its sheer

enormity it ensured that the absolute number of malignant neoplasms diagnosed in the fourth and fifth decades was greater in females compared to males. These studies also showed that carcinoma of the oral cavity is very common in our population in both sexes, probably due to eating of betel leaves, chalia (nuts), niswar, etc; and that colorectal adenocarcinoma is not only very common in both sexes, but also occurs commonly in younger age groups. Oesophageal and gastric carcinoma are also very common, the former, in our experience, especially in the province of Balochistan, which borders Iran, a region endemic for this cancer. Also the hot, spicy foods eaten in our country may be a significant contributing factor. Similarly, our practice shows a very high prevalence of hepatocellular carcinomas in both sexes (no doubt related to the terrible burden of hepatitis B+C infections in our population), laryngeal carcinomas, (again probably related to cigarette and huqqa smoking), and endometrial carcinomas. All types of thyroid lesions are very commonly seen in our practice, related to both iodine deficiency and autoimmune factors. A significant proportion of thyroid lesions are neoplastic. Papillary carcinomas of the thyroid are very common; we also regularly see follicular carcinomas.

It is not just that cancer of all kinds is very prevalent in Pakistan, but also that most cancers that we see (or indeed when the clinicians see these patients) are in advanced stages. It is only a small proportion of cancers, for example early precancerous breast and colonic lesions that we see; these are mainly in patients who come to clinicians at AKU. Otherwise, it is just too much cancer and advanced cancer at that. We will illustrate by again quoting from studies done in our section. A study on resection specimens of colorectal carcinoma showed that 83.33% cases were T3 and another 2.35% were T4. Radial margin was positive in 23.08% of rectal carcinomas, and 57.65% cases showed lymph node metastases. Of the cases with positive nodes, more than 73% had two or more positive nodes, which significantly worsens the prognosis compared to when a single node is involved. Similarly, a study on resection specimens of gastric carcinomas showed that 66% cases were T3 and 1% were T4. At least one peripheral resection margin was positive in 29% of cases. Lymph nodes were positive in 76% of cases. Of the cases with positive nodes, 35.52% were N2 and 18.42% were N3.

Another study conducted in our section on radical mastectomy specimens for breast carcinoma, showed that 41.66% of cases were T3 and another 3.33% were T4; 74.76% cases showed lymph node metastases. Of the cases with positive nodes, 32.5% were N2 and 31.25% were N3. Perinodal extension was present in 73.8% of cases. These findings are all indicative of extensive and advanced disease.

Renal and urinary bladder carcinomas too are commonly seen in our practice. A study on urothelial carcinomas of urinary bladder showed that almost 42% were high grade according to the WHO consensus classification of bladder carcinomas. The same study showed that over 34% of the tumours invaded the muscle wall of the urinary bladder. We see a lot of CNS tumours and we believe that their number is ever increasing. A study on CNS tumours showed that the largest group of CNS neoplasms were grade III and IV astrocytomas in adults, while among children, medulloblastomas were second only to pilocytic astrocytomas. Ovarian tumours of all types, both benign and malignant, are very common. A study on ovarian tumours carried out in our section showed that 40.18% of all ovarian tumours were malignant. According to this study, 40.88% of all surface epithelial tumours, 48% of sex cord-stromal tumours, and almost 20% of germ cell tumours were malignant. The most common malignant tumours were papillary serous carcinoma and endometrioid carcinoma.

A yet unpublished study on radical prostatectomy specimens shows that the majority of cases were pT3, ie tumour was no larger confined to the prostate, although clinical stage in the large majority of cases (83.63%) was T1. In this study, 31.66% cases were pT3a, 23.33% were pT3b and an additional 3.33% were pT4. So more than 58% cases showed advanced disease.

All the above figures amply illustrate the terrible cancer burden we carry. We still do not know the full magnitude of the problem but it is clear that whether they are carcinomas, or lymphomas or sarcomas of soft tissue and bone, all tumours are present in literally epidemic form. Add to this cancer burden the almost non-existent medical facilities at government level, illiteracy and poverty, the virtual lack of any insurance cover for the overwhelming majority of the population etc, and you can well imagine the magnitude of the disaster. Unfortunately, surgical skills, especially among surgeons practising in small towns, are also suspect as evidenced by numerous resection specimens which appear incompletely excised, showing positive excision margins, greatly increasing the risk of recurrence. This is true not just for gastric and colonic resection margins, for example, but also especially for soft tissue lesions (including sarcomas), and not only when these are intra-abdominal or deep seated in the limbs, but also unfortunately in superficially situated limb sarcomas where they are easily accessible. Compromised surgical techniques also result in the presence of very few lymph nodes in resection specimens from breast, colon, stomach etc; this results in compromised staging of the tumours in such cases.

Another reason for cancers being in an advanced stage when they first come to clinical attention or are resected is that patients themselves delay seeking medical attention until the condition is far advanced. This happens not only due to poverty, but also, and especially in the case of women, due to social and cultural norms; women feel shy and are reluctant to disclose their condition, even when carrying huge ovarian cysts manifesting as abdominal masses, or large, even ulcerated masses in their breasts.

It is also important to understand that cancer is not the only burden that the people of Pakistan carry. Infectious diseases, especially tuberculosis—alluded to half jokingly as our national disease by one of our colleagues, may be the single most dominant disease entity in the country (although no exact figures are available), and it may be single most common disease entity (neoplastic or non-neoplastic) that we see in our practice. Fungal infections are common as well; we see many giardia and amoebae in our biopsies, and Helicobacter appears rampant. We see many cases of villous atrophy (malabsorption), and non-neoplastic skin conditions. Malignant neoplasms of skin, such as squamous cell carcinoma, basal cell carcinoma and malignant melanomas are also very common, as are skin adnexal tumours (mostly benign).

Non-neoplastic and neoplastic bone and soft lesions constitute another major chunk of our practice; osteosarcomas (in the young) and soft tissue sarcomas are rampant. Primitive tumours of all types are very common; special mention in this connection can be made of rhabdomyosarcoma, neuroblastoma (Wilm's tumour), etc. Synovial sarcoma is very common, in our experience, in the younger age group. Both Hodgkin and non-Hodgkin lymphomas are extremely common in both adults and children (anaplastic large cell lymphomas are increasingly common in this age group). We see many gastrointestinal stromal tumours in the gut. So there is much neoplasia, benign and malignant, of all types.

With not even a well developed cancer registry, studies on prognosis and treatment outcomes remain so far the stuff of dreams.

Why so much disease? Why so much cancer? Genetics, immune and environmental factors all definitely play major roles. We personally feel that infections are important in this respect. Hepatitis B and C, for example, are again epidemic in our population—the sheer magnitude of cirrhosis cases that we see on liver biopsies in such patients, is depressing indeed.

We believe that environmental and industrial pollution, lack of clean water to drink, and lack of sanitation are all major factors. The plight of our poor patients who cannot afford to go to the doctor, who are deprived of the basic necessities of life like clean drinking water, and who live in unsanitized conditions, tears our hearts. Even the wealthy are exposed to unsanitary conditions, and terrible environmental pollution. Our government (and private sector as well) need to invest heavily in the health of our people if we truly want to make Pakistan a prosperous, modern country.

The practice of quality histopathology in a developing country like Pakistan is a great challenge. But at the same time, it gives us a great opportunity to try and serve our country to the best of our ability. We are placed in a position where we can in our own way bring positive change for our great country and its fantastic, hardworking people. This article only serves to highlight a few areas and challenges that we must cope with in our field. Only outlines have been given since space does not allow us to cover all aspects in any great detail. However, we hope that our colleagues in the West, doctors in general, and surgeons and histopathologists in particular, will appreciate the difficulties and challenges that are faced by practicing histopathologists in a developing country.

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## **60 Million Worldwide Carry Heart Disease Mutation**

January 23, 2009 (HealthDay News) -- About 60 million people worldwide carry a gene mutation that almost always causes heart disease, but the mutation is most common among people in India, according to a study by 25 researchers from four countries.

Heart disease is the leading cause of death in the world. By 2010, India will account for about 60 percent of the world's heart disease, said the researchers, who analyzed the DNA of about 800 patients at cardiac centers in India. The study was published in the Jan. 18 issue of *Nature Genetics*.

The mutation, a deletion of 25 letters of genetic code from the heart protein gene- cardiac **myosin binding protein C (MYBPC3)**, was discovered five years ago in two Indian families with a history of cardiomyopathy, an enlargement or abnormal thickening of the heart muscle that weakens the heart and reduces its ability to pump blood.

The genetic risk of heart disease is expressed as an odds ratio. A small effect would be 1:2 and a large effect would be 2:0. The researchers said the odds ratio for people with the MYBPC3 mutation is almost off the scale, 7:0. People with the mutation usually have few symptoms until middle age. But after that, most develop symptoms and are at risk for sudden cardiac death.

"The mutation leads to the formation of an abnormal protein. Young people can degrade the abnormal protein and remain healthy, but as they get older, it builds up and eventually results in the symptoms we see," study leader Kumarasamy Thangaraj, Center for Cellular and Molecular Biology in Hyderabad, India, said in a news release issued by the Wellcome Trust Sanger Institute.

The researchers believe the mutation arose about 30,000 years ago in India, and spread because its effects usually develop only after people with the mutation have had children.

"The bad news is that many of these mutation carriers have no warning that they are in danger, but the good news is, that we now know the impact of this mutation," Perundurai S. Dhandapany, of Madurai Kamaraj University in Madurai, India, said in the news release.

Genetic screening can identify carriers of the mutation at a young age. It may be possible to develop drugs to combat the abnormal protein caused by the mutation and postpone the onset of symptoms.

*SOURCE: Wellcome Trust Sanger Institute, news release, Jan. 18, 2009*

### **Blue Rubber Bleb Nevus Syndrome: Novel Lymphangiomas-Like Growth Pattern within the Uterus and Immunohistochemical Analysis**

**Rajal C. Patel, Debra L. Zynger and William B. Laskin**

Blue Rubber Bleb Nevus Syndrome is a rare, primarily sporadic condition characterized by vascular lesions principally involving the skin and gastrointestinal tract. Although considered a venous malformation, telangiectatic capillaries, arteriovenous malformations, and lymphangiomas have been reported, but a lymphangiomas-like growth pattern has not been described. This case of Blue Rubber Bleb Nevus Syndrome demonstrated a labyrinth of variably sized vascular spaces lined by an attenuated layer of bland endothelial cells, dissecting uterine tissues and sequestering remaining myometrium. Immunohistochemical profile of lesional endothelial cells from the myometrium included strong, diffuse CD31; variable CD34; strong, patchy D2-40; weak, patchy factor VIII-related antigen; focal linear subendothelial collagen type IV; Ki-67 in 1% of cells; and no GLUT-1 or WT1 expression. This report expands the morphological spectrum of vascular lesions in Blue Rubber Bleb Nevus Syndrome to include a lymphangiomas-like growth pattern and the immunohistochemistry suggests dual vascular and lymphatic differentiation, supporting the current belief that these lesions are malformations.

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### **New Classification of Melanocytic Nevi Based on Dermoscopy**

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The lack of consensus among clinicians and pathologists, owing to the mixture of clinical and histopathologic features used to define the various melanocytic nevi, underscores the need for a better classification system for these benign lesions. Most dermoscopic patterns of melanocytic nevi correspond to specific histopathologic correlates and, based on this, we recently introduced a new classification system of melanocytic nevi that is directed at

clinicians dealing with early diagnosis of melanoma, as well as pathologists, in order to promote better communication between these different specialists.

In contrast to large and intermediate-size congenital melanocytic nevi (CMN), which can be easily recognized because of their size (>1.5 cm or more), the clinical diagnosis of most other melanocytic nevi (MN) is only suboptimal and, accordingly, histopathology is the 'gold standard' in the diagnosis and classification of MN. Various attempts have been made to classify nevi based on their clinical (raised versus flat) or histopathologic features (Unna's, Miescher or Clark nevi) and, as a consequence, the current classification system is based on a mixture of clinical and histopathologic criteria. However, these do not reach a good interobserver agreement between clinicians and pathologists.<sup>[1,2]</sup> The decades of controversies and still-unsolved discussions regarding the questionable entity of 'dysplastic MN' highlight the problems relating to the current classification of MN.

The introduction of dermoscopy enabled clinicians to observe colors and structures within MN that are otherwise not visible to the unaided eye. Since these colors and structures correspond to well-defined histological correlates it is not surprising that dermoscopy allows clinicians to predict the histopathology diagnosis more precisely and, thereby, improve their clinical diagnostic accuracy. Besides this, dermoscopy and digital dermoscopic follow-up has led to new understanding regarding the evolution of MN and, recently, a new concept of nevo genesis.

Briefly, the new concept states that nevi develop via two different pathways, namely an endogenous (origin from dermal melanocytes) and exogenous (origin from epidermal melanocytes) pathway. The former leads to nevi that develop in early childhood and persist throughout a person's lifetime, revealing a dermoscopic globular pattern, while nevi with an epidermal origin develop mostly at puberty due to exogenous factors, such as UV exposure, and show a dynamic life-cycle. These latter nevi exhibit a reticular pattern by dermoscopy. Consequently, we recently proposed a new classification system of MN based on the overall dermoscopic appearance of MN and their related epidemiologic, clinical and histopathologic criteria. This classification system is designed particularly for clinicians dealing with the diagnosis and management of melanocytic skin lesions, as well as pathologists, in order to promote a better mutual comprehension between these different specialists. The diagnosis of MN is based on the assessment of four main dermoscopic criteria with specific underlying histopathologic correlates.

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## **Diagnostic Challenges of the Fine Needle Aspiration of Liver Nodules**

**Droc, Claudia; Aufman, Jeffrey; Centeno, Barbara .**

Fine needle aspiration of liver nodules poses several diagnostic challenges. One of the key diagnostic issues is differentiating between well differentiated hepatocellular carcinoma and morphologically similar benign entities. Also challenging is differentiating higher grade hepatocellular carcinomas from other malignancies such as metastatic adenocarcinomas and cholangiocarcinomas. To make an accurate diagnosis, authors correlate the clinical history and imaging characteristics of liver nodules with the cytomorphological features and results

of ancillary studies. By combining this information, the sensitivity of the fine needle aspiration of liver nodules approaches 92%.

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